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Description

The invention relates to novel compounds of the formula I which inhibit the enzyme TAFIa (activated thrombin-activatable fibrinolysis inhibitor), to process for their preparation and to the use thereof as medicaments.

The enzyme TAFIa is produced for example through thrombin activation from the thrombin-activatable fibrinolysis inhibitor zymogen (TAFI). The enzyme TAFI is also referred to as plasma procarboxypeptidase B, procarboxypeptidase U or procarboxypeptidase R and is a proenzyme similar to carboxypeptidase B (L. Bajzar, Arterioscler. Thromb. Vasc. Biol. 2000, pages 2511 – 2518).

During formation of a clot, thrombin is generated as the final product of the coagulation cascade and induces conversion of soluble plasma fibrinogen to an insoluble fibrin matrix. At the same time, thrombin activates the endogenous fibrinolysis inhibitor TAFI. Activated TAFI (TAFIa) is thus produced during thrombus formation and lysis from the zymogen TAFI through the action of thrombin; thrombomodulin in a complex with thrombin increases this effect about 1250-fold. TAFIa cleaves basic amino acids at the carboxy end of fibrin fragments. The loss of carboxy-terminal lysines as binding sites for plasminogen then leads to inhibition of fibrinolysis. Efficient inhibitors of TAFIa prevent the loss of these high-affinity lysine binding sites for plasminogen and, in this way, assist endogenous fibrinolysis by plasmin: TAFIa inhibitors have profibrinolytic effects.

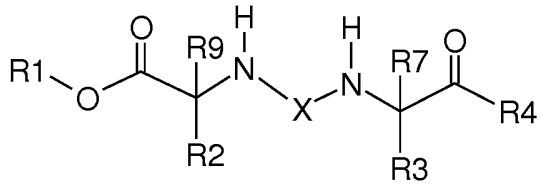
In order to maintain hemostasis in the blood, mechanisms which lead to the clotting of blood and to the breaking up of clots have developed; these are in equilibrium. If a disturbed equilibrium favors coagulation, fibrin is produced in larger quantities, so that pathological processes of thrombus formation may lead to serious pathological states in humans.

Just like excessive coagulation may lead to serious pathological states caused by thrombosis, an antithrombotic treatment entails the risk of unwanted bleeding through disturbance of the formation of a necessary hemostatic plug. Inhibition of TAFIa increases endogenous fibrinolysis - without influencing coagulation and platelet aggregation - i.e. the disturbed equilibrium is shifted in favor of fibrinolysis. It is thus possible both to counter the buildup of a clinically relevant thrombus, and to increase the lysis of a pre-existing clot. On the other hand, buildup of a hemostatic plug is not impaired, so that a hemorrhagic diathesis is probably not to be expected (Bouma et al., J. Thrombosis and Haemostasis, 1, 2003, pages 1566 - 1574).

Inhibitors of TAFIa have previously been described in the international application WO2005/105781.

The TAFIa inhibitors of the invention are suitable for a prophylactic and for a therapeutic use in humans suffering from disorders associated with thromboses, embolisms, hypercoagulability or fibrotic changes. They can be employed for secondary prevention and are suitable both for acute and for long-term therapy.

The invention therefore relates to the compound of the formula I



(I)

and/or a stereoisomeric form of the compound of the formula I and/or mixtures of these forms in any ratio, and/or a physiologically tolerated salt of the compound of the formula I, where

X is -S(O)2-,

R1 is 1) hydrogen atom,

2) -(C1-C6)-alkyl,

3) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl or

4) -(C1-C6)-alkylene-(C6-C14)-aryl,

R2 is a radical of the formula II

-(A1)m-A2 (II)

in which

m is the integer zero or 1,

A1 is 1) -(CH2)n- in which n is the integer zero, 1, 2 or 3,

2) -NH-(CH2)n- in which n is the integer zero, 1, 2 or 3,

3) -NH(C1-C6)-alkyl)-(CH2)n- in which n is the integer zero, 1, 2 or 3,

4) -NH((C3-C6)-cycloalkyl)-(CH2)n- in which n is the integer zero, 1, 2 or 3,

5) -O-(CH2)n- in which n is the integer zero, 1, 2 or 3, or

6) -(CH2)n-SOx- in which n is the integer zero 1, 2 or 3 and x is the integer zero, 1 or 2

