

“Peptidomimetic compounds and preparation of biologically active derivatives”

The present invention relates to novel cyclic peptidomimetic compounds having an azabicycloalkane structure, and the preparation of antagonists of integrins $\alpha v\beta 3$ and $\alpha v\beta 5$, useful for example, in the treatment of altered angiogenetic phenomena. The invention also concerns a process for the transformation of the functional groups of said cyclic peptidomimetic compounds and the biologically active derivatives thereof.

BACKGROUND OF THE INVENTION

10 A great number of physiological processes involve biologically active peptides, through their interactions with receptors and enzymes. However, peptides are not to be considered ideal drugs, given their poor metabolic stability, rapid excretion and low selectivity for specific receptors. A valid alternative involves the design of peptide analogues which are capable of mimicking the action of the natural peptide at the receptor level (peptidomimetic) [(a) Kahn, M. (Editor). Peptide Secondary Structure Mimetics. *Tetrahedron Symposia-in-Print* No. 50 **1993**, 49, 3433-3689. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1699-1720. (c) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, 36, 3039-3049. (d) Kitagawa, O.; Velde, D. V.; Dutta, D.; Morton, M.; Takusagawa, F.; Aubè, J. *J. Am. Chem. Soc.* **1995**, 117, 5169-5178. (e) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1244. (f) Aube, J. *Tetrahedron Symposia-in-Print* No. 50, **2000**, 56, 9725-9842].

25 During our research into peptide secondary structure mimetics, certain 6,5- and 7,5-azabicycloalkane aminoacids have been synthesised [(a) Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, 36, 625; (b) Colombo, L.; Di Giacomo, M.; Belvisi, L.; Manzoni, L.; Scolastico, C. *Gazz. Chim. It.* **1996**, 126, 543; (c) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Sardone, N.; Angiolini, M.; Belvisi, L.; Maffioli, S.; Manzoni, L.; Scolastico, C. *Tetrahedron* **1998**, 54, 5325-5336; (d) Angiolini, M.; Araneo, S.;

Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* 2000, 2571-2581; (e) Manzoni, L.; Colombo, M.; May, E.; Scolastico, C. *Tetrahedron* **2001**, 57, 249; (f) Belvisi, L.; Colombo, L.; Colombo, M.; Di Giacomo, M.; Manzoni, L.; Vodopivec, B.; Scolastico, C. *Tetrahedron* **2001**, 57, 6463; (g) EP 1 077 218; (h) Colombo, L.; Di Giacomo, M.; Vinci, V.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron*, **2003**, 59, 4501-4513; (i) Manzoni, L.; Colombo, M.; Scolastico, C. *Tetrahedron Lett.* **2004**, 45, 2623-2625; (l) Belvisi, L.; Colombo, L.; Manzoni, L.; Potenza, D.; Scolastico, C. *Synlett*, **2004**, 1449-1471.

These structures may be considered as conformationally constrained analogues of the Ala-Pro and Phe-Pro dipeptide units. [(a) Belvisi, L.; Bernardi, A.; Manzoni, L.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* 2000, 2563-2569; (b) Gennari, C.; Mielgo, A.; Potenza, D.; Scolastico, C.; Piarulli, U.; Manzoni, L. *Eur. J. Org. Chem.* 1999, 379].

The functionalisation of such molecules with heteroalkyl substituents is an aim of great interest, since the side chains may increase the affinity of the peptide for the receptor by interacting with the hydrophobic or hydrophilic sites of the receptor itself. A further advantage of such systems is the possibility of binding to different pharmacophoric groups and hence the possibility of creating a library, with the member components of which having different biological properties and activities. During our research into peptide secondary structure mimetics, certain 6,5- and 7,5-azabicycloalkane aminoacids have been synthesised which have been functionalised with heteroalkyl appendages [(a) Artale, E.; Banfi, G.; Belvisi, L.; Colombo, L.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron*, **2003**, 59, 6241-6250; (b) Bracci, A.; Manzoni, L.; Scolastico, C. *Synthesis* **2003**, 2363-2367; (c) Bravin, F. M.; Busnelli, G.; Colombo, M.; Gatti, F.; Manzoni, L.; Scolastico, C. *Synthesis*, **2004**, 353; (d) Manzoni, L.; Belvisi, L.; Colombo, M.; Di Carlo, E.; Forni, A.; Scolastico, C. *Tetrahedron Lett.* **2004**, 45, 6311-6315].

Furthermore, analogously to what occurs for non-substituted conformationally constrained dipeptide mimetics [Belvisi, L.; Bernardi, A.; Checchia, A.; Manzoni, L.; Potenza, D.; Scolastico, C.; Castorina, M.; Cupelli, A.; Giannini, G.; Carminati, P.; Pisano, C. *Org. Lett.* **2001**, 3, 1001, C. Scolastico, L.

Manzoni, G. Giannini. Brit. UK Pat. Appl. 2004. GB 2395480] such heteroalkyl substituted lactams may be incorporated into cyclic pseudo-peptides containing RGD sequence.

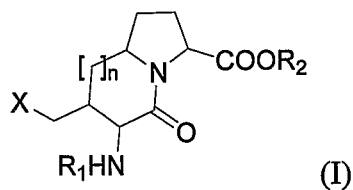
Such molecules may be selectively targeted to those tissues over-expressing certain receptors (*e.g.* epithelial cells involved in vascular growth), so as to be able to be used to inhibit angiogenesis and selectively control the release of any drugs optionally bound to the substituent groups on the lactam ring [Arap, W.; Pasqualini, R.; Ruoslahti, E. *Science*, **1998**, 279, 377].

The low number of “scaffolds” reported in the literature necessitates the design and synthesis of novel conformationally constrained dipeptide mimetics, functionalised with hetero-substituted side chains for interaction with various receptors.

DESCRIPTION OF THE INVENTION

It has now been found that certain conformationally constrained azabicyclic[X.Y.0]alkanes satisfy the characteristics required for the application of this kind of technology. Particularly, it has been found that compounds containing the conformationally constrained homoSer-Pro dipeptide unit structure are useful as drugs, particularly as drugs with antagonistic action towards the $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins.

Thus, according to one of the aspects thereof, the invention concerns compounds of general formula (I)



where:

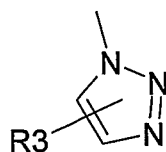
n has the value of 1 or 2,

R₁ is H, (C₁-C₄) linear or branched alkyl or a protective group;

R₂ is H or a protective group;

X is N₃, -NH-R₃, -N(R₃)₂, -NAlkR₃, -NH-CO-R₃, -NH-CS-R₃,
-NH-CO-NHR₃,

-NH-CS-NHR₃, or



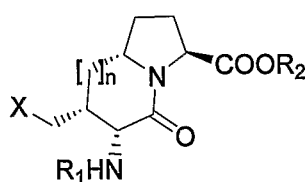
where

Alk = (C₁-C₄) linear or branched alkyl

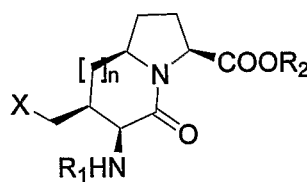
5 R₃ = H, a protective group, a biologically active molecule;

their salts, racemic mixtures, individual enantiomers, individual diastereoisomers and mixtures thereof in whatever proportion.

According to another aspect thereof, object of the invention are compounds of formulae (Ia) and (Ib)



(Ia)



(Ib)

where n, R₁, R₂ and X are as defined above and the wedge-shaped and dashed bonds indicate that the substituents are positioned above and below the plane respectively.

15 According to the present invention, the term “(C₁-C₄) alkyl” designates a linear or branched, saturated or unsaturated alkyl substituent comprising from 1 to 4 carbon atoms such as for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl. However, it is possible to use alkyl substituents containing a higher number of carbon atoms providing they are compatible with the reaction conditions of the
20 present invention.

According to the present invention, the expression “protective group” designates a protective group adapted to preserving the function to which it is bound, specifically the amino function or carboxyl function. Appropriate protective groups include for example benzyl, benzyloxycarbonyl, alkyl or benzyl esters, or other
25 substituents commonly used for the protection of such functions, which are well known to those skilled in the art, for example those described in conventional

manuals such as T. W. Green, Protective Groups in Organic Synthesis (Wiley, N.Y. 1981).

In the present description, by “biologically active molecule” is meant any molecule that may be used as a drug, or also as a “targeting” molecule, a
5 diagnostically useful molecule, or even a sugar etc.

Said biologically active molecule may be bound to compound of formula (I), either directly or through an appropriate spacer allowing or promoting binding, and optionally release into the site of action.

The salts of the compounds of formulae (I), (Ia) and (Ib) according to the
10 present invention comprise both those with mineral or organic acids allowing the expedient separation or crystallisation of the compounds of the invention, and those forming physiologically and pharmaceutically acceptable salts, such as for example hydrochloride, hydrobromide, sulphate, hydrogen sulphate, dihydrogen sulphate, maleate, fumarate, 2-naphthalenesulphonate, para-toluenesulphonate, oxalate etc.

15 Salts of the compounds of formulae (I), (Ia) and (Ib) according to the present invention also further include physiologically and pharmaceutically acceptable quaternary ammonium salts.

Said salts are prepared according to the well known techniques for the person skilled in the art.

20 When there is a free carboxyl group ($R_2=H$) present, the salts of the compounds of the invention also comprise salts with organic or mineral bases, such as for example alkaline metal or alkaline earth metal salts, such as sodium salts, potassium or calcium salts, or with an amine such as trometamol (tromethamine), or salts of arginine, lysine or any other physiologically and pharmaceutically acceptable
25 amine.

According to one preferred embodiment, object of the invention are compounds of formulae (I), (Ia) and (Ib) wherein n is 1, R_1 is benzyloxycarbonyl, R_2 is tert-butyl, X is N_3 or NH_2 .

According to another preferred embodiment, object of the invention are
30 compounds of formulae (I), (Ia) and (Ib) wherein n is 2, R_1 is benzyloxycarbonyl, R_2 is tert-butyl, R_3 is N_3 or NH_2 .

A process for the synthesis of such compounds is described in detail over the course of the present description, making reference to the synthetic schemes reported in the enclosed figures.

According to the present invention, compounds of formulae (I), (Ia) and (Ib)
5 may be prepared according to the processes described hereinafter.

Particularly, compounds of general formulae (Ia) 6,5-*trans*- and (Ib) 6,5-*cis*-fused, may be prepared according to a synthetic process outlined in Scheme 1 (wherein n=1), comprising the following stages:

- 10 a) hydrogenation of the isoxazolidine of compound 1 or of compound 2, for example with H₂, Pd/C in MeOH;
- b) protection of the amine group with a suitable protective group, such as for example Cbz, Boc, etc.;
- c) transformation of the free hydroxyl group into an azide through the Mitsunobu reaction, or by means of any other known method (for
15 example, transformation into mesylate and subsequent nucleophilic substitution with sodium azide), to give compounds of formulae 6, 9;
- d) reduction of the azide group into an amino group through the Staudinger reaction, or by means of hydrogenation to give compounds 7 and 10.

The compounds of general formulae (Ia) 7,5-*trans* and (Ib) 7,5-*cis* fused, may
20 be prepared according to a synthetic process outlined in Scheme 2 (wherein n=2), comprising the following stages:

- a) hydrogenation of the isoxazolidine of compound 3 or of compound 4, for example with H₂, Pd/C in MeOH;
- b) protection of the amine group with a suitable protective group, such as
25 for example Cbz, Boc, etc.;
- c) transformation of the hydroxyl group into an azide through the Mitsunobu reaction, or by means of any other known method (transformation into mesylate and subsequent nucleophilic substitution with sodium azide), to give compounds of formulae 12, 15;
- 30 d) reduction of the azide group into an amino group through the Staudinger reaction, or by means of hydrogenation to give compounds 13, 16.

To the resulting lactams, following the introduction of the azide group **6**, **9**, **12** and **15**, may be bound the desired biologically active molecules or compounds of biological importance such as sugars, through appropriate reactions known to those skilled in the art (Click chemistry).

5 Or moreover, to the amide or thioamide groups (compounds wherein X = NH-CO-R₃ or NH-CS-R₃) derived from lactams **7**, **10**, **13** and **16** may be bound appropriate substituents or known spacers, to give for example ureas or thioureas (*i.e.* to form compounds wherein X = -NH-CO-NHR₃, -NH-CS-NHR₃), prepared by reacting with isocyanates or isothiocyanates according to procedures known to the
10 person skilled in the art.

Practical examples are reported in the experimental section of the present description.

The tricyclic starting compounds **1-4** (n=1 and n=2, Figure 1) may be prepared according to the procedures described in Scheme A – Preparation of the
15 starting products.

The compounds of the present invention of formulae (I), (Ia) and (Ib) may be used as conformationally constrained scaffolds with the possibility to replicate the geometry of the backbone and of the side chains of a peptide residue within the active site, and be used for the preparation of biologically active compounds.

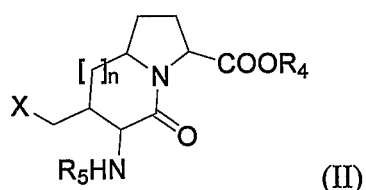
20 The need to conjugate drugs or other molecules of biological interest to systems of this kind is linked to the possibility for providing molecules having functional groups forming biologically stable bonds, for example containing nitrogen, present for example as an amino or amide group, azide or triazole.

Schemes 6-9 relates to conjugation examples through click chemistry
25 between sugars, fluorescein and biotin and compounds of general formula (I). Scheme 8 refers to the preparation of one utilized linker, taken as an example.

In pursuit of such aims, it has now been found that certain of the novel compounds of general formula (II), reported hereinafter, satisfy the required characteristics for the application of this type of technology. Particularly, it has been
30 found that compounds having general formula (II) are useful as drugs, particularly as drugs having antagonistic action against the $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins, particularly

those compounds deriving from the transformation of the compounds of formulae (I), (Ia) and (Ib) as set out above, wherein the peptide sequence RGD has been introduced.

Thus, in accordance with another aspect thereof, object of the invention are
5 novel compounds of formula (II)

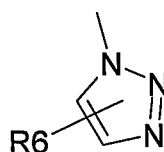


wherein:

n has the value of 1 or 2,

R₄ and R₅ together constitute the sequence Asp-Gly-Arg,

10 X is N₃, -NH-R₆, -N(R₆)₂, -NAlkR₆, -NH-CO-R₆, -NH-CS-R₆,
-NH-CO-NHR₆,
-NH-CS-NHR₆, or



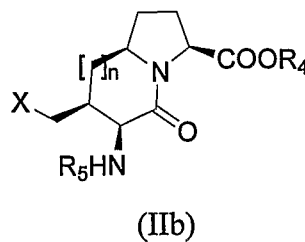
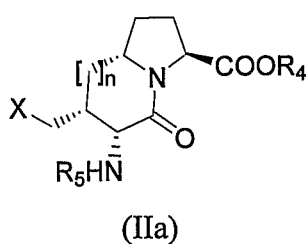
wherein

15 Alk = (C₁-C₄) linear or branched alkyl

R₆ = H, a protective group, a biologically active molecule;

their salts, racemic mixtures, individual enantiomers, individual diastereoisomers and mixtures thereof in whatever proportion.

According to one preferred aspect, the invention concerns compounds of
20 formulae (IIa) and (IIb)



wherein n, R₄, R₅ and X are as defined above and the wedge-shaped and

dashed bonds indicate that the substituents are positioned above and below the plane respectively.

The peptide sequence Asp-Gly-Arg is advantageously bound to compounds (II), (IIa) and (IIb) in such a manner whereby the carboxyl group is attached to the aminoacid arginine, and the amino group is attached to aspartic acid.

The details provided above for the variable substituents (alkyl, etc.) and the salts of the compounds of formula (I) are also applicable to the compounds of formulae (II), (IIa) and (IIb).

Thus, just as for the compounds of formula (I), X may represent an amino residue, an amide residue, a urea, a thiourea, said residues advantageously being substituted.

The Asp-Gly-Arg chain may be introduced by adapting the compounds of formulae (I), (Ia) and (Ib) described above, according to a process comprising the following stages:

- when R_2 is a protective group, chemoselective deprotection reaction of the carboxyl group of compound of general formula (I) and condensation with the appropriately protected Arg-Gly dipeptide;
- reduction of the oxazolidine by means of catalytic hydrogenation;
- transformation of the methyl ester of glycine into the benzyl ester through a transesterification reaction, followed by the simultaneous removal of the protective group from the glycine and the amino group from the aspartic acid by catalytic hydrogenation;
- condensation agent mediated intramolecular cyclisation and subsequent deprotection of the amino acid side chain protective groups.

The functional group protection and deprotection reactions may be carried out in accordance with known techniques.

Compounds (IIa) and (IIb) may hence be obtained, according to a process comprising the following stages (schemes 4-5):

- transformation of the hydroxyl group of compounds 17, 18, 19, 20 into the corresponding azides according to known procedures, for example through the Mitsunobu reaction, or mesylation and subsequent

nucleophilic substitution with sodium azide, to give compounds **21**, **23**, **25**, **27**;

- subsequent reduction by means of catalytic hydrogenation or Staudinger reaction
- 5 - transformation into the corresponding amides by means of coupling reactions using known reactions.
- Optional conjugation with molecules of biological interest by means of known reactions;
- subsequent deprotection of the aminoacid side chain protective groups
- 10 to give the compounds of formulae **22**, **24**, **26**, **28**.

To the resulting compounds, following the introduction of the azide group **21**, **23**, **25** and **27**, may be bound the desired biologically active molecules or compounds of biological importance such as for example sugars, through appropriate reactions known to those skilled in the art (Click chemistry).

- 15 Or even, to the amine groups of the previously prepared compounds may be bound appropriate substituents or known spacers, to give for example ureas or thioureas (*i.e.* to form compounds wherein $X = -NH-CO-NHR_3$, , $-NH-CS-NHR_3$, prepared by reaction with isocyanates or isothiocyanates in accordance with known procedures.

- 20 Examples and details of such reactions are provided in the experimental section of the present description.

- 25 According to one preferred embodiment, object of the invention are compounds of formulae (II), (IIa), and (IIb) wherein n is 1 and X is azide, amine, valeroyl amide and triazole, functionalized with a sugar, fluorescein, biotin and aliphatic chain.

- 25 According to one preferred embodiment, object of the invention are compounds of formulae (II), (IIa), and (IIb) wherein n is 2 and X is azide, amine, valeroyl amide and triazole, functionalized with a sugar, fluorescein, biotin and aliphatic chain.

- 30 The functional group protection and deprotection reactions may be carried out in accordance with known techniques, such as those described in the experimental

section of the present description.

The scheme for the preparation of valeroyl amides starting from compounds of general formula (I) is reported in schemes 4 and 5.

The preparation of compounds 6,5- and 7,5- *cis* is reported in scheme 4.

5 The preparation of compounds 6,5- and 7,5- *trans* is reported in scheme 5.

The preparation of functionalised triazoles starting from azides of compound of general formula (I) is reported in schemes 10-12.

Details of this kind of preparation for different, even if structurally analogous compounds, are provided in the Italian patent application N° MI2003A 002102 filed
10 on 30/10/2003, which will be available to the public at the publication date of the present application.

The compounds of formulae (II), (IIa) and (IIb) possess interesting pharmacological properties, particularly an antagonistic effect towards the $\alpha v \beta 3$ and $\alpha v \beta 5$ integrins, and display interesting antiangiogenic activities.

15 A further object of the present invention is hence the use of the compounds of general formulae (II), (IIa) and (IIb) for the preparation of drugs and/or compounds for diagnostic use, particularly useful for their antagonistic action towards the $\alpha v \beta 3$ and $\alpha v \beta 5$ integrins.

More particularly, the invention concerns the use of compounds of general
20 formulae (II), (IIa) and (IIb) for the preparation of drugs useful for the treatment of both altered angiogenic phenomena, and for those that may be encountered in metastasising tumour processes, retinopathies, acute renal damage and osteoporosis.

