(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 May 2002 (02.05.2002)

PCT

(10) International Publication Number
WO 02/34283 A2

(51) International Patent Classification⁷: **A61K 38/15**

(21) International Application Number: PCT/EP01/12369

(22) International Filing Date: 25 October 2001 (25.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0026345.9	27 October 2000 (27.10.2000)	GB
0029113.8	29 November 2000 (29.11.2000)	GB
00126150.2	30 November 2000 (30.11.2000)	EP
0102379.5	30 January 2001 (30.01.2001)	GB
0102380.3	30 January 2001 (30.01.2001)	GB
0102839.8	5 February 2001 (05.02.2001)	GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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(54) Title: VEGF INHIBITORS

(57) Abstract: The use of inhibitors of adhesion molecule expression, e.g. cyclopeptolides or cyclopeptides, in the preparation of a medicament for the treatment of vascular endothelial cell growth factormediated diseases and novel cyclopeptolides and cyclopeptides.

VEGF inhibitors

The present invention relates to inhibitors of the expression of the vascular endothelial cell growth factor (VEGF-inhibitors). VEGF is a secreted protein produced by a variety of cells in vascularized tissues where it plays a critical role in angiogenesis (formation of new blood vessels) by stimulating endothelial cell growth and modulating capillary permeability. Because of these activities, VEGF may play a prominent role in inflammatory processes and disease pathogenesis. VEGF-inhibitors exhibit pharmacological activity and are therefore useful as pharmaceuticals, e.g. in the treatment or prophylaxis of VEGF-mediated events.
VEGF-inhibitors may be useful in the treatment or prophylaxis of pathogenic processes, e.g. capillary nonperfusion, angiogenesis and neovascularization that contribute to diseases, e.g. including arteriosclerosis, cancer, chronic transplant rejection, psoriasis, rheumatoid arthritis and eye diseases, such as proliferative retinopathies and macular degeneration.

Cellular adhesion molecules, such as ICAM-1, are expressed on the surface of endothelial cells and keratinocytes, in response to pro-inflammatory mediators including TNFα, IFNγ, IL1 and LPS. Corresponding counter-ligands, e.g. LFA-1, VLA-4 and SLE^x, are expressed on the surface of circulating blood cells. Transendothelial migration of leucocytes during inflammatory processes, as well as extravascular cell-cell interactions, are regulated as a result of the interactions between these adhesion molecules and their counterligands.
Inhibitors of the stimulated expression of cellular adhesion molecules, especially inhibitors of VCAM-1 relative to E-selectin and ICAM-1 expression, exhibit pharmacological activity and are therefore useful as pharmaceuticals. The effect on VCAM-1 expression inhibition occurs at both transcriptional and posttranscriptional levels. Thus inhibitors of the stimulated expression of cellular adhesion molecules are useful for the treatment or prophylaxis of disease processes which involve expression of cellular adhesion molecules.
These disease processes include many acquired and inherited diseases/disorders where leucocyte trafficing plays a prominent role in the pathogenic process, most notably acute and chronic inflammation (e.g. allergy, asthma, psoriasis, reperfusion injury, rheumatoid arthritis and septic shock) and autoimmune states (e.g. multiple sclerosis). Other indications include tumor metastasis (e.g. melanoma, osteocarcinoma) and allograft/xenograft rejection, since it is known that inhibition of vascular adhesion molecules can greatly improve the prognosis of these processes. In addition, inhibitors of the expression of cellular adhesion molecules have therapeutic potential in hyperproliferative skin diseases (e.g. psoriasis) as well as various

malignancies. Inhibitors of the expression of cellular adhesion molecules are active in inhibiting TNFα- or IL6-induced HIV production in the U1 monocytic cell line, as evaluated by p24 ELISA and are therefore also useful in the treatment of immunodeficiences and virally caused diseases, especially in the treatment of AIDS.

We have found that inhibitors of adhesion molecule expression, especially VCAM-1 expression inhibitors, additionally act as VEGF-inhibitors. Compounds which act as inhibitors of adhesion molecule expression and additionally as VEGF-inhibitors offer potential for the treatment of many disease states.

In one aspect the present invention provides the use of inhibitors of adhesion molecule expression in the preparation of a medicament for the treatment of vascular endothelial cell growth factor-mediated diseases, e.g. including diseases as described above, e.g. diseases wherein processes, e.g. capillary nonperfusion, angiogenesis, neovascularization, tumor growth and metastasis, contribute to the pathogenesis or severity of said disease, such as

- eye diseases involving vision impairment or loss, e.g. proliferative retinopathies and macular degeneration, including ischemic retinopathies, uveoretinitis and degenerative eye diseases,
- arteriosclerosis associated with chronic transplant rejection and coronary heart disease,
- solid tumor malignancies and other cancers, e.g. Kaposi's sarcoma,
- psoriasis, rheumatoid arthritis.

In another aspect the present invention provides the use of inhibitors of adhesion molecule expression in the preparation of a medicament for the treatment of eye diseases leading to vision impairment or loss, such as proliferative retinopathies and macular degeneration, including ischemic retinopathies, uveoretinitis and degenerative eye diseases.

Treatment includes therapeutical treatment and prophylaxis.

Cyclopeptides are cyclic molecules comprising amino acid residues linked together by peptide bonds, cyclopeptolides further comprise one hydroxy substituted carboxylic acid residue which is linked through its hydroxyl substituent to the neighbouring acid residue by an ester linkage. Cyclopeptolides are e.g. described in WO 96/03430 and in WO 97/19104 for use as inhibitors

of adhesion molecule expression. According to the finding of the present invention cyclopept(ol)ides act additionally as VEGF-inhibitors.
The content of WO 96/03430 and WO 97/19104 is introduced herein by reference.
We have also found cyclopept(ol)ides, e.g. compounds of formula I_p, I_r and I_s, which are VEGF-inhibitors and additionally act as inhibitors of adhesion molecule expression.
Inhibitors of adhesion molecule expression which, according to the present invention, act additionally as VEGF-inhibitors, thus include cyclopeptides and cyclopeptolides, e.g. such as described above.

In another aspect the present invention provides the use of cyclopept(ol)ides, e.g. including cyclopeptolides of WO 96/03430 and WO 97/19104, e.g. of formula I, and of formula I_p, and I_r and cyclopeptides of formula I_s, in the preparation of a medicament for the treatment of vascular endothelial cell growth factor-mediated diseases.

Cyclopeptolides as described in WO 96/03430 and WO 97/19104 are of formula I, and in another aspect the present invention provides a compound of formula

$$\underline{\ulcorner\text{A - B - R}_1\text{Leu - Leu - Z - X - Y}\urcorner} \qquad \text{I}$$

wherein:
A is

- a glycolic acid residue optionally α-substituted by methyl or vinyl, optionally substituted by
  - halogen,alkoxy, optionally protected hydroxy or amino, $CSNH_2$, vinyl, -C≡CH, thiazolyl or $COOR_2$, wherein R_2 is H or lower alkyl, optionally substituted by
    - alkyl, halogen, cycloalkyl, optionally substituted thiazolyl, -C≡CH or $COOR_2$ wherein R_2 is as defined above;
- an α-hydroxy-substituted butyric or valeric acid residue β-substituted by
  - halogen, alkoxy, optionally protected hydroxy or amino, $CSNH_2$, vinyl, -C≡CH, thiazolyl or $COOR_2$, wherein R_2 is H or lower alkyl, optionally substituted by
    - alkyl, halogen, cycloalkyl, optionally substituted thiazolyl, -C≡CH or $COOR_2$, wherein R_2 is as defined above; or
- an α-hydroxy-substituted butyric acid residue optionally γ-substituted by R_6, wherein R_6 is
  - CN, $COOR_3$, wherein R_3 is hydrogen or optionally arylsubstituted alkyl, $CONR_4R_5$, wherein R_4 and R_5 are the same or different and represent hydrogen or alkyl or form together with the nitrogen to which they are attached a 3- to 6-membered ring, optionally containing a

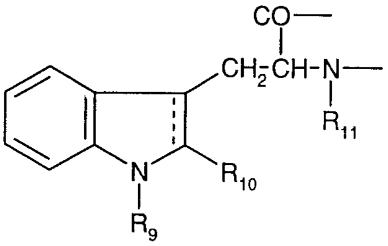
second heteroatom, COR_7, wherein R_7 represents hydrogen or lower alkyl, $CSNH_2$, or alkyl, optionally substituted by

- azido, halogen, alkoxy, optionally protected hydroxy or amino, $CSNH_2$, thiazolyl, vinyl, which may be substituted by alkyl, halogen or CN, cycloalkyl, tetrazolyl, -C≡CH, or $COOR'_2$, wherein R'_2 is hydrogen or lower alkyl, optionally substituted by alkyl, halogen, cycloalkyl, optionally substituted thiazolyl, -C≡CH or $COOR''_2$, wherein R''_2 is hydrogen or lower alkyl,

B is an α-amino-γ-methyl-substituted octanoic acid residue;

R_1 is hydrogen or methyl;

Z is a tryptophan residue, e.g. of formula



II

wherein R_9 is hydrogen, alkoxy, alkyl or benzyl, R_{10} is hydrogen or halogen, R_{11} is hydrogen or methyl and ---- is a single or double bond,

X is an α–amino-substituted (C_{2-14})carboxylic acid residue, and

Y is an α-amino- or N-methyl-α-amino substituted (C_{2-10})carboxylic acid residue;

in the preparation of a medicament for the treatment of vascular endothelial cell growth factor-mediated diseases.

In formula I the C-terminal to N-terminal orientation of the amino acid residues is in the clockwise direction, and the peptolide ester bond is between residues A and Y.

In a compound of formula I

A is preferably

- a glycolic acid residue which is optionally α-substituted by methyl, which methyl is optionally substituted by amino, hydroxy, chloro, alkoxy, optionally substituted thiazolyl, optionally substituted vinyl, cyclopropyl, $CSNH_2$ or -C≡CH;
- an α-hydroxy-substituted butyric or valeric acid residue which is optionally β-substituted by amino, hydroxy, chloro, alkoxy, optionally substituted thiazolyl, optionally substituted vinyl, cyclopropyl, $CSNH_2$ or -C≡CH;
- an α-hydroxybutyric acid residue, which is γ-substituted by

- CN, optionally protected CH_2OH, $COOR_{2'}$, wherein $R_{2'}$ is hydrogen or optionally arylsubstituted alkyl, $CONR_{3'}R_{4'}$, wherein $R_{3'}$ and $R_{4'}$ are the same or different and are hydrogen or alkyl, or $R_{3'}$ and $R_{4'}$ together with the nitrogen to which they are attached form a 5 or 6- membered ring optionally containing a second heteroatom, $COR_{5'}$, wherein $R_{5'}$ is hydrogen, or $-CH=CH_2$; alkyl optionally substituted by
  - azido, halogen, alkoxy, optionally protected amino or hydroxy, vinyl, optionally substituted by alkyl, halogen or CN; cycloalkyl, tetrazolyl, $-C\equiv CH$, optionally substituted thiazolyl, or $CSNH_2$;

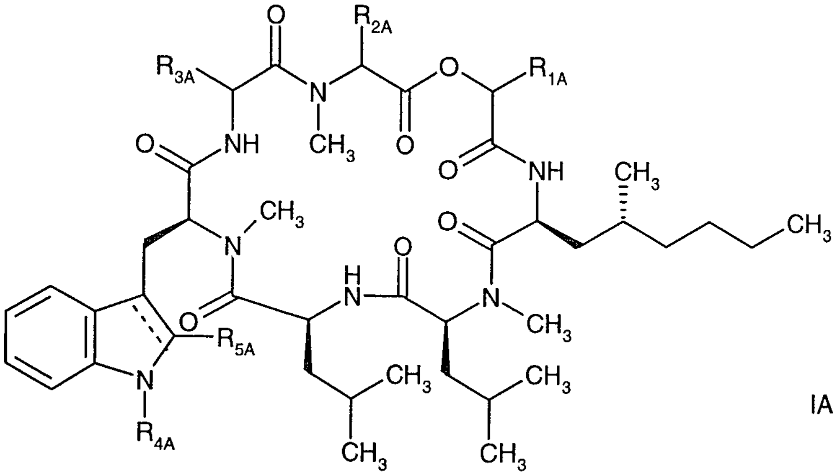
Z is preferably a tryptophan residue of formula II, wherein R_9 is hydrogen, alkoxy, alkyl or benzyl, R_{10} is hydrogen or halogen and R_{11} is hydrogen or methyl;

X is preferably an α-amino-substituted (C_{2-14})carboxylic acid residue, more preferably X is an α-amino-β- or γ-(C_{1-4}) alkyl-, especially methyl-, substituted octanoic or butyric acid residue,

Y is preferably an N-methyl-α-amino-substituted (C_{2-10})carboxylic acid residue, more preferably Y is an N-methyl-alanine or N-methyl-valine residue.

E.g. the compounds of formula I comprise asymmetric C-atoms and substituents attached to asymmetric C-atoms may be in either in the R or in the S configuration.

In another aspect the present invention provides the use as defined above of the compound 5-[8,11-Diisobutyl-14-(1-methoxy-1H-indol-3-ylmethyl)-7,13,19,20-tetramethyl-5,17-bis-(2-methyl-hexyl)-3,6,9,12,15,18,21-heptaoxo-1-oxa-4,7,10,13,16,19-hexaaza-cycloheneicos-2-yl]-pent-2-enoic acid methyl ester and of a compound of formula



IA

wherein R_{1A}, R_{2A} and R_{3A} are as defined in TABLE 1 below, and

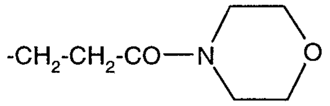
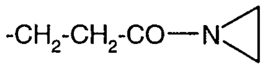
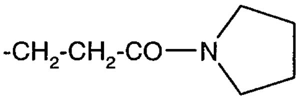
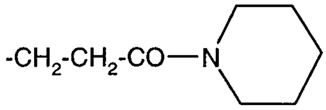
---- is a double bond in No.1 to 34, 36 and 38 to 46 and a single bond in No. 35 and 37;

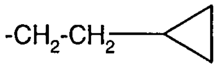
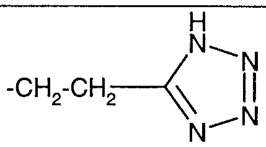
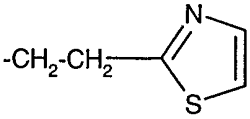
R_{4A} is methoxy in No. 1 to 16, 18 to 30, and 40 to 44, hydrogen in No. 17; 37 and 45, methyl in No. 31 and 46, ethyl in No. 32, benzyl in No. 33 and 35, a group of formula $-CH_2C(CH_3)_3$ in No. 34, isopropyl in No.36, n-propoxy in No. 38; ethoxy in No. 39; and

R_{5A} is hydrogen in No. 1 to 39 and 41 to 46 and Br in No. 40;

e.g. compounds such as exemplified in WO 96/03430 and WO 97/19104:

TABLE 1

No.	R_{1A}	R_{2A}	R_{3A}
1WO	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
2WO	$-CH_2-CH_2-CN$	$-CH(CH_3)_2$	$-CH(CH_3)_2$
3WO	$-CH_2-CH_2-COOCH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
4WO	$-CH_2-CH_2-COOH$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
5WO	$-CH_2-CH_2-CONH-CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
6WO		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
7WO	$-CH_2-CH_2-CON(CH_3)_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
8WO		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
9WO		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
10WO		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
11WO	$-CH_2CH_2CON(CH_3)(C_3H_7)$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
12WO	$-CH_2-CH_2-COOCH(CH_3)_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
13WO	$-CH_2-CH_2-COOCH_2CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
14WO	$-CH_2-CH_2-COO\ CH_2CH_2CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
15WO	$-CH_2-CH_2-CO-CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
16WO	$-CH_2-CH_2-CH_2-OH$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
17WO	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
18WO	$-CH_2-CH_2-CHO$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
19WO	$-CH_2-CH_2-CH=CH_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$

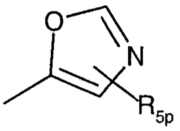
No.	R_{1A}	R_{2A}	R_{3A}
20 wo	$-CH_2-CH_2-CH=CH_2-CH_2-CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
21 wo	$-CH_2-CH_2-CH_2-N_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
22 wo	$-CH_2-CH_2-CH_2-NH_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
23 wo	$-CH_2-CH_2-CH=CBr_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
24 wo	$-CH_2-CH_2-C\equiv CH$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
25 wo	$-CH_2-CH_2-CH=CH-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
26 wo	$-CH_2-CH_2-CH_2-Cl$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
27 wo	$-CH_2-CH_2-CH_2-O-CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
28 wo		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
29 wo	$-CH_2-CH_2-COOCH(C_6H_5)_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
30 wo		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
31 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
32 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
33 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
34 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
35 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
36 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
37 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
38 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
39 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
40 wo	$-CH_2-CH_2-CN$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
41 wo	$-CH_2-CH_2-CS-NH_2$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
42 wo	$-CH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
43 wo		CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
44 wo	$-CH_2-CH_2-CH=CH-COOCH_3$	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
45 wo	CH_3	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$
46 wo	CH_3	CH_3	$-CH_2-CH(CH_3)-(CH_2)_3-CH_3$

A compound of formula I includes a compound of formula IA.

We also have found novel cyclopeptolides which are inhibitors of adhesion molecule expression, especially VCAM-1 relative to ICAM-1 and E-selectin expression inhibitors, and additionally act as VEGF-inhibitors, e.g. compounds of formula I_p, I_r and I_s.

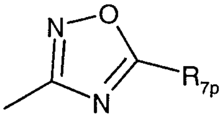
A substituent in γ-position of an α-hydroxy-substituted butyric acid residue in the meaning of A in a compound of formula I includes a substituent R_6 as defined above and we have found that R_6 may be also selected from the groups

- -COO-R_{2p}, wherein R_{2p} is alkyl substituted by CF_3,
- -CO-CH_2-O-R_{3p}, wherein R_{3p} is alkyl, cycloalkyl, alkoxyalkyl, hydroxyalkyl or acyloxyalkyl,
- -COO-CH_2-O-CO-R_{4p}, wherein R_{4p} is alkyl, e.g. alkyl substituted by a sugar residue;
- of formula



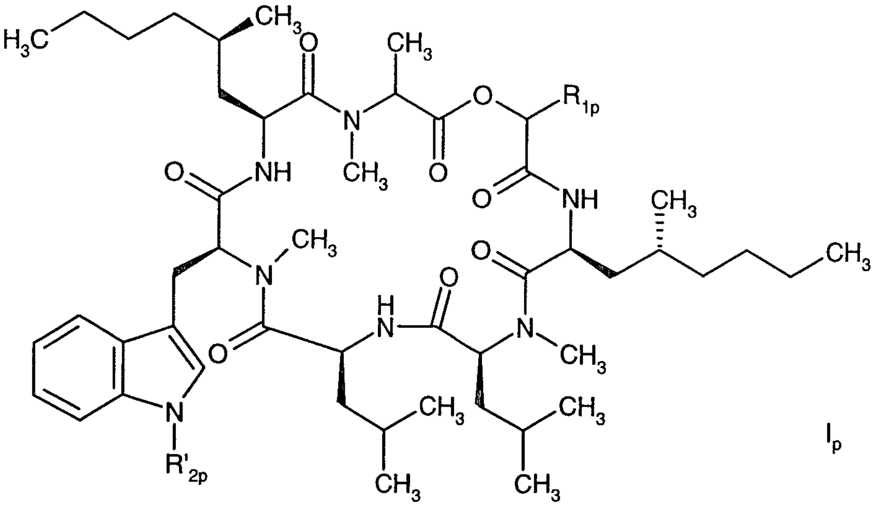
wherein R_{5p} is hydrogen or a substitutent, e.g. in position 2 of the ring system; such as alkyl, cyanoalkyl, alkoxyalkyl,

- -C(=N-R_{6p})NH_2, wherein R_{6p} is hydrogen or a substituent, e.g. hydroxy, and
- of formula



wherein R_{7p} is hydrogen or a substitutent, such as alkyl, e.g. (C_{1-6})alkyl.

In another aspect the present invention provides a compound, i.e. a cyclopeptolide, of formula

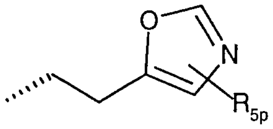


I_p

wherein

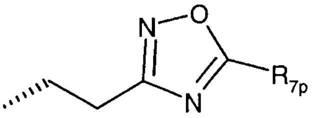
R_{1p} is selected from the groups

- $-CH_2-CH_2-COO-R_{2p}$, wherein R_{2p} is alkyl substituted by CF_3,
- $-CH_2-CH_2-CO-CH_2-O-R_{3p}$, wherein R_{3p} is alkyl, cycloalkyl, alkoxyalkyl, hydroxyalkyl or acyloxyalkyl,
- $-CH_2-CH_2-COO-CH_2-O-CO-R_{4p}$, wherein R_{4p} is alkyl,
- of formula



wherein R_{5p} is hydrogen or a substitutent, such as alkyl, cyanoalkyl, alkoxyalkyl, e.g. in position 2 of the ring system;

- $-CH_2-CH_2-C(=N-R_{6p})NH_2$, wherein R_{6p} is hydrogen or a substituent, e.g. hydroxy,
- a group of formula

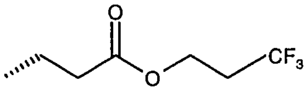
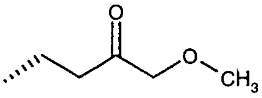
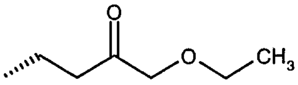


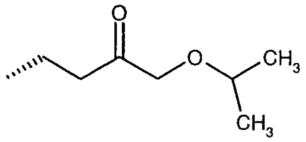
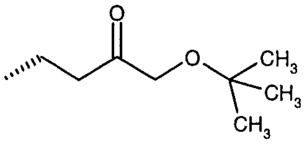
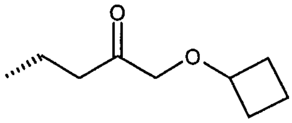
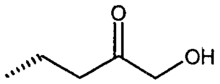
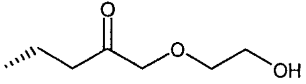
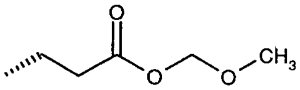
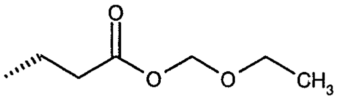
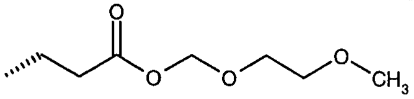
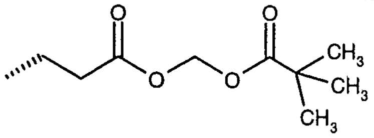
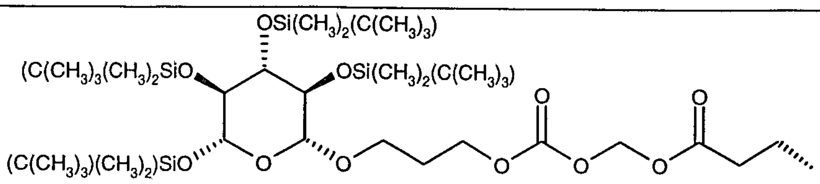
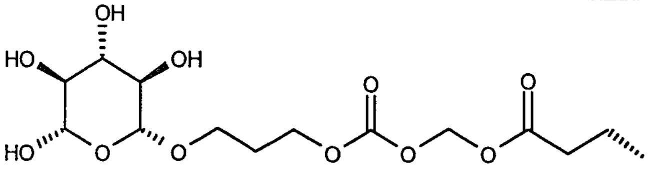
wherein R_{7p} is hydrogen or a substitutent, such as alkyl, e.g. (C_{1-6})alkyl; and

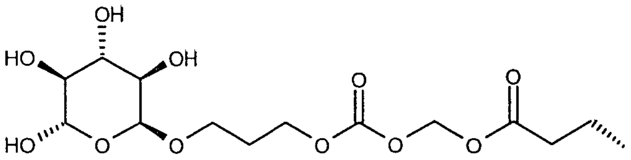
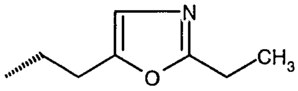
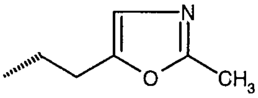
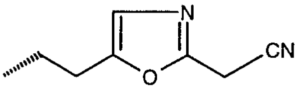
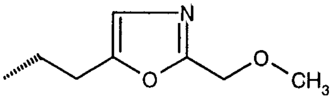
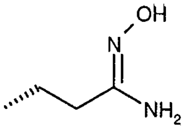
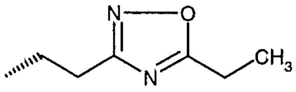
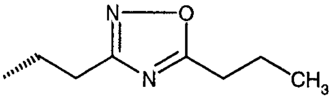
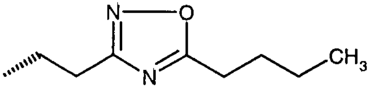
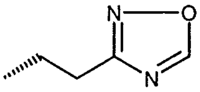
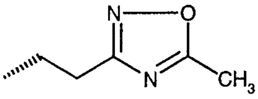
R'_{2p} is hydrogen, alkyl, alkoxy or aralkyl, preferably alkoxy, such as methoxy.

In another aspect the present invention provides a compound of formula I_p, wherein R'_{2p} is methoxy and R_{1p} is as defined in TABLE 2:

TABLE 2

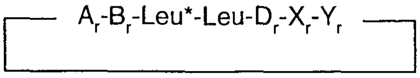
EX.	R_{1p}
1	
2	
3	

EX.	R_{1p}
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	

EX.	R_{1p}
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	

A compound of formula I includes a compound of formula IA, and, generically, a compound of formula I_p.