A2 is 1) Het, where Het means a 4- to 15-membered heterocyclic ring system having 4 to 15 ring atoms which are present in one, two or three ring systems connected together, and which comprise one, two, three or four identical or different heteroatoms from the series oxygen, nitrogen or sulfur, and are unsubstituted or substituted independently of one another once, twice or three times by -(C1-C3)-alkyl, halogen, -NH2,

-CF3 or -O-CF3,

2) -(C0-C6)-alkylene-NH2 ,

3) -(C1-C6)-alkylene-NH-C(=NH)-NH2,

4) -(C1-C6)-alkylene-NH-C(=NH)-(C1-C4)-alkyl,

5) -(C0-C4)-alkylene-O-NH-C(=NH)-NH2,

6) -(C0-C4)-alkylene-NH-C(O)-(C1-C6)-alkyl,

7) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-aryl, where aryl is unsubstituted or substituted by -NH2 or is substituted by -NH2 and once, twice or three times by R15,

8) -(C3-C8)-cycloalkyl-NH2, or

9) -(C0-C4)-alkylene-(C6-C14)-aryl, where aryl is unsubstituted or substituted by -NH2 or is substituted by -NH2 and once, twice or three times by R15,

R3 is 1) -(C1-C6)-alkyl,

2) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl,

3) -(C1-C6)-alkylene-(C6-C14)-aryl, where aryl is substituted independently of one another once, twice or three times by R15,
4) -(C0-C8)-alkylene-N(R5)-PG,
5) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-aryl, where aryl is substituted independently of one another once, twice or three times by R15,
6) -(C0-C4)-alkylene-(C6-C14)-aryl-(C0-C4)-alkylene-N(R5)-PG,
7) -(C0-C8)-alkylene-O-PG,
8) -(C0-C4)-alkylene-(C6-C14)-aryl-(C0-C4)-alkylene-O-PG,
9) -(C0-C8)-alkylene-C(O)-O-PG,
10) -(C0-C4)-alkylene-(C6-C14)-aryl-(C0-C4)-alkylene-C(O)-O-PG or
11) hydrogen atom,

R4 is -N(R6)2,

where R6 are identical or different and are independently of one another

1) hydrogen atom,
2) -(C1-C6)-alkyl,
3) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by R11, halogen, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or -O-(C1-C4)-alkyl,
4) -(C0-C6)-alkylene-(C6-C14)-aryl, where aryl and alkylene are unsubstituted or substituted independently of one another once, twice, three or four times by R11, halogen, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11, -C(O)-N(R8)2 or -O-(C1-C4)-alkyl,
5) -(C0-C8)-alkylene-N(R5)-PG,
6) -(C0-C4)-alkylene-(C6-C14)-aryl-(C0-C4)-alkyl-N(R5)-PG,
7) -(C0-C8)-alkylene-O-PG,
8) -(C0-C4)-alkylene-(C6-C14)-aryl-(C0-C4)-alkyl-O-PG,
9) -(C0-C8)-alkylene-C(O)-O-R11,
10) -(C0-C4)-alkylene-(C6-C14)-aryl-(C0-C4)-alkyl-C(O)-O-PG,
11) -(C0-C4)-alkylene-Het, where Het means a 4- to 15-membered heterocyclic ring system having 4 to 15 ring atoms

which are present in one, two or three ring systems connected together, and which comprise one, two, three or four identical or different heteroatoms from the series oxygen, nitrogen or sulfur, where Het or alkylene are unsubstituted or substituted independently of one another once, twice or three times by R11, halogen, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or -O-(C1-C4)-alkyl,