Biological tests for the evaluation of the activities of the compounds of general formulae (II), (IIa) and (IIb) towards the $\alpha v \beta 3$ and $\alpha v \beta 5$ integrins have been
25 performed using known tests also described in the literature [C. C. Kumar, H. Nie, C. P. Rogers, M. Malkowski, E. Maxwell, J. J. Catino, L. Armstrong, *J. Pharmacol. Exp. Ther.* **1997**, 283, 843] for example such as the one reported in patent application EP 1 077 218.

In such tests, certain compounds representative of the invention have shown
30 interesting biological and pharmacological activities.

Regarding their use as drugs according to the invention, the compounds of

general formulae (II), (IIa) and (IIb), their pharmaceutically acceptable salts, racemic mixtures, individual enantiomers, individual diastereoisomers and mixtures thereof in any proportion, are advantageously formulated into pharmaceutical compositions according to conventional techniques, well known to those skilled in the art.

5 Thus, according to another aspect thereof, the invention concerns pharmaceutical compositions containing, as active ingredient, at least one compound of general formulae (II), (IIa) or (IIb), the pharmaceutically acceptable salts, racemic mixtures, individual enantiomers, individual diastereoisomers and mixtures thereof in whatever proportion, in combination with one or more possible pharmaceutically
10 acceptable carriers or excipients.

The compositions of the invention may be prepared according to conventional techniques well known to those skilled in pharmaceutical techniques.

In order to obtain the desired prophylactic or therapeutic effect, the dose of active ingredient is advantageously administered in the form of a unit dose, one or
15 more times daily. The daily dosages are obviously selected by the health professional prescribing the drug depending on the biologically active molecule introduced.

As already mentioned, the compounds of formulae (II), (IIa) and (IIb) may be conjugated to various drugs, for example with a cytotoxic type drug, active towards the tumour pathology, or with appropriate ligands for diagnostic use.

20 In fact, the functionalised side chain ($-X$ substituent) of the compounds of the invention have been selected to be exploited as a site for the introduction of pharmacologically significant groups, in order to enhance protein-protein or protein-receptor interactions.

Thus, for example, in the compounds of formulae (II), (IIa) and (IIb) the
25 nitrogen residue contained in X is available for easy conjugation to a drug or a diagnostically useful compound.

According to another aspect thereof, the invention concerns the use of compounds of formulae (II), (IIa) and (IIb) as mediators for the transport and release of drugs.

30 Thus, the drug conjugated to the compounds of formulae (II), (IIa) or (IIb) is then transported to the desired site of action in order to fulfil its pharmacological

activity.

Conjugates of the compounds of formulae (II), (IIa) or (IIb) as described above, with cytotoxic and antitumour drugs, constitute an advantageous aspect of the present invention.

5 The present invention will now be described from the experimental viewpoint by way of purely illustrative, non-limiting examples.

EXPERIMENTAL SECTION

General Observations: The ^1H - and ^{13}C -NMR spectra have been recorded in CDCl_3 as indicated, at 200 (or 300, 400) and 50.3 (or 75.4, 100.6) MHz, respectively. Chemical shift values are indicated in ppm and the coupling constants in Hz. – Optical rotatory powers are measured using a Perkin-Elmer model 241 polarimeter. – Thin layer chromatography (TLC) is performed using Merck F-254 plates. Flash chromatography is performed using Macherey-Nagel 60, 230-400 mesh silica gel. Solvents are anhydriified in accordance with standard procedures and reactions requiring anhydrous conditions are carried out in nitrogen or argon atmosphere. Solutions containing the final products are anhydriified using Na_2SO_4 , filtered, and concentrated under reduced pressure using a rotary evaporator.

The ^1H -NMR and ^{13}C -NMR spectra have been recorded in the solvents indicated using a Brüker Avance-400 instrument at 400 MHz and 100.6 MHz respectively. Chemical shift values are indicated in ppm and the coupling constants in Hz. Optical rotatory powers are measured using a Perkin-Elmer model 241 polarimeter. Thin layer chromatography (TLC) is performed using Merck F-254 plates. Flash chromatography is performed using Macherey-Nagel 60, 230-400 mesh silica gel. Solvents are anhydriified in accordance with standard procedures and reactions requiring anhydrous conditions are carried out in an argon atmosphere. FAB^+ mass spectrometry has been performed using a VG 7070 EQ-HF spectrophotometer, ESI^+ mass spectrometry has been performed using a Bruker Esquire 3000 plus spectrophotometer.

FUNCTIONALISATION OF THE COMPOUNDS DERIVING FROM 1.3
30 DIPOLAR CYCLISATION (SCHEME 1, SCHEME 2, SCHEME 7 and SCHEME

9).

Example 1: protection of the free amino group

To a solution of product **5** or **14** (0.51 mmol) in anhydrous DCM (5 ml) under argon atmosphere and at room temp., are added in the following sequence TEA (184
 5 μ l, 1.33 mmol), Cbz-Cl (95 μ l, 0.61 mmol) and finally DMAP (15 mg, 0.126 mmol). The solution is kept under stirring for approx. 18 hours. After this period of time, it is taken up with DCM (5 ml) and washed with NH_4Cl (2 x 5ml). The organic phase, anhydrated over Na_2SO_4 , is taken to dryness and the crude product thus obtained is purified by flash chromatography (AcOEt/ETP 7:3 $\rightarrow$ 8:2) to give the desired product
 10 as a white foam (60%-78%).

Compound 5-Cbz

Yield: 78%. $[\alpha]_{\text{D}}^{22} = -13.7$ ($c = 1.0$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.6 (m, 1H, $H-5$), 1.7 (m, 1H, $H-7$), 2.06 (m, 1H, $H-8$), 2.2 (m, 1H, $H-8$), 2.23 (m, 1H, $H-7$), 2.3 (m, 1H, $H-5$), 2.75 (m, 1H, $H-4$), 2.92 (bs, 1H, OH), 3.6
 15 (dd, 1H, $H\text{CHOH}$), 3.71 (m, 1H, $H\text{CHOH}$), 3.72 (m, 1H, $H-6$), 4.38 (t, 1H, $H-3$), 4.48 (d, 1H, $H-9$), 5.15 (dd, 2H, CH_2Ph), 6.0 (d, 1H, NHCbz), 7.28-7.42 (m, 5H, *aromatic protons*). $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3): δ 171.7, 168.1, 156.7, 136.4, 128.5, 128.8, 127.9, 82.4, 66.9, 63.5, 58.9, 55.7, 52.1, 37.9, 32.5, 32.0, 31.6, 29.7, 29.2, 27.9. MS $[\text{FAB}^+]$: 419.3 $[\text{M}+1]^+$. Calculated elemental analysis $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_6$:
 20 C 63.14, H 7.23, N 6.69; observed C 62.16, H 7.25, N 6.67.

Compound 14-Cbz

Yield: 60%. $[\alpha]_{\text{D}}^{22} = -25.5$ ($c = 1.0$, CHCl_3). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.51 (m, 1H, $H-6$), 1.53 (m, 1H, $H-4$), 1.75 (m, 1H, $H-5$), 1.83 (m, 1H, $H-6$), 1.98 (m, 1H, $H-9$), 2.0 (m, 1H, $H-5$), 2.2 (m, 1H, $H-9$), 2.25 (m, 1H, $H-8$),
 25 2.33 (m, 1H, $H-8$), 3.4 (t, 1H, $H\text{CHOH}$), 3.72 (d, 1H, OH), 3.82 (d, 1H, $H\text{CHOH}$), 4.03 (t, 1H, $H-7$), 4.42 (dd, 1H, $H-3$), 4.5 (d, 1H, $H-10$), 5.15 (dd, 2H, CH_2Ph), 6.48 (d, 1H, NHCbz), 7.31-7.43 (m, 5H, *aromatic protons*). $^{13}\text{C NMR}$ (100.6 MHz, CDCl_3): δ 170.5, 170.3, 158.0, 136.0, 128.6, 128.2, 128.1, 81.6, 67.5, 64.5, 61.0, 58.7, 55.5, 42.5, 33.9, 32.1, 30.9, 29.7, 29.3, 28.0, 27.2. MS $[\text{ESI}^+]$: 433.3 $[\text{M}+\text{H}]^+$,

455.3 $[M+Na]^+$, Calculated elemental analysis $C_{23}H_{32}N_2O_6$: C 63.87, H 7.46, N 6.48 ; observed C 63.85, H 7.47, N 6.47.

Example 2: Synthesis of azide-derivatives.

To a solution of product **5-Cbz** or **14-Cbz** (0.29 mmol) in anhydrous DCM (4 ml) under argon atmosphere and at room temp., are added in the following sequence MsCl (846 μ l, 0.59 mmol) and TEA (165 μ l, 1.18 mmol). The solution is kept under stirring for approx. 45 minutes. After this period of time, it is taken up with DCM and washed with NH_4Cl . The organic phase, anhydrated over Na_2SO_4 is taken to dryness and the crude product thus obtained dissolved in DMF (3.2 ml) and, under argon atmosphere and at room temp., NaN_3 (154 mg, 2.37 mmol) is added. The reaction is kept under stirring at 80 °C for approx. 18 hours. After this period of time, the DMF is evaporated off to dryness, and the crude product dissolved in CH_2Cl_2 and washed with H_2O . The organic phase, anhydrated over Na_2SO_4 , is taken to dryness and the crude product thus obtained is purified by flash chromatography (AcOEt/ETP 7:3) to give the desired product as a white foam (76%-90%).

Compound 6.

Yield: 76%. $[\alpha]_D^{22} = +19.0$ ($c = 1.0$, $CHCl_3$). 1H -NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H, $C(CH_3)_3$), 1.61 (m, 1H, $H-5$), 1.72 (m, 1H, $H-7$), 2.08 (m, 1H, $H-8$), 2.14 (m, 1H, $H-8$), 2.24 (m, 1H, $H-7$), 2.31 (m, 1H, $H-5$), 2.9 (m, 1H, $H-4$), 3.28 (dd, 1H, $J =$ Hz, $HCHN_3$), 3.48 (dd, 1H, $HCHN_3$), 3.7 (m, 1H, $H-6$), 4.31 (t, 1H, $H-3$), 4.39 (d, 1H, $H-9$), 5.15 (s, 2H, CH_2Ph), 6.0 (bs, 1H, $NHCbz$), 7.28-7.42 (m, 5H, *aromatic protons*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.4, 166.7, 156.1, 136.3, 128.5, 128.1, 127.9, 81.9, 67.0, 59.0, 55.3, 55.8, 52.6, 35.4, 32.3, 31.8, 29.2, 28.0. MS $[ESI^+]$: 444.3 $[M+H]^+$. Calculated elemental analysis $C_{22}H_{29}N_5O_5$: C 59.58, H 6.59, N 15.79; observed C 59.57, H 6.58, N 15.81.

Compound 15

Yield: 90%. $[\alpha]_D^{22} = -13.8$ ($c = 1.0$, $CHCl_3$). 1H -NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H, $C(CH_3)_3$), 1.5 (m, 1H, $H-5$), 1.68 (m, 1H, $H-4$), 1.70 (m, 1H, $H-6$), 1.72 (m, 1H, $H-8$), 1.82 (m, 1H, $H-5$), 1.98 (m, 1H, $H-9$), 2.13 (m, 1H, $H-6$), 2.21 (m, 1H, $H-$

9), 2.34 (m, 1H, *H*-8), 3.26 (dd, 1H, *J* = 18.9 Hz, *J* = 12.1 Hz, *HCHN*₃), 3.65 (dd, 1H, *HCHN*₃), 4.09 (t, 1H, *J* = 9.0 Hz, *H*-7), 4.42 (dd, 1H, *H*-3), 4.46 (dd, 1H, *J* = 8.7 Hz, *J* = 2.0 Hz, *H*-10), 5.12 (dd, 2H, *J* = 15.7 Hz, *J* = 12.2 Hz, *CH*₂Ph), 6.08 (d, 1H, *J* = 7.18 Hz, *NHCbz*), 7.3-7.42 (m, 5H, *aromatic protons*). ¹³C NMR (100.6 MHz, CDCl₃): δ 170.5, 169.7, 156.6, 136.3, 128.5, 128.1, 81.6, 67.1, 60.9, 58.3, 55.9, 53.7, 40.9, 33.3, 31.9, 31.5, 28.0, 27.2. MS [ESI⁺]: 448.2 [M+H]⁺, 480.2 [M+Na]⁺, Calculated elemental analysis C₂₃H₃₁N₅O₅: C 60.38, H 6.83, N 15.31; observed C 60.36, H 6.84, N 15.32.

Example 3: Reduction of azide-derivatives.

To a solution of product **6** or **15** (0.034 mmol) in anhydrous DCM (350 μl) under argon atmosphere and at room temp., is added 1M Me₃P in toluene (51 μl, 0.051 mmol). After approx. 2 hours, upon completion of the reaction, the reaction is taken up with DCM (1 ml), and H₂O (1 ml) added, and the mixture is allowed under stirring for approx. 10 minutes. After this period of time, the two phases are separated. The organic phase, anhydrated over Na₂SO₄, is evaporated to dryness.

Compound 7.

Yield: 93%. [α]_D²² = -13.9 (*c* = 1.0, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.47 (s, 9H, C(CH₃)₃), 1.55 (m, 1H, *H*-5), 1.72 (m, 1H, *H*-7), 2.07 (m, 1H, *H*-8), 2.16 (m, 1H, *H*-8), 2.21 (m, 1H, *H*-7), 2.30 (m, 1H, *H*-5), 2.68 (m, 1H, *H*-4), 2.72-2.97 (m, 2H, *CH*₂NH₂), 3.73 (m, 1H, *H*-6), 4.31 (t, 1H, *H*-3), 4.41 (d, 1H, *H*-9), 5.15 (s, 2H, *CH*₂Ph), 6.4 (d, 1H, *NHCbz*), 7.23-7.42 (m, 5H, *aromatic protons*). ¹³C NMR (100.6 MHz, CDCl₃): δ 170.8, 168.1, 156.4, 136.6, 128.5, 128.0, 127.9, 81.8, 67.8, 58.9, 55.6, 53.0, 32.5, 32.0, 29.7, 29.3, 28.0. MS [ESI⁺]: 418.4 [M+H]⁺. Calculated elemental analysis C₂₂H₃₁N₃O₅: C 63.29, H 7.48, N 10.06; observed C 63.27, H 7.47, N 10.08.

Compound 16

Yield: 76%. [α]_D²² = -14.5 (*c* = 1.0, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 1.45 (s, 9H, C(CH₃)₃), 1.5 (m, 1H, *H*-5), 1.53 (m, 1H, *H*-4), 1.65 (m, 1H, *H*-6), 1.72 (m, 1H, *H*-8), 1.81 (m, 1H, *H*-5), 1.98 (m, 1H, *H*-9), 2.14 (m, 1H, *H*-6), 2.21 (m, 1H, *H*-

9), 2.33 (m, 1H, *H*-8), 2.83 (bs, 2H, CH_2NH_2), 4.08 (t, 1H, $J = 9.0$ Hz, *H*-7), 4.41 (m, 1H, *H*-3), 4.47 (d, 1H, $J = 8.5$ Hz, *H*-10), 5.13 (dd, 2H, $J = 15.7$ Hz, $J = 12.2$ Hz, CH_2Ph), 6.16 (d, 1H, $J = 7.0$ Hz, NHCbz), 7.28-7.42 (m, 5H, *aromatic protons*). ^{13}C NMR (100.6 MHz, CDCl_3): δ 170.6, 156.8, 136.2, 128.5, 128.0, 81.5, 67.0, 60.8, 58.3, 56.3, 44.4, 33.7, 32.0, 31.3, 28.0, 27.2. MS $[\text{ESI}^+]$: 432.5 $[\text{M}+\text{H}]^+$. Calculated elemental analysis $\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_5$: C 64.02, H 7.71, N 9.74; observed C 64.04, H 7.72, N 9.73

Example 4: Conjugation through “click reaction”.

To a solution of azide **6** or **15** (0.1 mmol) and of an appropriate alkynyl derivative (0.1 mmol) in $\text{H}_2\text{O}/t\text{-BuOH}$ 1:1 (500 μL .) a solution of sodium ascorbate 0.9 M (44 μL , 0.04 mmol, 0.4 mol eq) and a solution of $\text{Cu}(\text{OAc})_2$ 0.3 M (67 μL , 0.02 mmol, 0.2 mol eq) are added, respectively. The reaction mixture is kept under stirring at r. t. for about 18 hs. As the reaction is completed, compounds **31** or **33** have been extracted with CH_2Cl_2 (2 mL x 3) and the organic phase has been washed with a NaHCO_3 (5 mL x 1) saturated solution and brine (5 mL x 1). The organic phase, anhydrous over Na_2SO_4 , has been evaporated under reduced pressure. As concerns compounds **32**, **34**, **42-45** at the end of the reaction, the solvent is evaporated under reduced pressure. The crude products have been purified by flash chromatography on silica gel.

Compound 31

Column eluant: EtOAc/ETP 9:1

Yield : 80%. $[\alpha]_{\text{D}}^{22} = -9.2$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.45 (m, 1H, *H*-5), 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.66 (m, 1H, *H*-7), 1.96 (s, 3H, OCH_3), 1.98 (s, 3H, OCH_3), 2.01 (s, 3H, OCH_3), 2.08 (s, 3H, OCH_3), 2.13 (m, 1H, *H*-8), 2.15-2.22 (m, 2H, *H*-8, *H*-5), 2.23 (m, 1H, *H*-7), 2.29 (m, 1H, *H*-4), 3.6-3.73 (m, 2H, *H*-6, *H*-5 Glc), 4.06 (dd, 1H, $J = 2.0$ Hz, $J = 12.0$ Hz, *H*-6 Glc), 4.20 (dd, 1H, $J = 4.4$ Hz, $J = 12.0$ Hz, *H*-6 Glc), 4.27 (m, 1H, *H*-3), 4.35 (m, 1H, *H*-9), 4.43 (dd, 1H, $J = 4.4$ Hz, $J = 13.7$ Hz, *H*-CH-N), 4.60 (d, 1H, $J = 8.0$ Hz, *H*-1 Glc), 4.47 (d, 1H, $J = 12.4$ Hz, *H*-CH-O), 4.84 (d, 1H, $J = 12.4$ Hz, *H*-CH-O), 4.93 (m, 1H, *H*-2 Glc), 5.01 (m, 1H, *H*-4 Glc), 5.02-5.15 (m, 3H, *H*-3 Glc, CH_2Ph), 6.0 (m, 1H, NHCbz), 7.22-7.33 (m, 5H, *aromatic protons*), 7.48 (s, 1H, *H* triazole). ^{13}C NMR (100.6 MHz, CDCl_3): δ 170.7,

170.4, 169.4, 169.3, 166.5, 156.0, 143.7, 136.2, 128.6, 128.2, 128.1, 124.1, 99.6, 82.3, 72.8, 71.9, 68.4, 67.1, 62.7, 61.9, 58.8, 55.0, 53.0, 51.1, 36.8, 32.5, 30.3, 29.1, 28.0, 20.8, 20.6. MS [ESI⁺]: calc. per C₃₉H₅₁N₅O₁₅: 829.34; observed 852.4 [M+Na]⁺. Anal. elem. calc. C₃₉H₅₁N₅O₁₅: C 56.45, H 6.19, N 8.44; observed C 56.46, H 6.20, N 8.56.