In another aspect the present invention provides a compound, i.e. a cyclopeptolide, of formula



$$A_r\text{-}B_r\text{-Leu*-Leu-}D_r\text{-}X_r\text{-}Y_r \qquad I_r$$

wherein

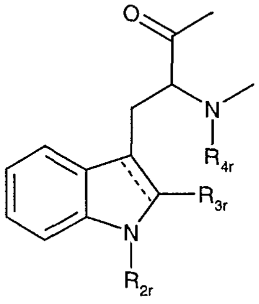
A_r is a glycolic acid residue; e.g. which is α-substituted by alkyl, which alkyl is optionally substituted by aryl, optionally protected hydroxy, cyano, heterocyclyl, iminoaminocarbenyl,, diazoketone or a group -COR, wherein R is OH, alkyl, alkoxy, alkenyloxy, amino;

B_r is an α-amino-γ -methyl-substituted octanoic acid residue;

Leu* is leucin or N-methyl leucin, preferably N-methyl leucin,

Leu is leucin;

D_r is a tryptophan residue, e.g. of formula



II_r

wherein

R_{2r} is hydrogen, alkoxy, alkyl or aralkyl,

R_{3r} is hydrogen or halogen,

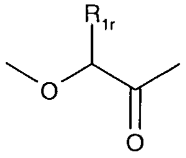
R_{4r} is hydrogen or alkyl, and

$\overline{\text{----}}$ is a single bond or a double bond,

X_r is an α-amino-substituted $(C_{2\text{-}14})$carboxylic acid residue, and

Y_r is an α-amino- or N-methyl-α-amino substituted $(C_{2\text{-}10})$-carboxylic acid residue wherein position α is trisubstituted, e.g. in addition to the α-amino- or N-methyl-α-amino substitution further disubstituted.

In formula I_r the ester bond is between residues A_r and Y_r. In a compound of formula I_r A_r is preferably a group of formula



wherein

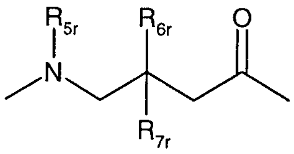
R_{1r} is alkyl, e.g. unsubstituted alkyl; or substituted alkyl, e.g. including alkyl substituted by

- cyano, a diazoketone, e.g. a group of formula $-CO-CH=N^+=N^-$;
- heterocyclyl, e.g. including a 5 or 6 membered ring (system) having 2 to 3 heteroatoms selected from N,O and S, such as a thiazolyl, oxadiazolyl, oxazolyl, e.g. unsubstituted heterocyclyl or substituted heterocyclyl, e.g. including heterocyclyl substituted by
- alkyl, e.g. (C_{1-6})alkyl, alkoxycarbonylalkyl, alkoxyalkyl, cyanoalkyl;
- a group COR_r', wherein R_r' is
  - OH, alkoxy, e.g. (C_{1-6})alkoxy, alkoxyalkoxy, alkoxyalkoxyalkoxy, alkylcarbonyloxyalkoxy; alkyl, e.g. including hydroxyalkyl, alkoxyalkyl;
  - alkenyloxy, amino, iminoaminocarbenyl, e.g. a group $-C(=NR_{8r})NH_2$, wherein R_{8r} is a substituent, e.g. hydroxy;
  - alkoxycarbonyloxyalkoxy, e.g. which alkyloxycarbonyloxyalkoxy is further substituted by a sugar residue;

D_r is preferably a tryptophan residue of formula II_r, wherein R_{2r} is hydrogen, R_{3r} is hydrogen; R_{4r} is alkoxy, such as methoxy; and ---- is a double bond;

X_r is preferably an α-amino (C_{4-8})carboxylic acid residue substituted in position β and/or γ, e.g. by alkyl, such as (C_{1-4})alkyl, e.g. an α-amino-butyric or octanoic acid residue, preferably octanoic acid residue, preferably substituted in position γ by alkyl, such as methyl;

Y_r is preferably a group of formula



wherein

R_{5r} is H or alkyl, e.g methyl;

R_{6r} is alkyl, e.g. methyl;

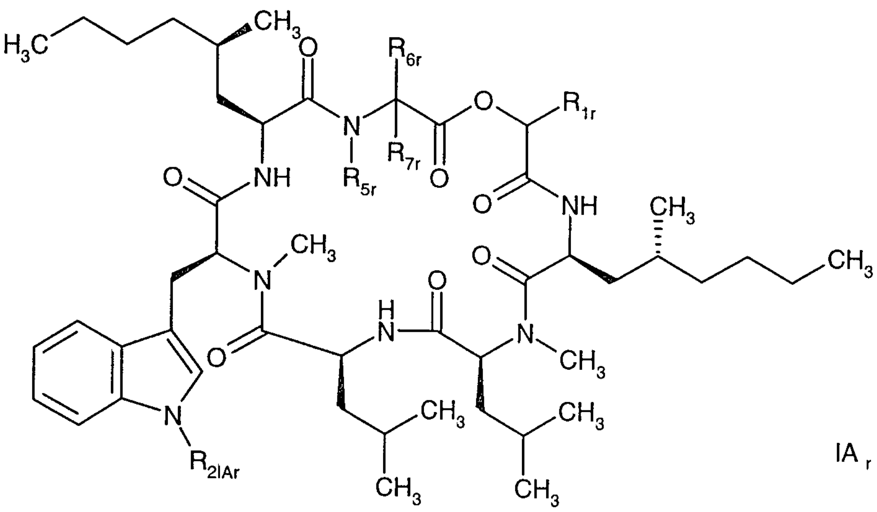
R_{7r} is

- alkyl, (C_{1-6})alkyl,e.g. unsubstituted alkyl or alkyl substituted by

- aryl, hydroxy or acyloxy, e.g. (C_{1-6})alkylcarbonyloxy or heterocyclylcarbonyloxy, e.g. imidazolylcarbonyloxy;
- alkenyl, e.g. (C_{2-6})alkenyl, such as (C_{3-5})alkenyl;
- a group -CHO or hydroxyiminocarbenyl, e.g. a group -C=N-OH, or

R_{6r} and R_{7r} together form a cycloalkyl ring, e.g. spiro attached to that carbon atom of the ring system where R_{6r} and R_{7r} are attached.

In another aspect the present invention provides a compound of formula



IA_r

wherein R_{1r}, R_{5r}, R_{6r} and R_{7r} are as defined above and R_{2IAr} has the meaning of R_{2r}, preferably methoxy.

A compound of formula I_r includes a compound of formula IA_r.

In another aspect the present invention provides a compound, i.e. a cyclopeptide, of formula

$$\boxed{A_s\text{-}B_s\text{-Leu*-Leu-}D_s\text{-}X_s} \qquad I_s$$

wherein

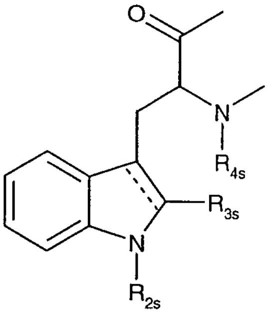
A_s is an α-amino carboxylic acid residue;

B_s is an α-amino-γ-methyl-substituted octanoic acid residue;

Leu* is leucin or N-methyl leucin, preferably N-methyl leucin,

Leu is leucin;

D_s is a tryptophan residue, e.g of formula



II$_s$

wherein

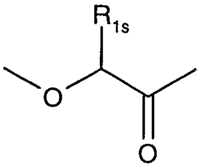
R$_{2s}$ is hydrogen, alkoxy, alkyl or aralkyl, R$_{3s}$ is hydrogen or halogen, R$_{4s}$ is hydrogen or alkyl, ---- is a single bond or a double bond, and

X$_s$ is an α-amino-carboxylic acid residue, e.g. an α-amino-substituted (C$_{2-14}$)carboxylic acid residue.

In formula I$_r$ and in formula I$_s$ the N-terminal to C-terminal orientation of the amino acid residues is in the clockwise direction.

In a compound of formula I$_s$

A$_s$ is preferably a group of formula

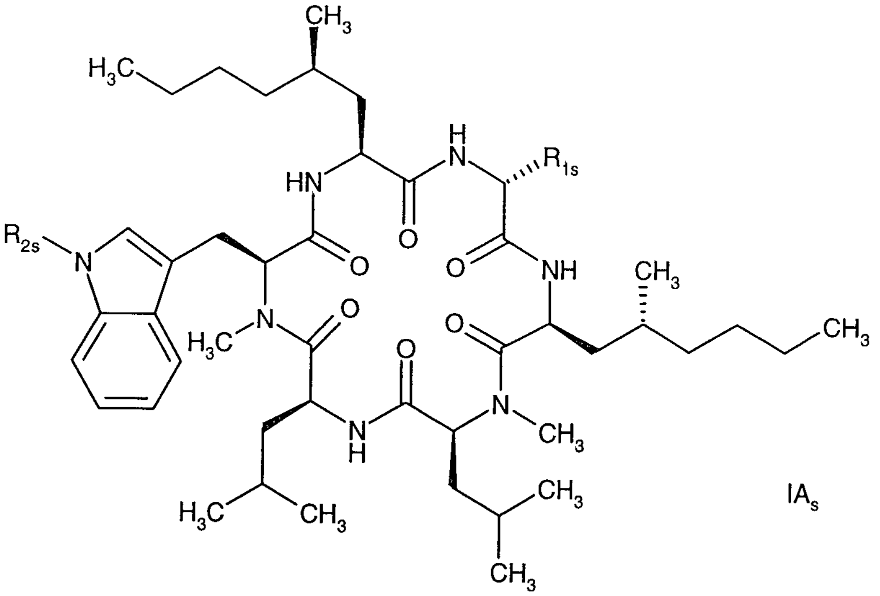


wherein R$_{1s}$ is alkyl or alkenyl, preferably alkyl,

D$_s$ is preferably a tryptophan residue of formula II$_s$, wherein R$_{4s}$ is hydrogen, R$_{3s}$ is hydrogen; R$_{2s}$ is alkoxy, such as methoxy; and ---- is a double bond; and

X$_s$ is preferably an α-amino (C$_{4-8}$)carboxylic acid residue, e.g. substituted in position β and/or γ, e.g. by alkyl, such as (C$_{1-4}$)alkyl, such as an α-amino-butyric or octanoic acid residue, preferably octanoic acid residue, preferably substituted in position γ by alkyl, such as methyl.

In another aspect the present invention provides a compound of formula



IA$_s$

wherein R_{1s} and R_{2s} are as defined above.

A compound of formula I_s includes a compound of formula IA_s.

In a compound of formula IA_s, R_{1s} is preferably alkyl and R_{2s} is preferably methoxy.

R_{1s} is more preferably substituted alkyl, e.g. substituted by a group $CY'_sR'_s$, wherein

Y'_s is S or O, preferably O; and

R'_s is H, OH, alkyl, alkenyl, cycloalkyl, aryl, alkoxy, e.g. (C_{1-6})alkoxy, alkenyloxy, cycloalkyloxy, e.g. (C_{3-7})cycloalkoxy, alkylthio, arylthio, amino, e.g. unsubstituted and substituted amino, e.g. amino substituted by one or more alkyl, e.g. (C_{1-6})alkyl or alkoxy, e.g. (C_{1-4})alkoxy; or R'_s is heterocyclyl, e.g. including a 5 or 6 membered ring system containing 1 to 4 heteroatoms selected from N, O and S; preferably from N and O; preferably aliphatic heterocyclyl, such as a pyrrolidine, piperidine, piperazine, hexahydro-1H-azepine, morpholine; including an anelleted heterocyclic ring system, e.g. a heterocyclic ring anelleted with a cycloalkyl ring, e.g. piperidine annelleted with cyclohexyl; and including spiro heterocyclyl, such as a heterocyclic ring spiro attached to another ring, e.g. such as a cycloalkyl, e.g. (C_{5-6})cycloalkyl, ring or spiro attached to another hetercyclic ring, e.g. a piperidine ring spiro attached to (C_{5-6})cycloalkyl, or 1,3-dioxacycloalkyl, such as 1,3-dioxa(C_{5-6})cycloalkyl, e.g. including unsubstituted heterocyclyl and substituted heterocyclyl, e.g. substituted by one or more groups, such as conventional in organic chemistry, e.g. substiuted by heterocyclyl, e.g. pyrrolidinyl, piperidinyl, alkyl.

More preferably preferably R'_s is OH, amino, alkoxy or heterocyclyl.

If not otherwise defined herein alkyl includes (C_{1-22})alkyl, such as (C_{1-6})alkyl, e.g. (C_{1-4})alkyl. Lower alkyl includes (C_{1-4})alkyl. Cycloalkyl includes (C_{3-7})cycloalkyl. Aryl includes phenyl. Heterocyclyl includes a 5 or 6 membered ring system having 1 to 4 heteroatoms, such as 1 to 3, e.g. selected from N, O, S. Heterocyclyl e.g. includes heterocyclyl anellated with another ring (system) and e.g. heterocylclyl spiro attached to another ring (system). Alkenyl includes (C_{2-22})alkenyl, e.g. (C_{2-6})alkenyl. Acyl includes alkylcarbonyl. Hydroxy includes unprotected hydroxy and protected hydroxy. Amino includes unsubstituted amino or substituted amino, e.g. including protected amino, e.g. amino substituted by one or two alkyl, aryl, alkoxy. Any group may be substituted or unsubstituted, e.g. subsitutents includes groups as conventional in organic chemistry, such as halogen, amino, nitro, cyano, hydroxy, cycloalkyl, aryl, alkoxy, aryloxy, alkylthio, arylthio, heterocyclyl, acyl and thioacyl, e.g. a group of formula CY'R', wherein Y' is S or O and R' is H, OH, amino, alkyl, alkenyl, cycloalkyl, aryl, alkoxy, e.g. (C_{1-6})alkoxy, alkenyloxy, alkylthio, arylthio or heterocyclyl.

The present invention beside cyclic pept(ol)ides includes open chain pept(ol)ides corresponding to cyclic pept(ol)ides as described herein, wherein a bond of the cyclic compound is split; e.g. the present invention includes open chain peptolides according to compounds of formula I; e.g. open chain compounds obtainable by either cleavage of the ester bond between residues Y and A or cleavage of an amide linkage between any other adjacent pair of the acid residues.

In another aspect the present invention provides the use of a compound of formula

$$\mathrm{H - Z - X - Y - A - B - R_1Leu - Leu\text{-}OR_{70}} \qquad \mathrm{IV}$$

or

$$\mathrm{HA - B - R_1Leu - Leu - Z - X - Y\text{-}OR_{70}} \qquad \mathrm{V}$$

wherein R_{70} is hydrogen or alkyl, and Z, X, Y, A, B, R_1Leu and Leu are as defined above, in the preparation of a medicament for the therapy, e.g. or prophylaxis, of vascular endothelial growth factor (VEGF)-mediated diseases.

Compounds provided by the present invention, including the compounds provided for the VEGF-inhibition use of the present invention, are hereinafter designated as "compound(s) of the present invention". A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

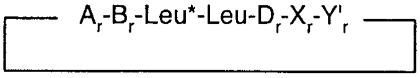
In another aspect the present invention provides a compound of formula I_p, I_r, I_s, IA_r and IA_s in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate; e.g. and/or in the form of an ester.

A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt or an acid addition salt. Metal salts include for example alkali or earth alkali salts; acid addition salts include salts of a compound of the present invention with an acid, e.g. hydrogen fumaric acid, fumaric acid, naphthalin-1,5-sulphonic acid, hydrochloric acid, deuterochloric acid; preferably hydrochloric acid.
A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.
A compound of the present invention may be converted into an ester and vice versa, in case of the presence of a group which is convertible into an ester, such as of a carboxylic acid group.
A compound of formula of the present invention may be in the form of an ester such as a physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the -COO- group of a carboxylic acid group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself is physilogically tolerable at dosages to be administered. The term "a compound of the present invention in the form of an ester" is thus to be understood as defining regular pro-drug forms of compounds of the present invention.
A compound of the present invention in the form of a salt or a solvate or an ester exhibit a similar order of pharmaceutical activity as a compound of the present invention in free from.
A compound of of the present invention may exist in the form of isomers and isomeric mixtures thereof, e.g. optical isomers, epimers, cis trans configurated isomers, conformers.
A compound of the present invention e.g. contains asymmetric carbon atoms and may thus exist in the form of diastereoisomeris and epimers and mixture thereof. Isomeric, diastereoisomeric and epimeric mixtures may be separated as appropriate, e.g. according to a method as conventional, to obtain pure isomers. Pure isomers may also be produced as appropriate, e.g. according, e.g. analogously, to a method as conventional, e.g. or as

described herein. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture, e.g. R-forms, S-forms and mixtures of R- and S-forms.

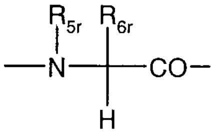
Any compound mentioned herein, e.g. including compounds according to the present invention may be obtained as appropriate, e.g. according to, e.g. analogously, to a process as conventional, e.g. as described in WO 96/03430 or in WO 97/19104, e.g. or as described herein.

In another aspect the present invention provides a process for the production of a compound of formula I_r comprising deprotonating the α-carbonyl atom in Y'_r in a compound of formula



$$\underline{\overline{A_r\text{-}B_r\text{-Leu*-Leu-}D_r\text{-}X_r\text{-}Y'_r}} \qquad III_r$$

wherein A_r, B_r, Leu*, Leu, D_r and X_r are as defined above and Y'_r is an α-amino- or N-methyl-α-amino substituted $(C_{2\text{-}10})$-carboxylic acid residue wherein position α is in addition to the α-amino- or N-methyl-α-amino substitution further monosubstituted;
e.g. Y' is a group of formula



$$-\overset{R_{5r}}{\overset{|}{N}}-\underset{\underset{H}{|}}{\overset{R_{6r}}{\overset{|}{C}}}-CO-$$

wherein R_{5r} and R_{6r} are as defined above; and reacting a deprotonated compound of formula III_r with an electrophile, e.g. including a compound of formula $R_{7r}X'_r$, wherein R_{7r} is as defined above and X'_r is a leaving group, e.g. bromide; to obtain a compound of formula I_r.

A compound of formula I_r is preferably produced by reacting a solution of a compound of formula III_r in a solvent which is inert under the reaction conditions, e.g. tetrahydrofurane, e.g. in the presence of a co-solvent, with a compound of formula $R_{7r}X'_r$, wherein R_{7r} is as defined above and X'_r is bromide, in the presence a base, e.g. phosphazene base P_4-t-But, at appropriate temperature, preferably at low temperature.
A compound of formula I_r wherein R_{5r}, R_{6r} and R_{7r} are as defined above and R_{1r} is a group of formula -C(=N-OH)-NH_2 or oxadiazolyl, may be obtained, e.g. by reaction of a compound of formula I_r wherein R_{1r} is a group of formula =CH-CH_2-CN and R_{5r}, R_{6r} and R_{7r} are as defined above with hydroxylamine to obtain a compound of formula I_r wherein R_{1r} is a group of formula

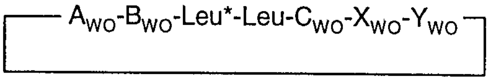
-C(=N-OH)-NH_2 and R_{5r}, R_{6r} and R_{7r} are as defined above; which compound may be further reacted, e.g. with a trimethyloxymethyl, e.g. unsubstituted or further substitued, e.g. substituted by alkyl, such as (C_{1-4})alkyl; to obtain a compound of formula I_r, wherein R_{1r} is an oxadiazolyl, e.g. an oxadiazol-2-yl, e.g. which oxadiazolyl is unsubstituted or substituted, e.g. substituted in position 5, e.g. by alkyl, such as (C_{1-4})alkyl. A compound of formula I_r obtained may be isolated and purified, e.g. according to a method as conventional.

A compoud of formula III_r may be obtained according to a method as conventional, e.g. by fermentative production of a cyclic peptide structure as an intermediate which may be chemically converted as desired; e.g. according to a method as conventional; or by chemical synthesis; e.g. according to a method as conventional, e.g. in peptide synthesis; e.g. according to a method as disclosed in WO 97/19104 or WO 96/03430; or as described herein.

If desired a group R_{1r} in a compound of formula I_r obtained may be converted further to obtain a compound of formula I_r wherein R_{1r} has another meaning than in the compound obtained according to the above described procedures.

In another aspect the present invention provides a process for the production of a compound of formula I_s comprising the steps

a) subjecting a compound of formula



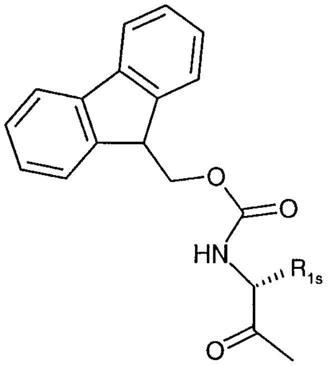
$$A_{WO}\text{-}B_{WO}\text{-Leu*-Leu-}C_{WO}\text{-}X_{WO}\text{-}Y_{WO} \qquad I_{WO}$$

wherein A_{WO} is an α-hydroxy-substituted butyric acid residue; B_{WO} is an α-amino-γ-methyl-substituted octanoic acid residue; Leu* is leucin or N-methyl leucin, Leu is leucin; C_{WO} is a tryptophan residue, X_{WO} is an α-amino-substituted (C_{2-14}) carboxylic acid residue and Y_{WO} is an α-amino- or α-methylamino-substituted (C_{2-14}) carboxylic acid residue, which is a compound of formula I of WO 96/03430, e.g. obtainable from a fermentation broth of a fungal strain NRRL 21123 as described in WO 96/03430, to ring opening;
e.g. by treatment with sodium tetrahydroborate, to obtain a diol of formula I_{WO}, wherein the bond between A_{WO} and Y_{WO} is opened and wherein A_{WO} is an α-hydroxy-substituted butyric acid residue which α-hydroxy-group is free, Y_{WO} is 1-hydroxy-2-amino- or 2-methylamino-substituted (C_{2-14})alkyl and B_{WO}, Leu*, Leu, C and X_{WO} are as defined above;

b) replacing in a compound obtained in step a) the residue Y_{WO} by a group which may be (e.g. reductively) removed, e.g. an allyloxy group; e.g. replacing the 1-hydroxy-2-amino- or 2-methylamino-substituted (C_{2-14})alkyl in the meaning of Y_{WO} in a compound obtained in step a) by an allyloxy group, e.g. by treatment with allyl alcohol/methane sulfonic acid and N-methyl morpholine;

c) splitting off a residue A_{WO} in a compound obtained in step b) to obtain a corresponding compound wherein A_{WO} is removed and B_{WO} is an α-amino-γ-methyl-substituted octanoic acid residue wherein the amine group in position α is free, e.g. by treatment of a compound obtained in step b) with methanesulfonic acid chloride/N-methyl morpholine and N-ethylthiourea;

d) converting in a compound obtained in step c) the free amine group in an α-amino-γ-methyl-substituted octanoic acid residue in the meaning of B_{WO} to obtain a compound of step c) wherein the amine group in position α in a group B_{WO} is acylated, e.g. acylated by a group

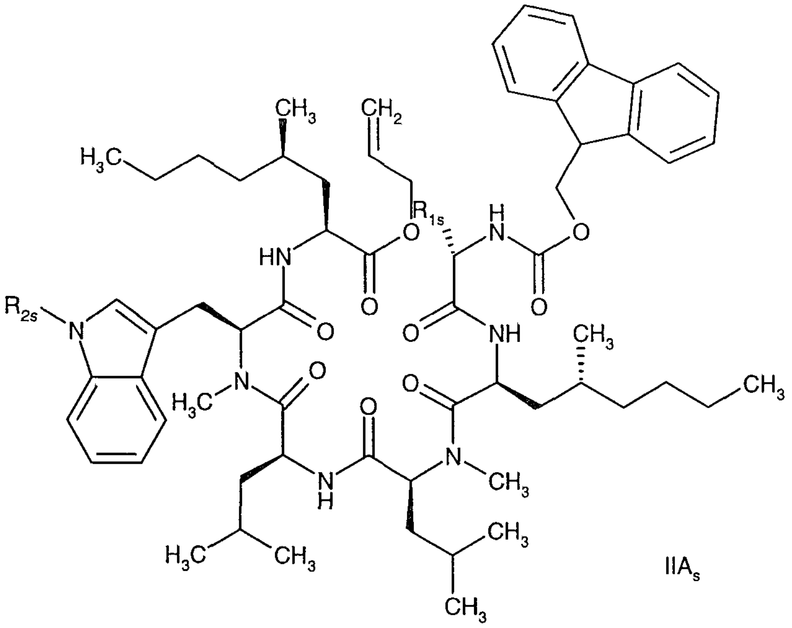


INT_s

e.g. by reaction of a compound obtained in step c) with an acid of formula INT_s-OH, e.g. in the presence of a coupling agent;

e) ring formation, e.g. ring closuring of a compound obtained in step d), e.g. reductive, to obtain a compound of formula I_s, wherein the substitutents are as defined above, e.g. forming an amide bond between a residue X_{WO} and a residue B_{WO} in the presence of a coupling agent, thereby removing the allyloxy group in a residue Y_{WO} and removing the acyl group in a group B_{WO}, e.g. in the presence of tetrakis(triphenylphosphane)-palladium.

A compound of formula I_s obtained may be isolated and purified, e.g. according to a method as conventional. E.g. for the preparation of a compound of formula IA_s wherein R_{1s} and R_{2s} are as defined above, a compound of formula



IIA$_s$

may be subjected to ring formation to obtain a compound of formula IA$_s$ wherein R_{1s} and R_{2s} are as defined above.