12) -(C1-C3)-fluoroalkyl,

13) -(C0-C4)-alkylene-CH(R11)-C(O)-NH2,

14) -(C0-C4)-alkylene-CH(R11)-C(O)-NH-(C1-C4)-alkyl, or

15) -(C0-C4)-alkylene-CH(R11)-C(O)-NH-CH(R12)-R13,

or the two R6 radicals form together with the N atom to which they are bonded a mono- or bicyclic ring having 4 to 9 ring atoms which is saturated, partly saturated or aromatic, where the ring is unsubstituted or substituted once or twice by -(C1-C4)-alkyl, -C(O)-O-R11, halogen, -(C1-C4)-alkyl-O-R11 or phenyl,

R5 is hydrogen atom or-(C1-C6)-alkyl,

PG is a protective group for the amino, carboxyl or for the hydroxy function,

R7 is hydrogen atom or -(C1-C6)-alkyl,

R8 is hydrogen atom or -(C1-C6)-alkyl,

R9 is hydrogen atom or -(C1-C6)-alkyl,

R11 and R12 are identical or different and are independently of one another

1) hydrogen atom,

2) -(C1-C6)-alkyl,

3) -(C0-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted independently of one another once, twice or three times by halogen, -OH or

-O-(C1-C4)-alkyl,

4) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by R13, halogen, -C(O)-O-R13, -(C1-C4)-alkyl-O-R13,

-O-(C1-C4)-alkyl or -(C0-C4)-alkylene-phenyl,

5) -(C0-C4)-alkylene-C(O)-N(R13)2 or

6) -(C0-C4)-alkylene-indolyl,

R13 is 1) hydrogen atom,
2) -(C1-C4)-alkyl,
3) -(C0-C4)-alkylene-C(O)-O-R14,
4) -(C0-C4)-alkylene-C(O)-R14 or
5) -(C0-C4)-alkylene-O-R14,
R14 is hydrogen atom, -(C1-C4)-alkyl, -NH2 or -OH, and
R15 is hydrogen atom, -(C1-C4)-alkyl, -O-CF3, -NH2, -OH, -CF3 or halogen.

The invention further relates to the compound of the formula I where
X is -S(O)2-,
R1 is 1) hydrogen atom or
2) -(C1-C4)-alkyl,
R2 is 1) -(C1-C6)-alkylene-NH2,
2) -(C0-C4)-alkylene-pyridyl-NH2,
3) -(C0-C4)-alkylene-piperidinyl-NH2,
4) -(C0-C4)-alkylene-thiazolyl-NH2,
5) -(C1-C6)-alkylene-NH-C(=NH)-NH2,
6) -(C0-C4)-alkylene-(C3-C8)-cycloalkyl-NH2,
7) -(C1-C6)-alkylene-NH-C(=NH)-(C1-C4)-alkyl,
8) -(C0-C4)-alkylene-O-NH-C(=NH)-NH2,
9) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-aryl, where aryl is unsubstituted or substituted by -NH2 or is substituted by -NH2 and once, twice or three times by R15,
10) -(C0-C4)-alkylene-NH-C(O)-(C1-C4)-alkyl
11) -(C0-C4)-alkylene-(C6-C14)-aryl, where aryl is unsubstituted or substituted by -NH2 or is substituted by -NH2 and once, twice or three times by R15, or
12) -(C1-C4)-alkylene-SOx-(C1-C4)-alkylene-NH2 in which x is the integer zero, 1 or 2
R3 is 1) -(C1-C4)-alkyl,
2) -(C0-C4)-alkylene-(C3-C8)-cycloalkyl,
3) -(C1-C6)-alkylene-aryl, where aryl is substituted independently of one another once, twice or three times by R15,
4) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-aryl, where aryl is substituted independently of one another once, twice