Compound 33

Column eluant: EtOAc/ETP 9:1

Yield : 84%. $[\alpha]_D^{22} = -46.9$ ($c = 1.0$, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 1.39 (m, 1H, *H*-6), 1.45 (s, 9H, C(CH₃)₃), 1.65 (m, 1H, *H*-8), 1.69 (m, 1H, *H*-6), 1.95 (m, 1H, *H*-9), 1.99 (s, 3H, OCH₃), 2.00 (s, 3H, OCH₃), 2.03 (s, 3H, OCH₃), 2.09 (s, 3H, OCH₃), 2.12-2.25 (m, 2H, H₄, *H*-9), 2.31 (m, 1H, *H*-8), 3.64 (m, 1H, *H*-5 Glc), 4.07 (m, 1H, *H*-7), 4.16 (dd, 1H, $J = 2.0$ Hz, $J = 9.6$ Hz, *H*-6 Glc), 4.27 (dd, 1H, $J = 4.8$ Hz, $J = 12.4$ Hz, *H*-6 Glc), 4.31 (m, 1H, *H*-CH-N), 4.46 (dd, 1H, $J = 8.8$ Hz, $J = 2.0$ Hz, *H*-10), 4.51 (m, 1H, *H*-3), 4.64-4.72 (m, 2H, *H*-1 Glc, *H*-CH-N), 4.79 (d, 1H, $J = 12.4$ Hz, *H*-CH-O), 4.92 (d, 1H, $J = 12.4$ Hz, *H*-CH-O), 5.01 (dd, 1H, $J \approx 0$ Hz, $J = 8$ Hz, *H*-2 Glc), 5.07-5.16 (m, 3H, *H*-4 Glc, CH₂Ph), 5.20 (t, 1H, $J = 9$ Hz, *H*-3 Glc), 6.17 (m, 1H, NHCbz), 7.20-7.31 (m, 5H aromatic protons), 7.40 (s, 1H, *H* triazole). ¹³C NMR (100.6 MHz, CDCl₃): δ 170.6, 170.4, 170.2, 169.4, 169.3, 169.1, 168.4, 156.9, 144.0, 136.1, 128.6, 128.2, 128.1, 123.7, 99.9, 81.7, 72.8, 71.9, 71.2, 70.7, 68.4, 67.3, 62.9, 61.9, 60.9, 60.4, 58.2, 56.1, 53.4, 52.0, 41.5, 32.9, 31.9, 30.8, 29.7, 28.0, 27.1, 20.7, 20.6. MS [ESI⁺]: Calc. for C₄₀H₅₃N₅O₁₅: 843.35; observed: 866.2 [M+Na]⁺, Anal. elem. calc. C₄₀H₅₃N₅O₁₅: C 56.93, H 6.33, N 8.30; observed C 56.95, H 6.34, N 8.32.

Compound 32

Column eluant : CHCl₃/MeOH 9:1

Yield : 74%. $[\alpha]_D^{22} = -10.8$ ($c = 1.0$, CHCl₃). ¹H NMR (400 MHz, CD₃OD): δ 1.49 (s, 9H, C(CH₃)₃), 1.53 (m, 1H, *H*-5), 1.66 (m, 1H, *H*-7), 1.98 (s, 1H, *H*-5), 2.01 (m, 1H, *H*-8), 2.13 (m, 1H, *H*-7), 2.18 (m, 2H, *H*-8), 2.98 (m, 1H, *H*-4), 3.22 (t, 1H, $J = 8.0$ Hz, *H*-2 Glc), 3.25-3.33 (m, 2H, *H*-4 Glc, *H*-5 Glc), 3.35 (m, 1H, *H*-3 Glc), 3.66-

3.74 (m, 2H, *H*-6, *H*-6 Glc), 3.89 (dd, 1H, *J* = 0 Hz, *J* = 12.0 Hz, *H*-6 Glc), 4.28-4.42 (m, 3H, *H*-9, *H*-CH-N, *H*-1 Glc), 4.50-4.57 (m, 2H, *H*-3, *H*-CH-N), 4.77(d, 1H, *J* = 12.4 Hz, *H*-CH-O), 4.95 (d, 1H, *J* = 12.4 Hz, *H*-CH-O), 5.13 (s, 2H, CH₂Ph), 7.27-7.42 (m, 5H, *aromatic protons*), 7.98 (s, 1H, *H* triazole). ¹³C NMR (100.6 MHz, CD₃OD): δ 174.4, 167.4, 157.1, 144.4, 136.7, 128.1, 127.7, 127.6, 124.6, 102.2, 81.9, 76.7, 76.6, 73.7, 70.3, 66.7, 61.6, 61.4, 59.0, 57.5, 51.7, 50.9, 38.2, 31.3, 28.9, 28.0, 26.8. MS [ESI⁺]: Calc. per C₃₁H₄₃N₅O₁₁: 661.30; observed 684.3 [M+Na]⁺. Anal. elem. calc. C₃₁H₄₃N₅O₁₁: C 56.27, H 6.55, N 10.58; observed C 56.26, H 6.56, N 10.59.

10 Compound 34

Column eluant: CHCl₃/MeOH 9:1

Yield : 72%. [α]_D²² = -49.2 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CD₃OD): δ 1.43 (m, 1H, *H*-6), 1.44 (s, 9H, C(CH₃)₃), 1.58 (m, 2H, 2 *H*-5), 1.75 (m, 1H, *H*-8), 1.80 (m, 1H, *H*-6), 1.93 (m, 1H, *H*-9), 2.18-2.34 (m, 4H, *H*4, *H*-8, *H*-9), 3.21 (dd, 1H, *J* ≈ 0Hz, *J* = 7.8 Hz, *H*-2 Glc), 3.27-3.33 (m, 2H, *H*-4 Glc, *H*-5 Glc), 3.35 (m, 1H, *H*-3 Glc) 3.68 (dd, 1H, *J* = 5.1 Hz, *J* = 11.9 Hz, *H*-6 Glc), 3.90 (dd, 1H, *J* = 0 Hz, *J* = 11.9 Hz, *H*-6 Glc), 4.16 (m, 1H, *H*-7), 4.36 (m, 1H, *H*-CH-N), 4.37 (m, 1H, *H*-1 Glc), 4.40 (dd, 1H, *H*-10), 4.56 (m, 1H, *H*-3), 4.63 (dd, 2H, *J* = 4.3 Hz, *J* = 13.7 Hz, *H*-CH-N), 4.76 (d, 1H, *J* = 12.6 Hz, *H*-CH-O), 4.95 (d, 1H, *J* = 12.5 Hz, *H*-CH-O), 5.13 (s, 2H, CH₂Ph), 7.24-7.42 (m, 5H, *aromatic protons*), 7.95 (s, 1H, *H* triazole). ¹³C NMR (100.6 MHz, CD₃OD): δ 171.2, 170.0, 157.2, 144.5, 136.7, 128.1, 127.7, 127.6, 124.5, 102.3, 81.5, 76.7, 76.6, 73.6, 70.2, 66.6, 61.6, 61.4, 61.0, 57.8, 56.0, 51.6, 39.8, 31.5, 31.1, 29.1, 26.8, 26.6. MS [ESI⁺]: Calc. per C₃₂H₄₅N₅O₁₁: 675.31, observed 676.2 [M+H]⁺, 698.3 [M+Na]⁺. Anal. elem. calc. C₃₂H₄₅N₅O₁₁: C 56.88, H 6.71, N 10.36; observed C 56.86 H 6.70, N 10.35.

Compound 42

Column eluant: CHCl₃/MeOH 9:1

Yield : 80%. [α]_D²² = - 4.1 (*c* = 1.0, MeOH). ¹H NMR (400 MHz, CD₃OD): δ 1.28 (m, 2H, CH₂ biotin), 1.31 (s, 9H, C(CH₃)₃), 1.39 (m, 1H, *H*-5), 1.42 (m, 1H, *H*-CH

biotin), 1.43-1.52 (m, 3H, *H*-7, CH₂ biotin), 1.53-1.67 (m, 5H, 2 NCH₂CH₂CH₂O linker, *H*CH biotin), 1.78-1.87 (m, 2H, *H*-5, *H*-8), 1.92-2.07 (m, 4H, *H*-7, *H*-8, CH₂ biotin), 2.56 (d, 1H, *J* = 12.8 Hz, *SH*CH biotin), 2.76 (dd, 1H, *J* = 12.8 Hz, *J* = 4.8 Hz, *SH*CH biotin), 2.82 (m, 1H, *H*-4), 3.05 (m, 1H, *SH*C- biotin), 3.10 (m, 2H, CH₂N linker), 3.18 (m, 2H, CH₂N linker), 3.33-3.45 (m, 4H, CH₂O linker), 3.40-3.45 (m, 4H, CH₂O linker), 3.45-3.505 (m, 4H, CH₂O linker), 3.53 (m, 1H, *H*-6), 3.98 (s, 2H, COCH₂O linker), 3.94 (s, 2H, COCH₂O linker), 4.12-4.18 (m, 2H, *NCH* biotin, *H*-9), 4.22 (m, 1H, *H*-CH-N), 4.30-4.41 (m, 5H, *H*-3, *H*-CH-N, *NCH* biotin, *NCH*₂C=), 4.95 (s, 2H, CH₂Ph), 7.10-7.27 (m, 5H, *aromatic protons*), 7.74 (s, 1H, *H* triazole). ¹³C NMR (100.6 MHz, CD₃OD): δ 174.4, 174.3, 170.2, 170.0, 167.2, 164.6, 157.0, 136.6, 128.0, 127.6, 127.4, 81.4, 70.1, 70.0, 69.7, 68.7, 68.5, 66.5, 61.9, 60.1, 58.9, 57.4, 55.6, 51.5, 50.8, 39.6, 38.1, 36.3, 36.2, 35.4, 33.8, 31.3, 29.3, 29.0, 28.9, 28.8, 28.3, 28.0, 27.9, 26.8, 25.4. MS [ESI⁺]: C₄₉H₇₄N₁₀O₁₃S: 1042.52; observed: 1043.7 [M+H]⁺, 1065.7 [M+Na]⁺. Anal. elem. calc. C₄₉H₇₄N₁₀O₁₃S: C 56.41, H 7.15, N 13.43; observed C 56.43, H 7.14, N 13.45.

Compound 44

Column eluant: CHCl₃/MeOH 9:1

Yield : 50%. [α]_D²² = -3.83 (*c* = 1.0, MeOH). ¹H NMR (400 MHz, CD₃OD): δ 1.21-1.34 (m, 12H, CH₂ biotin, *H*-6, C(CH₃)₃), 1.36-1.52 (m, 5H, 2 *H*-5, *H*CH biotin, CH₂ biotin), 1.53-1.79 (m, 7H, *H*CH biotin *H*-6, *H*-8, 2 NCH₂CH₂CH₂O linker), 1.77 (m, 1H, *H*-9), 1.99-2.18 (m, 5H, *H*-4, CH₂ biotin *H*-8, *H*-9), 2.55 (d, 1H, *J* = 12.8 Hz, *SH*CH biotin), 2.77 (dd, 1H, *J* = 12.8 Hz, *J* = 4.8 Hz, *SH*CH biotin), 3.05 (m, 1H, *SH*C- biotin), 3.10 (m, 2H, CH₂N linker), 3.18 (m, 2H, CH₂N linker), 3.32-3.40 (m, 4H, CH₂O linker), 3.40-3.45 (m, 4H, CH₂O linker), 3.45-3.50 (m, 4H, CH₂O linker), 3.89 (s, 2H, COCH₂O linker), 3.94 (s, 2H, COCH₂O linker), 3.99 (m, 1H, *H*-7), 4.14 (m, 1H, *NCH* biotin), 4.18 (m, 1H, *H*-CH-N), 4.23 (m, 1H, *H*-10), 4.30-4.37 (m, 3H, *NCH* biotin, *NCH*₂C=), 4.39 (m, 1H, *H*-3), 4.45 (m, 1, *H*-CH-N), 4.97 (s, 2H, CH₂Ph), 7.10-7.27 (m, 5H, *aromatic protons*), 7.75 (s, 1H, *H* triazole). ¹³C NMR (100.6 MHz, CD₃OD): δ 174.4, 171.1, 170.2, 170.0, 169.9, 164.6, 157.0, 136.6, 128.0, 127.6, 127.5, 81.4, 70.0, 69.7, 68.5, 68.4, 66.5, 61.9, 60.9, 60.1, 57.7, 55.8,

55.5, 51.6, 39.6, 39.5, 36.3, 36.2, 35.4, 33.8, 31.5, 31.4, 31.0, 29.2, 29.0, 28.9, 28.3, 28.0, 26.7, 26.5, 25.4. MS [ESI⁺]: Calc. per C₅₀H₇₆N₁₀O₁₃S: 1056.53, observed 1057.8 [M+H]⁺, Anal. elem. calc. C₅₀H₇₆N₁₀O₁₃S: C 56.80, H 7.25, N 13.25; observed C 55.81, H 6.24, N 13.24.

5 Compound 43 (isomers mixture)

Column eluant: CHCl₃/MeOH 8:2→CHCl₃/MeOH/H₂O 60:35:5

Yield : 91%. ¹H NMR (400 MHz, CD₃OD): δ 1.46 (s, 9H, C(CH₃)₃), 1.52 (m, 1H, H-5), 1.64 (m, 1H, H-7), 1.74 (m, 2H, NCH₂CH₂CH₂O), 1.82 (m, 1H, H-5), 1.87-2.04 (m, 3H, NCH₂CH₂CH₂O, H-8), 2.12 (m, 1H, H-7), 2.18 (m, 1H, H-8), 2.93 (m, 10 1H, H-4), 3.32 (m, 2H, CH₂N linker), 3.45-3.58 (m, 6H, CH₂N linker, CH₂O linker), 3.59-3.70-3.45 (m, 9H, CH₂O linker, H-6), 4.03 (s, 2H, COCH₂O linker), 4.09 (s, 2H, COCH₂O linker), 4.29 (m, 2H, H-9), 4.35 (m, 1H, H-CH-N), 4.41-4.55 (m, 4H, H-3, H-CH-N, NCH₂C=), 5.11 (s, 2H, CH₂Ph), 6.63-6.62 (m, 2H, aromatic protons fluorescein), 6.66-6.80 (m, 4H, aromatic protons, fluorescein), 7.26-7.42 (m, 5H, 15 aromatic protons Ph), 7.83 (s, 1H, H triazole), 8.05-8.18 (m, 2H, aromatic protons, fluorescein), 8.45 (m, 1H, aromatic proton, fluorescein). ¹³C NMR (100.6 MHz, CD₃OD): δ 172.8, 171.5, 168.8, 130.8, 129.5, 129.1, 128.9, 103.7, 83.3, 71.5, 71.4, 71.3, 71.2, 70.3, 70.0, 68.0, 60.4, 59.0, 52.9, 52.2, 39.6, 39.0, 37.6, 35.2, 32.7, 30.4, 30.2, 29.4. MS [ESI⁺]: Calc per C₆₀H₇₀N₈O₁₇: 1175.49; observed 1176.5 [M+H]⁺. 20 Anal. elem. calc. C₆₀H₇₀N₈O₁₇: C 61.32, H 6.00, N 9.53; observed C 61.33, H 6.01, N 9.55.

Compound 45

Column eluant: CHCl₃/MeOH 8:2→CHCl₃/MeOH/H₂O 60:35:5

Yield : 92%. ¹H NMR (400 MHz, CD₃OD): δ 1.37 (m, 1H, H-6), 1.43 (m, 9H, 25 C(CH₃)₃), 1.54 (m, 2H, 2 H-5), 1.64-1.84 (m, 5H, H-6, H-8, NCH₂CH₂CH₂O linker), 1.86-1.98 (m, 2H, H-9, NCH₂HCHCH₂O), 2.14-2.30 (m, 3H, H-4, H-8, H-9), 3.30 (m, 2H, CH₂N linker), 3.43 (m, 2H, CH₂N linker), 3.45-3.57 (m, 4H, CH₂O linker), 3.58-3.70 (m, 8H, CH₂O linker), 4.03 (s, 2H, COCH₂O linker), 4.08 (s, 2H, COCH₂O linker), 4.11 (m, 1H, H-7), 4.32 (m, 1H, H-CH-N), 4.39 (m, 1H, H-10), 4.47 (s, 2H,

NCH₂C=), 4.53 (m, 1H, *H*-3), 4.58 (m, 1, *H*-CH-N), 5.11 (s, 2H, CH₂Ph), 6.52-6.60 (m, 2H, *aromatic protons, fluorescein*), 6.66-6.76 (m, 4H, *aromatic protons, fluorescein*), 7.22-7.41 (m, 5H, *aromatic protons Ph*), 7.81 (s, 1H, *H* triazole), 8.05-8.20 (m, 2H, *aromatic protons, fluorescein*), 8.44 (m, 1H, *aromatic proton, fluorescein*). ¹³C NMR HETCOR (400 MHz, CD₃OD): δ 132.9, 129.3, 128.7, 127.8, 127.6, 127.5, 125.8, 125.3, 124.3, 123.5, 113.9, 102.3, 69.9, 69.6, 69.4, 68.9, 68.4, 66.5, 60.8, 57.6, 55.9, 51.5, 39.6, 37.65, 36.2, 33.8, 31.5, 31.4, 31.0, 29.0, 28.9, 26.7, 26.6. MS [ESI⁺]: Calc per C₆₁H₇₂N₈O₁₇: 1189.5; observed: 1190.2 [M+H]⁺, 1212.2 [M+Na]⁺, Anal. elem. calc. C₆₁H₇₂N₈O₁₇: C 61.61, H 6.10, N 9.42; observed C 61.60, H 6.11, N 9.43.

PREPARATION OF AMIDES OF THE CYCLIC PENTAPEPTIDE CONTAINING THE RGD SEQUENCE (SCHEME 4, SCHEME 5, SCHEME 11 and SCHEME 12)

Example 1: Synthesis of azide-derivatives.

To a solution of product **17-20** (0.055 mmol) in anhydrous DCM (700 μl) under argon atmosphere and at room temp., are added in the following sequence MsCl (8.5 μl, 0.11 mmol) and TEA (30 μl, 0.22 mmol). The solution is kept under stirring for approx. 30 minutes. After this period of time, the solvent is evaporated to dryness and the crude product filtered over silica gel (CH₂Cl₂/MeOH 9:1). The crude product thus obtained is dissolved in DMF (550 μl) and, under argon atmosphere and at room temp., NaN₃ (36 mg, 0.55 mmol) is added. The reaction is kept under stirring at 80 °C for approx. 18 hours. After this period of time, the DMF is evaporated off to dryness, and the crude product dissolved in CH₂Cl₂ and washed with H₂O. The organic phase, anhydrated over Na₂SO₄, is taken to dryness and the crude product thus obtained is purified by flash chromatography (CH₂Cl₂/iPrOH 9:1 → 8:2) to give the desired product as a white foam (30%-75%).

Compound 21

Yield: 62%. (White solid). [α]_D²² = -6.3 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, Acetone-D₆): δ 1.23 (s, 6H, C(CH₃)₂ Pmc), 1.38 (s, 9H, C(CH₃)₃), 1.44 (m, 1H, *H*β Arg), 1.47 (m, 1H, *H*-7), 1.49 (m, 1H, *H*-8), 1.51 (m, 1H, *H*β Arg), 1.60 (m, 1H, *H*γ Arg), 1.72 (m, 2H, CH₂CH₂Ar Pmc), 1.74 (m, 1H, *H*-5), 1.80 (m, 1H, *H*γ Arg), 2.02

(s, 3H, CH_3 Pmc), 2.1 74 (m, 1H, H -5), 2.12 (m, 1H, H -4), 2.18 (m, 1H, H -7), 2.3 (m, 1H, H -8), 2.48 (s, 3H, CH_3 Pmc), 2.50 (s, 3H, CH_3 Pmc), 2.54 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 2.60 (m, 1H, $H\beta$ Asp), 2.91 (m, 1H, $H\beta$ Asp), 3.17 (m, 1H, $H\delta$ Arg), 3.19 (m, 1H, CH_2N_3), 3.23 (m, 1H, $H\delta$ Arg), 3.48 (m, 1H, CH_2N_3), 3.6 (m, 1H, $H\alpha$ Gly), 3.8 (m, 1H, $H\alpha$ Gly), 4.0 (m, 1H, H -6), 4.17 (m, 1H, H -9), 4.4 (m, 1H, H -3), 4.63 (m, 1H, $H\alpha$ Arg), 4.72 (m, 1H, $H\alpha$ Asp), 6.14 (bs, 1H, $(\text{NH})_2\text{C}=\text{NH}$), 6.37 (bs, 2H, $(\text{NH})_2\text{C}=\text{NH}$), 7.32-7.48 (m, 2H, NH Arg, NH bicyclic), 7.8 (bs, 1H, NH Gly), 8.12 (bs, 1H, NH Asp). ^{13}C NMR HETCOR (400 MHz, Acetone- D_6): δ 67.5, 54.8, 51.8, 51.4, 50.2, 49.4, 45.8, 40.1, 39.9, 34.7, 32.8, 31.8, 31.5, 30.2, 28.1, 27.2, 26.8, 25.2, 21.3, 18.5, 17.5, 12.1. MS $[\text{FAB}^+]$: calculated for $\text{C}_{40}\text{H}_{59}\text{N}_{11}\text{O}_{10}\text{S}$: 885.42, observed: 886 $[\text{M} + \text{H}]^+$. Calculated analysis for $\text{C}_{40}\text{H}_{59}\text{N}_{11}\text{O}_{10}\text{S}$: C 54.22, H 6.71, N 17.39; observed C 54.20, H 6.72, N 17.37.