The compounds of the present invention exhibit pharmacological activity and are therefore useful as pharmaceuticals. E.g. the compounds of formula I, I_p, I_r and I_s are inhibitors of the stimulated expression of cellular adhesion molecules, especially inhibiting VCAM-1 relative to E-selectin and ICAM-1 expression, and additionally are inhibitors of the growth factor VEGF expression. Assays which may be used to detect the inhibition of VCAM-1, ICAM-1 and E-selectin expression by the compounds of the present invention are e.g. described in WO 97/19104 and the compounds of the present invention show activitiy in assays as described in WO 97/19104. Assays appropriate for the determination of downregulation of VEGF expression, e.g. assays to assess potential for VEGF-inhibition, are e.g. as follows:

A) Human VEGF soluble ELISA

U-138 MG cells, a non-tumorigenic human glioblastoma cell line, displays phenotypic characteristics of primary human glioblastoma cells (Ponten and MacIntyre, 1968, Acta Path Microbiol Scand 74:465-486) and are used for the human VEGF soluble ELISA. U-138 MG cells constitutively express VEGF, which can be upregulated under hypoxic culture conditions and switching the culture medium from a low to high concentration of fetal calf serum (FCS). Dose-response and time-course experiments are performed to determine the optimal conditions for inducing VEGF protein, whose secreted form ($VEGF_{165}$ isoform) is determined by soluble ELISA.

I. Growth conditions: U-138 MG cells are grown in T-75 flasks (Nunc) coated with 0.2% gelatin under standard conditions (37°C, 5% CO_2) with 1.5 x 10^6 cells/ml culture medium (CM = Minimum essential medium with Earle‘s salts [MEM; Gibco #61100] supplemented with 10% FCS, 2.2 g/l $NaHCO_3$, 1 mM sodium pyruvate, non-essential amino acids, 100 U/ml penicillin and 100 mg/ml of streptomycin). After mild trypsinization (0.25% trypsin + 0.1% EDTA for 5 min) and resuspension in CM, the cells are reseeded every 3-4 days at a 1:10 splitting ratio and given fresh CM every 3 days.

II. Experimental conditions: 96 well flat-bottom microtiter plates are precoated with 0.2% gelatin and seeded with 3 x 10^4 U-138 MG cells/well in 200 µl of assay growth medium, defined as 1:1 ratio of DMEM [Gibco #52100-047; supplemented with 3.7 g/l $NaHCO_3$] and Nutrient Mixture Ham's F12 [Gibco #21700-091; supplemented with 1.176 g/l $NaHCO_3$] containing 0.8% FCS The cells are incubated for 24 hours in these high-density, 'serum-starvation' conditions. The following day the culture medium is replaced with 150 µl/well of DMEM/F12 assay medium supplemented with 5% FCS and containing either (1) appropriate concentrations of the test compound, (2) corresponding concentrations of solvent/methanol-extracted medium, or (3) DMEM/F12 assay medium alone (5% FCS). The cells are incubated for 48 hr at 37° C. Each 96-well assay is performed with duplicate wells. After 48 hours in these 'low-to-high' serum conditions, the cell culture supernatants are transfered to a 96-well V-bottom plate (Costar # 3896) and spun down at 4° C for 15 min., 3000 x g, for subsequent analysis in the VEGF solid phase ELISA.

III. Cytotoxicity Control (cell loss based on nuclear stain): After harvesting the culture supernatants, the U-138 MG cell monolayer is fixed in 2% paraformaldehyde for 15 min at room temperature (RT) and rinsed in distilled water (Aquadest). The monolayer is covered with a 33% Giemsa solution in Aquadest for 2 min at RT. The wells are washed with Aquadest and air dried for at least 15 min. Microscopic evaluation is used to check that only the nuclei are stained, with essentially no cytoplasmic staining. Giemsa absorbance values are read on a microtiter plate reader at 550 nm and corrected for "blank" values (rows without cells) at 690 nm.

IV. Human VEGF Solid Phase ELISA: Harvested supernatant samples from the U-138 MG cells are evaluated for levels of $VEGF_{165}$ protein using a commercially-available human VEGF ELISA (R &D Systems #DVE00), according to manufacture's instructions.

The compounds of the present invention show activity in such assays.

A compound of the present invention may be administered in the form of a pharmaceutical composition.

In another aspects the present invention provides

- the therapeutical use of a compound of formula I_p, I_r and I_s; e.g. the use of a compound of formula I_p, I_r and I_s as a pharmaceutical;
- a therapeutic, e.g. pharmaceutical, composition comprising a compound of formula I_p, I_r or I_s, e.g. at least one compound, e.g. a therapeutically effective amount of at least one compound of formula I_p, I_r or I_s; beside one or more pharmaceutically acceptable carriers, diluents and/or excipients.

In another aspect the present invention provides the use of a compound of formula I, I_p, I_r or I_s, e.g. including a compound of formula IA, IA_r and IA_s, such as a compound of formula I_p, I_r or I_s, e.g. including a compound of formula IA_r and IA_s, e.g. in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate; and/or in the form of an ester; in the treatment, e.g. therapy or prophylaxis, of diseases wherein processes e.g. capillary nonperfusion, angiogenesis, neovascularization, tumor growth and metastasis contribute to the pathogenesis or severity of said disease, such as

- eye diseases involving vision impairment or loss, such as proliferative retinopathies and macular degeneration, including ischemic retinopathies, uveoretinitis and degenerative eye diseases,
- arteriosclerosis associated with chronic transplant rejection and coronary heart disease,
- solid tumor malignancies and other cancers, e.g. Kaposi's sarcoma,
- psoriasis, rheumatoid arthritis; and

a method for the treatment; e.g. or prophylaxis; of such diseases comprising administering a therapeutically or prophylactically effective amount of a compound of formula I_p, I_r or I_s, e.g. including a compound of formula IA_r and IA_s, e.g. in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate; and/or in the form of an ester; optionally in the form of a pharmaceutical composition, to a subject; e.g. to a patient, in need of such treatment.

Pharmaceutical compositions according to the present invention may be for parenteral, oral, aerosol or topical use, e.g. administration, and may comprise one or more pharmaceutically acceptable carriers, diluents and/or excipients; and may comprise one or more additives; e.g. stabilisers and the like. Appropriate dosage ranges of the compounds of the present invention in therapeutical use may be dependent on e.g. the condition or disease involved, whether the use is for treatment or prophylaxis, the mode of administration, the route of administration. In general satisfactory results may be obtained, e.g. in oral administration, at dosages of from about 0.05 to about 10 mg/kg/day, preferably from about 0.1 to about 7.5 mg/kg/day, more preferably from about 0.1 to about 2 mg/kg/day; Alternatively, for parenteral administration, e.g. by i.v. drip or infusion, e.g. dosages from about 0.01 to about 5 mg/kg/day, preferably from about 0.05 to about 1 mg/kg/day and more, preferably from about 0.1 to about 1.0 mg/kg/day may be appropriate; e.g. administered once, or, in divided doses, 2 to 4 times a day. Suitable daily dosages for human patients include thus from about 2.5 to about 500 mg p.o., preferably from about 5 to about 250 mg p.o., more preferably from about 5 to about 100 mg p.o.; or from about 0.5 to about 250 mg i.v., preferably from about 2.5 to about 125 mg i.v. and more preferably from about 2.5 to about 50 mg i.v.. The compounds of the present invention may be administered by any appropriate route, including enteral, parenteral and topical and by inhalator administration. Appropriate enteral administered forms include solutions for drinking, tablets or capsules. Appropriate parenteral forms include injectable solutions or suspensions. Appropriate forms for topical administration include e.g. creams, lotions; e.g. at a concentration range of 0.01 - 10 %, preferably from 0.1 to 1 %, by weight in such a topical formulation. Appropriate unit dosage forms for oral administration may comprise from 1 to 50 mg of a compound of the present invention, e.g. from 1 to 10 mg. A compound of the present invention may be administered to larger mammals, for example humans, e.g. by similar modes of administration; e.g. at similar or lower dosages; than known standards for indications, e.g. indications as described above.

A compound of the present invention may be used for pharmaceutical treatment according to the present invention alone, or in combination with one or more other pharmaceutically active agents. Such other pharmaceutically active agents include compounds which enhances the effectiveness of a compound of the present invention in a diseases as defined above. Combinations include fixed combinations, in which two or more pharmaceutically active agents are in the same formulation; kits, in which two or more pharmaceutically active agents in separate formulations are sold in the same package, e.g. with instruction for co-administration; and free combinations in which the pharmaceutically active agents are packaged separately, but instruction for simultaneous or sequential administration are given.

In another aspect the present invention provides a compound as defined in any one of examples 26 to 104.

In the following examples all temperatures are in degree Centigrade and are uncorrected. The following abbreviations are used:

EX.: Example	m.p.: melting point
DCC: dicyclohexylcarbodiimide	DMF: N,N-dimethylformamide
THF: tetrahydrofurane	DIEA: diisopropylethylamine
EtAc: ethyl acetate	c-Hex: cyclohexane
TFA: trifluoro acetic acid	RT = room temperature

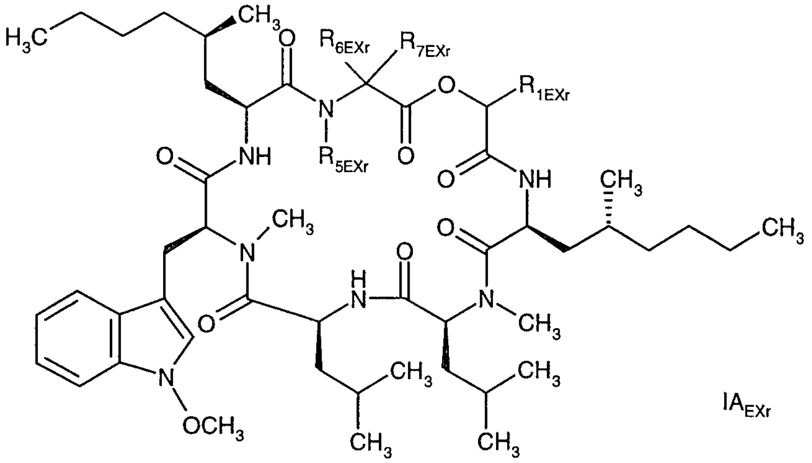
HATU: [O-(7-azabenzotriazol-1-yl)]-1,1,3,3-tetramethyluronium hexafluorophosphate

BOP: (Benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate

P_4-t-Bu: Phosphazene Base P_4-t-Bu (1M-solution in n-hexane, FLUKA Art.Nr. 79421)

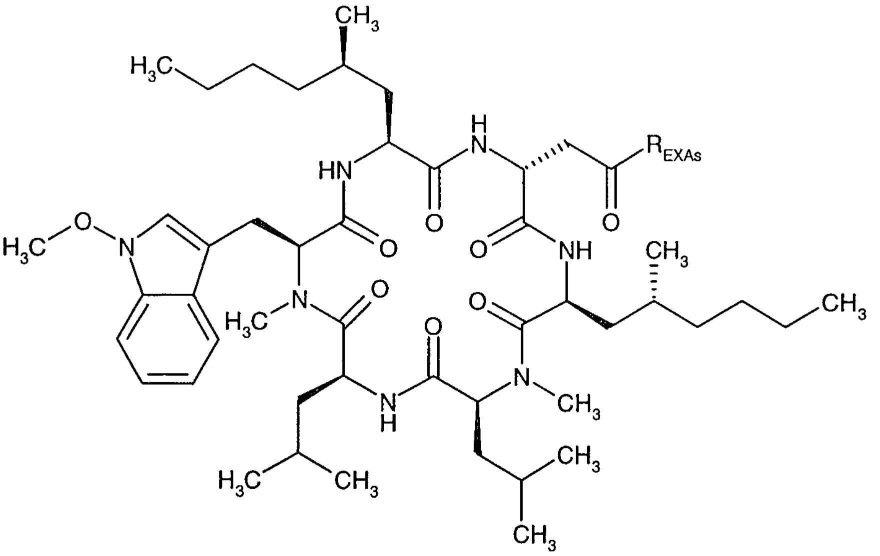
Flash column chromatography is carried out on silica gel.

According to Examples 1 to 25 a compound of formula I_p is as defined above, wherein R_{1p} is as defined in examples 1 to 25 (TABLE 2) and R_{2p} is methoxy. According to Examples 26 to 84, the production of compounds of formula



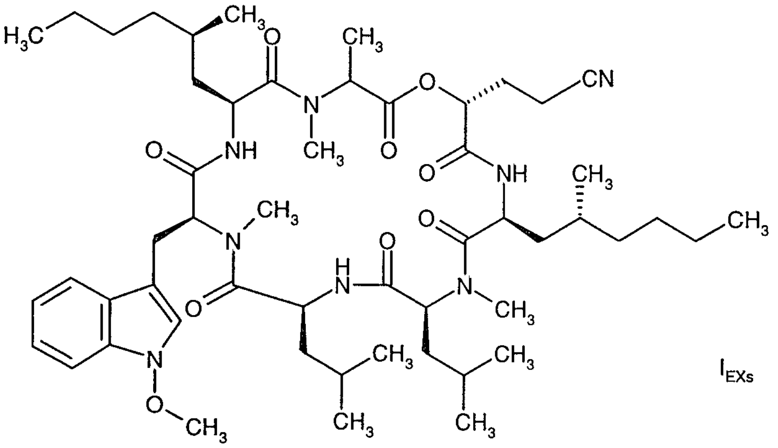
IA_{EXr}

wherein R_{1EXr}. R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in the corresponding examples (TABLE 3 to TABLE 10), is described. According to Examples 85 the production of a compound of formula IA_s as defined above, wherein R_{2s} is methoxy and R_{1s} is as defined in the corresponding example, is described. According to examples 86 to 104 the production of a compound of formula



IA_{EXAs}

wherein R_{EXAs} is as defined in TABLE 11, is described. The production of a compound of formula

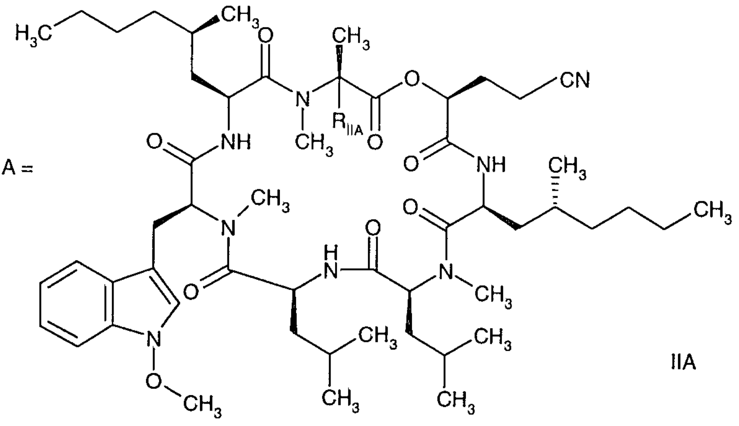


I_{EXs}

is carried out according to WO 96/03430, example 3, Compound A.

The production of a compound of formula IIA wherein R_{IIA} is hydrogen, a group of formula $-CH_2-CH=CH_2$ or a group of formula $-CH_2-O-CO-C(CH_3)_3$; is known, see e.g. WO97/19104; e.g. a compound IIA wherein R_{IIA} is a group of formula $-CH_2-CH=CH_2$ or a group of formula $-CH_2-O-CO-C(CH_3)_3$ may be obtained by reaction of a compound of formula IIA, wherein R_{IIA} is hydrogen, with a compound of formula $Br-CH_2-CH=CH_2$, or $Cl-CH_2-O-CO-C(CH_3)_3$, in the presence of phosphazane P4, in THF at -78°.

Compound of formula IIA =



IIA

If not otherwise indicated ^{1}H-NMR Spectra are determined in DMSO-d_6 (500 MHz), and ^{13}C-NMR Spectra in DMSO-d_6 (125.8 MHz). In most cases only selected signals of the major conformation are given.

Example 1

Production of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-COO-CH_2-CH_2-CF_3$

To a solution of 100 mg of compound A of example 3 of WO 96/03430, 15 mg of DMAP, 0.4 ml of 3,3,3-trifluoro-1-propanol and 50 mg of DCC are added and the mixture obtained is stirred at RT for ca. 18 hours. To the mixture obtained a mixture of EtAc/c-HEX is added and the mixture obtained is extracted with saturated NaH_2PO_4 solution. The organic layer obtained is dried, the solvent is evaporated off, the evaporation residue is subjected to chromatography, the fraction comprising the product is poured over a LH20 column and the organic solution obtained is subjected to lyophilisation. A compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-COO-CH_2-CH_2-CF_3$ in the from of an 1:1 mixture of 2 conformers is obtained. ^{13}C-NMR(125.8 MHz, $CDCl_3$): 173.670, 173.160, 172.486, 172.345, 172.085, 171.824, 171.412, 170.939, 169.771, 169.664, 169.641, 169.107, 168.397, 168.344, 168.008, 132.453, 132.256, 124.161, 123.757, 122.829, 122.513, 122.411, 121.947, 119.959, 119.668, 118.845, 118.401, 108.655, 108.441, 106.801, 74.493, 73.609, 66.905, 65.788, 65.505, 64.662, 61.160, 59.891, 59.522, 57.302, 57.200, 47.996, 47.854, 47.263, 47.210, 46.913, 46.421, 41.262, 39.855, 39.660, 39.186, 38.996, 38.261, 37.568, 37.107, 36.982, 36.897, 36.838, 33.464, 33.383, 33.227, 33.151, 30.740, 30.153, 29.441, 29.350, 29.314, 29.144, 29.100, 28.801, 28.674, 28.580, 27.299, 25.876, 25.230, 24.692, 24.438, 24.198, 23.937, 23.681, 23.509, 23.180, 22.992, 22.970, 22.891, 22.783, 22.369, 21.865, 21.673, 19.797, 19.651, 19.273, 19.224, 19.055, 14.136, 14.107, 14.069, 14.040, 13.946, 13.580.

Example 2

Production of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-CO-CH_2-O-CH_3$

A) Production of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-CO-C=N^+=N^-$

2.0 g of an solution of a compound of example 5 of WO 96/03430 in 30 ml of THF, cooled in an ice bath is treated with 0.33 ml of triethylamine and 0.29ml of 2-methyl-propylchloroformate. To the mixture obtained 15 ml of an 1M etheral diazomethane solution is added and the mixture obtained is stirred at RT for ca. 15 hours. To the mixture obtained saturated aqueous $NaHCO_3$ and EtAc are added and the phases formed are separated. The organic layer obtained is washed, dried, the solvent is evaporated off and the evaporation residue is subjected to flash column chromatography. A compound of formula I_p wherein R_1 = $-CH_2-CH_2-CO-C=N^+=N^-$ in the form of an amorphous powder is obtained.

^{13}C-NMR: 194.22, 173.61; 171.62; 171.1; 170.57; 170.55; 168.91; 168.15 (carbonyls); 75.5; 60.71, 59.12; 57.67; 48.36; 46.87; 46.69 (alpha-C´s)

B) Production of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-CO-CH_2-O-CH_3$

To a solution of 200 mg of a compound of formula I_p wherein R_{1N} = $-CH_2-CH_2-CO-C{=}N^+{=}N^-$ in 5ml of dry methanol, 0.05ml of borontrifluoride-diethyletherat are added and the mixture obtained is stirred at room temperature for ca. 3 hours. To the mixture obtained saturated aqueous $NaHCO_3$ and EtAc are added and the phases formed are separated. The organic layer obtained is washed, dried, the solvent is evaporated off and the evaporation residue is subjected to flash column chromatography. A compound of formula I_p wherein R_1 = $-CH_2-CH_2-CO-CH_2-CO-CH_3$ in the form of an amorphous powder is obtained. ^{13}C-NMR: 207.04, 173.57; 171.58; 170.99; 170.57; 170.54; 168.84; 168.18 (carbonyls); 75.34; 60.76, 59.05; 57.68; 48.31; 46.90; 46.68 (alpha-C´s); 77.47(-CH2O); 58.91 (-OMe).

Analogously as described in example 2, but using appropriate starting materials, compounds of formula I_p, wherein R_{1p} is as defined in examples 3 to 8, are obtained:

EXAMPLE 3: R_{Ip} = $-CH_2-CH_2-CO-CH_2-O-CH_2-CH_3$

^{13}C-NMR: 206.99, 173.62; 171.65; 170.98; 170.58; 170.54; 168.87; 168.18 (carbonyls); 75.66; 60.73, 58.93; 57.67; 48.33; 46.90; 46.65 (alpha-C´s); 66.50(CH3CH2O); 75.39 (-COCH2O-).

EXAMPLE 4: R_{Ip} = $-CH_2-CH_2-CO-CH_2-O-CH(CH_3)_2$

^{13}C-NMR: 206.81, 173.69; 171.61; 170.96; 170.59; 170.56; 168.91; 168.18 (carbonyls); 75.51; 60.70, 58.95; 57.65; 48.35; 46.89; 46.64 (alpha-C´s); 71.88 ((CH3)2CHO-); 73.52 (2H; -OCH2-).

EXAMPLE 5: R_{Ip} = $-CH_2-CH_2-CO-CH_2-O-C(CH_3)_3$

^{13}C-NMR: 206.71, 173.73; 171.57; 170.96; 170.59; 170.58; 168.93; 168.20 (carbonyls); 75.49; 60.69, 59.00; 57.66; 48.35; 46.89; 46.63 (alpha-C´s); 66.50((CH3)3CO-).

EXAMPLE 6: R_{Ip} = $-CH_2-CH_2-CO-CH_2-O-$cyclobutyl

^{1}HNMR: 4.6/1.87/1.72/1.64/1.62/1.46 (6 x m; 5 x 1H, 1 x 2H; cyclobutyloxy).

EXAMPLE 7: R_{Ip} = $-CH_2-CH_2-CO-CH_2OH$

^{13}C-NMR: 210.03, 173.49; 171.70; 170.99; 170.55; 170.52; 168.78; 168.19 (carbonyls); 75.29; 60.82; 58.86; 57.68; 48.20; 46.88; 46.66 (alpha-C´s); 68.09 (CH2OH) .

EXAMPLE 8: R_{Ip} = $-CH_2-CH_2-CO-CH_2-O-CH_2-CH_2OH$

^{13}C-NMR: 173.57; 171.66; 170.99; 170.58; 170.56; 168.84; 168.19 (carbonyls); 76.27; 60.65; 58.90; 57.68; 48.32; 46.90; 46.66 (alpha-C´s); 73.09/70.28(2x-CH2O-).

Example 9

Production of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-COO-CH_2-OCH_3$

200 mg of a solution of a compound of example 5 of WO 96/03430 in 20 ml of toluene, cooled in an ice bath, is treated with 0.21 ml of P_4-t-Bu and 100 mg of chloromethylmethylether and the mixture obtained is stirred for ca. 1 hour at ca. 5°. To the mixture obtained aqueous HCl and EtAc are added, the phases formed are separated, the organic layer is washed , dried, the solvent is evaporated off and the evaporation residue is subjected to flash column chromatography. A compound of formula I_p wherein R_1 = $-CH_2-CH_2-COO-CH_2-O-CH_3$ in the form of an amorphous powder is obtained. ^{13}C-NMR: 173.28; 171.82; 171.08; 170.53; 170.52; 168.60; 168.12 (ring carbonyls); 172.32 (-C(=O)O-); 90.04 (-OCH2O-); 57,32 (-CH2OCH3).

Analogously as described in example 9 but using appropriate starting materials compounds of formula I_p wherein R_{1p} is as defined in the examples 10 to 12 are obtained:

EXAMPLE 10: R_{1p} = $-CH_2-CH_2-COO-CH_2-O-CH_2-CH_3$

^{13}C-NMR: 173.28; 171.81; 171.09; 170.52 ; 170.52 (2x); 168.61; 168.12 (ring carbonyls); 172.34 (-C(=O)O-); 88.77 (-OCH2O-); 65.55 (-OCH2CH3).

EXAMPLE 11: R_{1p} = $-CH_2-CH_2-COO-CH_2-O-CH_2-CH_2-OCH_3$

^{13}C-NMR: 173.28; 171.81; 171.08; 170.53; 170.53; 168.60; 168.12 (ring carbonyls); 172.27 (-C(=O)O-); 88.97 (-OCH2O-); 71.45/69.29 (-OCH2CH2O-).

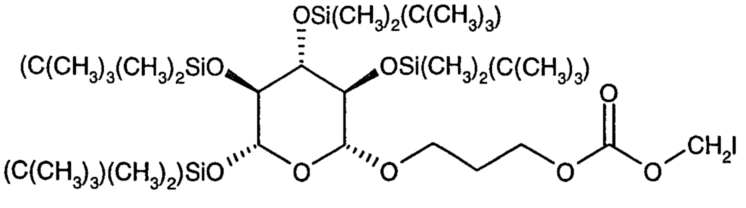
EXAMPLE 12: R_{1p} = $-CH_2-CH_2-COO-CH_2-O-CO-C(CH_3)_3$

^{13}C-NMR: 173.18; 171.86; 171.10; 170.51; 170.45; 168.49; 168.05 (ring carbonyls); 171.64 (-C(=O)O-); 176.77. (-C(=O)O-); 79.71 (-OCH2O-).

EXAMPLE 13

Production of a compound of formula I_p wherein R_{1p} is as defined in Table 2 under "Ex. 13"

To a solution of 200 mg of a compound of example 5 of WO 96/03430 in 20 ml of toluene, 0.21 ml of P_4-t-Butyl and 240 mg of a compound of formula

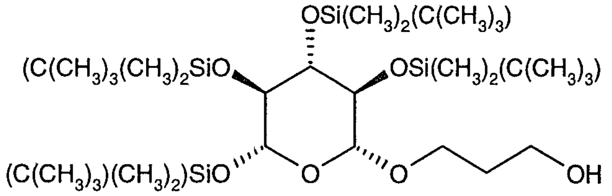


EX13

is added. The mixture obtained is stirred for ca. 15 minutes at ca. 5° and aqueous HCl and EtAc are added. The phases formed are separated, the organic layer is washed, dried and the solvent is evaporated off. The evaporation residue obtained is subjected to molecular size exclusion chromatography (Sephadex®-LH20, eluent: methanol) and flash column chromatography. A compound of formula I_p wherein R_{1p} is as defined in Table 2 under "Ex. 13" is obtained. ^{13}C-NMR: 173.27; 171.85; 171.61; 170.54; 170.30; 168.56; 168.02 (ring carbonyls); 171.08 (-<u>C</u>(=O)O-); 82.02 (-O<u>C</u>H2O-); 153.76 (-O(C=O)O-); 101.88; 82.02; 78.73; 77.57; 70.04; 64.02 (C1-C6-sugar part).