or three times by R15,
5) -(C1-C6)-alkylene-NH-PG,
6) -(C1-C6)-alkylene-O-PG,
7) -(C1-C6)-alkyl, or
8) hydrogen atom,
where PG is t-butyl-, t-butyloxycarbonyl or benzyloxycarbonyl,
R4 is -N(R6)2,
where R6 are identical or different and are independently of one another
1) hydrogen atom,
2) -(C1-C6)-alkyl,
3) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by R11, halogen, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or
-O-(C1-C4)-alkyl,
4) -(C0-C4)-alkylene-C(R11)(R12)-(C3-C12)-cycloalkyl, where cycloalkyl is unsubstituted or substituted independently of one another once, twice or three times by R11, halogen, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or
-O-(C1-C4)-alkyl,
5) -(C0-C4)-alkylene-Het, where Het means a 4- to 15-membered heterocyclic ring system having 4 to 15 ring atoms which are present in one, two or three ring systems connected together, and which comprise one, two, three or four identical or different heteratoms from the series oxygen, nitrogen or sulfur, where Het or alkylene are unsubstituted or substituted independently of one another once, twice or three times by R11, halogen, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or -O-(C1-C4)-alkyl,
6) -(C0-C6)-alkylene-aryl, where aryl or alkylene is unsubstituted or substituted independently of one another once, twice or three times by R11, halogen, -C(O)-O-R11, -(C0-C4)-alkyl-O-R11 or -O-(C1-C4)-alkyl,
7) -(C0-C4)-alkylene-C(R11)(R12)-aryl, where aryl or alkylene is unsubstituted or substituted independently of one another once, twice or three times by R11, halogen, -C(O)-O-R11, -(C0-C4)-alkyl-O-R11 or -O-(C1-C4)-alkyl,

8) 1,2,3,4-tetrahydronaphthalenyl,
9) -(C0-C4)-alkylene-CH(R11)-C(O)-NH2,
10) -(C0-C4)-alkylene-CH(R11)-C(O)-NH-(C1-C4)-alkyl,
11) -(C0-C4)-alkylene-CH(R11)-C(O)-NH-CH(R12)-R13,
12) -(C0-C6)-alkylene-C(O)-O-R11, where alkylene is unsubstituted or substituted independently of one another once or twice by R11, halogen,
-C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or -O-(C1-C4)-alkyl,
13) -(C0-C4)-alkylene-C(R11)(R12)-C(O)-O-R11, or
14) -(C1-C3)-fluoroalkyl,
or the two R6 radicals form together with the N atom to which they are bonded a mono- or bicyclic ring having 4 to 9 ring atoms which is saturated, partly saturated or aromatic, where the ring is unsubstituted or substituted once or twice by -(C1-C4)-alkyl, -C(O)-O-R11, halogen, -(C1-C4)-alkyl-O-R11 or phenyl,
R7 is hydrogen atom or -(C1-C4)-alkyl,
R9 is hydrogen atom or -(C1-C4)-alkyl,
R11 and R12 are identical or different and are independently of one another
1) hydrogen atom,
2) -(C1-C4)-alkyl,
3) -(C0-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted independently of one another once, twice or three times by halogen, -OH or
-O-(C1-C4)-alkyl,
4) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by R13, halogen, -C(O)-O-R13,
-(C1-C4)-alkyl-O-R13,
-O-(C1-C4)-alkyl or -(C0-C4)-alkylene-phenyl,
5) -(C0-C4)-alkylene-C(O)-N(R13)2 or
6) -(C0-C4)-alkylene-indolyl,
R13 is 1) hydrogen atom,
2) -(C1-C4)-alkyl,
3) -(C0-C4)-alkylene-C(O)-O-R14,
4) -(C0-C4)-alkylene-C(O)-R14 or
5) -(C0-C4)-alkylene-O-R14,

R14 is hydrogen atom, -(C1-C4)-alkyl, -NH2 or -OH, and
R15 is hydrogen atom, -(C1-C4)-alkyl, -O-CF3, -NH2, -OH, -CF3 or halogen.