Compound 23

Yield: 30%. (White solid). $[\alpha]_{\text{D}}^{22} = -65.15$ ($c = 1.0$, Acetone). ^1H NMR (400 MHz, Acetone- D_6): δ 1.18 (s, 6H, $\text{C}(\text{CH}_3)_2$ Pmc), 1.3 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.44 (m, 1H, H -8), 1.45 (m, 3H, H -6, $H\gamma$ Arg), 1.5 (m, 1H, $H\beta$ Arg), 1.57 (m, 1H, $H\beta$ Arg), 1.62 (m, 1H, H -4), 1.65 (m, 1H, H -5), 1.7 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 1.73 (m, 2H, H -5, H -9), 1.95 (m, 1H, H -9), 1.96 (s, 3H, CH_3 Pmc), 1.98 (m, 1H, H -6), 2.13 (m, 1H, H -8), 2.46 (s, 3H, CH_3 Pmc), 2.48 (s, 3H, CH_3 Pmc), 2.55 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 2.7 (m, 1H, $H\beta$ Asp), 2.78 (m, 1H, $H\beta$ Asp), 3.07 (m, 1H, HCHN_3), 3.11 (m, 2H, $H\delta$ Arg), 3.56 (m, 1H, HCHN_3), 3.63 (m, 1H, $H\alpha$ Gly), 3.87 (m, 1H, H -7), 3.93 (m, 1H, $H\alpha$ Gly), 4.33 (m, 1H, $H\alpha$ Asp), 4.35 (m, 1H, H -3), 4.42 (m, 1H, $H\alpha$ Arg), 4.64 (m, 1H, H -10), 6.25 (bs, 1H, $(\text{NH})_2\text{C}=\text{NH}$), 6.36 (bs, 2H, $(\text{NH})_2\text{C}=\text{NH}$), 7.46 (m, 1H, NH bicyclic), 7.77-7.9 (m, 2H, NH Gly, NH Arg), 8.05 (bs, 1H, NH Asp). ^{13}C NMR HETCOR (400 MHz, Acetone- D_6): δ 61.2, 58.9, 53.5, 53.3, 53.1, 51.4, 43.6, 40.3, 39.6, 36.3, 33.3, 33.1, 31.6, 28.7, 27.3, 26.9, 26.1, 25.8, 25.5, 21.0, 18.0, 16.9, 11.4. MS $[\text{ESI}^+]$: calculated for $\text{C}_{41}\text{H}_{61}\text{N}_{11}\text{O}_{10}\text{S}$: 899.43, observed: 900.9 $[\text{M} + \text{H}]^+$. Calculated analysis for $\text{C}_{41}\text{H}_{61}\text{N}_{11}\text{O}_{10}\text{S}$: C 54.71, H 6.83, N 17.12; observed C 54.73, H 6.82, N 17.11.

Compound 25

Yield: 60%. (White solid). $[\alpha]_D^{22} = -65.83$ ($c = 1.15$, CHCl_3). ^1H NMR (400 MHz, Acetone- D_6): δ 1.27 (m, 1H, $H-5$), 1.30 (s, 6H, $\text{C}(\text{CH}_3)_2$ Pmc), 1.45 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.52 (m, 1H, $H\beta$ Arg), 1.59 (m, 1H, $H-7$), 1.60 (m, 1H, $H\gamma$ Arg), 1.62 (m, 1H, $H\beta$ Arg), 1.81 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 1.98 (m, 1H, $H\gamma$ Arg), 2.0 (m, 1H, $H-8$), 2.1 (s, 3H, CH_3 Pmc), 2.38 (m, 1H, $H-5$), 2.42 (m, 1H, $H-7$), 2.43 (m, 1H, $H-8$), 2.56 (s, 3H, CH_3 Pmc), 2.58 (s, 3H, CH_3 Pmc), 2.6 (m, 1H, $H\beta$ Asp), 2.62 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 2.9 (m, 1H, $H-4$), 2.95 (m, 1H, $H\beta$ Asp), 3.19 (m, 1H, $H\delta$ Arg), 3.25 (m, 1H, $H\delta$ Arg), 3.37 (m, 2H, CH_2N_3), 3.62 (d, 1H, $J = 13.3$ Hz, $H\alpha$ Gly), 4.1 (m, 1H, $H-6$), 4.12 (m, 1H, $H\alpha$ Gly), 4.25 (m, 2H, $H-9$), 4.39 (m, 1H, $H-3$), 4.6 (m, 1H, $H\alpha$ Arg), 4.67 (m, 1H, $H\alpha$ Asp), 6.12 (bs, 1H, $(\text{NH})_2\text{C}=\text{NH}$), 6.35 (bs, 2H, $(\text{NH})_2\text{C}=\text{NH}$), 7.32-7.48 (m, 2H, NH Arg, NH bicyclic), 7.82 (bs, 1H, NH Gly), 8.1 (bs, 1H, NH Asp). ^{13}C NMR HETCOR (400 MHz, Acetone- D_6): δ 62.5, 55.7, 53.4, 51.2, 42.7, 40.6, 40.3, 36.3, 35.5, 34.9, 33.4, 33.3, 30.0, 28.4, 28.3, 27.5, 26.0, 22.1, 20.8, 17.9, 16.7, 13.2, 11.4. MS $[\text{FAB}^+]$: calculated for $\text{C}_{40}\text{H}_{59}\text{N}_{11}\text{O}_{10}\text{S}$: 885.42, observed: 886 $[\text{M} + \text{H}]^+$. Calculated analysis for $\text{C}_{40}\text{H}_{59}\text{N}_{11}\text{O}_{10}\text{S}$: C 54.22, H 6.71, N 17.39; observed C 54.21, H 6.73, N 17.38.

Compound 27

Yield: 75%. (White solid). $[\alpha]_D^{22} = -35.74$ ($c = 1.2$, CHCl_3). ^1H -NMR (400 MHz, CDCl_3): δ 1.32 (s, 6H, $\text{C}(\text{CH}_3)_2$ Pmc), 1.46 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.48 (m, 1H, $H-6$), 1.5 (m, 1H, $H\beta$ Arg), 1.60 (m, 1H, $H\gamma$ Arg), 1.62 (m, 1H, $H\beta$ Arg), 1.65 (m, 1H, $H-5$), 1.7 (m, 1H, $H-4$), 1.73 (m, 1H, $H-8$), 1.82 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 1.96 (m, 1H, $H\gamma$ Arg), 2.02 (m, 1H, $H-9$), 2.1 (m, 1H, $H-5$), 2.11 (s, 3H, CH_3 Pmc), 2.21 (m, 1H, $H-8$), 2.23 (m, 1H, $H-9$), 2.45 (m, 1H, $H\beta$ Asp), 2.56 (s, 3H, CH_3 Pmc), 2.58 (s, 3H, CH_3 Pmc), 2.64 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 2.87 (m, 1H, $H\beta$ Asp), 3.18 (m, 2H, $H\delta$ Arg), 3.22 (m, 1H, HCHN_3), 3.53 (d, 1H, $J = 13.0$ Hz, $H\alpha$ Gly), 3.62 (m, 1H, HCHN_3), 4.24 (m, 1H, $H-7$), 4.26 (m, 1H, $H\alpha$ Gly), 4.41 (m, 2H, $H-10$), 4.59 (m, 1H, $H\alpha$ Arg), 4.61 (m, 1H, $H-3$), 4.96 (m, 1H, $H\alpha$ Asp), 6.32 (bs, 3H, $(\text{NH})_2\text{C}=\text{NH}$), 7.46-7.58 (m, 3H, NH Gly, NH Arg, NH bicyclic), 7.9 (bs, 1H, NH Asp). ^{13}C NMR HETCOR (400 MHz, CDCl_3): δ 63.4, 58.9, 55.0, 53.8, 51.9, 49.7, 44.3, 40.5, 39.3, 35.2, 33.0, 32.5, 32.6, 31.2, 28.0, 27.8, 26.7, 25.3, 21.3, 18.6, 17.3, 11.9. MS $[\text{FAB}^+]$:

calculated for $C_{41}H_{61}N_{11}O_{10}S$: 899.43, observed: 901 $[M + H]^+$. Calculated analysis for $C_{41}H_{61}N_{11}O_{10}S$: C 54.71, H 6.83, N 17.12; observed C 54.70, H 6.83, N 17.11.

Example 2: Hydrogenation of the azide group.

To a solution of product **21, 23, 25 or 27** (0.03 mmol) in MeOH (1 ml) is
5 added a catalytic quantity of C-Pd 10%. The suspension is kept stirring under hydrogen atmosphere for approx. 4 hours. After this period of time the reaction mixture is filtered over a bed of Celite, the collected organic phase is evaporated to dryness and used in the subsequent reaction without any further purification.

Example 3: Synthesis of the amide.

10 To a solution of product **21-NH₂, 23-NH₂, 25-NH₂ or 27-NH₂** (0.027 mmol) in anhydrous DCM (700 μ l) under argon atmosphere and at room temp., are added in the following sequence: valeroyl chloride (6.5 μ l, 0.054 mmol) and TEA (15 μ l, 0.11 mmol). The solution is kept stirring for approx. 1.5 hours. After this period of time the solvent is evaporated to dryness and the crude product is purified by flash
15 chromatography ($CH_2Cl_2/iPrOH$ 85:15) to give the desired product as a white foam (40%-57%).

Compound 22-PG

Yield: 40%. (White solid). $[\alpha]_D^{22} = -83.1$ ($c = 0.48$, Acetone). 1H NMR (400 MHz, Acetone- D_6): δ 0.9 (t, 3H, $J = 7.4$ Hz, $COCH_2CH_2CH_2CH_3$), 1.32 (s, 6H, $C(CH_3)_2$
20 Pmc), 1.35 (m, 2H, $COCH_2CH_2CH_2CH_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.54 (m, 2H, $H\gamma$ Arg), 1.55 (m, 2H, $COCH_2CH_2CH_2CH_3$), 1.6 (m, 1H, $H-5$), 1.62 (m, 1H, $H\beta$ Arg), 1.8 (m, 1H, $H-7$), 1.85 (m, 2H, CH_2CH_2Ar Pmc), 1.9 (m, 1H, $H\beta$ Arg), 1.92 (m, 1H, $H-8$), 2.08 (m, 1H, $H-5$), 2.1 (s, 3H, CH_3 Pmc), 2.12 (m, 2H, $COCH_2CH_2CH_2CH_3$),
25 2.19 (m, 1H, $H-7$), 2.20 (m, 1H, $H-8$), 2.24 (m, 1H, $H-4$), 2.57 (s, 3H, CH_3 Pmc), 2.59 (s, 3H, CH_3 Pmc), 2.67 (m, 2H, CH_2CH_2Ar Pmc), 2.78 (m, 1H, $H\beta$ Asp), 2.82 (m, 1H, $HCHNHCO$), 2.84 (m, 1H, $H\beta$ Asp), 3.27 (m, 2H, $H\delta$ Arg), 3.48 (m, 1H, $H\alpha$ Gly), 3.57 (m, 1H, $HCHNHCO$), 3.69 (m, 1H, $H-6$), 4.14 (m, 1H, $H\alpha$ Gly), 4.18 (m, 1H, $H-9$), 4.43 (m, 1H, $H\alpha$ Arg), 4.62 (m, 1H, $H-3$), 4.8 (m, 1H, $H\alpha$ Asp), 6.5 (m, 3H, $(NH)_2C=NH$), 7.08 (m, 1H, $NHCO(CH_2)_3CH_3$), 7.12 (bs, 1H, NH Arg), 7.88
30 (m, 1H, NH Asp), 8.0 (bs, 1H, NH bicyclic), 8.4 (bs, 1H, NH Gly). ^{13}C NMR

HETCOR (400 MHz, Acetone-D6): δ 61.9, 60.5, 51.7, 51.3, 50.5, 45.1, 40.5, 40.4, 40.1, 37.7, 36.4, 32.9, 31.7, 30.8, 30.7, 28.2, 28.0, 27.6, 26.4, 25.9, 22.5, 21.6, 18.6, 17.1, 16.6, 11.8. MS [FAB⁺]: calculated for C₄₅H₆₉N₉O₁₁S: 943.48, observed: 944 [M + H]⁺, 966 [M + Na]⁺. Calculated analysis for C₄₅H₆₉N₉O₁₁S: C 57.25, H 7.37, N 13.35; observed C 57.23, H 7.36, N 13.36.

Compound 24-PG

Yield: 40%. (White solid). $[\alpha]_D^{22} = -15.9$ ($c = 1.0$, Acetone). ¹H NMR (400 MHz, Acetone-D6): δ 0.9 (t, 3H, J = 7.4 Hz, COCH₂CH₂CH₂CH₃), 1.31 (s, 6H, C(CH₃)₂ Pmc), 1.33 (m, 2H, COCH₂CH₂CH₂CH₃), 1.47 (s, 9H, C(CH₃)₃), 1.49 (m, 1H, H γ Arg), 1.51 (m, 1H, H β Arg), 1.6 (m, 1H, H γ Arg), 1.62 (m, 2H, COCH₂CH₂CH₂CH₃), 1.65 (m, 1H, H-6), 1.67 (m, 1H, H-5), 1.69 (m, 1H, H-4), 1.71 (m, 1H, H-8), 1.76 (m, 2H, CH₂CH₂Ar Pmc), 1.79 (m, 1H, H-6), 1.96 (m, 2H, H-5, H-9), 2.07 (m, 1H, H β Arg), 2.1 (s, 3H, CH₃ Pmc), 2.13 (m, 2H, COCH₂CH₂CH₂CH₃), 2.35 (m, 1H, H-8), 2.38 (m, 1H, H-9), 2.53 (m, 1H, H β Asp), 2.57 (s, 3H, CH₃ Pmc), 2.59 (s, 3H, CH₃ Pmc), 2.68 (m, 2H, CH₂CH₂Ar Pmc), 2.95 (m, 1H, H β Asp), 3.07 (m, 1H, HCHNHCO), 3.21 (m, 2H, H δ Arg), 3.38 (d, 1H, J = 14.3 Hz, H α Gly), 3.64 (m, 1H, HCHNHCO), 4.25 (m, 1H, H-7), 4.31 (m, 1H, H α Gly), 4.41 (m, 1H, H-3), 4.46 (m, 1H, H-10), 4.52 (m, 1H, H α Arg), 4.83 (m, 1H, H α Asp), 6.32 (bs, 1H, (NH)₂C=NH), 6.5 (bs, 2H, (NH)₂C=NH), 7.12 (m, 1H, NHCO(CH₂)₃CH₃), 7.3 (m, 1H, NH Gly), 7.49 (m, 1H, NH Arg) 7.60 (m, 1H, NH bicyclic), 8.02 (m, 1H, NH Asp). ¹³C NMR HETCOR (400 MHz, Acetone-D6): δ 62.0, 59.4, 55.9, 51.8, 50.0, 43.9, 41.1, 40.5, 39.5, 35.7, 35.0, 33.1, 32.7, 32.2, 31.5, 27.8, 27.7, 27.4, 27.1, 26.2, 26.0, 22.3, 21.0, 18.0, 16.8, 13.5, 11.6. MS [FAB⁺]: calculated for C₄₆H₇₁N₉O₁₁S: 957.5, observed: 958 [M + H]⁺. Calculated analysis for C₄₆H₇₁N₉O₁₁S: C 57.66, H 7.47, N 13.16; observed : C 57.69, H 7.46, N 13.15.

Compound 26-PG

Yield: 54%. (White solid). $[\alpha]_D^{22} = -84.4$ ($c = 0.75$, Acetone). ¹H NMR (400 MHz, Acetone-D6): δ 0.9 (t, 3H, J = 7.3 Hz, COCH₂CH₂CH₂CH₃), 1.3 (m, 2H, COCH₂CH₂CH₂CH₃), 1.32 (s, 6H, C(CH₃)₂ Pmc), 1.34 (m, 1H, H-5), 1.45 (s, 9H, C(CH₃)₃), 1.5 (m, 1H, H γ Arg, H β Arg), 1.54 (m, 2H, COCH₂CH₂CH₂CH₃), 1.6 (m,

1H, $H\gamma$ Arg), 1.63 (m, 1H, $H-7$), 1.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar Pmc}$), 2.0 (m, 1H, $H-8$), 2.08 (m, 1H, $H\beta$ Arg), 2.1 (s, 3H, CH_3 Pmc), 2.12 (m, 2H, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.4 (m, 1H, $H-7$), 2.43 (m, 1H, $H-8$, $H-5$), 2.56 (m, 1H, $H\beta$ Asp), 2.57 (s, 3H, CH_3 Pmc), 2.59 (s, 3H, CH_3 Pmc), 2.68 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar Pmc}$), 2.74 (m, 1H, $H-4$), 3.01 (dd, 1H, $J = 16.6$ Hz, $J = 7.0$ Hz, $H\beta$ Asp), 3.12 (m, 1H, HCHNHCO), 3.19 (m, 1H, HCHNHCO), 3.21 (m, 2H, $H\delta$ Arg), 3.43 (d, 1H, $J = 14.2$ Hz, $H\alpha$ Gly), 4.17 (m, 1H, $H-6$), 4.2 (m, 1H, $H\alpha$ Gly), 4.25 (m, 1H, $H-9$), 4.3 (m, 1H, $H-3$), 4.55 (m, 1H, $H\alpha$ Arg), 4.58 (m, 1H, $H\alpha$ Asp), 6.32 (bs, 1H, $(\text{NH})_2\text{C}=\text{NH}$), 6.48 (bs, 2H, $(\text{NH})_2\text{C}=\text{NH}$), 6.67 (m, 1H, $\text{NHCO}(\text{CH}_2)_3\text{CH}_3$), 7.33 (m, 1H, NH bicyclic), 7.42 (m, 1H, NH Arg), 7.58 (m, 1H, NH Gly), 8.032 (m, 1H, NH Asp). ^{13}C NMR HETCOR (400 MHz, Acetone- D_6): δ 62.5, 55.7, 53.4, 51.2, 42.7, 40.6, 40.3, 36.3, 35.5, 34.9, 33.4, 33.3, 33.4, 30.0, 28.4, 28.3, 27.5, 26.0, 22.1, 20.8, 17.9, 16.7, 13.2, 11.4. MS $[\text{FAB}^+]$: calculated for $\text{C}_{45}\text{H}_{69}\text{N}_9\text{O}_{11}\text{S}$: 943.48, observed: 944 $[\text{M} + \text{H}]^+$, 966 $[\text{M} + \text{Na}]^+$. Calculated analysis for $\text{C}_{45}\text{H}_{69}\text{N}_9\text{O}_{11}\text{S}$: C 57.25, H 7.37, N 13.35; observed C 57.26, H 7.36, N 13.34.