<u>Production of a compound of formula EX13</u>

To a solution of 2.4 g of a compound of formula



EX13-A

and 3 ml of pyridine in 70 ml of CH_2Cl_2, cooled to ca. 5°, 0.6 ml of chloromethyl chloroformate are added, the mixture obtained is stirred for ca. 3 hours at RT and aqueous 1N HCl and Etac are added. The phases formed are separated, the organic layer is washed, dried and the solvent is evaporated off. To the evaporation residue obtained, dissolved in acetone/acetonitrile, 15 g of NaI and 60 mg of 18-crown-6 are added and the mixture obtained is kept at ca. 60° for ca. 2 hours. To the mixture obtained, cooled down to RT, EtAc and water are added, the phases formed are separated, the organic layer is washed, dried and the solvent is evaporated off. A compound of formula EX13 is obtained and used without further purification.

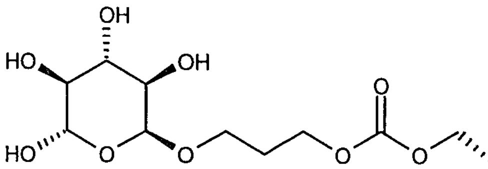
Example 14

Production of a compound of formula I_p wherein R_{1p} is as defined in Table 2 under "Ex. 14"

To 246 mg of the cyclopeptolide obtained according to Example 13 in 16 ml of CH_3CN, 2 ml of aqueous hydrogenfluoride (40w/w%) are added, the mixture obtained is stirred for ca. 90 minutes at RT, saturated aqueous $NaHCO_3$ and EtAc are added and the phases formed are separated. The organic layer obtained is washed, dried and the solvent is evaporated off. The evaporation residue is subjected to flash column chromatography and filtration through Sephadex®-LH20 (eluent:methanol). The fractions comprising a compound of formula I_p, wherein R_{1p} is as defined in Table 2 under "Ex. 14", are subjected to lyophilisation from benzene. ^{13}C-NMR: 173.27; 171.84; 171.09; 170.51; 170.48; 168.59; 168.06 (ring carbonyls); 171.71 (-C(=O)O-); 82.19 (-OCH2O-); 153.84 (-O(C=O)O-); 103.35; 77.32; 77.16; 73.87; 70.51; 61.53 (C1-C6-sugar part).

Example 15

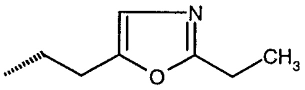
Production of a compound of formula I_p wherein R_{1p} is a compound of formula



is carried out analogously to the method described in example 14, but using the appropriate starting materials. ^{13}C-NMR: 173.27; 171.71; 171.09; 170.51; 170.48; 168.59; 168.06 (ring carbonyls); 171.84 (-C(=O)O-); 82.18 (-OCH2O-); 153.84 (-O(C=O)O-); 99.13; 73.73; 73.29; 72.37; 70.70; 61.36 (C1-C6-sugar part).

Example 16

Production of a compound of formula I_p wherein R_{1p} is a compound of formula



A solution of 150 mg of a compound obtained in example 2 A) in 10 ml of propionitrile is treated with 10 mg of rhodium(II)acetate, the mixture obtained is stirred for ca. 20 hours at RT and EtAc is added. The mixture obtained is extracted with brine, the organic layer obtained is dried, the solvent is evaporated off and the evaporation residue is subjected to flash column chromatography. A compound of formula I_p is obtained wherein R_{1p} is as defined in Table 2 under "Ex. 16", in the form of a powder. ^{13}C-NMR: 172.95; 171.99; 171.04; 170.48; 170.43; 168.37; 168.26 (carbonyls); 164.63 / 150,77 / 123.03 (oxazol).

Analogously as described in example 16 but using appropriate starting materials compounds of formula I_p wherein R_{1p} is as defined in the examples 17 to 19 are obtained:

EXAMPLE 17

R_{1p} is as defined in Table 2 under "Ex. 17": ^{13}C-NMR: 172.96; 172.00; 171.05; 170.48; 170.44; 168.37; 168.27 (carbonyls); 160.42 / 150.93 / 123.24 (oxazol).

EXAMPLE 18

R_{1p} is as defined in Table 2 under "Ex. 18": ^{13}C-NMR: 172.93; 172.03; 171.05; 170.48; 170.42; 168.28; 168.25 (carbonyls); 154.11 / 152.71 / 123.74 (oxazol), 115.84 (-CN).

EXAMPLE 19

R_{1p} is as defined in Table 2 under "Ex. 19": ^{13}C-NMR: 172.94; 172.02; 171.03; 170.47; 170.42; 168.31; 168.27 (carbonyls); 160.14 / 152.20 / 123.52 (oxazol); 66.01 (oxazolyl-$\underline{C}$H2O-); 58.77 (-OCH3).

Example 20

Production of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-C(=N-OH)NH_2$

4 g of compound A of example 3 of WO 96/03430, 2.76 g of hydroxylamin hydrochloride, 14 ml of triethylamine in 40 ml of isopropanol are sonicated for 30 minutes at RT and the mixture obtained is stirred at ca. 60° for ca. 7 hours. To the mixture obtained 600 ml of EtAc/c-HEX (1:1) are added and the mixture obtained is washed with 1 M NaH_2PO_4 solution. The organic layer obtained is dried, the solvent is evaporated off, the evaporation residue obtained is subjected to chromatography on silica gel and size exclusion on Sephadex LH20 (methanol) and lyophilisation from dioxane. A compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-C(=N-OH)NH_2$ in the form of a powder is obtained. m.p. = 109-114°.

Example 21

Production of a compound of formula I_p wherein R_{1p} is as defined in Table 2 under "Ex. 21"

To 150 mg of a compound of formula I_p wherein R_{1p} = $-CH_2-CH_2-C(=N-OH)NH_2$, dissolved in 2 ml of dry toluene, 100 µl of trimethylorthopropionate and 5 µl of methanesulfonic acid are added, the mixture obtained is stirred at ca. 60°C for ca. 7 hours, the solvent is evaporated off, the evaporation residue obtained is subjected to chromatography on silica gel, size exclusion on Sephadex LH20 (methanol) and lyophilisation from dioxane. A compound of formula I_p wherein R_{1p} is as defined in Table 2 under "Ex. 21", in the form of a 1:1 mixture of 2 conformers, in the form of a powder is obtained.

^{13}C-NMR(125.8 MHz, $CDCl_3$): 180.954, 180.577, 173.827, 173.105, 172.434, 172.421, 171.479, 170.779, 169.710, 169.596, 169.523, 169.499, 169.351, 169.024, 168.478, 168.281, 168.231, 132.454, 132.275, 124.195, 123.660, 122.926, 122.577, 122.359, 121.841, 120.254, 119.747, 118.943, 118.279, 108.715, 108.662, 108.458, 106.639, 74.128, 73.647, 66.794, 65.852, 65.565, 65.005, 61.273, 59.786, 59.7576, 57.270, 48.076, 47.705, 47.225, 47.203, 46.908, 46.281, 41.191, 39.919, 39.835, 39.663, 38.999, 38.097, 37.642, 37.480, 37.363, 37.138, 37.997, 36.947, 36.897, 36.824, 29.473, 29.414.

Analogously as described in example 21 but using appropriate starting materials compounds of formula I_p wherein R_{1p} is as defined in examples 22 to 25 are obtained:

EXAMPLE 22

R_{1p} is as defined in Table 2 under "Ex. 22": 1:1 Mixture of 2 conformers. ^{13}C-NMR(125.8 MHz, $CDCl_3$):180.130, 179.739, 173.918, 173.094, 172.487, 172.444, 171.479, 170.831, 170.804, 169.707, 169.594, 169.517, 169.481, 169.370, 169.033, 168.497, 168.309, 168.237, 132.541, 132.366, 124. 268, 123.737, 122.926, 122.587, 122.396, 121.883, 120.259, 119.777, 118.972, 118.346, 108.759, 108.723, 108.472, 106.757, 74.102, 73.666, 66.854, 65.808, 65.522, 65.156, 61.300, 59.829, 59.627, 57.323, 48.120, 47.782, 47.301, 47.270, 46.992, 46.368, 41.246, 39.926, 39.881, 39.731, 39.066, 38.249, 37.657, 37.507, 37.356, 37.148, 37.026, 36.924, 36.876, 29.486, 29.470, 29.348, 29.212, 29.115, 29.016, 28.797, 28.716, 28.549, 28.465, 28.425, 27.822, 25.280, 24.745, 24.458, 24.212, 24.080, 23.689, 23.487, 23.144, 23.020, 22.995, 22.920, 22.887, 22.820, 22.533, 22.422, 21.931, 21.768, 20.116, 20.091, 19.822, 19.562, 19.311, 19,263, 19.104, 14.147, 14.110, 14.076, 14.050, 13.852, 13.651, 13.611, 13.555.

EXAMPLE 23

R_{1p} is as defined in Table 2 under "Ex. 23": 1:1 mixture of 2 conformers; ^{3}C-NMR(125.8 MHz, $CDCl_3$): 180.302, 179.913, 173.921, 173.084, 172.495, 172.444, 171.479, 170.803, 169.707, 169.587, 169.508, 169.466, 169.362, 169.024, 168.497, 168.309, 168.233, 132.546, 132.372, 124.274, 123.740, 122.924, 122.580, 122.395, 121.882, 120.257, 119.773, 118.966, 118.345, 108.767, 108.718, 108.469, 106.762, 74.077, 73.651, 66.869, 65.801, 65.514, 65.166, 61.298, 59.830, 59.625, 57.319, 48.121, 47.783, 47.305, 47.270, 46.998, 46.372, 41.251, 39.940, 39.879, 39.730, 39.073, 38.255, 37.655, 37.512, 37.354, 37.154, 37.031, 36.930, 36.874, 29.486, 29.471, 29.217, 29.115, 29.026, 28.796, 28.712, 28.599, 28.573, 28.546, 27.835, 28.546, 27.835, 26.277, 26.266, 25.281, 24.745, 24.459, 24.214, 24.085, 23.686, 23.483, 23.150, 23.016, 22.994, 22.918, 22.524, 22.418, 22.194, 22.162, 21.932, 21.766, 19.822, 19.561, 19.321, 19.266, 19.100, 14.145, 14.105, 14.073, 14.047, 13.849, 13.557, 13.479.

EXAMPLE 24

R_{1p} is as defined in Table 2 under "Ex. 24": 1:1 mixture of 2 conformers; ^{13}C-NMR(125.8 MHz, $CDCl_3$): 173.857, 173.161, 172.469, 171.430, 170.826, 170.720, 169.573, 169.476, 169.321, 169.280, 169.200, 168.632, 168.385, 168.102, 165.177, 164.598, 132.576, 132.305, 124.283, 123.754, 122.937, 122.601, 122.419, 122.003, 120.201, 119.711, 119.082, 118.514, 108.972, 108.715, 108.526, 106.798, 75.017, 74.644, 66.648, 65.849, 65.557, 65.272, 61.446, 59.766, 59.559, 57.326, 48.024, 47.909, 47.350, 47.113, 46.910, 46.134, 41.241, 40.088, 39.963, 39.890, 39.720, 39.074, 38.905, 38.218, 37.668, 37.345, 37.265, 37.161, 37.001, 36.845, 29.500, 29.324, 29.241, 29.131, 28.942, 28.753, 28.685, 28.621, 27.941, 25.279, 24.760, 24.483, 24.232, 24.035, 23.692, 23.526, 23.148, 23.021, 22.999, 22.972, 22.896, 22.831, 22.498, 21.940, 21.720, 19.813, 19.541, 19.337, 19.153, 14.160, 14.121, 14.080, 14.048, 13.703, 13.354.

EXAMPLE 25

R_{1p} is as defined in Table 2 under "Ex. 25": 1:1 mixture of 2 conformers; ^{13}C-NMR(125.8 MHz, $CDCl_3$): 176.866, 176.382, 173.954, 173.096, 172.479, 172.443, 171.473, 170.813, 170.761, 169.873, 169.640, 169.569, 169.482, 169.044, 168.470, 168.264, 132.574, 132.371, 124.282, 123.750, 122. 936, 122.609, 122.397, 121.908, 120.261, 119.766, 119.011, 118.372, 108.839, 108.728, 108.491, 106.760, 74.502, 73.828, 66.741, 65.808, 65.516, 65.323, 61.323, 59.837, 59.660, 57.319, 48.111, 47.801, 47.274, 46.983, 46.276, 41.232, 39.986, 39.874, 39.712, 39.065, 38.948, 38.241, 37.652, 37.434, 37.329, 37.179, 37.020, 36.935, 36.864, 29.466, 29.359, 29.326, 29.218, 29.120, 28.964, 28.782, 28.693, 28.552, 27.903, 25.285, 24.744, 24.464, 24.211, 24.099, 23.681, 23.480, 23.153, 23.019, 22.994, 22.915, 22.809, 22.586, 22.452, 21.938, 21.756, 19.819, 19.534, 19.315, 19.274, 19.109, 14.145, 14.105, 14.070, 14.040, 13.845, 13.505, 12.322.

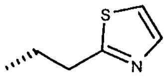
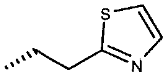
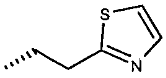
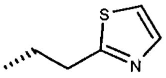
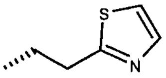
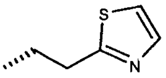
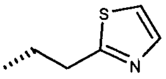
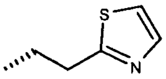
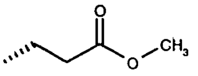
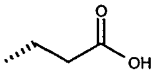
Example 26

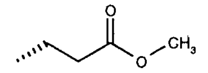
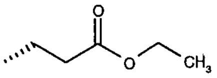
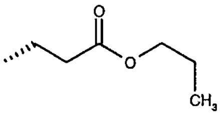
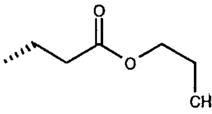
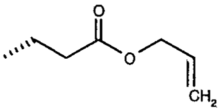
Production of a compound of formula IA_{EXr}, wherein R_{1EXr}, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$

To a solution of 100 mg of a compound of formula IA_{EXr}, wherein R_{1EXr}, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is hydrogen, allyl bromide in dry THF and 0.6 ml of P_4-t-But is added at -78 ° and the mixture obtained is stirred for ca. 3 hours and treated with 100 µl of acetic acid. The mixture obtained is diluted with toluene and the mixture obtained is extracted with aqueous NaH_2PO_4 and brine. The organic layer is separated off, dried and the solvent is evaporated off. The evaporation residue obtained is purified by pouring over sephadex (LH20) and chromatography over silica gel. A compound of formula IA_{EXr}, wherein R_{1EXr}, R_{5EXr} and R_{6EXr} are CH_3 and R_{7EXr} is $-CH_2-CH=CH_2$ is obtained. ^{1}H-NMR: 8.60 (d, J=10.0Hz, 1H), 8.31 (d, J=6.0Hz, 1H), 7.58 (d, J=9.6Hz, 1H), 7.52 (d, J=8.0Hz, 1H), 7.41 (d, J=8.3Hz, 1H), 7.36 (s, 1H), 7.19 (t, J=7.6Hz, 1H), 7.03 (t, J=7.5Hz, 1H), 5.51 (m, 1H), 5.05 (d, J=15.5Hz, 1H), 5.02 (d, J=9.9Hz, 1H), 4.93 (td, J=9.8, 4.7Hz, 1H), 4.75 (dd, J=9.1, 5.6Hz, 1H), 4.66 (m, 1H), 4.56 (q, J=7.0Hz, 1H), 4.17 (m, 1H), 4.11 (dd, J=9.7, 5.4Hz, 1H), 3.99 (s, 3H), 3.26 (dd, J=15.0, 5.6Hz, 1H), 3.00 (dd, J=15.0, 9.1Hz, 1H), 2.89 (s, 3H), 2.75 (s, 3H), 2.47 (dd, J=13.6, 7.3Hz, 1H), 2.41 (dd, J=13.6, 6.8Hz, 1H), 2.40 (s, 3H), 1.62 (t, J=7.0Hz, 2H), 1.27 (s, 3H), 0.93 (d, J=6.5Hz, 3H), 0.92 (d, J=6.6Hz, 3H), 0.85 (d, J=6.6Hz, 3H), 0.83 (t, J=7.2Hz, 3H), 0.82 (t, J=7.0Hz, 3H), 0.77 (d, J=6.5Hz, 3H), 0.49 (d, J=6.6Hz, 3H), 0.03 (d, J=6.6Hz, 3H), -0.16 (ddd, J=13.6, 10.6, 3Hz, 1H).

Analogously as described in example 26 but using appropriate starting materials the compounds of formula IA_{EXr}, wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as described in TABLE 3, are obtained:

TABLE 3

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
27	$-CH_2CH_2CN$	CH_3	CH_3	CH_3	91°-93°
28	$-CH_2CH_2CN$	CH_3	CH_3	$-CH_2-CH=CH_2$	89°-91°
29		CH_3	CH_3	CH_3	-
30		CH_3	CH_3	$-CH_2-CH_3$	-
31		CH_3	CH_3	$-CH_2-CH_2-CH_3$	-
32		CH_3	CH_3	$-CH_2-CH=CH_2$	-
33		CH_3	CH_3	$-CH_2-C(=CH_2)(CH_3)$	-
34		CH_3	CH_3	$-CH_2-CH=C(CH_3)_2$	-
35		CH_3	CH_3	$-CH_2-C_6H_5$	-
36		CH_3	CH_3	$-CH_2-O-CO-C(CH_3)_3$	-
37		CH_3	CH_3	$-CH_2-CH_2-CH_3$	-
38		CH_3	CH_3	$-CH_2-CH=CH_2$	-

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
39		CH_3	CH_3	$-CH_2-CH=CH_2$	-
40		CH_3	CH_3	$-CH_2-CH=CH_2$	-
41		CH_3	CH_3	$-CH_2-CH_2-CH_3$	-
42		CH_3	CH_3	$-CH_2-CH=CH_2$	-
43		CH_3	CH_3	$-CH_2-CH=CH_2$	-

Example 44

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is $-CH_2-CH_2-CO-NH_2$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$

A compound of formula IA_{EXr}, wherein R_{1EXr} is $-CH_2-CH_2-COOH$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ is heated in a mixture of tert-butanol/water and HCl, the mixture obtained is treated with isobutyl chlorformate in the presence of an amine in apolar solvent and quenched with aqueous ammonium hydroxide. A compound of formula IA_{EXr} wherein R_{1EXr} is $-CH_2-CH_2-CO-NH_2$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ is obtained. ^{13}C-NMR: 173.545, 173.044, 171.873, 171.481, 171.378, 170.740, 168.770, 168.611, 133.014, 132.166, 124.034, 123.272, 122.683, 119.721, 108.555, 107.140, 75.931, 66.174, 64.172, 60.643, 57.713, 50.592, 48.356, 47.465, 47.137, 40.944, 38.926, 37.379, 36.991, 36.822, 36.358, 31.673, 30.991, 29.210, 28.956, 28.811, 28.633, 28.475, 26.085, 24.971, 23.896, 23.430, 23.070, 22.974, 22.826, 21.910, 20.488, 19.366, 18.818, 14.458, 14.389.

Example 45

Production of a compound of formula IA_{EXr}, wherein R_{1EXr} and R_{5EXr} are as defined in example 36 and R_{7EXr} is $-CH_2OH$

The compound of example 36 is stirred at temperatures from RT to 50° in 50 ml of methanol together with 150 mg of lithium carbonate. The mixture obtained is diluted with cyclohexane:EtAc = 2:1 and the mixture obtained is extracted with saturated $NaHPO_4$. The organic layer obtained is dried and the solvent is evaporated off. The residue obtained is purified by chromatography on silica gel and sephadex (LH20). A compound of example 36 wherein R_{7EXr} is $-CH_2OH$ is obtained. m.p.: 130-135 °.

Example 46

Production of a compound of formula IA_{EXr}, wherein R_{1EXr} and R_{5EXr} are as defined in example 36 and R_{7EXr} is -CHO

To a solution of 400 mg of a compound of example 45 in CH_2Cl_2, 192 mg of 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Des Martin periodinane) and 360 µl of pyridine are added and the mixture obtained is stirred at RT for ca. 3 hours. The mixture obtained is diluted with cyclohexane:EtAc = 2:1 and the mixture obtained is extracted with sat. $NaHPO_4$. The organic layer is dried and the solvent is evaporated off. The evaporation residue obtained is subjected to chromatography. A compound of example 45, wherein R_{7EXr} is -CHO obtained. ^{13}C-NMR ($CDCl_3$): 194.299, 182.091, 170.177, 170.105, 167.547, 167.260, 132.5, 122.693, 121.877, 119.826, 119.063, 108.488, 108.375, 107.671, 105.208, 71.878, 67.958, 65.821, 65.654, 61.718, 57.499, 48.354, 47.802, 42.564, 40.896, 40.485, 37.564, 37.178, 36.855, 36.394, 32.542, 31.406, 30.875, 29.680, 29.564, 29.449, 29.348, 29.294, 29.229, 29.056, 28.958, 28.838, 25.603, 25.095, 24.547, 23.333, 23.183, 22.986, 22.921, 21.861, 21.622, 19.687, 19.562, 19.284, 18.811, 18.702, 16.498, 15.251, 14.103.

Example 47

Production of a compound of formula IA_{EXr}, wherein R_{1EXr} and R_{5EXr} are as defined in example 36 and R_{7EXr} is -C=N-OH

To a solution of 250 mg of a compound of example 46 in 20 ml of THF, 30 mg of NaOAc and 27 mg of NH_2OH in the form of a hydrochloride, dissolved in 5 ml of water, are added and the mixture obtained is stirred at 60° for ca. 1 hour. The mixture obtained is diluted with cyclohexane:EtAc = 2:1 and the mixture obtained is extracted with saturated $NaHPO_4$. The organic layer obtained is dried, the solvent is evaporated off and the evaporation residue obtained is subjected to chromatography on silica gel and sephadex (LH20/MeOH). A compound of example 46, wherein R_{7EXr} is -C=N-OH is obtained.

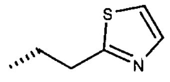
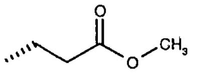
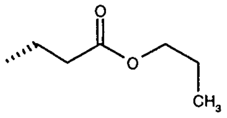
Example 48

Production of a compound of formula IA_{EXr}, wherein R_{1EXr} and R_{5EXr} are as defined in example 28 and R_{7EXr} is $-CH_2-CH_2-CH_2OH$

A compound of example 28 is treated with borane dimethylsulfide complex at 0° and oxidatively worked up with Na_2CO_3/H_2O_2. A compound of example 28, wherein R_{7EXr} is $-CH_2-CH_2-CH_2OH$ is obtained. ^{13}C-NMR: 174.168, 172.083, 171.677, 171.422, 168.792, 168.709, 122.431, 119.732, 108.198, 106.389, 74.275, 65.056, 64.264, 61.433, 61.008, 58.160, 39.499, 39.026, 36.760, 36.686, 36.638, 35.759, 33.136, 29.971, 29.130, 29.082, 28.885, 28.566, 27.994, 27.539, 26.728, 24.646, 23.572, 22.836, 22.675, 22.640, 22.554, 21.693, 21.075, 18.975, 18.070, 18.018, 17.668, 13.118, 13.058.

Analogously as described in example 48 but using appropriate starting materials the compounds of formula IA_{EXr}, wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in TABLE 4, are obtained:

TABLE 4

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
49		CH_3	CH_3	$-CH_2-CH_2-CH_2OH$	-
50		CH_3	CH_3	$-CH_2-CH_2-CH_2OH$	-
51		CH_3	CH_3	$-CH_2-CH_2-CH_2OH$	-

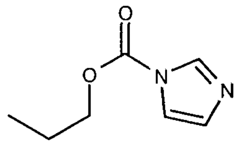
Example 52

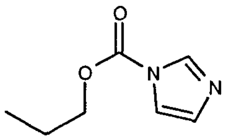
Production of a compound of formula IA_{EXr}, wherein R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in example 51 and R_{1EXr} is $-CH_2-CH_2-COOH$

A compound of example 51 is saponified by treatment with NaOH in a mixture of THF/water. A compound of formula 51, wherein R_{1EXr} is $-CH_2-CH_2-COOH$ is obtained. ^{13}C-NMR: 173.931, 173.383,171.804,171.728, 171.649, 170.681, 168.510, 168.407, 132.152, 123.980, 123.224, 122.744, 120.537, 119.947, 119.530, 108.637, 107.027, 75.260, 66.206, 64.095, 60.931, 60.628, 57.734, 48.182, 47.410, 47.147, 38.865, 37.323, 36.903, 36.754, 36.359, 33.106, 30.631, 30.341, 29.218, 28.977, 28.852, 28.663, 28.391, 28.184, 26.064, 24.947, 23.875, 23.445, 23.066, 22.936, 22.819, 21.981, 20.465, 19.140, 19.077, 18.824, 14.468, 14.403.