The invention further relates to the compound of the formula I where
X is -S(O)2-,
R1 is 1) hydrogen atom or
2) -(C1-C4)-alkyl,
R2 is 1) -(C1-C6)-alkylene-NH2,
2) -(C1-C4)-alkylene-pyridyl-NH2,
3) -(C1-C4)-alkylene-piperidinyl-NH2,
4) -(C1-C6)-alkylene-NH-C(=NH)-NH2,
5) -(C0-C4)-alkylene-(C3-C6)-cycloalkyl-NH2,
6) -(C1-C6)-alkylene-NH-C(=NH)-(C1-C4)-alkyl,
7) -(C1-C4)-alkylene-O-NH-C(=NH)-NH2,
8) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted by -NH2 or is substituted by -NH2 and once, twice or three times by R15,
9) -(C1-C4)-alkylene-NH-C(O)-(C1-C6)-alkyl,
10) -(C1-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted by $-NH_2$ or is substituted by $-NH_2$ and once, twice or three times by R15,
11) -(C1-C4)-alkylene-SO2-(C1-C4)-alkylene-NH2 or
12) -(C1-C4)-alkylene-S-(C_1-C_4)-alkylene-NH2,
R3 is 1) -(C1-C4)-alkyl,
2) -(C1-C4)-alkylene-(C3-C6)-cycloalkyl,
3) -(C1-C4)-alkylene-phenyl, where phenyl is substituted independently of one another once, twice or three times by R15,
4) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-phenyl, where phenyl is substituted independently of one another once, twice or three times by R15,
5) hydrogen atom,
R4 is -N(R6)2,
where R6 are identical or different and are independently of one another
1) hydrogen atom,

2) -(C1-C4)-alkyl,

3) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl is selected from the group of cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethylbicyclo[3.1.1]heptanyl, decahydronaphthalenyl, tetrahydronaphthalenyl, octahydro-4,7-methanoindenyl or bicyclo[2.2.1]heptanyl and in which cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by -(C1-C4)-alkyl, -C(O)-O-R11 or -(C1-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted by halogen,

4) -(C0-C4)-alkylene-C(R11)(R12)-(C3-C12)-cycloalkyl, where cycloalkyl is selected from the group of cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethylbicyclo[3.1.1]heptanyl, decahydronaphthalenyl, tetrahydronaphthalenyl, octahydro-4,7-methanoindenyl or bicyclo[2.2.1]heptanyl and in which cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by -(C1-C4)-alkyl, -C(O)-O-R11 or -(C1-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted by halogen,

5) -(C0-C4)-alkylene-Het, where Het is selected from the group of acridinyl, azepinyl, azetidinyl, aziridinyl, benzimidazalinyl, benzimidazolyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dibenzofuranyl, dibenzothiophenyl, dihydrofuran[2,3-b]-tetrahydrofuranyl, dihydrofuranyl, dioxolyl, dioxanyl, 2H, 6H-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolidinyl, 2-isothiazolinyl, isothiazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, morpholinyl, naphthyridinyl, octahydroiso-

quinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, oxothiolanyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridothiophenyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydropyridinyl,
6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienoimidazolyl, thienooxazolyl, thienopyridine, thienothiazolyl, thiomorpholinyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl,
1,3,4-triazolyl and xanthenyl, where Het or alkylene is unsubstituted or substituted independently of one another once or twice by -(C1-C4)-alkyl,

6) -(C1-C6)-alkylene-phenyl, where phenyl or alkylene are unsubstituted or substituted independently of one another once or twice by halogen, phenyl, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11, -O-(C1-C4)-alkyl or -(C1-C4)-alkyl,

7) -(C0-C4)-alkylene-C(R11)(R12)-phenyl, where phenyl is unsubstituted or substituted independently of one another once, twice or three times by phenyl or fluorine,

8) 1,2,3,4-tetrahydronaphthalenyl,

9) -(C0-C4)-alkylene-CH(R11)-C(O)-NH2,

10) -(C0-C4)-alkylene-CH(R11)-C(O)-NH-(C1-C4)-alkyl,

11) -(C0-C4)-alkylene-CH(R11)-C(O)-NH-CH(R12)-R13,

12) -(C1-C6)-alkylene-C(O)-O-R11, where alkylene is unsubstituted or substituted independently of one another once or twice by halogen, phenyl,
-C(O)-O-R11, -(C1-C4)-alkyl-O-R11, -O-(C1-C4)-alkyl or -(C1-C4)-alkyl,