Compound 28-PG

Yield: 57%. (White solid). $[\alpha]_{\text{D}}^{22} = -13.78$ ($c = 1.02$, Acetone). ^1H NMR (400 MHz, Acetone- D_6): δ 0.92 (t, 3H, $J = 7.4$ Hz, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.32 (s, 6H, $\text{C}(\text{CH}_3)_2$ Pmc), 1.34 (m, 2H, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.45 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.48 (m, 1H, $H\gamma$ Arg), 1.50 (m, 1H, $H\beta$ Arg), 1.58 (m, 1H, $H\gamma$ Arg), 1.6 (m, 2H, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.62 (m, 1H, $H-6$), 1.65 (m, 1H, $H-5$), 1.67 (m, 1H, $H-4$), 1.7 (m, 1H, $H-8$), 1.75 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar Pmc}$), 1.78 (m, 1H, $H-6$), 1.97 (m, 2H, $H-5$, $H-9$), 2.06 (m, 1H, $H\beta$ Arg), 2.1 (s, 3H, CH_3 Pmc), 2.12 (m, 2H, $\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.33 (m, 1H, $H-8$), 2.38 (m, 1H, $H-9$), 2.54 (m, 1H, $H\beta$ Asp), 2.56 (s, 3H, CH_3 Pmc), 2.58 (s, 3H, CH_3 Pmc), 2.67 (m, 2H, $\text{CH}_2\text{CH}_2\text{Ar Pmc}$), 2.94 (m, 1H, $H\beta$ Asp), 3.05 (m, 1H, HCHNHCO), 3.2 (m, 2H, $H\delta$ Arg), 3.37 (d, 1H, $J = 14.3$ Hz, $H\alpha$ Gly), 3.65 (m, 1H, HCHNHCO), 4.24 (m, 1H, $H-7$), 4.3 (m, 1H, $H\alpha$ Gly), 4.4 (m, 1H, $H-3$), 4.45 (m, 1H, $H-10$), 4.5 (m, 1H, $H\alpha$ Arg), 4.85 (m, 1H, $H\alpha$ Asp), 6.33 (bs, 1H, $(\text{NH})_2\text{C}=\text{NH}$), 6.48 (bs, 2H, $(\text{NH})_2\text{C}=\text{NH}$), 7.13 (m, 1H, $\text{NHCO}(\text{CH}_2)_3\text{CH}_3$), 7.27 (m, 1H, NH Gly), 7.48 (m, 1H, NH Arg), 7.61 (m, 1H, NH

bicyclic), 8.04 (m, 1H, *NH* Asp). ^{13}C NMR HETCOR (400 MHz, Acetone- D_6): δ 63.1, 59.2, 55.7, 51.7, 49.9, 43.6, 40.8, 40.3, 39.6, 35.9, 34.8, 33.0, 32.6, 32.2, 31.4, 27.8, 27.7, 27.5, 27.3, 26.1, 26.0, 22.1, 21.0, 17.9, 16.9, 13.3, 11.4. MS $[\text{FAB}^+]$: calculated for $\text{C}_{46}\text{H}_{71}\text{N}_9\text{O}_{11}\text{S}$: 957.5, observed: 958 $[\text{M} + \text{H}]^+$. Calculated analysis for
 5 $\text{C}_{46}\text{H}_{71}\text{N}_9\text{O}_{11}\text{S}$: C 57.66, H 7.47, N 13.16; observed : C 57.67, H 7.48, N 13.14.

Example 4: Conjugation through “click reaction”

To a solution of azide **25** (0.1 mmol) and of an appropriate alkynyl derivative (0.1 mmol) in $\text{H}_2\text{O}/t\text{-BuOH}$ 1:1 (500 μL .) a solution of sodium ascorbate 0.9 M (44 μL , 0.04 mmol, 0.4 mol eq) and a solution of di $\text{Cu}(\text{OAc})_2$ 0.3 M (67 μL , 0.02 mmol, 0.2
 10 mol eq) are added, respectively. The reaction mixture has been kept under stirring at r. t. for about 18 hs. At the reaction completed, the solvent is evaporated under reduced pressure and the product is isolated by flash chromatography on silica gel.

Compound 46

Yield: 67%. (White solid). $[\alpha]_{\text{D}}^{22} = -70.5$ ($c = 0.89$, MeOH). ^1H NMR (400 MHz, CD_3OD): δ 1.31 (s, 6H, $\text{C}(\text{CH}_3)_2$ Pmc), 1.44 (m, 1H, *H γ* Arg), 1.48 (s, 9H, $\text{C}(\text{CH}_3)_3$),
 15 1.51 (m, 1H, *H β* Arg), 1.56 (m, 1H, *H γ* Arg), 1.6-1.7 (m, 2H, *H-5 H-7*), 1.84 (t, 2H, $\text{J} = 6.8$ Hz, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 1.87 (m, 1H, *H-8*), 2.06 (m, 1H, *H β* Arg), 2.1 (s, 3H, CH_3 Pmc), 2.32-2.46 (m, 3H, *H-5, H-7, H-8*), 2.55 (s, 3H, CH_3 Pmc), 2.56 (s, 3H, CH_3 Pmc), 2.59 (m, 1H, *H β* Asp), 2.67 (7, 2H, $\text{J} = 6.8$ Hz, $\text{CH}_2\text{CH}_2\text{Ar}$ Pmc), 3.06 (dd,
 20 1H, $\text{J} = 16.6$ Hz, $\text{J} = 7.2$ Hz, *H β* Asp), 3.14-3.22 (m, 2H, *H δ* Arg), 3.26 (m, 1H, *H-2* Glc) 3.30-3.34 (m, 3H, *H-4, H-4* Glc, *H-5* Glc), 3.38 (m, 1H, *H-3* Glc), 3.47 (d, 1H, $\text{J} = 13.9$ Hz, *H α* Gly), 3.7 (m, 1H, *H-6* Glc), 3.91 (d, 1H, $\text{J} = 10.8$, *H-6* Glc), 4.01 (m, 1H, *H-6*), 4.16 (dd, 1H, $\text{J} = 6.5$ Hz, $\text{J} = 11.0$ Hz, *H-9*), 4.27 (d, 1H, $\text{J} = 14.4$ Hz, *H α* Gly), 4.3 (m, 1H, *HCH-N*) 4.35-4.46 (m, 3H, *H-3, H-1* Glc, *HCH-N*), 4.47 (m, 1H,
 25 *H α* Asp), 4.55 (m, 1H, *H α* Arg), 4.83 (m, 1H, *OHCH-*), 4.93 (d, 1H, $\text{J} = 12.9$ Hz, *OHCH-*), 8.02 (s, 1H, *H* triazole). ^{13}C NMR (100.6 MHz, CD_3OD): δ 174.3 172.4, 172.0, 171.4, 170.7, 168.8, 156.6, 153.3, 144.4, 135.1, 134.7, 133.4, 125.2, 123.5, 118.0, 101.6, 80.8, 76.6, 76.5, 73.6, 70.3, 62.3, 61.4, 55.5, 53.0, 51.5, 51.3, 51.0, 41.7, 40.2, 36.5, 34.5, 33.0, 32.4, 32.2, 30.1, 27.6, 27.0, 25.6, 21.0, 17.5, 16.4, 10.9.
 30 MS $[\text{ESI}^+]$: calc. for $\text{C}_{49}\text{H}_{73}\text{N}_{11}\text{O}_{16}\text{S}$: 1103.5, observed: 1104.5 $[\text{M} + \text{H}]^+$, 1126.5 $[\text{M}$

+ Na]⁺. Anal. calc. for C₄₉H₇₃N₁₁O₁₆S: C 53.3, H 6.66, N 13.95; observed C 53.28, H 6.64, N 13.92.

Compound 48

Yield: 81%. (White solid). $[\alpha]_D^{22} = -73.3$ ($c = 0.92$, Acetone). ¹H NMR (400 MHz, Acetone-d₆): δ 0.98 (t, 3H, $J = 7.2$ Hz, CH₃), 1.35 (m, 1H, *H*-5), 1.37 (s, 6H, C(CH₃)₂ Pmc), 1.42 (m, 2H, CH₂), 1.5 (s, 9H, C(CH₃)₃), 1.54 (m, 2H, *H* β Arg, *H* γ Arg), 1.58 (m, 1H, *H* γ Arg), 1.65 (m, 1H, *H*-7), 1.67 (m, 2H, CH₂), 1.9 (t, 2H, $J = 6.8$ Hz, CH₂CH₂Ar Pmc), 2.07 (m, 1H, *H*-8), 2.12 (m, 1H, *H* β Arg), 2.15 (s, 3H, CH₃ Pmc), 2.26 (m, 1H, *H*-5), 2.40-2.49 (m, 2H, *H*-7, *H*-8), 2.62 (s, 3H, CH₃ Pmc), 2.64 (s, 3H, CH₃ Pmc), 2.65-2.76 (m, 5H, CH₂CH₂Ar Pmc, CH₂, *H* β Asp), 3.07 (dd, 1H, $J = 16.8$ Hz, $J = 6.8$ Hz, *H* β Asp), 3.26 (m, 2H, *H* δ Arg), 3.34 (m, 3H, *H*-4), 3.53 (d, 1H, $J = 14.0$ Hz, *H* α Gly), 4.11 (m, 1H, *H*CH-N), 4.22-4.31 (m, 2H, *H*-6, *H* α Gly), 4.34 (m, 1H, *H*-9), 4.48 (m, 1H, *H*-3), 4.52 (m, 1H, *H*CH-N), 4.62 (m, 1H, *H* α Arg), 4.65 (m, 1H, *H* α Asp), 6.43 (bs, 1H, *NH* guanidine), 6.58 (bs, 2H, *NH* guanidine), 7.42 (d, 1H, $J = 4.0$ Hz, *NH* scaffold), 7.59 (d, 1H, $J = 8.8$ Hz, *NH* Arg), 7.66 (d, 1H, $J = 8.0$ Hz, *NH* Gly), 7.76 (s, 1H, *H* triazole), 8.50 (d, 1H, $J = 7.6$ Hz, *NH* Asp). ¹³C NMR (100.6 MHz, Acetone-d₆): δ 174.2, 172.2, 171.8, 170.8, 169.4, 157.1, 153.5, 148.1, 135.8, 135.7, 135.2, 123.8, 122.4, 118.5, 80.7, 74.0, 63.2, 56.2, 54.0, 52.2, 52.0, 51.7, 43.5, 41.1, 37.3, 35.5, 33.8, 33.6, 33.2, 32.2, 30.5, 28.0, 26.8, 26.7, 26.6, 25.7, 22.6, 21.7, 18.6, 17.5, 13.9, 12.0. MS [ESI⁺]: calc. for C₄₆H₆₉N₁₁O₁₀S: 967.49, observed: 968.5 [M + H]⁺. Anal. calc. for C₄₆H₆₉N₁₁O₁₀S: C 57.07, H 7.18, N 15.91; observed C 57.08, H 7.20, N 15.92.

Compound 50

Yield: 62%. (White solid). $[\alpha]_D^{22} = -26.5$ ($c = 1.06$, MeOH). ¹H NMR (400 MHz, CD₃OD): δ 1.3 (s, 6H, C(CH₃)₂ Pmc), 1.36-1.52 (m, 14H, *H*-5, *H* γ Arg, CH₂ biotin, C(CH₃)₃, *H* β Arg, *H* γ Arg), 1.53-1.67 (m, 5H, *H*-7, *H* γ Arg, *H*CH biotin, CH₂ biotin), 1.71 (m, 1H, *H*CH biotin), 1.72 (m, 2H, NCH₂CH₂CH₂O linker), 1.78 (m, 2H, NCH₂CH₂CH₂O linker), 1.82 (m, 2H, CH₂CH₂Ar Pmc), 1.87 (m, 1H, *H*-8), 2.04 (m, 1H, *H* β Arg), 2.08 (s, 3H, CH₃ Pmc), 2.18 (m, 2H, CH₂ biotin), 2.27-2.44 (m, 3H, *H*-5, *H*-7, *H*-8), 2.54 (s, 3H, CH₃ Pmc), 2.56 (s, 3H, CH₃ Pmc), 2.57 (m, 1H, *H* β Asp),

2.63-2.72 (m, 3H, CH₂CH₂Ar Pmc, SHCH biotin), 2.91 (dd, 1H, J = 12.7 Hz, J = 5.0 Hz, SHCH biotin), 3.04 (dd, 1H, J = 16.7 Hz, J = 7.3 Hz, H β Asp), 3.12-3.27 (m, 5H, 2H δ Arg, H-4, SHC- biotin, CH₂N linker), 3.33 (m, 2H, CH₂N linker) 3.41 (d, 1H, J = 14.3 Hz, H α Gly), 3.47-3.55 (m, 4H, CH₂O linker), 3.56-3.66 (m, 8H, CH₂O linker), 3.98 (m, 1H, H-4), 4.06 (s, 2H, COCH₂O linker), 4.11 (s, 2H, COCH₂O linker), 4.13 (m, 1H, H-9), 4.17-4.32 (m, 3H, HCH-N, H α Gly, NCH biotin), 4.33-4.55 (m, 5H, H-3, HCH-N, H α Arg, H α Asp, NCH biotin), 7.40 (m, 1H, NH Asp), 7.80 (s, 1H, H triazole). ¹³C NMR (100.6 MHz, Acetone-d₆): δ 175.6, 173.7, 173.5, 172.7, 172.1, 170.2, 158.0, 154.7, 146.1, 136.5, 136.1, 134.9, 125.5, 124.9, 119.4, 82.2, 74.9, 71.6, 71.5, 71.3, 70.0, 69.9, 63.7, 63.4, 61.6, 57.1, 56.8, 54.4, 52.8, 52.5, 43.3, 41.6, 41.1, 37.9, 37.8, 37.7, 36.9, 35.9, 35.2, 34.4, 33.8, 33.6, 31.5, 30.8, 30.5, 30.4, 29.8, 29.6, 29.0, 28.4, 27.1, 27.0, 26.9, 22.4, 19.0, 17.9, 12.3. MS [ESI⁺]: calc. for C₆₇H₁₀₄N₁₆O₁₈S₂: 1484.72, observed: 1485.9 [M + H]⁺, 743.6 [M + 2H]²⁺. Anal. calc. for C₆₇H₁₀₄N₁₆O₁₈S₂: C 54.16, H 7.06, N 15.08; observed C 54.14, H 7.05, N 15.06.

Example 5: Deprotection of the end-products pentapeptides

To products **22-PG**, **24-PG**, **26-PG**, **28-PG**, **46**, **48**, **50** or **52** (0.015) is added a solution of CF₃COOH/thioanisole/1,2-ethanedithiol/anisole 90:5:3:2 (1 ml). Said mixture is kept stirring for approx. 2 hours. After this period of time, the solvent is evaporated to dryness, the crude product is dissolved in H₂O and washed with iPr₂O (twice). The aqueous phases are evaporated to dryness.

Compound 22.

Yield: 99%. (White solid). [α]_D²² = -67.75 (*c* = 0.72, MeOH). ¹H NMR (400 MHz, D₂O): δ 0.84 (t, 3H, J = 7.4 Hz, NHCH₂CH₂CH₂CH₃), 1.26 (m, 2H, NHCH₂CH₂CH₂CH₃), 1.42 (m, 1H, H-5), 1.5 (m, 2H, H γ Arg), 1.53 (m, 2H, NHCH₂CH₂CH₂CH₃), 1.64 (m, 1H, H β Arg), 1.72 (m, 1H, H-7), 1.82 (m, 1H, H β Arg), 1.95 (m, 1H, H-8), 2.14 (m, 1H, H-5), 2.2 (m, 2H, NHCH₂CH₂CH₂CH₃), 2.23 (m, 1H, H-7), 2.25 (m, 1H, H-8), 2.36 (m, 1H, H-4), 2.79 (m, 2H, H β Asp), 3.07 (m, 1H, HCHNHCO), 3.17 (m, 2H, H δ Arg), 3.24 (m, 1H, HCHNHCO), 3.56 (d, 1H, J = 14.3 Hz, H α Gly), 3.66 (t, 1H, J = 10.4 Hz, H-6), 4.04 (d, 1H, J = 14.3 Hz, H α Gly),

4.26 (d, 1H, $J = 10.1$ Hz, $H-9$), 4.3 (m, 1H, $H\alpha$ Arg), 4.63 (m, 1H, $H\alpha$ Asp), 4.74 (m, 1H, $H-3$). ^{13}C NMR HETCOR (100.6 MHz, D_2O): δ 61.3, 59.9, 51.8, 51.7, 49.7, 44.5, 40.4, 39.8, 38.0, 36.9, 35.6, 30.8, 29.0, 28.9, 27.7, 27.3, 24.3, 21.5, 12.8. MS $[\text{ESI}^+]$: calculated for $\text{C}_{29}\text{H}_{44}\text{N}_9\text{O}_{10}$: 735.32, observed: 622 $[\text{M} - \text{TFA}]^+$. Calculated analysis for $\text{C}_{29}\text{H}_{44}\text{N}_9\text{O}_{10}$: C 47.34, H 6.04, N 14.93; observed C 47.35, H 6.04, N 14.91.

Compound 24.

Yield: 98%. (White solid). $[\alpha]_{\text{D}}^{22} = -22.5$ ($c = 1.0$, MeOH). ^1H NMR (400 MHz, D_2O): δ 0.84 (t, 3H, $J = 7.3$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.25 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.50 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.53 (m, 1H, $H\gamma$ Arg), 1.55 (m, 1H, $H-6$), 1.6 (m, 2H, $H\beta$ Arg, $H-5$), 1.73 (m, 1H, $H-4$), 1.83 (m, 1H, $H-6$), 1.85 (m, 1H, $H-8$), 1.91 (m, 1H, $H\gamma$ Arg), 1.94 (m, 1H, $H-5$), 2.01 (m, 2H, $H\beta$ Arg, $H-9$), 2.22 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.26 (m, 1H, $H-8$), 2.41 (m, 1H, $H-8$), 2.75 (dd, 1H, $J = 17.0$ Hz, $J = 6.7$ Hz, $H\beta$ Asp), 3.01 (m, 1H, HCHNHCO), 3.05 (m, 1H, $H\beta$ Asp), 3.18 (m, 2H, $H\delta$ Arg), 3.4 (dd, 1H, $J = 14.0$ Hz, $J = 3.9$ Hz, HCHNHCO), 3.5 (d, 1H, $J = 14.5$ Hz, $H\alpha$ Gly), 4.2 (m, 1H, $H-7$), 4.25 (d, 1H, $J = 14.5$ Hz, $H\alpha$ Gly), 4.4 (dd, 1H, $J = 8.8$ Hz, $J = 4.7$ Hz, $H-10$), 4.45 (dd, 1H, $J = 10.6$ Hz, $J = 4.2$ Hz, $H\alpha$ Arg), 4.58 (m, 1H, $H-3$), 4.67 (dd, 1H, $J = 7.6$ Hz, $H\alpha$ Asp). ^{13}C NMR HETCOR (100.6 MHz, D_2O): δ 62.9, 59.5, 55.0, 52.0, 50.8, 43.2, 41.6, 40.1, 38.3, 36.0, 33.5, 32.0, 31.9, 30.8, 27.7, 27.5, 27.5, 25.7, 21.6, 12.4. MS $[\text{ESI}^+]$: calculated for $\text{C}_{30}\text{H}_{46}\text{F}_3\text{N}_9\text{O}_{10}$: 749.33, observed: 636.7 $[\text{M} - \text{TFA}]^+$. Calculated analysis for $\text{C}_{30}\text{H}_{46}\text{F}_3\text{N}_9\text{O}_{10}$: C 48.06, H 6.18, N 16.81; observed C 48.04, H 6.17, N 16.82.

Compound 26.