Example 53

Production of a compound of formula IA_{EXr}, wherein R_{1EXr}, R_{5EXr} and R_{6EXr} are as defined in example 50 and R_{7EXr} is a group of formula



A compound of example 50 is treated with carbonyldiimidazole in apolar solvent. a compound of example 50 formula I, wherein wherein R_{7EXr} is a group of formula  is obtained. ^{13}C-NMR: 176.868, 173.261, 172.976, 171.978, 171.801, 170.637, 168.466, 168.227, 164.596, 137.793, 130.732, 129.974, 123.881, 122.745, 120.690, 119.975, 119.473, 119.057, 118.008, 108.636, 106.785, 75.114, 68.155, 66.216, 63.043, 61.990, 60.722, 60.102, 57.756, 54.200, 51.758, 48.916, 48.238, 38.182, 37.482, 36.834, 36.775, 36.395, 30.581, 30.071, 29.209, 28.984, 24.941, 23.839, 22.931, 22.805, 22.017, 20.451, 19.165, 19.061, 14.469, 14.402.

Example 54

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is $-CH_2-CH_2-(C=N-OH)-NH_2$, R_{5EXr} *and* R_{6EXr} *are* CH_3, *and* R_{7EXr} is $-CH_2-CH=CH_2$

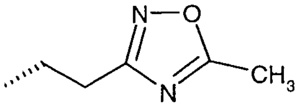
4 g of a compound of formula IIA wherein R_{IIA} is a group of formula $-CH_2-CH=CH_2$, 2.76 g of hydroxylamin hydrochloride, 14 ml of triethylamine and 40 ml of isopropanol are sonicated for ca. 30 minutes at RT and stirred at ca. 60 ° for ca. 7 hours. The reaction mixture obtained is diluted with 600 ml of EtAc/cyclohexane (1:1) and washed with aqueous 1 M NaH_2PO_4 solution. The phases obtained are separated, the organic layer is dried, the solvent is evaporated off, the evaporation residue obtained is subjected to chromatography and size exclusion. Compound-containing fractions are subjected to lyophilisation from dioxane. A compound of formula IA_{EXr} wherein R_{1EXr} is $-CH_2-CH_2-(C=N-OH)-NH_2$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ is obtained in the form of a powder.

Example 55

Analogously as described in example 54 but using appropriate starting materials a compound of formula IA_{EXr} wherein R_{1EXr} is $-CH_2-CH_2-(C=N-OH)-NH_2$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-O-CO-C(CH_3)_3$ is obtained. ^{13}C-NMR: 176.726, 172.658, 171.860, 171.472, 170.518, 170.017, 168.041, 151.236, 131.937, 123.463, 123.053, 122.500, 119.846, 118.710, 108.443, 106.436, 73.963, 65.835, 63.873, 60.523, 57.382, 47.810, 47.081, 46.996, 38.426, 37.048, 36.484, 36.225, 31.076, 28.781, 28.590, 28.548, 28.326, 28.157, 26.950, 26.835, 26.499, 24.580, 23.439, 23.148, 22.696, 22.453, 22.400, 21.692, 19.956, 18.764, 17.416, 14.037, 13.969.

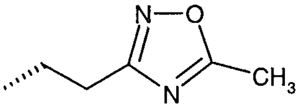
Example 56

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula



, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$

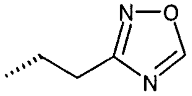
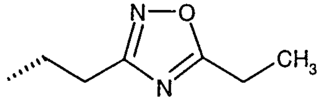
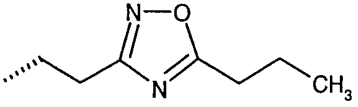
To 150 mg of a compound obtained according to example 54, dissolved in 2 ml of dry toluene, 100 µl of trimethylorthopropionate and 5 µl of methanesulfonic acid are added and the mixture obtained is stirred at ca. 60° for ca. 7 hours. From the mixture obtained the solvent is evaporated off and the evaporation residue obtained is subjected to chromatography and size exclusion on Sephadex LH20 (methanol) Compound-containing fractions are subjected to lyophilisation. A compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula

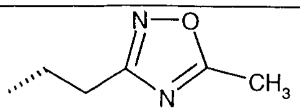
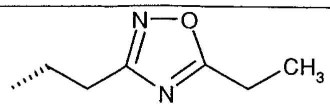
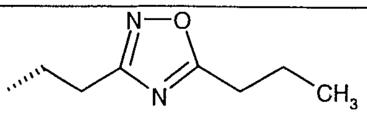
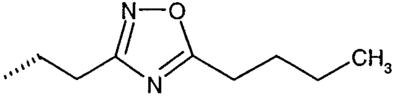
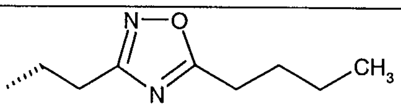


, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ is obtained in the form of a powder. ^{13}C-NMR: 176.721, 172.712, 171.648, 171.494, 170.717, 170.221, 169.390, 167.942, 167.870, 132.223, 131.891, 123.509, 122.878, 122.430, 119.670, 119.276, 118.585, 108.423, 106.516, 73.632, 65.830, 63.707, 60.489, 57.498, 47.754, 47.081, 46.908, 40.796, 38.458, 36.405, 36.094, 30.302, 28.800, 28.637, 28.581, 28.562, 28.341, 28.020, 24.576, 23.381, 23.238, 22.666, 22.542, 22.404, 21.757, 21.651, 20.038, 18.824, 18.675, 18.526, 14.038, 13.988, 11.873.

Analogously as described in example 56 but using appropriate starting materials compounds of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in TABLE 5 are obtained:

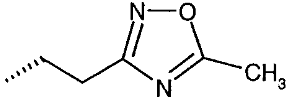
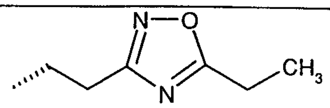
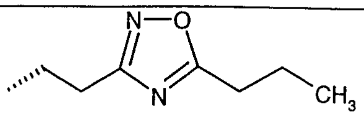
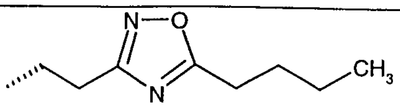
TABLE 5

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
57		CH_3	CH_3	$-CH_2-CH=CH_2$	-
58		CH_3	CH_3	$-CH_2-CH=CH_2$	-
59		CH_3	CH_3	$-CH_2-CH=CH_2$	-

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
60		CH_3	CH_3	$-CH_2-O-CO-C(CH_3)_3$	-
61		CH_3	CH_3	$-CH_2-O-CO-C(CH_3)_3$	-
62		CH_3	CH_3	$-CH_2-O-CO-C(CH_3)_3$	-
63		CH_3	CH_3	$-CH_2-O-CO-C(CH_3)_3$	-
64		CH_3	CH_3	$-CH_2-CH=CH_2$	-

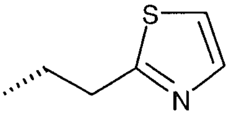
Compounds of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in TABLE 6 may be obtained by treatment of compounds obtained according to of examples 60 to 63 with lithium carbonate:

TABLE 6

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
65		CH_3	CH_3	$-CH_2OH$	-
66		CH_3	CH_3	$-CH_2OH$	-
67		CH_3	CH_3	$-CH_2OH$	-
68		CH_3	CH_3	$-CH_2OH$	-

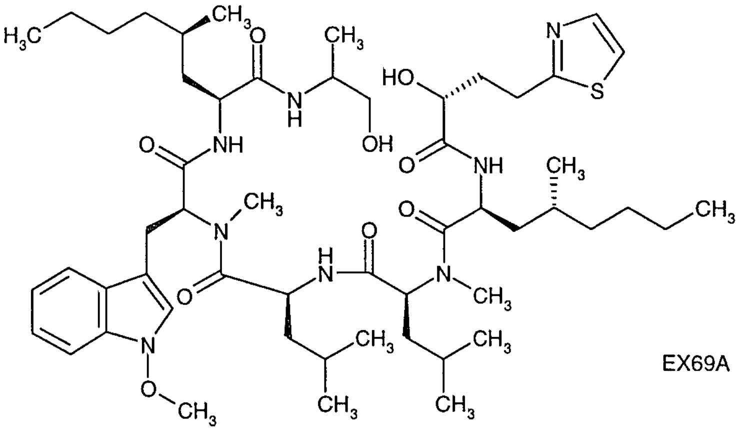
Example 69

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula



, R_{5EXr} is hydrogen and R_{6EXr} and R_{7EXr} together with the carbon atom to which they are attached form cyclopropyl (compound of formula EX69C)

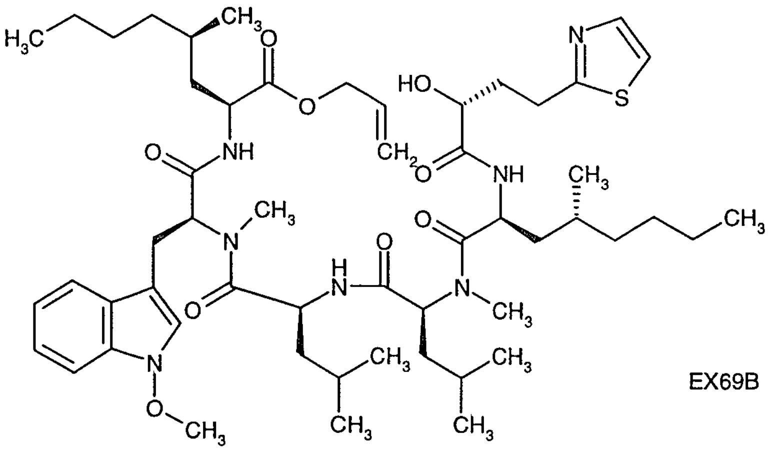
A) Compound of formula EX69A



EX69A

A solution of 1.8 g of the compound of example 7 of WO 97/19104 in 10 ml of methanol is treated with 1 g of $NaBH_4$ in small portions at RT. The reaction mixture is poured onto dilute hydrochloric acid and the mixture obtained is extracted with EtAc. The organic extract obtained is washed with aqueous $NaHCO_3$, dried and the solvent is evaporated off. The evaporation residue obtained is subjected to reversed phase chromatography (RP-8, gradient water/methanol 80 to 100% methanol). A compound of formula EX69A is obtained.

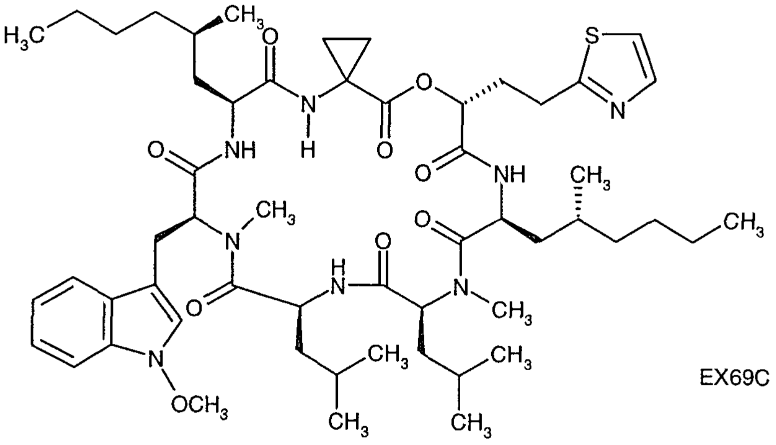
B) Compound of formula EX69B



EX69B

A solution of 1.87 g of a compound of formula EX69A in 10 ml of allyl alcohol is treated with 590 µl of methanesulfonic acid at 0° for ca. 5 hours and at RT for ca. 15 hours. To the mixture obtained 2.5 ml of N-methylmorpholine are added at 0° and the mixture obtained is heated to ca. 60° for ca. 6 hours. The mixture obtained is poured onto diluted hydrochloric acid and the mixture obtained is extracted with EtAc. The phases are separated and the organic layer obtained is washed with aqueous $NaHCO_3$ solution and dried and the solvent is evaporated off. The evaporation residue obtained is subjected to chromatography. A compound of formula EX69B in the form of a solid is obtained.

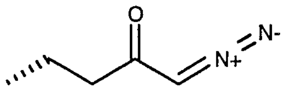
C) Compound of formula EX69C


EX69C

To a solution of 50 mg of the compound of a compound of formula EX69B 1 ml of acetonitrile 60 mg of dimethylaminopyridine, 19 µl of TFA and 57 µl of DCC. To the mixture obtained 30 mg of N-butoxycarbonyl-aminocyclopropylcarboxylic acid are added in small portions at RT and the mixture obtained is stirred for ca, 3 hours. The mixture obtained is poured onto diluted aqueous hydrochloric acid and the mixture obtained is extracted with EtAc. The organic extract obtained is washed with aqueous $NaHCO_3$ solution, dried and the solvent is evaporated off. The evaporation residue obtained is subjected to gel permeation chromatography (Sephadex LH-20, methanol/EtAc 1:1). The product fractions obtained are evaporated. The evaporation residue obtained is treated with 1.5 ml of THF and the solution obtained is treated with 5 mg of tetrakis-triphenylphosphine palladium and 42 µl of pyrrolidine at 0° for ca. 1 hours. The mixture obtained is diluted with EtAc, washed with diluted hydrochloric acid, Na_2CO_3 solution and brine, dried and the solvent is evaporated off. The evaporation residue obtained is dissolved in 1 ml of toluene, 200 µl of TFA are added and the mixture obtained is stirred for ca. 4 hours at RT. The mixture obtained is diluted with EtAc, the mixture obtained is washed with diluted hydrochloric acid, $NaHCO_3$ solution and brine, dried and the solvent is evaporated off. The evaporation residue obtained is mixed with 2 ml of acetonitrile and diisopropylethylamine is added to adjust a slightly basic pH. The mixture obtained is added to a solution of 57 mg of [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and 9 µl of diisopropylethylamine in 10 ml of acetonitrile during ca. 10 hours. The mixture obtained is diluted with EtAc and the organic phase is washed and dried and the solvent is evaporated off. The evaporation residue is subjected to silica gel chromatography (gradient toluene/methanol 0.5% to 3%) and gel permeation chromatography. A compound of formula EX69C is obtained in the form of a solid. ^{1}H-NMR ($CDCl_3$): 8.72^b/7.91^a (2d, 9.5Hz; $PrLeu^6$ NH), 7.98^b/7.84^a (d, 3.3Hz; thiazole), 7.49^a (d, 8Hz; $PrLeu^2$ NH), 7.49^a/7.42^b (2d, 8Hz; MMTrp 4'-H), 7.37^a/7.35^b (2d, 8Hz; MMTrp 7'-H), 7.29^b (d, 9Hz; $PrLeu^2$ NH), 7.23^b/7.20^a (2d, 3.3Hz; thiazole), 7.18^a/7.17^b (2ddd, 1Hz, 7Hz, 8Hz; MMTrp 6'-H), 7.01^a/6.98^b (2s; MMTrp 2'-H), 6.97^a (s; NH), 6.92^b/6.91^a (2ddd, 1Hz, 7Hz, 8Hz; MMTrp 5'-H), 6.31^b (d, 12Hz; Leu NH), 6.30^b (MeAla NMe), 5.94^a (d, 5.5Hz; Leu NH), 5.53^b (dd, 9.5Hz, 3.5Hz; CHBA α-H), 5.36^a (dd, 2Hz, 10Hz; CHBA α-H), 5.24^b (dd, 3.2Hz, 11.7Hz; MMTrp α-H), 4.95^b (ddd, 2.5Hz, 9Hz, 12Hz; $PrLeu^2$ α-H), 4.87^a (ddd, 5.2Hz, 9.4Hz, 9.7Hz; $PrLeu^2$ α-H), 4.67^b (m; Leu α-H), 4.67^a (m; $PrLeu^6$ α-H), 4.57^b (ddd, 4Hz, 9.5Hz, 11Hz; $PrLeu^6$ α-H), 4.54^a (dd, 5Hz, 10Hz; MeLeu α-H), 4.07^a (m; MMTrp α-H), 4.07^a (m; Leu α-H), 4.03^b/3.98^a/3.96^c (3s; MMTrp N1'-OMe), 3.74^b (dd, 3.3Hz, 15.6Hz; MMTrp β-H), 3.67^a (m; MMTrp β-CH_2), 3.50^b (dd, 5.1Hz, 10.4Hz; MeLeu α-H), 3.42^c (s; NMe), 3.25^b (s; MeLeu NMe), 3.19^b (m; MMTrp β'-H), 2.92^b (s; MMTrp NMe), 2.79^c (s; NMe), 2.56^a (s; MeLeu NMe), 2.39^a (s; MMTrp NMe), 1.02^a (d, 6.5Hz; MeLeu δ-CH_3), 0.97 (m; cyPr), 0.53^c/0.49^a (2d, 6.6Hz; Leu δ-CH_3), 0.18^c/-0.13^a (2d, 6.6Hz; Leu δ'-CH_3), -0.55^a (ddd, 3.2Hz, 11Hz, 14.4Hz; Leu β'-H).

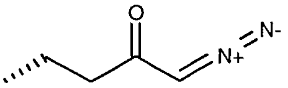
Example 70

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula



, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$

A cooled solution of 2.0 g of a compound obtained according to Example 38 in 30 ml of THF is treated with 0.333 ml of triethylamine and 0.29 ml of 2-methyl-propylchloroformate. To the mixture obtained 15 ml of 1M diazomethane in ether solution is added and the mixture obtained is stirred at RT for ca. 15 hours and saturated aqueous $NaHCO_3$ and EtAc is added. The phases formed are separated and the organic layer is washed, dried and the solvent is evaporated off. The evaporation residue obtained is subjected to chromatography. A compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula



,R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ is obtained.
^{13}C-NMR: 193.72, 173.47; 171.92; 171.63; 171.15; 170.67; 168.68; 168.35 (carbonyls); 75.55; 64.13, 60.69; 57.74; 48.32; 47.41; 47.18 (alpha-C's); 54.23 (-$\underline{C}$HN2).

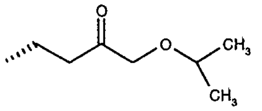
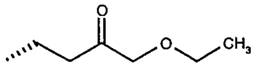
Example 71

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula $-CH_2-CH_2-CO-CH_2OH$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$

To a solution of 200 mg of compound obtained according to Example 38 in 20 ml of trifluoroethanol and 0.05 ml of water, 0.05 ml of borontrifluoride-diethyletherat are added in one portion, the mixture obtained is stirred for ca.15 minutes at RT and saturated aqueous $NaHCO_3$ and ethylacetate is added. The phases obtained are separated, the organic layer is washed, dried and the solvent is evaporated off. The evaporation residue is subjected to chromatography. A compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula $-CH_2-CH_2-CO-CH_2OH$, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ is obtained.
^{13}C-NMR: 210.15, 173.26; 171.88; 171.75; 171.12; 170.57; 168.48; 168.40 (carbonyls); 75.23; 64.16, 60.82; 57.81; 48.04; 47.44 (alpha-C's); 68.01 (-CH2OH).

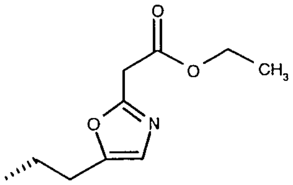
Analogously as described in example 71, but using appropriate starting materials, compounds of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in TABLE 7 are obtained:

TABLE 7

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
72		CH_3	CH_3	$-CH_2-CH=CH_2$	-
73		CH_3	CH_3	$-CH_2-CH=CH_2$	-

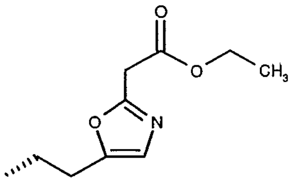
Example 74

Production of a compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula



, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$

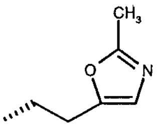
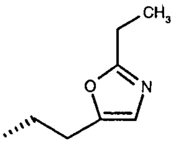
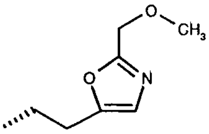
A solution of 150 mg of a compound obtained according to example 70 in 6 ml of α-cyano-EtAc is treated with 10 mg of rhodium(II)acetate and the mixture obtained is stirred for ca. 20 hours at RT. To the mixture obtained EtAc and brine is added, the phases obtained are separated, the organic layer obtained is dried and the solvent is evaporated off. The evaporation residue obtained is subjected to molecular size exclusion chromatography through sephadex®-LH20 (eluent methanol) and flash column chromatography (eluent. cyclohexane: 2-propanol = 4 :1). A compound of formula IA_{EXr} wherein R_{1EXr} is a group of formula

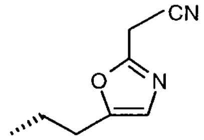


, R_{5EXr} and R_{6EXr} are CH_3, and R_{7EXr} is $-CH_2-CH=CH_2$ in the form of an amorphous powder is obtained. ^{13}C-NMR: 172.97; 172.08; 171.95; 171.10; 170.49; 168.37; 168.25 (carbonyls); 157.00 / 152.83 / 123.35 (oxazol), 168.00 (-$\underline{C}$OOEt).

Analogously as described in example 74, but using appropriate starting materials, compounds of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in TABLE 8 are obtained:

TABLE 8

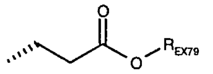
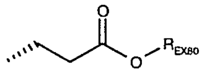
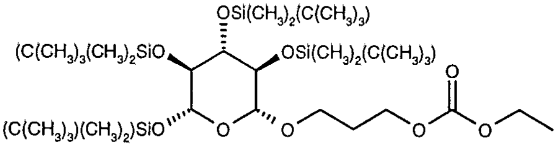
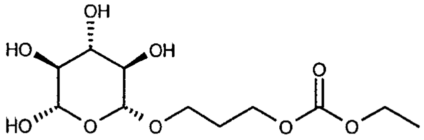
EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
75		CH_3	CH_3	$-CH_2-CH=CH_2$	-
76		CH_3	CH_3	$-CH_2-CH=CH_2$	-
77		CH_3	CH_3	$-CH_2-CH=CH_2$	-

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
78		CH_3	CH_3	$-CH_2-CH=CH_2$	-

Examples 79 and 80

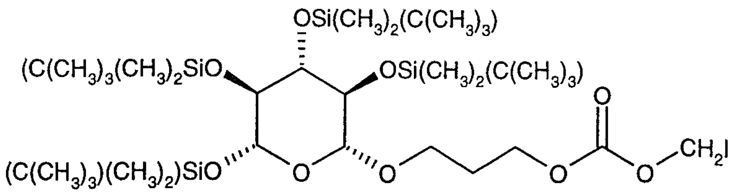
Production of compounds of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr} and R_{6EXr} are as defined in TABLE 9

TABLE 9

<table>
<tr><th>EX.</th><th>R_{1EXr}</th><th>R_{5EXr}</th><th>R_{6EXr}</th><th>R_{7EXr}</th><th>m.p.</th></tr>
<tr><td>79</td><td> </td><td>CH₃</td><td>CH₃</td><td>-CH₂-CH=CH₂</td><td>-</td></tr>
<tr><td>80</td><td> </td><td>CH₃</td><td>CH₃</td><td>-CH₂-CH=CH₂</td><td>-</td></tr>
<tr><td colspan="6">R_{EX79} = 
R_{EX80} =  </td></tr>
</table>

A) Compound of Example 79

To an ice bath cooled solution of 200 mg of a compound obtained according to Example 38 in 20 ml toluene is added 0.21 ml of P_4-t-Butyl and 240 mg of a compound of formula



EX79-i

The mixture obtained is stirred for ca. 15 minutes at ca. 5° and aqueous HCl and EtAc are added. The phases formed are separated, the organic layer is washed, dried and the solvent is evaporated off. The evaporation residue obtained is subjected to molecular size exclusion chromatography (Sephadex®-LH20, eluent: methanol) and flash column chromatography (eluent: cyclohexane:EtAc:methanol = 20:10:1). A compound of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr} and R_{6EXr} are as defined in TABLE 9 under Ex. 79 is obtained. ^{13}C-NMR: 173.23; 171.98; 171.54; 170.95; 170.66; 168.41; 168.11 (ring carbonyls); 82.05 (-OCH2O-); 153.72 (-O(C=O)O-); 101.89; 82.05; 78.74; 77.60; 70.05; 64.03 (C1-C6-sugar part).

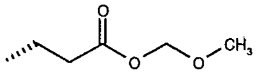
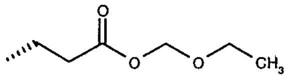
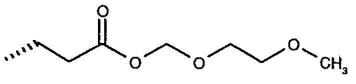
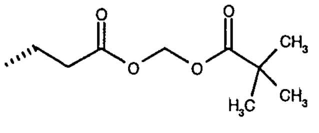
B) Compound of Example 80

To 246 mg of the compound obtained according to Example 79 in 16 ml of acetonitrile 2 ml of aqueous hydrogenfluoride (40w/w%) are added, the mixture obtained is stirred for ca. 90 minutes at RT, saturated aqueous $NaHCO_3$ and EtAc are added and the phases formed are separated. The organic layer obtained is washed, dried and the solvent is evaporated off. The evaporation residue is subjected to flash column chromatography (eluent: cyclohexane:EtAc:methanol=20:10:5) and filtration through Sephadex®-LH20 (eluent: methanol). The fractions comprising a compound of example 80 as defined in TABLE 9 are subjected to lyophilisation from benzene. ^{13}C-NMR: 173.23; 171.97; 171.62; 171.01; 170.65; 168.44; 168.16 (ring carbonyls); 171.82 (-C(=O)O-); 82.18 (-OCH2O-); 153.81 (-O(C=O)O-); 103.35; 77.33; 77.16; 73.87; 70.52; 61.54 (C1-C6-sugar part).

A compound of formula EX79-i may be obtained according to example 13, "Production of a compound of formula EX13."

Analogously as described in example 79, but using appropriate starting materials, compounds of formula IA_{EXr} wherein R_{1EXr}, R_{5EXr}, R_{6EXr} and R_{7EXr} are as defined in TABLE 10 are obtained:

TABLE 10

EX.	R_{1EXr}	R_{5EXr}	R_{6EXr}	R_{7EXr}	m.p.
81		CH_3	CH_3	$-CH_2-CH=CH_2$	-
82		CH_3	CH_3	$-CH_2-CH=CH_2$	-
83		CH_3	CH_3	$-CH_2-CH=CH_2$	-
84		CH_3	CH_3	$-CH_2-CH=CH_2$	-

Additional compound characterization data

EX.29: ^{1}H-NMR: 8.66 (d, J=10.0Hz, 1H), 8.34 (d, J=6.2Hz, 1H), 7.78 (d, J=9.6Hz, 1H), 7.78 (d, J=3.3Hz, 1H), 7.70 (d, J=3.3Hz, 1H), 7.57 (d, J=7.9Hz, 1H), 7.41 (d, J=8.2Hz, 1H), 7.37 (s, 1H), 7.18 (dd, J=8.2, 7.1Hz, 1H), 6.98 (dd, J=7.9, 7.1Hz, 1H), 4.96 (td, J=10.0, 5.1Hz, 1H), 4.80 (dd, J=9.3, 5Hz, 1H), 4.68 (td, J=8.7, 7.3Hz, 1H), 4.62 (dd, J=10.5, 3.9Hz, 1H), 4.15 (m, 1H), 4.13 (m, 1H), 4.00 (s, 3H), 3.26 (dd, J=15.0, 5Hz, 1H), 3.08 (dd, J=15.0, 9.3Hz, 1H), 2.98 (m, 1H), 2.97 (s, 3H), 2.84 (m, 1H), 2.79 (s, 3H), 2.40 (s, 3H), 2.09 (m, 1H), 1.91 (m, 1H), 1.65 (t, J=6.8Hz, 2H), 1.34 (s, 6H), 0.94 (d, J=6.5Hz, 3H), 0.92 (d, J=6.6Hz, 3H), 0.88 (d, J=6.5Hz, 3H), 0.86 (t, J=7.2Hz, 3H), 0.84 (t, J=7.2Hz, 3H), 0.78 (d, J=6.5Hz, 3H), 0.44 (d, J=6.6Hz, 3H), -0.13 (d, J=6.6Hz, 3H), -0.32 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.30: ^{1}H-NMR: 8.64 (d, J=10.0Hz, 1H), 8.32 (d, J=6.2Hz, 1H), 7.80 (d, J=9.5Hz, 1H), 7.67 (d, J=3.3Hz, 1H), 7.59 (d, J=3.3Hz, 1H), 7.54 (d, J=7.9Hz, 1H), 7.39 (d, J=8.2Hz, 1H), 7.37 (s, 1H), 7.16 (dd, J=8.2, 7.1Hz, 1H), 6.95 (dd, J=7.9, 7.1Hz, 1H), 4.95 (td, J=9.9, 5.1Hz, 1H), 4.78 (dd, J=9.7, 5.1Hz, 1H), 4.68 (dd, J=10.1, 3.1Hz, 1H), 4.66 (td, J=8.7, 7.3Hz, 1H), 4.14 (m, 1H), 4.09 (dd, J=9.0, 6.3Hz, 1H), 3.98 (s, 3H), 3.25 (dd, J=15.1, 5.1Hz, 1H), 3.06 (dd, J=15.1, 9.7Hz, 1H), 2.96 (m, 1H), 2.93 (s, 3H), 2.82 (m, 1H), 2.77 (s, 3H), 2.39 (s, 3H), 2.08 (m, 1H), 1.89 (m, 1H), 1.62 (m, 2H), 1.24 (s, 3H), 0.93 (d, J=6.5Hz, 3H), 0.91 (d, J=6.6Hz, 3H), 0.85 (d, J=6.5Hz, 3H), 0.84 (t, J=7.2Hz, 3H), 0.82 (t, J=7.2Hz, 3H), 0.78 (d, J=6.5Hz, 3H), 0.64 (t, J=7.2Hz, 3H), 0.43 (d, J=6.6Hz, 3H), -0.13 (d, J=6.6Hz, 3H), -0.34 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.31: ^{1}H-NMR: 8.61 (d, J=10.0Hz, 1H), 8.34 (d, J=6.2Hz, 1H), 7.80 (d, J=9.5Hz, 1H), 7.67 (d, J=3.3Hz, 1H), 7.60 (d, J=3.3Hz, 1H), 7.57 (d, J=7.9Hz, 1H), 7.39 (d, J=8.2Hz, 1H), 7.34 (s, 1H), 7.16 (dd, J=8.2, 7.1Hz, 1H), 6.95 (dd, J=7.9, 7.1Hz, 1H), 4.93 (td, J=9.9, 5.1Hz, 1H), 4.79 (dd, J=9.3, 5.3Hz, 1H), 4.68 (dd, J=10.1, 3.1Hz, 1H), 4.66 (td, J=8.7, 7.3Hz, 1H), 4.18 (m, 1H), 4.10 (dd, J=8.8, 6.6Hz, 1H), 3.97 (s, 3H), 3.28 (dd, J=15.0, 5.3Hz, 1H), 3.04 (dd, J=15.0, 9.3Hz, 1H), 2.91 (m, 1H), 2.89 (s, 3H), 2.81 (m, 1H), 2.77 (s, 3H), 2.39 (s, 3H), 2.07 (m, 1H), 1.90 (m, 1H), 1.62 (m, 2H), 1.26 (s, 3H), 0.93 (d, J=6.5Hz, 3H), 0.91 (d, J=6.6Hz, 3H), 0.85 (d, J=6.5Hz, 3H), 0.84 (t, J=7.2Hz, 3H), 0.83 (t, J=7.2Hz, 3H), 0.81 (t, J=7.2Hz, 3H), 0.78 (d, J=6.5Hz, 3H), 0.45 (d, J=6.6Hz, 3H), -0.08 (d, J=6.6Hz, 3H), -0.26 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.32: ^{1}H-NMR: 8.64 (d, J=10.0Hz, 1H), 8.33 (d, J=6.0Hz, 1H), 7.78 (d, J=9.5Hz, 1H), 7.68 (d, J=3.3Hz, 1H), 7.60 (d, J=3.3Hz, 1H), 7.54 (d, J=8.0Hz, 1H), 7.39 (d, J=8.1Hz, 1H), 7.34 (s, 1H), 7.16 (ddd, J=8.1, 7.1, 0.8Hz, 1H), 6.95 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 5.45 (m, 1H), 5.05 (d, J=17.5Hz, 1H), 5.02 (d, J=12.0Hz, 1H), 4.95 (td, J=9.6, 5.3Hz, 1H), 4.80 (dd, J=9.8, 5.1Hz, 1H), 4.68 (dd, J=9.0, 3.6Hz, 1H), 4.65 (td, J=8.8, 7.6Hz, 1H), 4.15 (m, 1H), 4.10 (t, J=8.0Hz, 1H), 3.98 (s, 3H), 3.35 (dd, J=15.0, 5.1Hz, 1H), 3.06 (dd, J=15.0, 9.8Hz, 1H), 2.98 (ddd, J=15.8, 8.4, 6.2Hz, 1H), 2.94 (s, 3H), 2.87 (td, J=15.8, 6.3Hz, 1H), 2.77 (s, 3H), 2.53 (dd, J=13.1, 7.8Hz, 1H), 2.40 (s, 3H), 2.24 (dd, J=13.1, 6.3Hz, 1H), 2.05 (m, 1H), 1.96 (m, 1H), 1.62 (t, J=7.0Hz, 2H), 1.26 (s, 3H), 0.94 (d, J=6.5Hz, 3H), 0.91 (d, J=6.6Hz, 3H), 0.85 (d, J=6.6Hz, 3H), 0.83 (t, J=7.2Hz, 3H), 0.82 (t, J=7.1Hz, 3H), 0.78 (d, J=6.5Hz, 3H), 0.42 (d, J=6.6Hz, 3H), -0.13 (d, J=6.6Hz, 3H), -0.35 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.33: ^{1}H-NMR: 8.68 (d, J=10.0Hz, 1H), 8.34 (d, J=6.2Hz, 1H), 7.87 (d, J=9.5Hz, 1H), 7.68 (d, J=3.3Hz, 1H), 7.61 (d, J=3.3Hz, 1H), 7.50 (d, J=7.9Hz, 1H), 7.40 (d, J=8.2Hz, 1H), 7.34 (s, 1H), 7.17 (dd, J=8.2, 7.1Hz, 1H), 6.96 (dd, J=7.9, 7.1Hz, 1H), 4.96 (td, J=9.9, 5.1Hz, 1H), 4.81 (dd, J=9.3, 5.3Hz, 1H), 4.78 (bs, 1H), 4.67 (m, 1H), 4.67 (m, 1H), 4.61 (bs, 1H), 4.14 (m, 1H), 4.10 (dd, J=9.6, 5.7Hz, 1H), 3.99 (s, 3H), 3.26 (dd, J=15.0, 5.3Hz, 1H), 3.07 (dd, J=15.0, 9.3Hz, 1H), 2.95 (s, 3H), 2.91 (m, 1H), 2.81 (m, 1H), 2.77 (s, 3H), 2.53 (d, J=13.0, 7.8Hz, 1H), 2.39 (s, 3H), 2.17 (d, J=13.0, 6.3Hz, 1H), 2.05 (AB, 1H), 2.05 (AB, 1H), 1.62 (m, 2H), 1.58 (s, 3H), 1.34 (s, 3H), 0.95 (d, J=6.5Hz, 3H), 0.93 (d, J=6.6Hz, 3H), 0.86 (d, J=6.5Hz, 3H), 0.85 (t, J=7.2Hz, 3H), 0.83 (t, J=7.2Hz, 3H), 0.80 (d, J=6.6Hz, 3H), 0.41 (d, J=6.6Hz, 3H), -0.15 (d, J=6.6Hz, 3H), -0.36 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.34: ^{1}H-NMR: 8.64 (d, J=10.0Hz, 1H), 8.34 (d, J=6.0Hz, 1H), 7.81 (d, J=9.5Hz, 1H), 7.68 (d, J=3.3Hz, 1H), 7.59 (d, J=3.3Hz, 1H), 7.54 (d, J=8.0Hz, 1H), 7.41 (d, J=8.1Hz, 1H), 7.36 (s, 1H), 7.18 (ddd, J=8.1, 7.1, 0.8Hz, 1H), 6.98 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 4.97 (td, J=9.6, 5.3Hz, 1H), 4.81 (m, 1H), 4.80 (m, 1H), 4.72 (dd, J=9.1, 3.6Hz, 1H), 4.67 (td, J=8.8, 7.6Hz, 1H), 4.14 (m, 1H), 4.12 (t, J=7.2Hz, 1H), 4.00 (s, 3H), 3.36 (dd, J=15.1, 5.1Hz, 1H), 3.07 (dd, J=15.1, 9.6Hz, 1H), 3.00 (s, 3H), 2.94 (m, 1H), 2.86 (m, 1H), 2.79 (s, 3H), 2.53 (m, 2H), 2.41 (s, 3H), 2.06 (m, 1H), 1.93 (m, 1H), 1.64 (m, 2H), 1.63 (s, 3H), 1.58 (s, 3H), 1.26 (s, 3H), 0.95 (d, J=6.5Hz, 3H), 0.93 (d, J=6.7Hz, 3H), 0.87 (d, J=6.5Hz, 3H), 0.86 (t, J=7.2Hz, 3H), 0.84 (t, J=7Hz, 3H), 0.80 (d, J=6.5Hz, 1H), 0.44 (d, J=6.6Hz, 3H), -0.13 (d, J=6.6Hz, 3H), -0.32 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.35: ^{1}H-NMR: 8.74 (d, J=10.0Hz, 1H), 8.36 (d, J=6.1Hz, 1H), 7.82 (d, J=9.5Hz, 1H), 7.79 (d, J=3.3Hz, 1H), 7.68 (d, J=3.3Hz, 1H), 7.55 (d, J=8.0Hz, 1H), 7.42 (d, J=8.1Hz, 1H), 7.36 (s, 1H), 7.20 (m, 3H), 7.18 (dd, J=8.1, 7.1Hz, 1H), 7.01 (m, 1H), 6.98 (dd, J=8.0, 7.1Hz, 1H), 6.92 (m, 1H), 5.00 (td, J=9.7, 5.4Hz, 1H), 4.85 (dd, J=9.8, 5.1Hz, 1H), 4.73 (dd, J=8.0, 5Hz, 1H), 4.64 (td, J=8.7, 7.3Hz, 1H), 4.17 (m, 1H), 4.10 (dd, J=9.3, 7Hz, 1H), 4.00 (s, 3H), 3.32 (m, 1H), 3.18 (m, 1H), 3.07 (s, 3H), 3.03 (m, 1H), 3.01 (m, 1H), 2.85 (AB;), 2.79 (s, 3H), 2.43 (s, 3H), 2.06 (m, 1H), 1.94 (m, 1H), 1.65 (t, J=6.8Hz, 2H), 1.26 (s, 3H), 0.94 (d, J=6.5Hz, 3H), 0.92 (d, J=6.7Hz, 3H), 0.88 (d, J=6.5Hz, 3H), 0.86 (t, J=7.2Hz, 3H), 0.77 (t, J=7.2Hz, 3H), 0.76 (d, J=6.5Hz, 3H), 0.44 (d, J=6.6Hz, 3H), -0.13 (d, J=6.6Hz, 3H), -0.38 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.36: ^{1}H-NMR: 8.63 (d, J=10.0Hz, 1H), 8.33 (d, J=6.1Hz, 1H), 7.70 (d, J=9.2Hz, 1H), 7.65 (d, J=3.3Hz, 1H), 7.57 (d, J=3.3Hz, 1H), 7.56 (d, J=7.9Hz, 1H), 7.39 (d, J=8.2Hz, 1H), 7.35 (s, 1H), 7.16 (t, J=7.5Hz, 1H), 6.96 (t, J=7.5Hz, 1H), 4.98 (td, J=10.0, 5.1Hz, 1H), 4.78 (dd, J=10.0, 4.5Hz, 1H), 4.67 (dd, J=10.5, 3.9Hz, 1H), 4.67 (td, J=8.7, 7.3Hz, 1H), 4.12 (m, 1H), 4.10 (m, 1H), 3.98 (s, 3H), 3.23 (dd, J=15.1, 4.5Hz, 1H), 3.06 (m, 1H), 3.04 (s, 3H), 2.98 (dd, J=15.0, 8.4Hz, 1H), 2.88 (m, 1H), 2.77 (s, 3H), 2.41 (s, 3H), 2.07 (m, 1H), 1.95 (m, 1H), 1.62 (t, J=7.0Hz, 2H), 1.36 (s, 3H), 1.12 (s, 9H), 0.93 (d, J=6.5Hz, 3H), 0.91 (d, J=6.7Hz, 3H), 0.85 (d, J=6.5Hz, 3H), 0.84 (t, J=7.2Hz, 3H), 0.82 (t, J=7.2Hz, 3H), 0.78 (d, J=6.4Hz, 3H), 0.39 (d, J=6.6Hz, 3H), -0.18 (d, J=6.6Hz, 3H), -0.44 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.37: ^{1}H-NMR: 173.222, 172.925, 171.863, 171.483, 170.651, 168.357, 168.304, 132.138, 123.874, 123.271, 122.784, 119.937, 119.084, 108.759, 106.872, 74.877, 66.243, 64.177, 60.697, 57.732, 51.772, 48.184, 47.360, 47.116, 38.816, 38.741, 37.480, 36.854, 36.757, 36.380, 30.536, 29.969, 29.223, 29.028, 28.958, 28.876, 28.631, 28.394, 26.078, 24.942, 23.845, 23.590, 23.101, 22.926, 22.807, 22.013, 20.452, 19.109, 19.042, 18.866, 17.981, 14.527, 14.464, 14.408.

EX.38: Mass Spectroscopy: ESI-MS: M.H+ 1036.6 (calc. 1036.7); M.Na+ 1058.7 (calc. 1058.6) (M-H).2Na+ 1080.6 (calc. 1080.6) negative mode: M-H-1034.7 (calc. 1034.7) TLC: Silicagel 60 (Merck HPTLC); Rf = 0.23 in toluene:MeOH = 85:15

EX.39: ^{13}C-NMR: 173.269, 172.956, 172.001, 171.796, 171.024, 170.643, 168.480, 168.261, 132.683, 132.145, 123.876, 123.278, 122.780, 119.958, 119.610, 119.065, 108.766, 106.857, 74.971, 66.241, 64.126, 60.698, 57.751, 51.794, 48.223, 47.362, 47.181, 38.778, 37.448, 36.861, 36.784, 36.385, 30.783, 30.130, 29.212, 29.043, 28.963, 28.868, 28.651, 28.424, 26.065, 24.942, 23.834, 23.553, 23.086, 22.946, 22.808, 22.011, 20.453, 19.135, 18.974, 18.844, 14.459, 14.399.

EX.40: ^{1}H-NMR ($CDCl_3$):8.72 (d, J=9.9Hz, 1H), 8.20 (d, J=6Hz, 1H), 7.71 (d, J=9.5Hz, 1H), 7.54 (d, J=8Hz, 1H), 7.40 (d, J=8.1Hz, 1H), 7.33 (s, 1H), 7.17 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 6.99 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 5.52 (m, 1H), 4.95 (ddd, J=5, 10, 4.7Hz, 1H), 4.92 (dd, J=10.5, 4.4Hz, 1H), 4.64 (m, 1H), 4.52 (dd, J=10.3, 3.5Hz, 1H), 4.00 (s, 3H), 3.00 (s, 3H), 2.76 (s, 3H), 2.38 (s, 3H), 1.28 (s, 3H), 0.40 (d, J=6.5Hz, 3H), -0.12 (d, J=6.5Hz, 3H), -0.51 (ddd, J=3.6, 11.1, 14.5Hz, 1H).

EX.41: ^{13}C-NMR 173.208, 172.553, 171.854, 171.796, 171.504, 170.667, 168.337, 168.308, 132.131, 123.877, 123.296, 122.783, 119.884, 119.049, 108.784, 106.861, 74.846, 66.239, 65.912, 64.199, 60.661, 57.738, 48.200, 47.366, 47.107, 38.876, 38.753, 37.502, 36.858, 36.748, 36.392, 30.539, 30.095, 29.220, 29.040, 28.958, 28.868, 28.643, 28.410, 26.097, 24.950, 23.834, 23.599, 23.102, 22.926, 22.806, 21.998, 20.447, 19.118, 19.074, 18.909, 17.962, 14.581, 14.463, 14.409, 10.747.

EX.42: ^{1}H-NMR: 8.73 (d, J=10.0Hz, 1H), 8.22 (d, J=6.1Hz, 1H), 7.73 (d, J=9.5Hz, 1H), 7.55 (d, J=8.0Hz, 1H), 7.41 (d, J=8.2Hz, 1H), 7.35 (s, 1H), 7.19 (ddd, J=8.2, 7.1, 0.8Hz, 1H), 7.00 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 5.53 (m, 1H), 5.11 (d, J=16.0Hz, 1H), 5.09 (d, J=10.1Hz, 1H), 4.96 (td, J=10.1, 4.8Hz, 1H), 4.93 (dd, J=9.8, 4.7Hz, 1H), 4.66 (td, J=8.4, 7.7Hz, 1H), 4.53 (dd, J=9.2, 3.7Hz, 1H), 4.22 (m, 1H), 4.08 (m, 1H), 4.06 (dd, J=10.7, 6.6Hz, 1H), 4.00 (s, 3H), 3.95 (dd, J=10.7, 6.6Hz, 1H), 3.18 (dd, J=15.0, 4.7Hz, 1H), 3.10 (dd, J=15.0, 9.8Hz, 1H), 3.02 (s, 3H), 2.78 (s, 3H), 2.64 (dd, J=13.0, 7.5Hz, 1H), 2.40 (s, 3H), 2.35 (m, 1H), 2.35 (m, 1H), 2.26 (ddd, J=17.1, 7.2, 4.5Hz, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.62 (ABXY, 2H), 1.26 (s, 3H), 0.95 (d, J=6.5Hz, 3H) 0.93 (d, J=6.6Hz, 3H), 0.92 (t, J=7.3Hz, 3H), 0.87 (d, J=6.5Hz, 3H), 0.86 (t, J=7.2Hz, 3H), 0.84 (t, J=7.2Hz, 3H), 0.80 (d, J=6.5Hz, 3H), 0.42 (d, J=6.6Hz, 3H), -0.01 (d, J=6.6Hz, 3H), -0.50 (ddd, J=13.7, 10.4, 3.3Hz, 1H).

EX.43: ^{1}H-NMR: 8.72 (d, J=10Hz, 1H), 8.72 (d, J=10Hz, 1H), 8.23 (d, J=6.1Hz, 1H), 7.74 (d, J=9.5Hz, 1H), 7.55 (d, J=8Hz, 1H), 7.41 (d, J=8.1Hz, 1H), 7.35 (s, 1H), 7.18 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 7.00 (ddd, J=8.0, 7.1, 0.8Hz, 1H), 5.95 (m;), 5.53 (m, 1H), 5.33 (dq, J=17.2, 1Hz;), 5.26 (dq, J=10.8, 1Hz;), 5.10 (d, J=17Hz, 1H), 5.07 (d, J=11Hz, 1H), 4.95 (ddd, J=5, 10, 4.7Hz, 1H), 4.92 (dd, J=10.5, 4.4Hz, 1H), 4.66 (m, 1H), 4.63 (ddt, J=14, 5.2Hz, 1H), 4.55 (ddt, J=14, 5.6Hz, 1H), 4.53 (dd, J=10.3, 3.5Hz, 1H), 4.22 (m, 1H), 4.09 (dd, J=5.4, 10Hz, 1H), 4.00 (s, 3H), 3.02 (s, 3H), 2.78 (s, 3H), 2.40 (s, 3H), 1.30 (s, 3H), 0.42 (d, J=7Hz, 3H), -0.09 (d, J=7Hz, 3H), -0.51 (ddd, J=3.6, 11.1, 14.5Hz, 1H) (In CDCl$_3$ instead of DMSO-D$_6$).

EX.49: ^{13}C-NMR: 172.976, 171.873, 171.594, 170.549, 169.129, 168.498, 168.138, 142.772, 132.215, 123.817, 123.265, 122.855, 120.971, 119.840, 119.081, 108.814, 106.838, 106.603, 73.950, 66.240, 64.161, 60.925, 57.850, 48.060, 47.492, 47.215, 36.781, 36.719, 36.463, 31.246, 30.556, 29.196, 29.041, 28.956, 28.817, 28.699, 28.040, 24.939, 23.747, 23.686, 23.047, 22.924, 22.791, 22.145, 20.463, 19.176, 18.881, 14.455, 14.402.

EX.50: ^{1}H-NMR: 8.72 (d, J=10.1Hz, 1H), 8.22 (d, J=6.2Hz, 1H), 7.77 (d, J=9.5Hz, 1H), 7.55 (d, J=7.8Hz, 1H), 7.42 (d, J=8.1Hz, 1H), 7.34 (s, 1H), 7.19 (t, J=7.6Hz, 1H), 7.02 (t, J=7.5Hz, 1H), 4.96 (m, 1H), 4.93 (m, 1H), 4.68 (dd, J=9.3, 7.5Hz, 1H), 4.57 (dd, J=10.5, 3.4Hz, 1H), 4.48 (t, J=5.6Hz, 1H), 4.23 (m, 1 H), 4.09 (dd, J=9.9, 5.4Hz), 4.00 (s, 3H), 2.99 (s, 3H), 2.78 (s, 3H), 2.40 (s, 3H), 0.43 (d, J=6.5Hz, 3H), -0.09 (d, J=6.5Hz, 3H), -0.47 (m, 1H).

EX.51: ^{13}C-NMR: 173.225, 172.589, 171.885, 171.780, 171.600, 170.637, 168.417, 168.312, 132.138, 123.897, 123.264, 122.779, 119.914, 119.026, 108.790, 106.871, 74.939, 66.240, 65.898, 64.096, 60.898, 60.731, 60.660, 57.758, 48.195, 47.402, 47.145, 38.824, 37.447, 36.864, 33.414, 30.565, 30.190, 29.208, 29.041, 28.972, 28.865, 28.671, 28.417, 28.098, 26.149, 24.949, 23.821, 23.571, 23.486, 23.076, 22.930, 22.811, 22.030, 21.975, 20.460, 19.327, 19.150, 19.039, 18.936, 14.463, 14.403, 10.726.

EX.54: ^{13}C-NMR: 173.057, 171.958, 171.843, 171.294, 170.781, 168.863, 168.223, 151.543, 132.874, 132.318, 123.854, 123.395, 122.869, 120.250, 119.890, 119.065, 108.827, 106.814, 73.872, 66.222, 64.181, 60.874, 57.783, 48.111, 47.599, 47.212, 38.816, 36.812, 30.947, 28.671, 28.429, 26.759, 24.935, 23.813, 23.548, 23.072, 22.915, 22.772, 22.086, 20.394, 19.196, 14.419.

EX.57: ^{13}C-NMR: 172.794, 171.579, 171.493, 170.641, 170.196, 168.627, 167.977, 167.904, 132.208, 131.833, 123.514, 122.885, 122.385, 119.638, 119.269, 118.645, 108.367, 106.514, 74.161, 65.817, 63.658, 60.500, 57.506, 47.808, 47.057, 46.968, 40.708, 38.525, 36.369, 36.091, 30.191, 28.779, 28.670, 28.572, 28.365, 28.045, 27.787, 24.583, 23.472, 23.376, 23.215, 22.662, 22.537, 22.398, 21.814, 21.743, 20.041, 18.865, 18.691, 18.436, 14.027, 13.974.