Yield: 99%. (White solid). $[\alpha]_{\text{D}}^{22} = -64.9$ ($c = 0.68$, MeOH). ^1H NMR (400 MHz, D_2O): δ 0.83 (t, 3H, $J = 7.3$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.19 (m, 1H, $H-5$), 1.23 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.45 (m, 2H, $H\gamma$ Arg), 1.48 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.5 (m, 1H, $H\beta$ Arg), 1.55 (m, 1H, $H-7$), 1.60 (m, 1H, $H-5$), 1.63 (m, 1H, $H-7$), 1.85 (m, 1H, $H-8$), 2.05 (m, 1H, $H\beta$ Arg), 2.15 (t, 2H, $J = 7.4$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.42 (m, 2H, CH_2NHCO), 2.45 (m, 1H, $H-8$), 2.72 (dd, 1H, $J = 17$ Hz, $J = 7.1$ Hz, $H\beta$ Asp), 2.76 (m, 1H, $H-4$), 3.06 (dd, 1H, $J = 17$ Hz, $J = 7.1$ Hz, $H\beta$ Asp), 3.15 (m,

2H, $H\delta$ Arg), 3.48 (d, 1H, $J = 14.6$ Hz, $H\alpha$ Gly), 3.98 (m, 1H, $H-6$), 4.25 (m, 2H, $H-9$, $H\alpha$ Gly), 4.36 (t, 1H, $J = 7.0$ Hz, $H-3$), 4.5 (t, 1H, $J = 7.2$ Hz, $H\alpha$ Asp), 4.57 (dd, 1H, $J = 10.1$ Hz, $J = 3.4$ Hz, $H\alpha$ Arg). ^{13}C NMR (100.6 MHz, D_2O): δ 177.7, 174.8, 174.5, 174.0, 173.0, 171.6, 170.2, 62.1, 56.0, 52.9, 51.6, 51.3, 42.3, 40.3, 40.1, 35.8, 35.6, 33.2, 32.8, 32.6, 30.1, 27.5, 26.9, 24.3, 21.6, 13.0. MS $[\text{ESI}^+]$: calculated for $\text{C}_{29}\text{H}_{44}\text{F}_3\text{N}_9\text{O}_{10}$: 735.32, observed: 622 $[\text{M} - \text{TFA}]^+$. Calculated analysis for $\text{C}_{29}\text{H}_{44}\text{F}_3\text{N}_9\text{O}_{10}$: C 47.34, H 6.04, N 14.93; observed C 47.33, H 6.05, N 14.92.

Compound 28.

Yield: 99%. (White solid). $[\alpha]_{\text{D}}^{22} = -12.6$ ($c = 1.0$, MeOH). ^1H NMR (400 MHz, D_2O): δ 0.85 (t, 3H, $J = 7.3$ Hz, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.25 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.51 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.52 (m, 1H, $H\gamma$ Arg), 1.54 (m, 1H, $H-6$), 1.62 (m, 2H, $H\beta$ Arg, $H-5$), 1.75 (m, 1H, $H-4$), 1.82 (m, 1H, $H-6$), 1.84 (m, 1H, $H-8$), 1.9 (m, 1H, $H\gamma$ Arg), 1.93 (m, 1H, $H-5$), 2.0 (m, 2H, $H\beta$ Arg, $H-9$), 2.2 (m, 2H, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.22 (m, 1H, $H-8$), 2.4 (m, 1H, $H-8$), 2.73 (dd, 1H, $J = 17.0$ Hz, $J = 6.7$ Hz, $H\beta$ Asp), 3.0 (m, 1H, HCHNHCO), 3.04 (m, 1H, $H\beta$ Asp), 3.15 (m, 2H, $H\delta$ Arg), 3.42 (dd, 1H, $J = 14.0$ Hz, $J = 3.9$ Hz, HCHNHCO), 3.47 (d, 1H, $J = 14.5$ Hz, $H\alpha$ Gly), 4.17 (m, 1H, $H-7$), 4.22 (d, 1H, $J = 14.5$ Hz, $H\alpha$ Gly), 4.39 (dd, 1H, $J = 8.8$ Hz, $J = 4.7$ Hz, $H-10$), 4.46 (dd, 1H, $J = 10.6$ Hz, $J = 4.2$ Hz, $H\alpha$ Arg), 4.56 (m, 1H, $H-3$), 4.65 (dd, 1H, $J = 7.6$ Hz, $H\alpha$ Asp). ^{13}C NMR HETCOR (100.6 MHz, D_2O): δ 62.8, 59.3, 55.2, 51.8, 50.6, 43.0, 41.4, 40.0, 38.1, 35.7, 33.2, 31.8, 31.7, 30.5, 27.4, 27.3, 27.0, 25.5, 21.4, 12.8. MS $[\text{ESI}^+]$: calculated for $\text{C}_{30}\text{H}_{46}\text{F}_3\text{N}_9\text{O}_{10}$: 749.33, observed: 636.7 $[\text{M} - \text{TFA}]^+$. Calculated analysis for $\text{C}_{30}\text{H}_{46}\text{F}_3\text{N}_9\text{O}_{10}$: C 48.06, H 6.18, N 16.81; observed C 48.05, H 6.19, N 16.83.

Compound 47

Yield: 99%. (White solid). $[\alpha]_{\text{D}}^{22} = -69.0$ ($c = 0.76$, MeOH). ^1H NMR (400 MHz, D_2O): δ 1.33 (m, 1H, $H-5$), 1.5 (m, 2H, $H\gamma$ Arg), 1.56 (m, 1H, $H\beta$ Arg), 1.63 (m, 1H, $H-7$), 1.82 (m, 1H, $H-8$), 2.02 (m, 1H, $H\beta$ Arg), 2.33-2.46 (m, 3H, $H-5$, $H-7$, $H-8$), 2.67 (dd, 1H, $J = 16.9$ Hz, $J = 7.0$ Hz, $H\beta$ Asp), 3.01 (dd, 1H, $J = 16.9$ Hz, $J = 7.0$ Hz, $H\beta$ Asp), 3.14 (m, 2H, $H\delta$ Arg), 3.20-3.29 (m, 2H, $H-4$, $H-2$ Glc), 3.33 (m, 1H, $H-5$ Glc), 3.37-3.45 (m, 2H, $H-3$ Glc, $H-4$ Glc), 3.48 (d, 1H, $J = 14.7$ Hz, $H\alpha$ Gly),

3.67 (dd, 1H, $J = 6.1$ Hz, $J = 12.5$ Hz, *H*-6 Glc), 3.85 (dd, 1H, $J = 1.8$ Hz, $J = 12.5$ Hz, *H*-6 Glc), 4.0 (m, 1H, *H*-6), 4.17-4.3 (m, 3H, *HCH*-N, *H* α Arg, *H*-9), 4.37-4.44 (m, 3H, *HCH*-N, *H* α Asp, *H*-3), 4.48 (d, 1H, $J = 8.0$ Hz, *H*-1 Glc), 4.55 (m, 1H, *H* α Arg), 4.79 (d, 1H, $J = 126.0$ Hz, *OHCH*-), 4.93 (d, 1H, $J = 126.0$ Hz, *OHCH*-), 7.51 (m, 1H, *NH* Asp), 8.01 (s, 1H, *H* triazole). ^{13}C NMR (100.6 MHz, D_2O): δ 174.9, 174.8, 174.0, 173.0, 171.6, 169.2, 156.7, 143.6, 126.0, 101.4, 76.0, 75.8, 73.0, 69.7, 62.2, 61.9, 60.8, 58.5, 55.8, 54.3, 52.9, 51.6, 51.5, 51.3, 46.7, 42.4, 40.4, 36.2, 33.3, 32.7, 32.2, 30.0, 27.0, 24.4. MS [ESI^+]: calc. for $\text{C}_{31}\text{H}_{47}\text{N}_{11}\text{O}_{13}$: 781.34, observed: 782.5 [$\text{M} + \text{H}$] $^+$. Anal. calc. for $\text{C}_{33}\text{H}_{48}\text{F}_3\text{N}_{11}\text{O}_{15}$: C 44.25, H 5.40, N 17.20; observed: C 44.27, H 5.41, N 17.22.

Compound 49

Yield: 99%. (White solid). $[\alpha]_{\text{D}}^{22} = -68.3$ ($c = 0.77$, MeOH). ^1H NMR (400 MHz, D_2O): 0.82 (m, 3H, CH_3), δ 1.17-1.33 (m, 3H, *H*-5, CH_2), 1.42-1.66 (m, 5H, 2*H* γ Arg, *H* β Arg, CH_2 , *H*-7), 1.83 (m, 1H, *H*-8), 2.0 (m, 1H, *H* β Arg), 2.3-2.46 (m, 3H, *H*-5, *H*-7, *H*-8), 2.66 (m, 1 H, CH_2), 2.68 (m, 1H, *H* β Asp), 2.99 (m, 1H, *H* β Asp), 3.13 (m, 2H, *H* δ Arg), 3.24 (m, 1H, *H*-4), 3.46 (d, 1H, $J = 14.7$ Hz, *H* α Gly), 3.99 (m, 1H, *H*-6), 4.1-4.29 (m, 3H, *HCH*-N, *H* α Arg, *H*-9), 4.31-4.43 (m, 3H, *HCH*-N, *H* α Asp, *H*-3), 4.54 (m, 1H, *H* α Arg), 7.52 (m, 1H, *NH* Asp), 7.80 (s, 1H, *H* triazole). ^{13}C NMR (100.6 MHz, D_2O): δ 174.6, 174.0, 173.9, 173.0, 171.6, 170.8, 169.1, 156.7, 148.1, 124.4, 62.2, 55.8, 52.9, 51.8, 51.6, 51.2, 42.4, 40.4, 36.3, 36.1, 33.2, 32.7, 32.2, 30.6, 30.2, 30.0, 27.0, 24.4, 23.7, 21.4, 13.0. MS [ESI^+]: calc. for $\text{C}_{28}\text{H}_{43}\text{N}_{11}\text{O}_7$: 645.33, observed: 646.2 [$\text{M} + \text{H}$] $^+$. Anal. calc. for $\text{C}_{30}\text{H}_{44}\text{F}_3\text{N}_{11}\text{O}_9$: C 47.43, H 5.84, N 20.28; observed C 47.42, H 5.83, N 20.26.

Compound 51

Yield: 99%. (White solid). $[\alpha]_{\text{D}}^{22} = -27.3$ ($c = 0.67$, MeOH). ^1H NMR (400 MHz, D_2O): δ 1.25-1.41 (m, 3H, *H*-5, CH_2 biotin), 1.45-1.67 (m, 8H, 2 CH_2 biotin, 2*H* γ Arg, *H* β Arg, *H*-7), 1.68-1.79 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{O}$ linker), 1.83 (m, 1H, *H*-8), 2.02 (m, 1H, *H* β Arg), 2.18 (t, 2H, $J = 7.2$ Hz, CH_2 biotin), 2.33-2.46 (m, 3H, *H*-5, *H*-7, *H*-8), 2.64 (dd, 1 H, $J = 16.8$ Hz, $J = 6.8$ Hz, *H* β Asp), 2.69 (dd, 1H, $J = 13.2$ Hz, $J = 4.8$ Hz, *SHCH* biotin), 3.01 (dd, 1H, $J = 16.8$ Hz, $J = 7.6$ Hz, *H* β Asp), 3.14

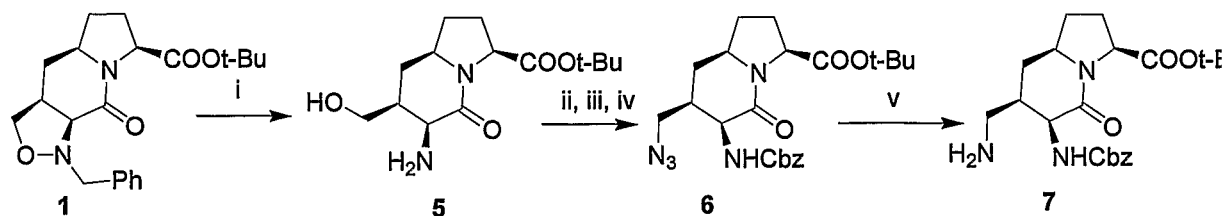
(m, 2H, $H\delta$ Arg), 3.19 (m, 2H, CH_2N linker), 3.22-3.30 (m, 4H, $H-4$, SHC -biotin, CH_2N linker), 3.47 (m, 1H, $H\alpha$ Gly), 3.48-3.55 (m, 4H, CH_2O linker), 3.56-3.65 (m, 9H, CH_2O linker), 3.99 (m, 1H, $H-6$), 4.07 (s, 2H, $COCH_2O$ linker), 4.12 (s, 2H, $COCH_2O$ linker), 4.16 (m, 1H, $H-9$), 4.20-4.30 (m, 2H, $HCH-N$, $H\alpha$ Gly), 4.33-4.43
 5 (m, 4H, $HCH-N$, $H\alpha$ Asp, $H-3$, NHC biotin), 4.47 (s, 2H, $NCH_2C=$) 4.52-4.58 (m, 2H, $H\alpha$ Arg, NHC biotin), 7.49 (m, 1H, NH Asp), 7.87 (s, 1H, H triazole). ^{13}C NMR (100.6 MHz, D_2O): δ 174.6, 174.7, 173.9, 172.9, 171.7, 171.6, 171.5, 169.2, 144.4, 124.5, 70.0, 69.9, 69.6, 69.4, 68.5, 68.4, 62.1, 62.2, 55.7, 55.4, 52.9, 51.6, 51.4, 51.3, 42.3, 40.4, 39.7, 36.3, 36.2, 36.1, 35.5, 33.9, 33.4, 32.7, 32.2, 30.0, 28.3, 27.7, 27.0,
 10 25.2, 24.4. MS [ESI^+]: calc. for $C_{49}H_{78}N_{16}O_{15}S$: 1162.56, observed: 1163.6 [$M + H$] $^+$, 582.4 [$M + 2H$] $^{2+}$. Anal. calc. for $C_{51}H_{79}F_3N_{16}O_{17}S$: C 47.96, H 6.23, N 17.54; observed C 47.97, H 6.24, N 17.56.

Compound 53 (isomers mixture)

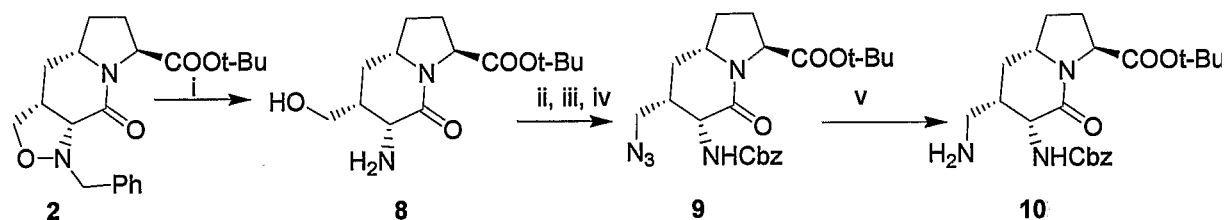
Yield: 99%. (Yellow solid). 1H NMR (400 MHz, DMSO- d_6): δ 1.14 (m, 1H, $H-5$),
 15 1.3-1.53 (m, 4H, $2H\gamma$ Arg, $H\beta$ Arg, $H-7$), 1.66 (m, 2H, $NCH_2CH_2CH_2O$ linker), 1.71 (m, 1H, $H-8$), 1.79 (m, 2H, $NCH_2CH_2CH_2O$ linker), 1.96-2.08 (m, 2H, $H\beta$ Arg, $H-7$), 2.20 (m, 1H, $H-5$), 2.24 (m, 1H, $H-8$), 2.52 (m, 1H, $H\beta$ Asp), 2.94 (m, 1H, $H\beta$ Asp), 3.03-3.20 (m, 3H, $H\delta$ Arg, $H-4$), 3.24 (m, 2H, CH_2N linker), 3.30 (m, 1H, $H\alpha$ Gly), 3.34-3.56 (m, 14H, CH_2N linker, CH_2O linker), 3.92 (s, 2H, $COCH_2O$ linker), 3.93
 20 (m, 1H, $HCH-N$), 3.96 (s, 2H, $COCH_2O$ linker), 3.99-4.09 (m, 2H, $H-6$, $H\alpha$ Gly), 4.16 (m, 1H, $H-9$), 4.26-4.44 (m, 6H, $HCH-N$, $H-3$, $NCH_2C=$, $H\alpha$ Asp, $H\alpha$ Arg), 6.51-6.62 (m, 4H, H aromatics fluorescein), 6.7 (m, 2H, H aromatics fluorescein), 7.27 (m, 1H, NH scaffold), 7.36 (m, 1H, H aromatic fluorescein), 7.53 (m, 1H, NH Gly), 7.58 (m, 3H, NH guanidine), 7.66 (s, 1H, H aromatic fluorescein), 7.92 (s, 1H,
 25 H triazole), 8.02 (m, 1H, NH Asp), 8.07 (m, 1H, H aromatic fluorescein), 8.16 (m, 1H, H aromatic fluorescein), 8.24 (m, 1H, H aromatic fluorescein), 8.44 (s, 1H, H aromatic fluorescein), 8.53 (m, 1H, NH Arg), 8.65 (m, 1H, NH linker), 8.80 (m, 1H, NH linker), 9.93 (m, 1H, NH linker), 10.18 (m, 1H, $COOH$). ^{13}C NMR (100.6 MHz, DMSO- d_6): δ 173.2, 172.6, 170.9, 170.8, 170.5, 169.5, 169.4, 168.6, 168.5, 168.3,
 30 168.2, 168.0, 167.8, 164.6, 159.6, 156.5, 151.8, 144.6, 140.8, 136.3, 134.6, 129.2,

129.1, 128.1, 126.4, 124.8, 124.2, 123.6, 123.2, 122.2, 112.6, 109.1, 102.2, 70.2,
70.1, 69.8, 69.7, 69.6, 69.6, 69.4, 68.1, 61.9, 54.8, 52.6, 52.5, 51.1, 50.7, 50.3, 42.6,
36.8, 36.7, 36.1, 35.6, 35.5, 33.8, 33.7, 33.5, 32.8, 32.2, 29.5, 29.2, 29.1, 27.8, 25.3.
MS [ESI⁺]: calc. for C₆₀H₇₄N₁₄O₁₉: 1294.53, observed: 1295.6 [M + H]⁺, 648.3 [M +
5 2H]²⁺. Anal. calc. for C₆₂H₇₅F₃N₁₄O₂₁: C 52.84, H 5.36, N 13.91; observed C 52.85,
H 5.35, N 13.91.

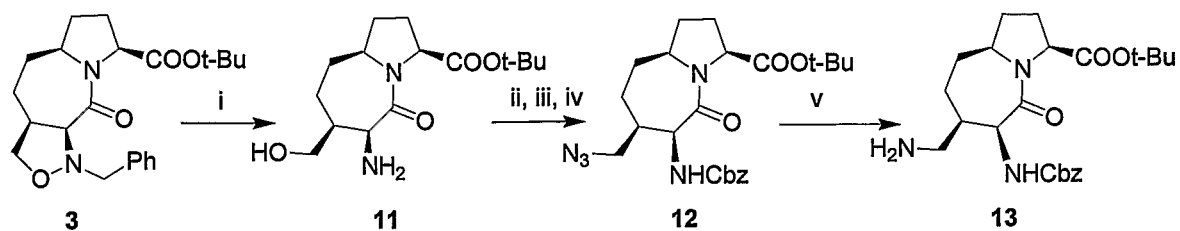
Scheme 1.



Reagents and conditions: i) H_2 , Pd/C; ii) Cbz-Cl, TEA, DCM (78%); iii) MsCl, TEA, DCM; iv) NaN_3 , DMF, 80 °C, (76% over two steps); v) Me_3P , H_2O , DCM (99%).