EX.58: ^{13}C-NMR: 172.793, 171.624, 171.490, 170.701, 170.218, 169.325, 167.941, 167.887, 132.224, 131.875, 123.513, 122.874, 122.404, 119.651, 119.241, 118.561, 108.417, 106.504, 73.725, 65.830, 63.691, 60.454, 57.505, 47.744, 47.085, 46.937, 38.462, 37.150, 36.386, 36.083, 30.265, 28.802, 28.632, 28.583, 28.562, 28.372, 28.019, 27.789, 24.583, 23.388, 23.213, 22.657, 22.542, 22.408, 21.767, 20.041, 19.527, 18.824, 18.633, 18.470, 14.029, 13.991, 10.537.

EX.59: ^{13}C-NMR: 179.599, 172.741, 171.635, 171.496, 170.709, 170.229, 169.341, 167.952, 167.886, 132.237, 131.885, 123.511, 122.883, 122.416, 119.645, 119.246, 118.574, 108.436, 106.507, 73.738, 65.839, 63.697, 60.441, 57.514, 47.750, 47.086, 46.945, 40.830, 38.465, 37.171, 36.391, 36.099, 30.279, 28.812, 28.638, 28.589, 28.562, 28.383, 28.031, 27.778, 27.566, 24.590, 23.388, 23.216, 22.660, 22.548, 22.414, 21.772, 20.049, 19.607, 18.823, 18.655, 18.472, 14.046, 13.402.

EX.60: ^{13}C-NMR: 177.138, 177.013, 173.056, 172.225, 171.901, 170.629, 170.130, 169.670, 168.371, 168.011, 132.232, 123.833, 123.298, 122.835, 120.058, 118.994, 108.819, 106.795, 74.283, 66.231, 63.823, 60.837, 57.822, 48.092, 47.312, 47.184, 38.730, 37.373, 36.847, 36.695, 36.487, 31.158, 29.180, 29.006, 28.961, 28.872, 28.695, 28.431, 28.203, 27.215, 27.094, 24.936, 23.873, 23.767, 23.497, 23.029, 22.790, 22.748, 22.089, 21.856, 20.395, 19.381, 19.096, 18.850, 17.429, 14.432, 14.383, 12.246.

EX.61: ^{13}C-NMR: 180.929, 176.998, 173.070, 172.212, 171.898, 170.636, 170.136, 169.587, 168.387, 168.006, 132.215, 123.838, 123.297, 122.816, 120.045, 118.984, 108.812, 106.787, 74.380, 66.229, 63.826, 60.818, 57.828, 48.084, 47.333, 47.196, 38.685, 36.847, 36.678, 36.491, 31.148, 29.179, 29.008, 28.961, 28.875, 28.718, 28.434, 28.146, 27.099, 24.941, 23.772, 23.482, 23.019, 22.841, 22.791, 22.751, 22.095, 21.978, 20.399, 19.903, 19.099, 18.830, 17.414, 14.432, 14.385, 10.838.

EX.62: ^{13}C-NMR: 179.987, 176.986, 173.064, 172.211, 171.894, 170.644, 170.141, 169.600, 168.384, 167.999, 132.217, 123.832, 123.292, 122.809, 120.030, 118.987, 108.809, 106.785, 74.385, 66.229, 63.826, 60.796, 57.830, 48.087, 47.337, 47.196, 38.678, 37.367, 36.846, 36.671, 36.499, 31.146, 29.177, 29.006, 28.964, 28.873, 28.731, 28.438, 28.134, 27.922, 27.151, 24.945, 23.701, 23.483, 23.018, 22.837, 22.791, 22.754, 22.093, 21.971, 20.393, 19.908, 19.096, 18.861, 17.412, 14.426, 14.383, 13.772.

EX.63: ^{13}C-NMR:180.133, 176.986, 173.063, 172.210, 171.891, 170.683, 170.141, 169.597, 168.377, 168.007, 132.160, 123.825, 123.289, 119.997, 118.992, 108.591, 106.771, 74.371, 66.227, 66.056, 63.825, 60.773, 57.821, 48.083, 47.328, 47.182, 38.676, 36.847, 36.668, 31.155, 29.181, 29.008, 28.962, 28.419, 27.098, 25.771, 24.941, 23.766, 23.477, 23.012, 22.836, 22.792, 22.092, 21.946, 20.396, 19.090, 18.850, 17.405, 14.433, 14.391, 13.846.

EX.64: ^{13}C-NMR: 172.727, 171.671, 171.486, 170.695, 170.220, 169.338, 167.937, 167.869, 132.231, 131.881, 123.507, 122.869, 122.395, 119.627, 119.216, 118.559, 108.421, 106.500, 73.731, 65.819, 63.679, 60.416, 57.503, 47.736, 47.084, 46.936, 40.820, 36.379, 36.091, 30.260, 28.794, 28.621, 28.574, 28.554, 28.370, 28.112, 28.112, 28.016, 25.396, 24.576, 23.367, 23.200, 22.636, 22.531, 22.398, 21.759, 21.552, 20.030, 18.815, 18.648, 18.459, 14.026, 13.981, 13.442.

EX.65: ^{1}H-NMR: 8.64 (d, J=10.0 Hz, 1H), 8.25 (d, J=6.3 Hz, 1H), 7.83 (d, J=9.6 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.39 (d, J=8.2 Hz, 1H), 7.33 (s, 1H), 7.16 (t, J=7.6 Hz, 1H), 6.98 (t, J=7.8 Hz, 1H), 5.37 (t, J=5.2 Hz, 1H), 4.94 (dt, J=9.7, 5.5 Hz, 1H), 4.79 (dd, J=10.1, 4.7 Hz, 1H), 4.68 (dd, J=10.2, 3.1 Hz, 1H), 4.66 (m, 1 H), 4.12 (dd, J=10.5, 5.1 Hz, 1H), 4.09 (m, 1H), 3.99 (s, 3H), 3.61(d, J=5.2 Hz, 2H), 3.09 (s, 3H), 2.76 (s, 3H), 2.53 (s, 3H), 2.39 (s, 3H), 1.31 (s, 3H), 0.44 (d, J=6.6 Hz, 3H), -0.18 (d, J=6.6 Hz, 3H), -0.51 (m, 1H).

EX.66: ^{1}H-NMR: 8.65 (d, J=9.9 Hz, 1H), 8.25 (d, J=6.2 Hz, 1H), 7.83 (d, J=9.6 Hz, 1H), 7.44 (d, J=8.0 Hz, 1H), 7.39 (d, J=8.2 Hz, 1H), 7.33 (s, 1H), 7.15 (t, J=7.3 Hz, 1H), 6.97 (t, J=7.5

Hz, 1H), 5.37 (bs, 1H), 4.94 (dt, J=9.7, 5.5 Hz, 1H), 4.81 (dd, J=9.7, 5.0 Hz, 1H), 4.69 (dd, J=10.0, 3.1 Hz, 1H), 4.66 (m, 1 H), 4.12 (dd, J=10.5, 4.7 Hz, 1H), 4.11 (m, 1H), 3.99 (s, 3H), 3.60(bs, 2H), 3.18 (s, 3H), 2.89 (q, J=7.5 Hz, 2 H), 2.77 (s, 3H), 2.39 (s, 3H), 1.30 (s, 3H), 1.27 (t, J=7.5 Hz), 0.39 (d, J=6.6 Hz, 3H), -0.20 (d, J=6.6 Hz, 3H), -0.53 (m, 1H).

EX.67: ^{1}H-NMR: 8.65 (d, J=10.0 Hz, 1H), 8.25 (d, J=6.3 Hz, 1H), 7.83 (d, J=9.6 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.39 (d, J=8.2 Hz, 1H), 7.33 (s, 1H), 7.15 (t, J=7.6 Hz, 1H), 6.97 (t, J=7.2 Hz, 1H), 5.36 (bt, J=4.4 Hz, 1H), 4.94 (dt, J=9.6, 5.5 Hz, 1H), 4.81 (dd, J=9.8, 4.9 Hz, 1H), 4.69 (dd, J=10.0, 3.2 Hz, 1H), 4.67 (m, 1 H), 4.12 (m, 2H), 3.98 (s, 3H), 3.59 (bd, J=4.4 Hz, 2H), 3.07 (s, 3H), 2.85 (t, J=7.4 Hz, 2 H), 2.77 (s, 3H), 2.39 (s, 3H), 1.72 (tq, J=7.3 Hz, 2H), 1.30 (s, 3H), 0.94 (t, J=7.3 Hz), 0.39 (d, J=6.6 Hz, 3H), -0.19 (d, J=6.6 Hz, 3H), -0.52 (m, 1H).

EX.68: ^{1}H-NMR: 8.65 (d, J=9.9 Hz, 1H), 8.25 (d, J=6.2 Hz, 1H), 7.83 (d, J=9.6 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.39 (d, J=8.2 Hz, 1H), 7.33 (s, 1H), 7.15 (t, J=7.6 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 5.37 (t, J=4.4 Hz, 1H), 4.94 (dt, J=9.4, 5.5 Hz, 1H), 4.81 (dd, J=9.8, 4.9 Hz, 1H), 4.69 (dd, J=10.0, 3.2 Hz, 1H), 4.67 (m, 1 H), 4.12 (m, 2H), 3.98 (s, 3H), 3.60(bd, J=4.4 Hz, 2H), 3.07 (s, 3H), 2.87 (t, J=7.5 Hz, 2 H), 2.76 (s, 3H), 2.39 (s, 3H), 1.68 (tt, J=7.4 Hz, 2 H), 1.34 (tq, J=7.4 Hz, 2 H), 1.30 (s, 3H), 0.88 (t, J=7.4 Hz), 0.39 (d, J=6.6 Hz, 3H), -0.19 (d, J=6.6 Hz, 3H), -0.51 (m, 1H).

EX.72: ^{13}C-NMR: 207.23, 173.42; 171.93; 171.71; 171.13; 170.72; 168.59; 168.37 (carbonyls); 75.39; 64.10, 60.64; 57.72; 48.29; 47.43; 47.16 (alpha-C´s); 72.06 ((CH3)2$\underline{C}$HO-); 73.47 (-$\underline{C}$H2O-).

EX.73: ^{13}C-NMR: 07.28, 173.35; 171.95; 171.73; 171.13; 170.69; 168.54; 168.38 (carbonyls); 75.57; 64.11, 60.68; 57.76; 48.26; 47.43; 47.18 (alpha-C´s); 66.21 (CH3$\underline{C}$H2O-).

EX.75: ^{13}C-NMR: 172.98; 172.05; 171.95; 171.14; 170.50; 168.42; 168.24 (carbonyls); 160.25 / 151.70 / 122.85 (oxazol).

EX.76: ^{13}C-NMR: 172.97; 172.04; 171.98; 171.13; 170.48; 168.42; 168.22 (carbonyls); 164.40 / 151.58 / 122.71 (oxazol).

EX.77: ^{13}C-NMR: 172.96; 172.08; 171.99; 171.11; 170.4;168.37; 168.25 (carbonyls); 160.04 / 153.08 / 123.30 (oxazol); 65.94 (oxazolyl-$\underline{C}$H2O-); 57.8 (-OCH3).

EX.78: ^{13}C-NMR: 172.93; 172.06; 172.01; 171.12; 170.48; 168.33; 168.23 (carbonyls); 153.94 / 153.58 / 123.64 (oxazol), 115.80 (-CN).

EX.81: ^{13}C-NMR: 173.27; 171.97; 171.78; 171.05; 170.68; 168.51; 168.23 (ring carbonyls); 172.19 (-$\underline{C}$(=O)O-); 90.14 (-O$\underline{C}$H2O-); 57,47 (-CH2O$\underline{C}$H3).

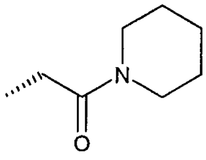
EX.82: ^{13}C-NMR: 173.28; 171.97; 171.78; 171.04; 170.67; 168.51; 168.22 (ring carbonyls); 172.20 (-C(=O)O-); 88.91 (-OCH2O-); 65.68 (-OCH2CH3).

EX.83: ^{13}C-NMR: 173.25; 171.98; 171.78; 171.05; 170.68; 168.48; 168.23 (ring carbonyls); 172.16 (-C(=O)O-); 89.19 (-OCH2O-); 71.38/69.35 (-OCH2CH2O-).

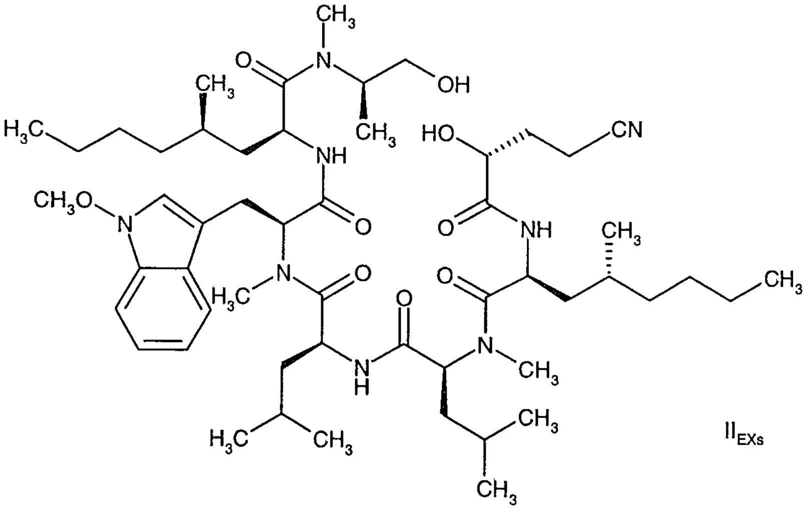
EX.84: ^{13}C-NMR: 173.21; 172.03; 171.83; 171.03; 170.66; 168.30; 168.15 (ring carbonyls); 171.46 (-C(=O)O-); 79.85 (-OCH2O-).

Example 85

Production of a compound of formula IA$_s$, wherein R$_{2s}$ is methoxy and R$_{1s}$ is a group of formula



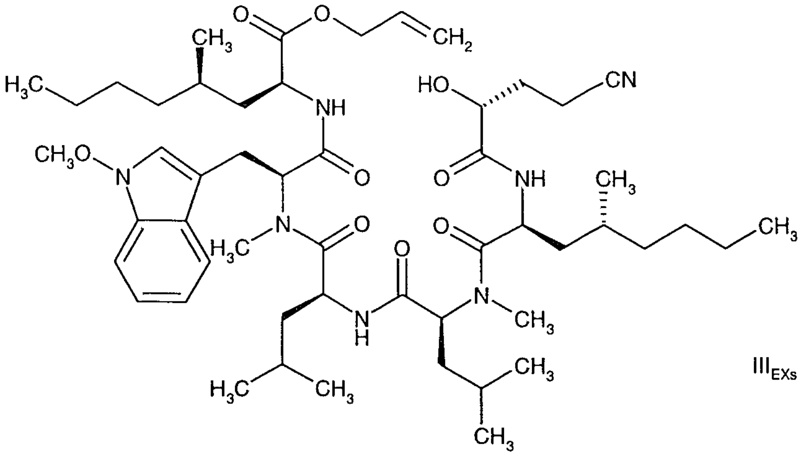
A) Production of a compound of formula



II$_{EXs}$

To a solution of 30 g of a compound of formula I$_{EXs}$ in 300 ml of methanol 6.6 g of $NaBH_4$ are added at 0° and the reaction mixture obtained is warmed up to RT and stirred overnight. To the mixture obtained a mixture of EtAc/c-Hex (1/2) is added and the mixture obtained is stirred with an aqueous NaH_2PO_4 solution for ca. 20 minutes. The phases obtained are separated and the organic layer obtained is dried, the solvent is evaporated off and the evaporation residue obtained is subjected to chromatography. A compound of formula II$_{EXs}$ in the form of a solid is obtained.

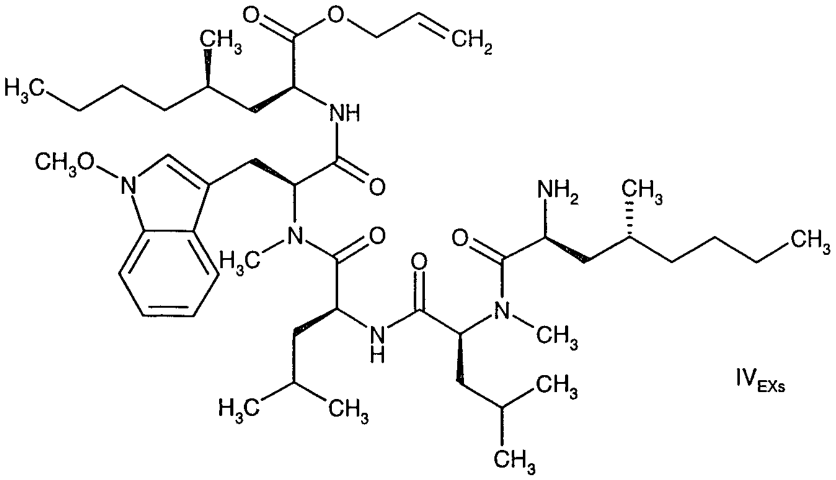
B) Production of a compound of formula



IIIEXs

To a solution of 24 g of a compound of formula II_{EXs} in 150 ml of dry allylic alcohol 8 ml of methanesulfonic acid is added and the mixture obtained is stirred at RT overnight. To the mixture obtained 35 ml of N-methylmorpholine are added, the mixture obtained is stirred for ca. 72 hours at ca. 40°, the solvent is evaporated off and the evaporation residue obtained is subjected to chromatography. A compound of formula III_{EXs} in the form of a mixture of 3 conformers (0.58 : 0.27 : 0.17) is obtained. C^{13}-NMR(125.8 MHz, $CDCl_3$) - only selected signals: 173.641, 173.129, 172.710, 172.515, 171.398, 169.182, 132.234, 131.920, 123.421, 122.885, 122.132, 120.233, 119.308, 118.854, 118.253, 108.608, 106.616, 69.645, 65.602, 61.492, 51.189, 47.184, 40.018, 38.962, 37.233, 36.652, 30.900, 30.512, 29.629, 29.427, 28.939, 28.917, 24.857, 23.695, 22.950, 22.920, 22.827, 22.719, 22.231, 19.309, 18.830, 18.712, 14.055, 13.992, 13.034.

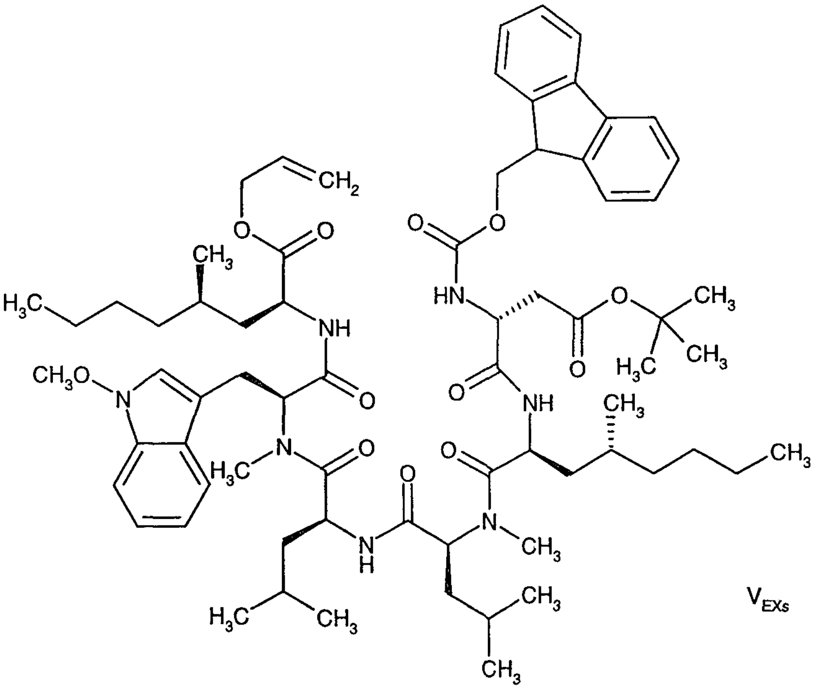
C) Production of a compound of formula



IVEXs

To 14 g of a compound of formula III_{EXs} in 150 ml of CH_2Cl_2, cooled to 0°, 4.86 ml of N-methylmorpholine and 3.44 ml of methanesulfonic acid chloride are added and the reaction mixture obtained is allowed to warm up to RT within ca. 3 hours. To the mixture obtained 200 ml of a mixture of EtAc/c-Hex (1:2) are added and the mixture obtained is extracted with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ solution and brine. The solvent of the organic layer obtained is evaporated off and the evaporation residue obtained is heated with 12.5 g of N-ethylthiourea in 45 ml of dry ethanol under argon atmosphere at ca. 80° for ca. 48 hours. From the mixture obtained the solvent is evaporated off. To the evaporation residue obtained 300 ml of toluene are added and the mixture obtained is extracted with 20% aqueous K_2HPO_4. the organic layer obtained is dried, the solvent is evaporated off and the evaporation residue is subjected to chromatography. A compound of formula IV_{EXs} in the form of an 1 : 2 mixture of 2 conformers is obtained. C^{13}-NMR(125.8 MHz, $CDCl_3$): 172.839, 172.688, 172.611, 172.073, 171.057, 169.974, 169.746, 169.490, 166.823, 166.761, 132.252, 131.978, 131.609, 123.408, 122.907, 122.562, 122.103, 121.527, 120.259, 119.793, 118.828, 118.710, 118.602, 118.408, 118.338, 118.160, 108.625, 108.296, 106.778, 106.570, 76.330, 65.877, 65.566, 61.397, 53.839, 51.113, 50.548, 48.156, 48.031, 47.535, 47.123, 39. 594, 39.364, 39.306, 38.823, 38.668, 37.845, 37.353, 37.307, 36.840, 36.084, 35.404, 28.926, 29.561, 29.503, 29.383, 29.251, 29.081, 29.030, 28.923, 28.272, 28.224, 24.791, 24.736, 24.445, 23.636, 23.452, 23.222, 23.098, 22.965, 22.928, 22.731, 22.663, 21.607, 21.419, 19.114, 19.006, 18.890, 18.852, 18.555, 14.067, 13.982, 12.888, 12.847.

D) Production of a compound of formula



V_{EXs}

2.8 g of a compound of formula IV_{EXs}, 1.51 g of N-(9-fluorenyl-methoxycarbonyl)-D-asparaginic acid mono-tert.butylester and 1.89 g of HATU are dissolved in 30 ml of DMF and 1.71 ml of DIEA are slowly added at ca. 0 ° to the mixture obtained. The mixture obtained is left for ca. 1.5 hours and a mixture of EtAc/ c-Hex (1/2) is added. the mixture obtained is extracted with 1M aqueous HCl, saturated $NaHCO_3$ solution and brine, the solvent is evaported off and the evaporation residue obtained is subjected to chromatography.A compound of formula V_{EXs} is obtained in the form of a solid.

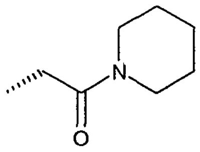
E) Production of a compound of formula IA_s, wherein R_{2s} is methoxy and R_{1s} is a group -CH_2-COOtert.butyl

A compound of formula V_{EXs} is dissolved in a mixture of 60 ml of THF and 232 µl of pyrrolidine. The mixture obtained is stirred at ca. 0° for ca. 3 hours, 1 ml of pyrrolidine is added and the mixture obtained is allowed to warm up to RT overnight. To the mixture obtained a mixture of EtAc/ c-Hex (1/2) is added, the mixture obtained is extracted with 1M aqueous HCl and brine and from the organic layer obtained the solvent is evaporated off. The evaporation residue obtained is dissolved in 1.8 l of acetonitrile, the solution obtained is cooled to 0° and 5.3 g of a coupling reagent (BOP, equivalent to HATU) and 2.6 ml of DIEA are added and the mixture obtained is stirred at RT for ca. 24 hours. From the mixture obtained the solvent is evaporated off, the evaporation residue obtained is dissolved in EtAc, the mixture obtained is extracted with 1M aqueous HCl, saturated $NaHCO_3$ solution and brine, the solvent of the organic layer obtained is evaporated off and the evaporation residue obtained is subjected to chromatography. A compound of formula IA_s wherein R_{2s} is methoxy and R_{1s} is a group -CH_2-COOtert.butyl in the form of a 4:1 mixture of 2 conformers is obtained. C^{13}-NMR(125.8 MHz, d_6-DMSO): 173.077, 172.815, 172.324, 171.752, 169.695, 169.198, 169.151, 132.033, 123.597, 123.302, 122.885, 120.178, 119.170, 108.784, 107.092, 80.286, 66.234, 62.111, 58.539, 52.056, 49.590, 45.544, 27.264, 37.157, 36.883, 36.771, 29.898, 29.230, 29.110, 28.762, 28.024, 25.007, 23.649, 23.369, 22.919, 22.809, 22.742, 21.586, 19.750, 19.400, 19.311, 14.434, 14.305.

F) Production of a compound of formula IA_s, wherein R_{2s} is methoxy and R_{1s} is a group -CH_2-COOH

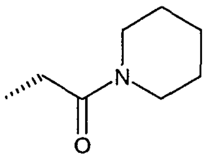
A compound of formula IA_s, wherein R_{2s} is methoxy and R_{1s} is a group -CH_2-COOH is obtained from a compound obtained according to example 85, step E) by treatment with TFA in toluene. H^1-NMR(500 MHz, d_6-DMSO) - selected signals of the major conformation: 8.31 (bs, 1H), 7.92 (bs, 1H), 7.62 (d, J=7.7 Hz, 1H), 7.41 (s, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.07 (d, J=7.5 Hz, 1H), 4.65 (m, 3H), 4.40 (m, 2H), 4.23 (m, 1H), 3.97 (s, 3H), 2.78 (s, 3H), 0.23 (t, 6H).