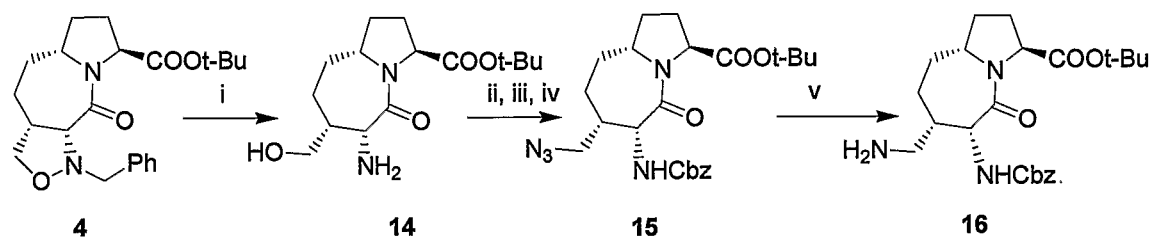


Reagents and conditions: i) H_2 , Pd/C; ii) Cbz-Cl, TEA, DCM (80%); iii) MsCl, TEA, DCM; iv) NaN_3 , DMF, 80 °C, (85% over two steps); v) Me_3P , H_2O , DCM (98%).

Scheme 2.

Reagents and conditions: i) H_2 , Pd/C; ii) Cbz-Cl, TEA, DCM (75%); iii) MsCl, TEA, DCM; iv) NaN_3 , DMF, 80 °C, (80% over two steps); v) Me_3P , H_2O , DCM (98%).

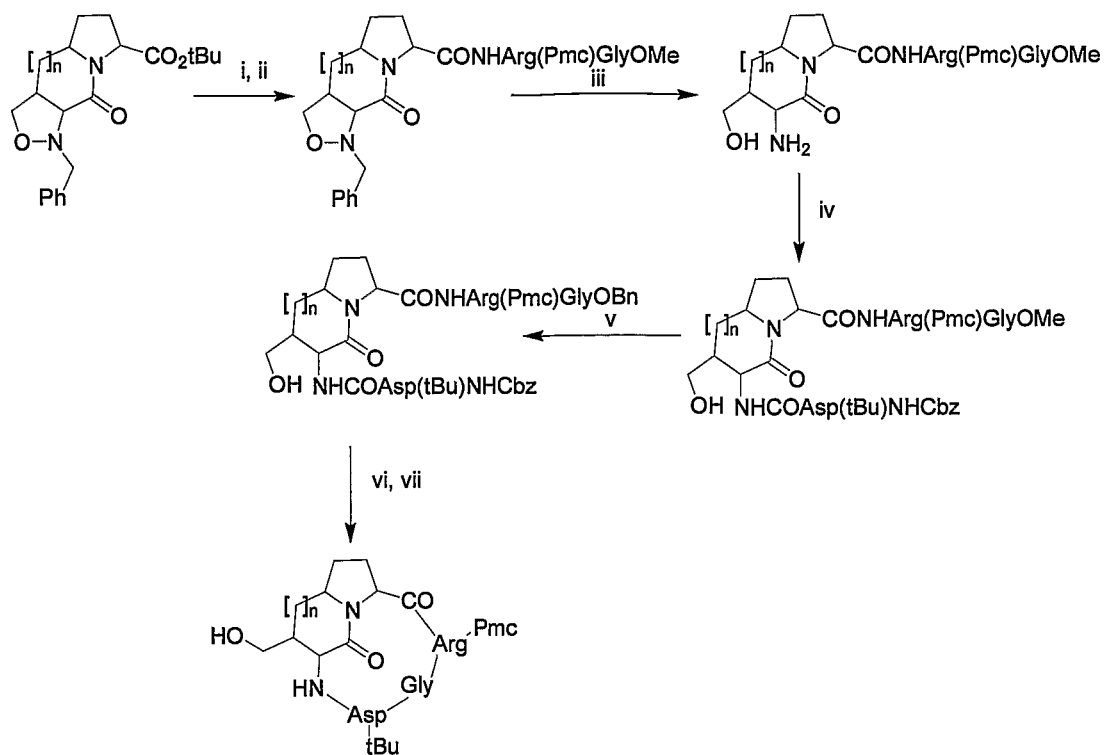
5



Reagents and conditions: i) H_2 , Pd/C; ii) Cbz-Cl, TEA, DCM (60%); iii) MsCl, TEA, DCM; iv) NaN_3 , DMF, 80 °C, (90% over two steps); v) Me_3P , H_2O , DCM (99%).

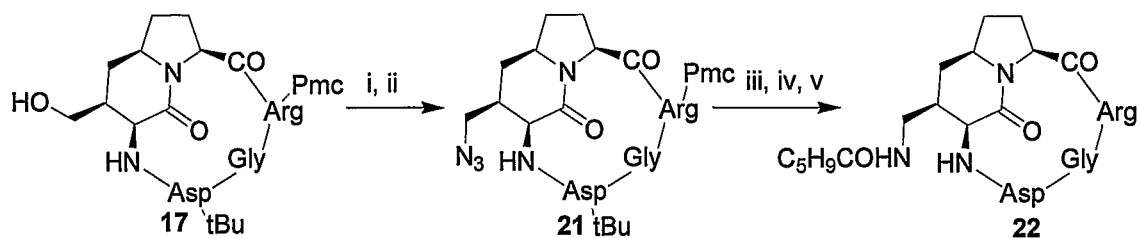
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Scheme 3



Reagents and conditions: i) TFA, DCM; ii) $\text{NH}_2\text{Arg(Pmc)GlyOMe}$, DIC, HOBT; iii)
 5 H_2 , Pd/C; iv) CbzNHAsp(tBu)OH , DIC, HOBT; v) BnOH , Ti(OiPr)_4 ; vi) H_2 , Pd/C;
 vii) HATU, HOAt, DIPEA.

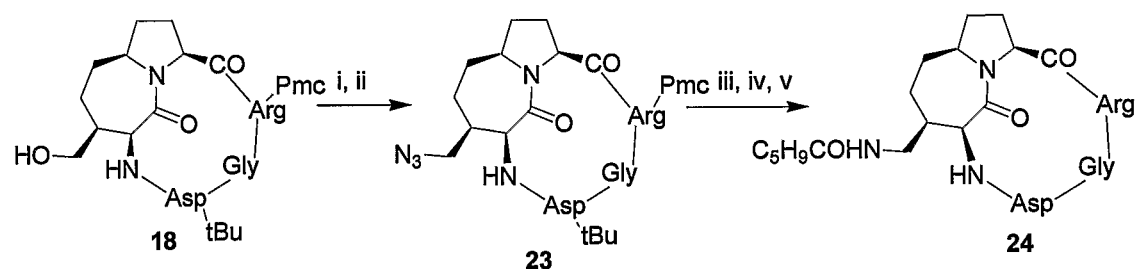
Scheme 4

Synthesis of 6,5-*cis*.

5

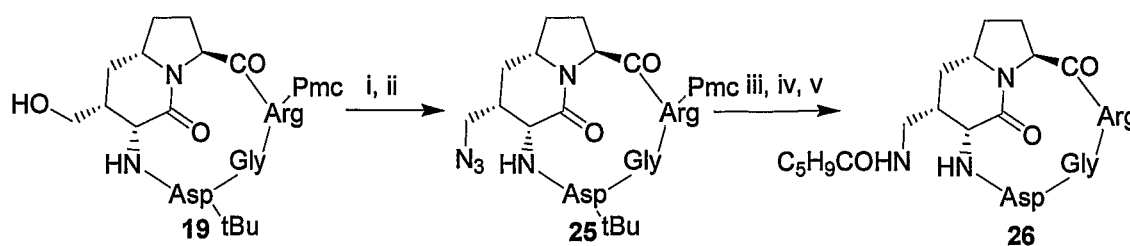
Reagents and conditions: i) MsCl , TEA, DCM; ii) NaN_3 , DMF, 80°C , (62% over two steps); iii) H_2 , Pd-C 10%, MeOH, iv) $\text{C}_5\text{H}_9\text{COCl}$, TEA, DCM (40% over two steps); v) TFA/thioanisole/1,2-ethanedithiol/anisole 90:5:3:2.

10

Synthesis of 7,5-*cis*.

Reagents and conditions: i) MsCl , TEA, DCM; ii) NaN_3 , DMF, 80°C , (60% over two steps); iii) H_2 , Pd-C 10%, MeOH, iv) $\text{C}_5\text{H}_9\text{COCl}$, TEA, DCM (43% over two steps); v) TFA/thioanisole/1,2-ethanedithiol/anisole 90:5:3:2.

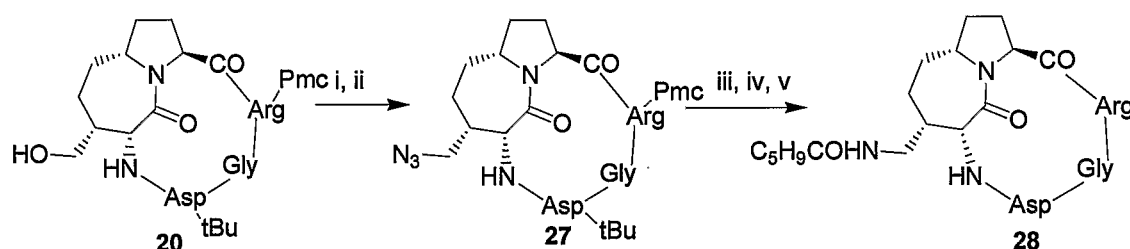
15

Scheme 5.Synthesis of 6,5-*trans*.

- 5 Reagents and conditions: i) MsCl, TEA, DCM; ii) NaN₃, DMF, 80°C, (60% over two steps); iii) H₂, Pd-C 10%, MeOH, iv) C₅H₉COCl, TEA, DCM (54% over two steps); v) TFA/thioanisole/1,2-ethanedithiol/anisole 90:5:3:2.

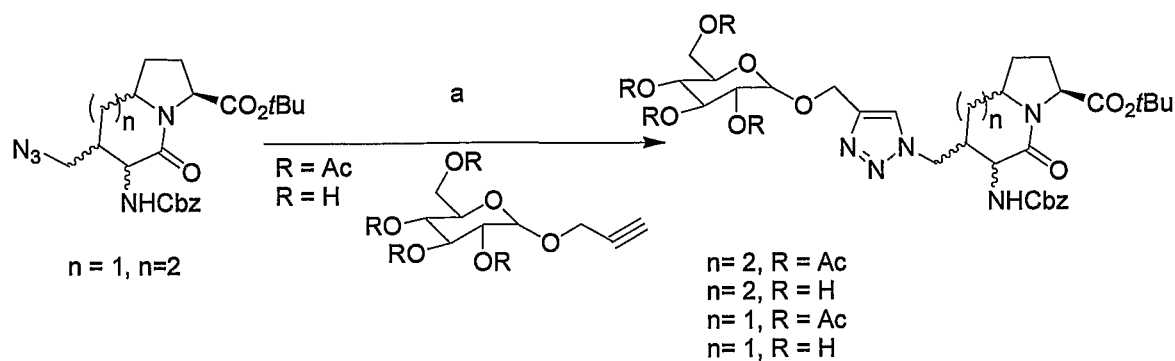
Synthesis of 7,5-*trans*.

10



Reagents and conditions: i) MsCl, TEA, DCM; ii) NaN₃, DMF, 80°C, (75% over two steps); iii) H₂, Pd-C 10%, MeOH, iv) C₅H₉COCl, TEA, DCM (57% over two steps); v) TFA/thioanisole/1,2-ethanedithiol/anisole 90:5:3:2.

Schema 6



5

Schema 6. 1,3-dipolar cycloaddition between pseudopeptides and the propargyl 2,3,4,6-tetra-O-acetyl- β -D-glucose. Reagents and conditions: (a) Na-ascorbate, $\text{Cu}(\text{OAc})_2$, $t\text{BuOH}/\text{H}_2\text{O}$ 1:1.

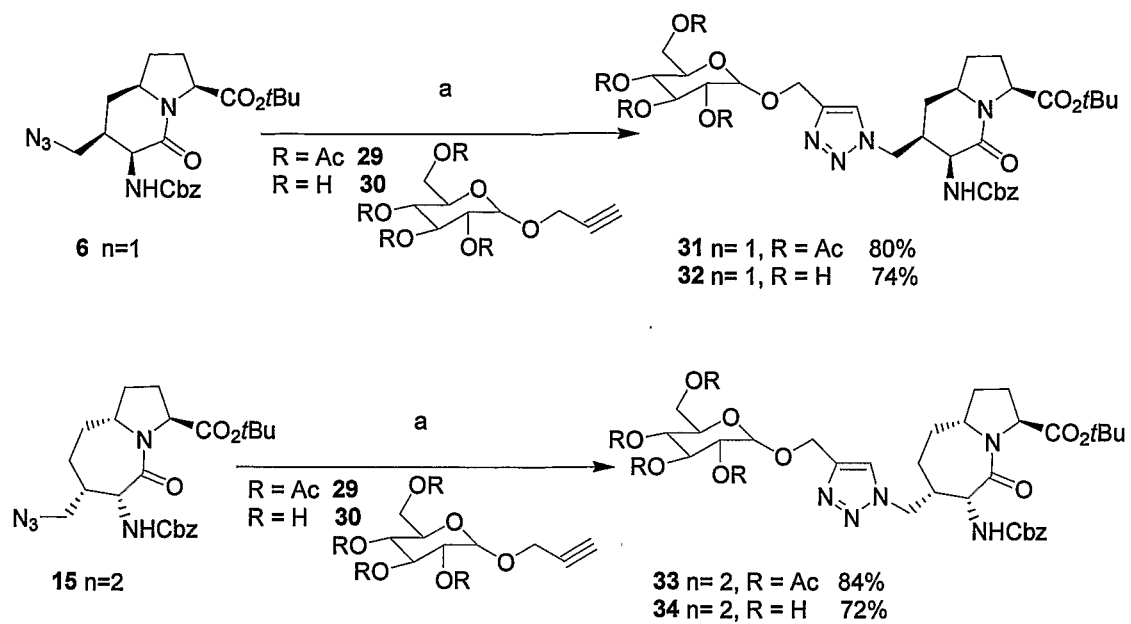
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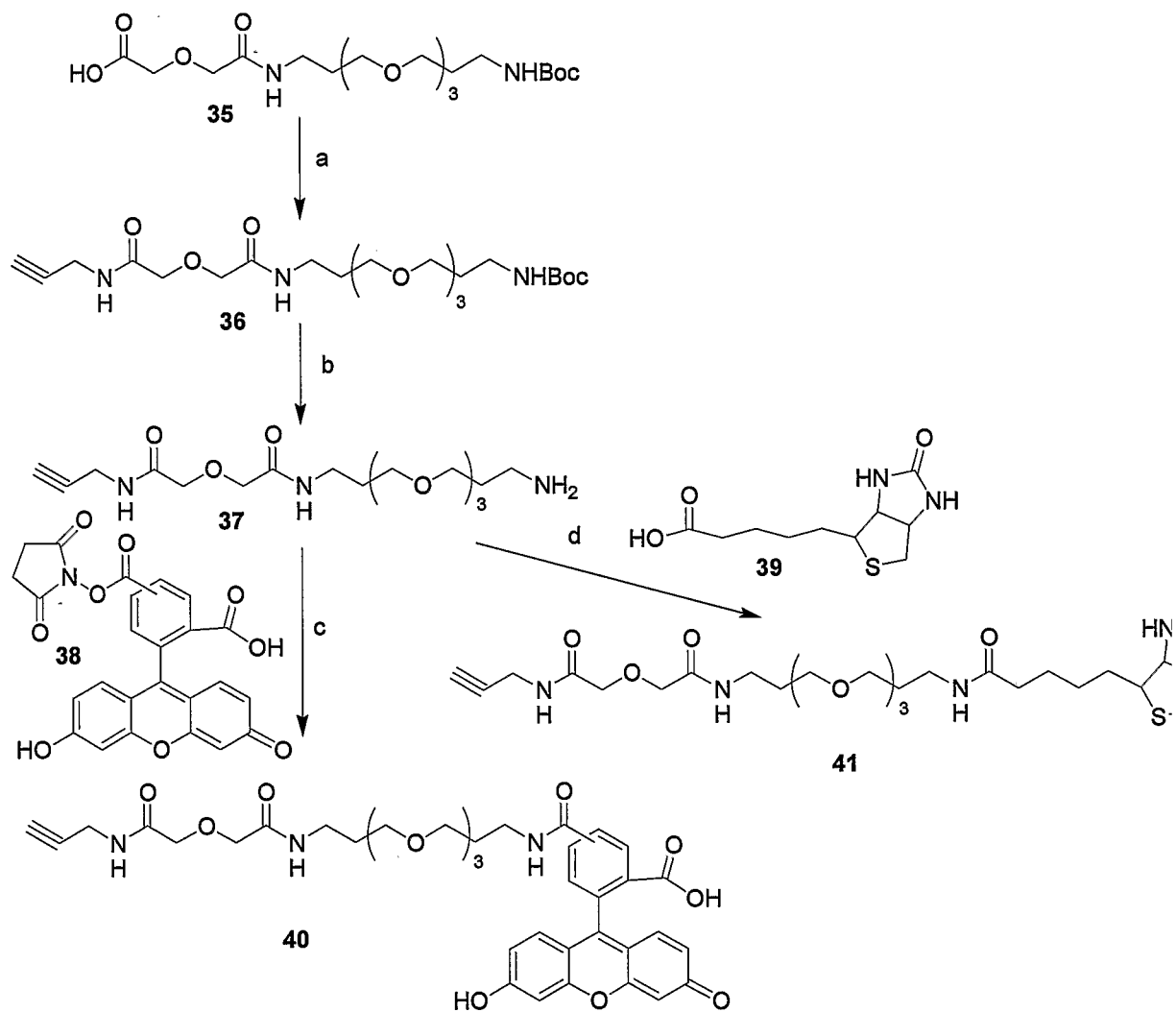
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Schema 7

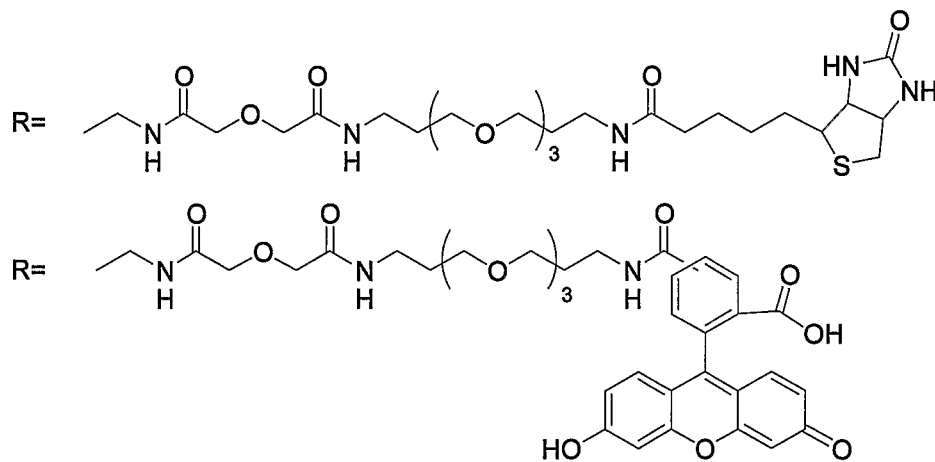
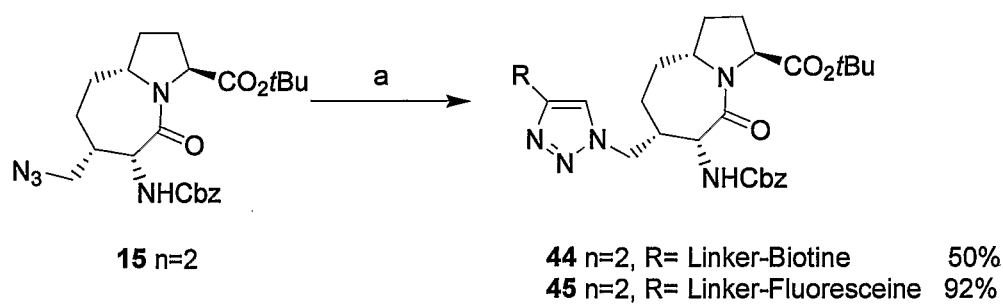
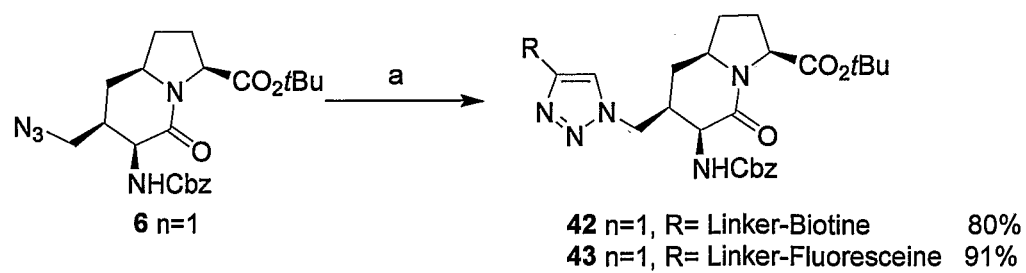


- 5 Reagents and conditions: **6** or **15**, propargyl 2,3,4,6-tetra-O-acetyl- β -D-glucose or propargyl β -D-glucose, Na-ascorbate, $\text{Cu}(\text{OAc})_2$, $t\text{BuOH}/\text{H}_2\text{O}$ 1:1.