G) Production of a compound of formula IA$_s$, wherein R$_{2s}$ is methoxy and R$_{1s}$ is a group of



formula

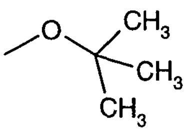
50 mg of compound obtained in example 85, step F) is treated with piperidine and HATU in DMF and to the mixture obtained DIEA is slowly added at ca. 0°. The mixture obtained is left for ca. 1.5 hours and a mixture of EtAc/c-Hex (1/2) is added. The mixture obtained is extracted with 1M aqueous HCl, saturated NaHCO$_3$ solution and brine, the solvent is evaported off and the evaporation residue obtained is subjected to chromatography. A compound of formula IA$_s$, wherein R$_{2s}$ is methoxy and R$_{1s}$ is a group of

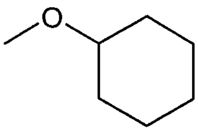


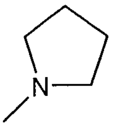
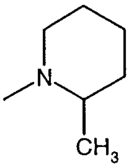
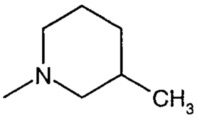
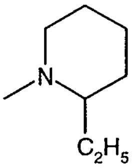
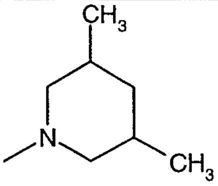
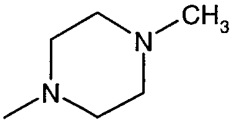
formula is obtained in the form of a mixture of 2 conformers. C^{13}-NMR(125.8 MHz, CDCl$_3$): 172.887, 172.585, 172.099, 171.978, 171.819, 171.610, 170.790, 169.982, 169.381, 169.244, 168.854, 132.323, 123.396, 122.938, 122.023, 120.189, 120.077, 118.859, 118.662, 108.695, 118.616, 71.615, 65.843, 65.677, 62.517, 59.021, 57.996, 52.115, 49.788, 48.984, 48.744, 48.343, 42.947, 40.798, 40.559, 39.769, 38.071, 37.426, 37.368, 37.197, 36.521, 32.499, 30.012, 29.939, 29.909, 29.769, 29.337, 29.270, 29.073, 24.963, 24.456, 24.393, 23.467, 23.022, 22.883, 22.845, 22.784, 22.037, 20.185, 19.970, 18.788, 14.020.

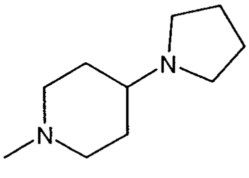
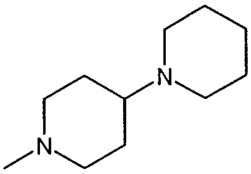
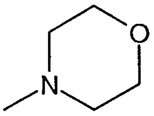
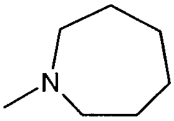
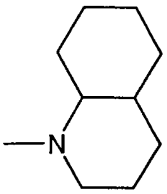
Analogously as described in example 85 but using appropriate starting materials, compounds of formula IA$_{EXAs}$ wherein R$_{EXAs}$ is as defined in TABLE 11 below, are obtained having the ^{1}H-NMR data (500MHz; CDCl$_3$) as shown in TABLE 11:

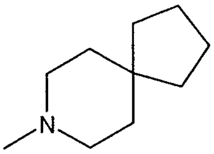
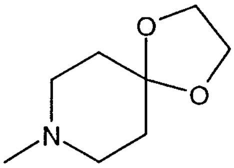
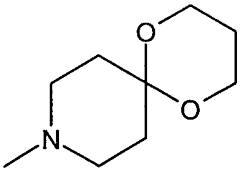
TABLE 11

EX.	R$_{EXAs}$	^{1}H-NMR
86		8.28(d, J= 9.9Hz, 1H), 8.12(d, J= 9.7Hz, 1H), 7.03(s, 1H), 6.23(d, J= 9.5Hz, 1H), 5.91(d, J= 4.4Hz, 1H), 4.49 (dd, J= 10.9, 4.5Hz, 1H),4.28(m, 1H), 4.03(s, 3H), 3.81(dd, J= 15.5, 2.8Hz, 1H), 3.59(q, J= 10.4Hz, 2H),

EX.	R_{EXAs}	^{1}H-NMR
		3.02(dd, J= 15.5, 11.2 Hz, 1H), 2.95(dd, J= 17.2, 3.1Hz, 1H),2.94(s, 3H), 2.56(s, 3H), 2.48(dd, J= 17.2, 4.8Hz, 1H), 0.93 (s, 9H), 0.45(d, J= 6.3Hz, 3H), 0.10(d, J= 6.4Hz, 3H), -0.34(m, 1H).
87		8.41 (d, J= 9.7Hz, 1H), 8.30(d, J= 9.4Hz, 1H), 7.04(s, 1H), 6.46(d, J= 8.5Hz, 1H), 5.94(d, J= 3.8Hz, 1H), 5.36(d, J= 8.3 Hz, 1H), 4.36(m, 1H), 4.32(dd, J= 10.7, 4.1Hz, 1H), 4.03(s, 3H), 3.83(dd, J= 15.5, 3.1Hz, 1H), 3.03(dd, J= 15.5, 11.0Hz, 1H), 2.95(s, 3H), 2.68(dd, J= 15.4, 3.9Hz, 1H), 2.59(s, 3H), 2.35(dd, J= 15.4, 3.9Hz, 1H), 0.41(d, J= 6.6Hz, 3H), 0.22(d, J= 6.5Hz, 3H), -0.22(m, 1H).
88	$-N(CH_3)_2$	8.39(d, J= 10.0Hz, 1H), 8.32(d, J= 9.6Hz, 1H), 7.03(s, 1H), 6.49(d, J= 8.0Hz, 1H), 5.94(d, J= 3.6Hz, 1H), 4.42(dd, J= 10.6, 4.3Hz, 1H), 4.26(m, 1H), 4.03(s, 3H), 3.83(dd, J= 15.5, 2.8Hz, 1H), 3.15(dd, J= 16.6, 3.1Hz, 1H), 3.01(dd, J= 15.5, 11.2Hz, 1H), 2.97(s, 3H), 2.94(s, 3H), 2.72(s, 3H), 2.61(s, 3H), 2.34(dd, J= 16.6, 4.5Hz, 1H), 0.40(d, J= 6.3Hz, 3H), 0.13(d, J= 6.4Hz, 3H), -0.30(m, 1H).
89	$-NH-C(CH_3)_3$	8.37(d, J= 9.9Hz, 1H),8.26(d, J= 9.4Hz, 1H),7.05(s, 1H), 6.42(d, J= 8.6Hz, 1H),6.06(d, J= 3.8Hz, 1H), 5.38(s, 1H), 4.36(dd, J= 10.3, 3.5Hz, 1H), 4.30(m, 1H), 4.03(s, 3H), 3.80(dd, J= 15.5, 3.2Hz, 1H), 3.04(dd, J= 15.5, 10.9Hz, 1H), 2.94(s, 3H), 2.63(dd, J= 15.5, 4.1Hz, 1H), 2.60(s, 3H), 2.33(dd, J= 15.5, 4.3Hz, 1H), 1.23(s, 3H), 0.42(d, J= 6.5Hz, 3H), 0.20(d, J= 6.5Hz, 3H), -0.04(m, 1H).
90	$-N(CH_3)(OCH_3)$	8.36(d, J= 9.3Hz, 1H),7.03(s, 1H), 6.40(d, J= 8.7Hz, 1H), 5.88(d, J= 3.8Hz, 1H), 4.46(dd, J= 11.0, 4.5Hz, 1H), 4.29(m, 1H), 4.03(s, 3H), 3.81(dd, J= 15.4, 2.9Hz, 1H), 3.71(s, 3H), 3.28(bd, 1H), 3.01(dd, J= 15.4, 11.2Hz, 1H), 3.00(s, 3H), 2.93(s, 3H), 2.59(s, 3H), 2.42(dd, J= 17.5, 4.8Hz, 1H), 0.41(d, J= 6.3Hz, 3H), 0.11(d, J= 6.3Hz,

EX.	R_{EXAs}	^{1}H-NMR
		3H), -0.34(m, 1H).
91		8.52(d, J= 8.4Hz, 1H), 8.45(d, J= 9.8Hz, 1H),7.03(s, 1H), 6.45(d, J= 8.4Hz, 1H), 5.90(d, J= 3.6Hz, 1H), 4.43(dd, J= 10.8, 4.4Hz, 1H), 4.36(m, 1H), 4.03(s, 3H), 3.83(dd, J= 15.5, 2.9Hz, 1H), 3.48-3.09 (series of m, 4H), 2.94(s, 3H), 2.60(s, 3H), 2.33(dd, J= 15.4, 4.2Hz, 1H), 0.42(d, J= 6.4Hz, 3H), 0.13(d, J= 6.4Hz, 3H), -0.28(m, 1H).
92		7.03(s, 1H), 6.52(d, J= 7.6Hz, 1H), 5.95(bs, 1H), 4.02(s, 3H), 3.02(dd, J= 15.4, 11.2Hz, 1H), 2.95(s, 3H), 2.62(s, 3H), 0.41(d, J= 5.8Hz, 3H), 0.13(d, J= 6.3Hz, 3H), -0.31(m, 1H). Mixture of isomers
93		8.52(d, J= 9.2Hz, 1H), 8.39(d, J= 9.9Hz, 1H), 7.03(s, 1H), 6.51(bs, 1H), 5.99(bs, 1H), 4.42(m, 1H), 4.23(m, 1H), 4.02(s, 3H), 3.82(bd, J= 16.2Hz, 1H), 3.21(dd, J= 16.3, 3.4Hz, 1H), 3.01(dd, J= 16.2, 9.9Hz, 1H), 2.95(s, 3H), 2.62(s, 3H), 2.36(m, 1H), 0.39(d, J= 6.4Hz, 3H), 0.14(bs, 3H), -0.33(m, 1H).Mixture of isomers
94		8.38(d, J= 10.4Hz, 1H), 7.03(s, 1H), 6.53(m, 1H), 6.00(m, 1H), 4.41(m, 1H), 4.24(m, 1H), 4.02(s, 3H), 3.83(m, 1H), 3.32(m, 1H), 3.02(m, 1H), 2.94(s, 3H), 2.62(s, 3H), 0.41(d, J= 6.5Hz, 3H), 0.13(d, J= 6.5Hz, 3H), -0.31(m, 1H). Mixture of isomers
95		7.03(s, 1H), 6.49(d, J= 8.0Hz, 1H), 5.98(d, J= 4.0Hz, 1H), 4.03(s, 3H), 3.83(dd, J= 15.5, 2.7Hz, 1H), 3.22(dd, J= 16.5, 3.1Hz, 1H), 3.02(dd, J= 16.5, 12.1Hz, 1H), 2.95(s, 3H), 2.62(s, 3H), 0.41(d, J= 6.4Hz, 3H), 0.18(d, J= 6.4Hz, 3H), -0.24(m, 1H). Mixture of isomers
96		8.31(bs, 1H), 8.23(d, J= 10.0Hz, 1H), 7.03(s, 1H), 6.45(bs, 1H), 5.95(d, J= 3.8Hz, 1H), 4.42(dd, J= 10.6, 4.5Hz, 1H), 4.23(m, 1H), 4.03(s, 3H), 3.82(dd, J= 15.5, 2.8Hz, 1H), 3.01(dd, J= 15.5, 11.2Hz, 1H), 2.94(s, 3H), 2.61(s, 3H), 0.40(d, J= 6.4Hz, 3H), 0.10(d, J= 6.4Hz, 3H), -0.34(m, 1H).

EX.	R_{EXAs}	^{1}H-NMR
97		8.31(d, J= 9.5Hz, 1H), 8.18(d, J= 9.3Hz, 1H), 7.03(s, 1H), 6.41(d, J= 7.5Hz, 1H), 5.96(d, J= 3.8Hz, 1H), 4.39(dd, J= 10.5, 4.5Hz, 1H), 4.29(bd, J= 11.1Hz, 1H), 4.03(s, 3H), 3.83(dd, J= 15.4, 2.8Hz, 1H), 3.11(bd, J= 11.1Hz, 1H), 3.01(dd, J= 15.5, 10.5Hz, 1H), 2.94(s, 3H), 2.61(s, 3H), 0.39(d, J= 6.3Hz, 3H), 0.13(d, J= 6.4Hz, 3H), -0.35(m, 1H).
98		7.03(s, 1H), 6.44(d, J= 7.9Hz, 1H), 5.97(bs, 1H), 4.38(dd, J= 10.0, 4.0Hz, 1H), 4.20(m, 1H), 4.03(s, 3H), 3.83(dd, J= 15.4, 2.8Hz, 1H), 3.28(bd, J= 14.2Hz, 1H), 2.99(dd, J= 15.5, 11.2Hz, 1H), 2.94(s, 3H), 2.62(s, 3H), 2.38(dd, J= 16.3, 4.2Hz, 1H), 0.39(d, J= 6.3Hz, 3H), 0.11(d, J= 6.3Hz, 3H), -0.34(m, 1H).
99		8.33(d, J= 10.0Hz, 1H), 8.26(d, J= 9.5Hz, 1H), 7.03(s, 1H), 6.46(d, J= 8.2Hz, 1H), 5.93(d, J= 3.9Hz, 1H), 4.42(dd, J= 10.6, 4.5Hz, 1H), 4.21(m, 1H), 4.03(s, 3H), 3.83(dd, J= 15.4, 3.1Hz, 1H), 3.75-3.61 (m, 4H), 3.49-3.27 (m, 4H), 3.13(dd, J= 16.5, 3.2Hz, 1H), 3.01(dd, J= 15.4, 11.1Hz, 1H), 2.94(s, 3H), 2.61(s, 3H), 2.34(dd, J= 15.4, 4.2Hz, 1H), 0.40(d, J= 6.4Hz, 3H), 0.08(d, J= 6.4Hz, 3H), -0.35(m, 1H).
100		8.27(d, J= 9.5Hz, 1H), 7.03(s, 1H),6.49(d, J= 7.8Hz, 1H), 5.98(d, J= 3.5Hz, 1H),4.39(dd, J= 10.7, 4.3Hz, 1H), 4.25 (m, 1H), 4.03(s, 3H), 3.81(dd, J= 15.4, 2.9Hz, 1H), 3.20 (dd, J= 16.5, 3.8Hz, 1H), 3.02(dd, J= 15.5, 11.1Hz, 1H), 2.95(s, 3H),2.61(s, 3H),2.36(dd, J= 16.5,4.4Hz,1H), 0.41 (d, J= 6.4Hz, 3H), 0.14(d, J= 6.5Hz, 3H), -0.27(m, 1H).
101		7.03(s, 1H), 6.48(d, J= 7.7Hz, 1H), 5.93(bs, 1H), 4.24(m, 1H), 4.03(s, 3H), 3.82(m, 1H), 3.02(m, 1H), 2.94(s, 3H), 2.1(s, 3H), 0.39(d, J= 6.4Hz, 3H), 0.13(d, J= 6.4Hz, 3H), -0.34(m, 1H). Mixture of isomers

EX.	R_{EXAs}	^{1}H-NMR
102		8.40 (d, J=9.9 Hz, 1H), 8.27 (d, J=9.5 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 7.41 (d, J=8.2 Hz, 1H), 7.25 (t, J=8.1 Hz, 1H), 7.07 (d, J=8.1 Hz, 1H), 7.03 (s, 1H), 6.50 (d, J=7.9 Hz, 1H), 5.95 (d, J=3.6 Hz, 1H), 4.42 (dd, J=10.4, 4.5 Hz, 1H), 4.03 (s, 3H), 3.82 (dd, J=15.4, 2.9 Hz, 1H), 3.19 (dd, J=16.5, 3.2 Hz, 1H), 3.02 (dd, J=15.4, 11.2 Hz, 1H), 2.94 (s, 3H), 2.62 (s, 3H), 2.34 (dd, J=16.5, 4.5 Hz, 1H), 0.39 (d, J=6.5 Hz, 3H), 0.13 (d, J=6.5 Hz, 3H), -0.33 (m, 1H).1:2 mixture of 2 conformers
103		8.25(d, J= 9.5Hz, 1H),7.03(s, 1H), 6.48(d, J= 8.0Hz, 1H), 5.96(d, J= 3.7Hz, 1H),4.42(dd, J= 10.5, 4.5Hz, 1H), 4.21 (bd, J= 11.6 Hz, 1H), 4.02(s, 3H), 3.99(m, 4H), 3.82(dd, J= 15.5, 2.8Hz, 1H), 3.56-3.33(m, 4H), 3.20(dd, J= 16.4, 3.2 Hz, 1H), 3.01(dd, J= 15.5, 11.2 Hz, 1H), 2.94(s, 3H), 2.61(s, 3H), 2.36(dd, J= 16.4, 4.5Hz, 1H), 0.39(d, J= 6.3Hz, 3H), 0.11(d, J= 6.4Hz, 3H), -0.36(m, 1H).
104		8.27(d, J= 9.5Hz, 1H), 7.03(s, 1H), 6.48(d, J= 8.0Hz, 1H), 5.95(d, J= 3.8Hz, 1H), 4.42(dd, J= 10.5, 4.5Hz, 1H), 4.22(m, 1H), 4.02(s, 3H), 3.96-3.86(m, 4H), 3.82(dd, J= 15.5, 2.8Hz, 1H), 3.48-3.29(m, 4H), 3.19(dd, J= 16.5, 3.2 Hz, 1H), 3.01(dd, J= 15.5, 11.2 Hz, 1H), 2.94(s, 3H), 2.61(s, 3H), 2.35(dd, J= 16.5, 4.6Hz, 1H), 0.39(d, J= 6.3Hz, 3H), 0.11(d, J= 6.4Hz, 3H), -0.34(m, 1H).

Patent Claims

1. The use of inhibitors of adhesion molecule expression in the preparation of a medicament for the treatment of vascular endothelial cell growth factor-mediated diseases.

2. The use according to claim 1, wherein an inhibitor of adhesion molecule expression is a cyclopeptolide or a cyclopeptide.

3. The use according to claim 2, wherein a cyclopeptolide is a compound of formula

$$\underline{\text{A - B - R}_1\text{Leu - Leu - Z - X - Y}} \qquad \text{I}$$

wherein:

A is

- a glycolic acid residue optionally α-substituted by methyl or vinyl, optionally substituted by
  - halogen,alkoxy, optionally protected hydroxy or amino, $CSNH_2$, vinyl, -C≡CH, thiazolyl or $COOR_2$, wherein R_2 is H or lower alkyl, optionally substituted by
    - alkyl, halogen, cycloalkyl, optionally substituted thiazolyl, -C≡CH or $COOR_2$ wherein R_2 is as defined above;
- an α-hydroxy-substituted butyric or valeric acid residue β-substituted by
  - halogen, alkoxy, optionally protected hydroxy or amino, $CSNH_2$, vinyl, -C≡CH, thiazolyl or $COOR_2$, wherein R_2 is H or lower alkyl, optionally substituted by
    - alkyl, halogen, cycloalkyl, optionally substituted thiazolyl, -C≡CH or $COOR_2$, wherein R_2 is as defined above; or
- an α-hydroxy-substituted butyric acid residue optionally γ-substituted by R_6, wherein R_6 is
  - CN, $COOR_3$, wherein R_3 is hydrogen or optionally arylsubstituted alkyl, $CONR_4R_5$, wherein R_4 and R_5 are the same or different and represent hydrogen or alkyl or form together with the nitrogen to which they are attached a 3- to 6-membered ring, optionally containing a second heteroatom, COR_7, wherein R_7 is hydrogen or lower alkyl, $CSNH_2$, or alkyl, optionally substituted by
    - azido, halogen, alkoxy, optionally protected hydroxy or amino, $CSNH_2$, thiazolyl, vinyl, which may be substituted by alkyl, halogen or CN, cycloalkyl, tetrazolyl, -C≡CH, or $COOR'_2$, wherein R'_2 is hydrogen or lower alkyl, optionally substituted by alkyl,

halogen, cycloalkyl, optionally substituted thiazolyl, -C≡CH or COOR"$_2$, wherein R"$_2$ is hydrogen or lower alkyl,

B is an α-amino-γ-methyl-substituted octanoic acid residue;

R_1 is hydrogen or methyl;

Z is a tryptophan residue,

X is an α–amino-substituted (C_{2-14})carboxylic acid residue, and

Y is an α-amino- or N-methyl-α-amino substituted (C_{2-10})carboxylic acid residue.

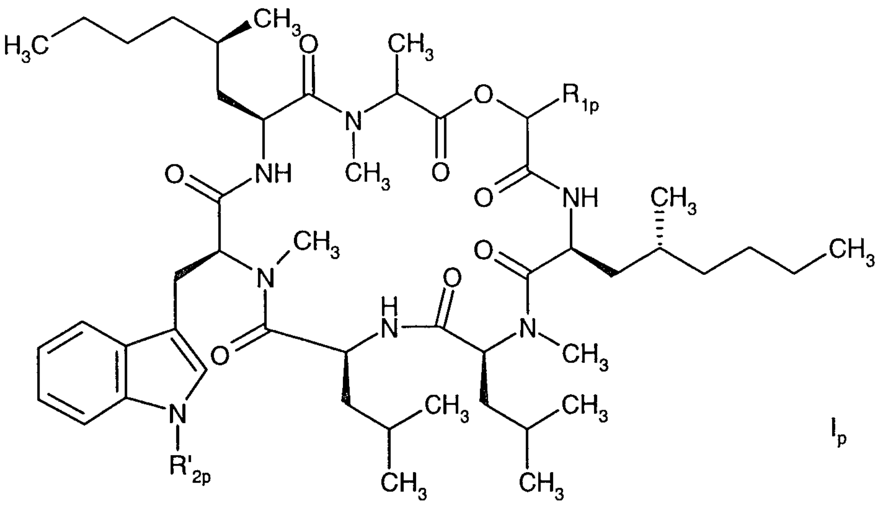
4. The use according to any one of claims 2 to 3, wherein a cyclopeptolide or cyclopeptide is of formula I_p or I_r or I_s as defined in claims 8 to 10.

5. The use according to any preceding claim, wherein the vascular endothelial cell growth factor-mediated disease is selected from
   - eye diseases involving vision impairment or loss,
   - arteriosclerosis associated with chronic transplant rejection and coronary heart disease,
   - solid tumor malignancies and other cancers, or
   - psoriasis, rheumatoid arthritis.

6. The use according to any preceding claim, wherein the vascular endothelial cell growth factor-mediated diseases are selected from eye diseases leading to vision impairment or loss.

7. The use according to claim 6, wherein eye diseases leading to vision impairment or loss are selected from ischemic retinopathies, uveoretinitis and degenerative eye diseases.

8. A compound of formula

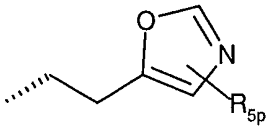


I_p

wherein

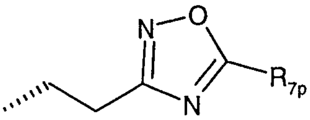
R_{1p} is selected from the group

- $-CH_2-CH_2-COO-R_{2p}$, wherein R_{2p} is alkyl,
- $-CH_2-CH_2-CO-CH_2-O-R_{3p}$, wherein R_{3p} is alkyl, cycloalkyl, alkoxyalkyl, hydroxyalkyl or acyloxyalkyl,
- $-CH_2-CH_2-COO-CH_2-O-CO-R_{4p}$, wherein R_{4p} is alkyl,
- of formula



wherein R_{5p} is hydrogen or a substitutent,

- $-CH_2-CH_2-C(=N-R_{6p})NH_2$, wherein R_{6p} is hydrogen or a substituent,
- a group of formula



wherein R_{7p} is hydrogen or a substitutent, and

R'_{2p} is hydrogen, alkyl, alkoxy or aralkyl.

9. A compund of formula

$$\boxed{A_r\text{-}B_r\text{-Leu*-Leu-}D_r\text{-}X_r\text{-}Y_r} \qquad I_r$$

wherein

A_r is a glycolic acid residue,

B_r is an α-amino-γ-methyl-substituted octanoic acid residue;

Leu* is leucin or N-methyl leucin, preferably N-methyl leucin,

Leu is leucin;

D_r is a tryptophan residue,

X_r is an α-amino-substituted (C_{2-14})carboxylic acid residue, and

Y_r is an α-amino- or N-methyl-α-amino substituted (C_{2-10})-carboxylic acid residue wherein position α is trisubstituted.

10. A compound of formula

$$\boxed{A_s\text{-}B_s\text{-Leu*-Leu-}D_s\text{-}X_s} \qquad I_s$$

wherein

A_s is an α-amino carboxylic acid residue;

B_s is an α-amino-γ-methyl-substituted octanoic acid residue;

Leu* is leucin or N-methyl leucin, preferably N-methyl leucin,

Leu is leucin;

D_s is a tryptophan residue, and

X_s is an α-amino-carboxylic acid residue.

11. A compound of formula I_p, I_r, or I_s as defined in claims 8 to 10, in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate.

12. Use of a compound of formula I_p, I_r or I_s defined in claims 8 to 11, as a pharmaceutical.

13. Pharmaceutical composition comprising a compound of formula I_p, I_r or I_s, as defined in claims 8 to 11, beside one or more pharmaceutically acceptable carriers, diluents and/or excipients.

14. A method for the treatment of diseases which are mediated by expression of adhesion molecules and/or by expression of the growth factor VEGF, which comprises administering a pharmaceutically effective amount of a compound of formula I_p, I_r or I_s, as defined in claims 8 to 11, to a subject in need of such treatment.