Schema 8. Conjugation of fluorescein and biotin to the linker.

- 5 Reagents and conditions: (a) Propargylamine, HBTU, DIPEA, CH_2Cl_2 ; (97%). (b) TFA, CH_2Cl_2 . (c) 38, TEA, THF; (78% over two steps) (d) 39, HBTU, DIPEA, CH_2Cl_2 ; (60% over two steps).

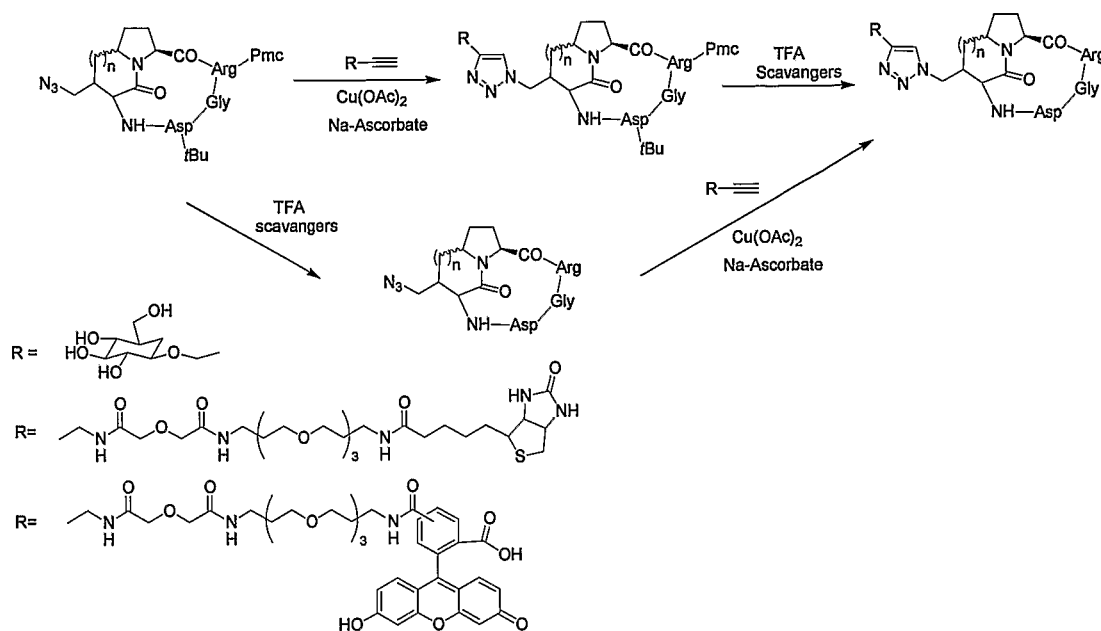
Scheme 9

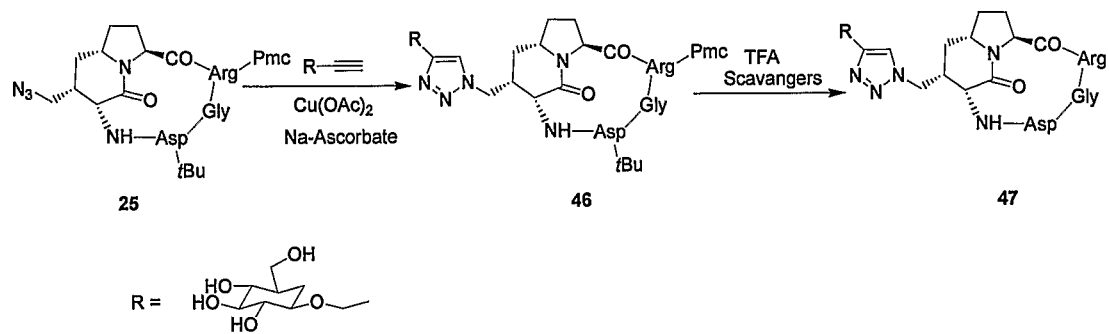


Reagents and conditions: **6** or **15** and **40** or **41**, Na-ascorbate, $\text{Cu}(\text{OAc})_2$, $t\text{BuOH}/\text{H}_2\text{O}$

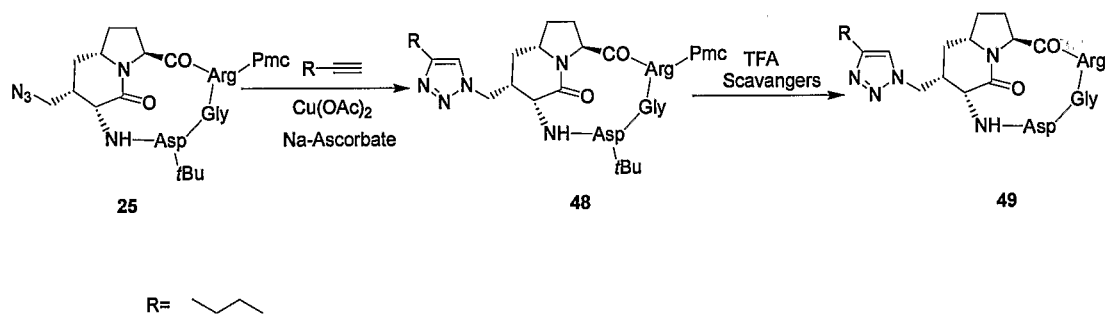
5 1:1.

Schema 10



Scheme 11

Reagents and conditions: (a) **25**, propargyl β -D-glucose, Na-ascorbate, $Cu(OAc)_2$,
 5 $tBuOH/H_2O$ 1:1



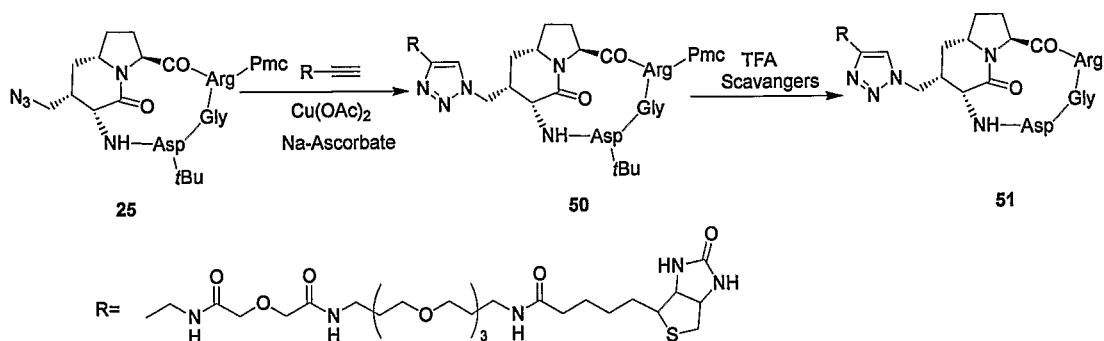
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Reagents and conditions: (a) **25**, n-hexyne, Na-ascorbate, $Cu(OAc)_2$, $tBuOH/H_2O$ 1:1

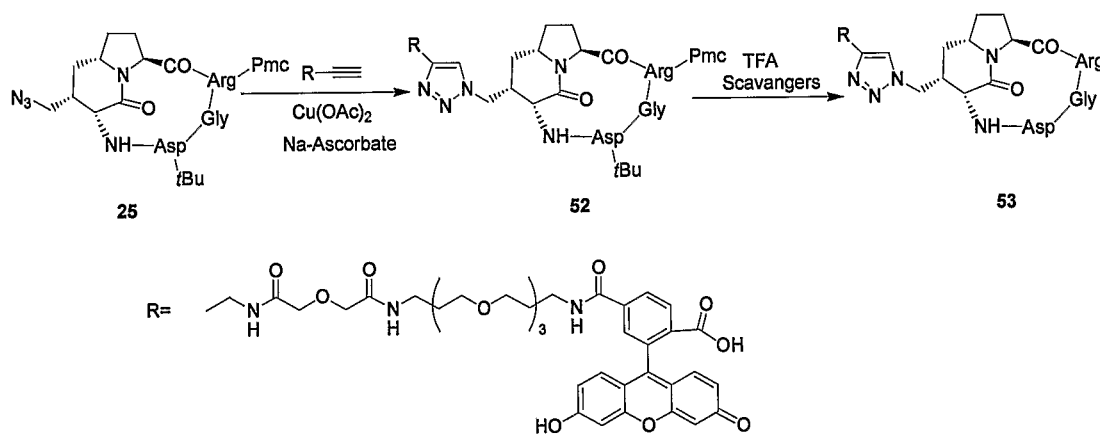
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Schema 12



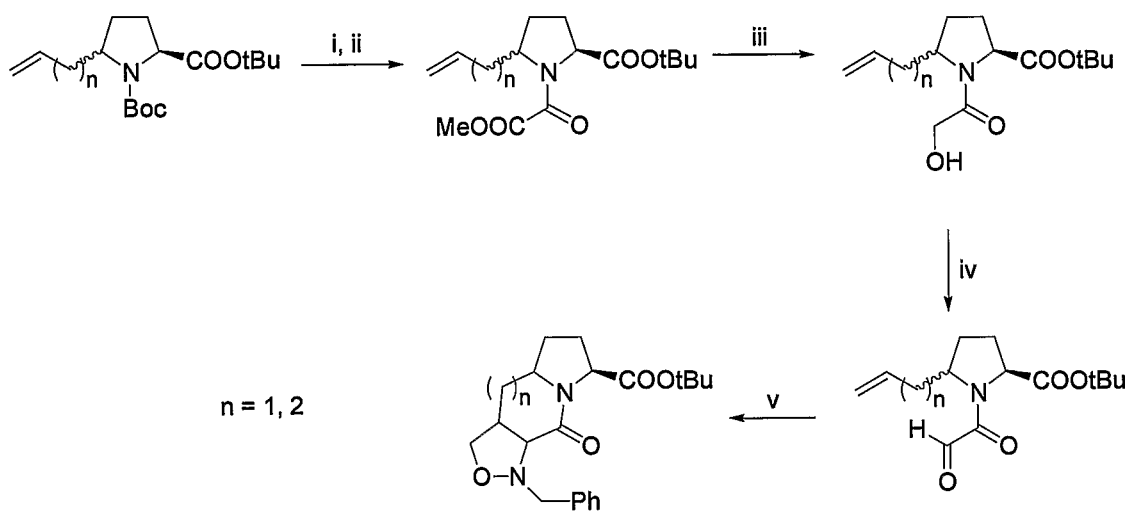
5 Reagents and conditions: (a) **25**, **41**, Na-ascorbate, $\text{Cu}(\text{OAc})_2$, $t\text{BuOH}/\text{H}_2\text{O}$ 1:1



Reagents and conditions: (a) **25**, **40**, Na-ascorbate, $\text{Cu}(\text{OAc})_2$, $t\text{BuOH}/\text{H}_2\text{O}$ 1:1

Scheme A

Preparation of the starting products



5

 $n = 1 \text{ or } 2$

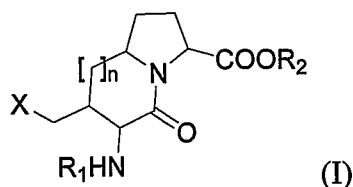
Reagents and conditions: HClO_4 , AcOtBu , 0°C ; ii. Amberlyst A-21, ClCOCOOMe , -20°C ; iii. LiBH_4 , THF, 0°C ; iv. $(\text{COCl})_2$, DMSO, TEA, CH_2Cl_2 , -60°C ; v. Bn-NH-

10 $\text{OH}\cdot\text{HCl}$, NaHCO_3 , $\text{EtOH}/\text{H}_2\text{O}$, 80°C ; vi.

15

CLAIMS

1. Compounds of general formula (I):



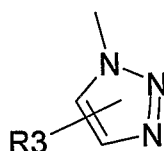
wherein:

5 n has the value of 1 or 2,

R₁ is H, (C₁-C₄) alkyl or a protective group;

R₂ is H or a protective group;

X is N₃, -NH-R₃, -N(R₃)₂, -NAlkR₃, -NH-CO-R₃, -NH-CS-R₃, -NH-CO-NHR₃, -NH-CS-NHR₃, or



10

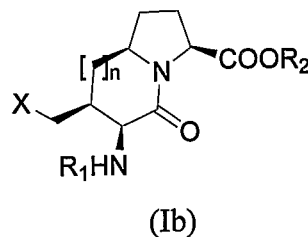
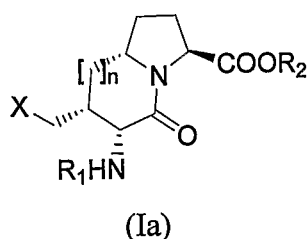
wherein:

Alk = (C₁-C₄) linear or branched alkyl

R₃ = H, a protective group, a biologically active molecule;

15 their salts, racemic mixtures, individual enantiomers, individual diastereoisomers and mixtures thereof in whatever proportion.

2. Compounds according to claim 1, of general formulae (Ia) and (Ib)



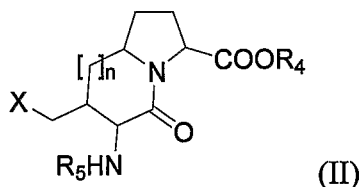
20 wherein n, R₄, R₅ and X are defined according to claim 1 and the wedge-shaped and dashed bonds indicate that the substituents are positioned above and below the plane respectively.

3. A process for the preparation of the compounds of formulae (I), (Ia)

and (Ib) as defined in claims 1 to 3 characterised by the following steps of schemes 1 or 2:

- a) hydrogenation of the isoxazolidine of compounds 1-4;
- b) protection of the amine group with a protective group;
- 5 c) transformation of the free hydroxyl group into an azide to give the compounds of formulae **6, 9, 12, 15**;
- d) reduction of the azide group into an amine by means of the Staudinger reaction or by means of hydrogenation to give the compounds of formulae (I), (Ia) or (Ib) wherein X is NH₂;
- 10 e) optional transformation of said compounds into other compounds of formulae (I), (Ia) or (Ib) and/or into a salt thereof
- f) or from compounds **6, 9, 12, 15**, 1,3-dipolar reaction (click chemistry) with a biologically interesting molecule (sugar, fluorescein, biotin) linked to a suitable linker
- 15 g) possible transformation of said compounds into different compounds having formula (I), (Ia) or (Ib) and/or into their salts.

4. Compounds of general formula (II):

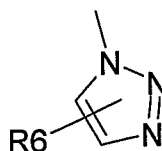


wherein:

20 n has the value of 1 or 2,

R₄ and R₅ together constitute the sequence Asp-Gly-Arg,

X is N₃, -NH-R₆, -N(R₆)₂, -NAlkR₆, -NH-CO-R₆, -NH-CS-R₆, -NH-CO-NHR₆, -NH-CS-NHR₆, or



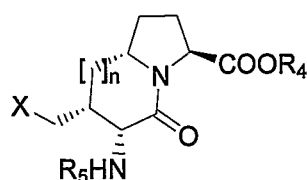
25 wherein

Alk = (C₁-C₄) linear or branched alkyl

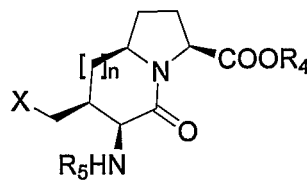
$R_6 =$ H, a protective group, a biologically active molecule, therein comprising a sugar;

their salts, racemic mixtures, individual enantiomers, individual diastereoisomers and mixtures thereof in whatever proportion.

- 5 5. Compounds according to claim 1, of general formulae (IIa) and (IIb)



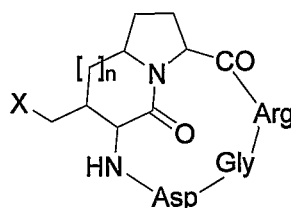
(IIa)



(IIb)

- wherein n, R_4 , R_5 and X are as defined in claim 4 and the wedge-shaped and dashed bonds indicate that the substituents are positioned above and below the plane
10 respectively.

6. Compound according to claims 4 or 5 having the following structure:



7. Compounds according to claims 4-6 wherein X is NH_2 .
8. Compounds according to claims 4-6 wherein X is a substituted or
15 unsubstituted amide.
9. Compounds according to claims 4-6 wherein X is a substituted or unsubstituted urea or thiourea.
10. Compounds according to claims 4-6 wherein X is a substituted or unsubstituted triazole system.
- 20 11. Compounds according to claims 4 to 10 or their pharmaceutically acceptable salts thereof, wherein R_6 is a drug.
12. Compounds according to claim 11 wherein said drug is a cytotoxic and/or antitumour drug.
13. Compounds of claims 4-12 for their use as drugs.
- 25 14. Use of the compounds of claims 1-2 and 4-10 for the preparation of

antagonist drugs towards $\alpha v \beta 3$ and $\alpha v \beta 5$ integrins.

15. Use of compounds of claims 1-2 and 4-10 for the preparation of drugs with antiangiogenic activity.

16. Use according to claim 1-2 or 4-10 for the preparation of drugs intended for the treatment and/or the prophylaxis of altered angiogenic processes, metastasised tumour processes, retinopathies, acute renal damage and osteoporosis.

17. Compounds according to claims 4 to 10 or their pharmaceutically acceptable salts thereof, wherein R_6 is a diagnostic agent.

18. Use of compounds of claims 4 to 10 as drug carriers.

19. A pharmaceutical composition containing at least one compound of formulae (II), (IIa) or (IIb), or their pharmaceutically acceptable salts thereof, according to claims 4 to 12, as active ingredient, optionally in combination with one or more pharmaceutically acceptable carriers or excipients.

20. Use of compounds of claims 4 to 10 as carriers for diagnostic compounds.

21. A process for the preparation of the compounds of formulae (II), (IIa) and (IIb) as defined in claims 4 to 12 characterised by the following steps of schemes 3 to 5:

- transformation of the hydroxyl group into the corresponding azide in accordance with a procedure known to those skilled in the art (through the Mitsunobu reaction, or mesylation and subsequent nucleophilic substitution with sodium azide) to give compounds **21, 23, 25, 27**;
- subsequent reduction by means of catalytic hydrogenation or the Staudinger reaction
- transformation into the corresponding amides by means of a coupling reaction;
- optional conjugation with molecules of biological interest;
- subsequent deprotection of the aminoacid side chain protective groups to give the compounds of formulae **22, 24, 26, 28**
- or from compounds **21, 23, 25, 27** 1,3-dipolar reaction (click chemistry) with a biologically interesting molecule (sugar, fluorescein, biotin)

linked to a suitable linker

- subsequent elimination of protective groups of the amino acids side chains.