13) -(C0-C4)-alkylene-C(R11)(R12)-C(O)-O-R11, or

14) -(C1-C3)-fluoroalkyl,
or the two R6 radicals form together with the N atom to which they are bonded a mono- or bicyclic ring selected from the group of pyrrolidine, piperidine, 2-aza-bicyclo[3.2.2]nonane and 7-aza-bicyclo[2.2.1]heptane, where the ring is unsubstituted or substituted once or twice by -(C1-C4)-alkyl, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or phenyl,
R7 is hydrogen atom or -(C1-C4)-alkyl,
R9 is hydrogen atom or -(C1-C4)-alkyl,
R11 and R12 are identical or different and are independently of one another
1) hydrogen atom,
2) -(C1-C4)-alkyl,
3) -(C0-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted independently of one another once, twice or three times by -OH, halogen or -O-(C1-C4)-alkyl,
4) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl is selected from the group of cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethylbicyclo[3.1.1]heptanyl, decahydronaphthalenyl, tetrahydronaphthalenyl, octahydro-4,7-methanoindenyl or bicyclo[2.2.1]heptanyl and in which cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by -(C1-C4)-alkyl, -C(O)-O-R13 or phenyl, or
5) -(C0-C4)-alkylene-indolyl,
R13 is 1) hydrogen atom,
2) -(C1-C4)-alkyl,
3) -(C0-C4)-alkylene-C(O)-O-R14,
4) -(C0-C4)-alkylene-C(O)-R14 or
5) -(C0-C4)-alkylene-O-R14, and
R14 is hydrogen atom, -(C1-C4)-alkyl, -NH2 or -OH and
R15 is hydrogen atom, -(C1-C4)-alkyl, -O-CF3, -NH2, -OH, -CF3 or halogen.

The invention further relates to the compound of the formula I where
X is -S(O)2-,

R1 is 1) hydrogen atom or
2) -(C1-C4)-alkyl,
R2 is 1) -(C1-C6)-alkylene-NH2,
2) -(C1-C4)-alkylene-pyridyl-NH2,
3) -(C1-C4)-alkylene-piperidinyl-NH2,
4) -(C1-C4)-alkylene-NH-C(=NH)-NH2,
5) -(C1-C6)-alkylene-NH-C(=NH)-(C1-C4)-alkyl,
6) -(C1-C4)-alkylene-(C3-C6)-cycloalkyl-NH2,
7) -(C1-C4)-alkylene-O-NH-C(=NH)-NH2,
8) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-phenyl,
9) -(C1-C4)-alkylene-NH-C(O)-(C1-C6)-alkyl,
10) -(C1-C4)-alkylene-phenyl-NH2,
11) -(C1-C4)-alkylene-SO2-(C1-C4)-alkylene-NH2 or
12) -(C1-C4)-alkylene-S-(C1-C4)-alkylene-NH2,
R3 is 1) -(C1-C4)-alkyl,
2) -(C1-C4)-alkylene-(C3-C6)-cycloalkyl,
3) -(C1-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted by -OH,
4) -(C1-C6)-alkylene-NH-C(O)-O-(C1-C4)-alkylene-phenyl,
5) hydrogen atom,
R4 is -N(R6)2,
where R6 are identical or different and are independently of one another
1) hydrogen atom,
2) -(C1-C6)-alkyl,
3) -(C0-C4)-alkylene-(C3-C8)-cycloalkyl, where cycloalkyl is selected from the group of cyclohexyl, cyclopentyl, cyclopropyl, adamantanyl, 1,7,7-trimethylbicyclo[3.1.1]heptanyl, decahydronaphthalene, octahydro-4,7-methanoindenyl or bicyclo[2.2.1]heptanyl and in which cycloalkyl is unsubstituted or substituted independently of one another once, twice or three times by -(C1-C4)-alkyl or phenyl,
4) -C(R11)(R12)-adamantanyl,
5) -CH(R11)-C(O)-NH-CH(R12)-R13,
6) -(C0-C4)-alkylene-Het, where Het is selected from the group of benzimidazolyl, isoxazolyl, piperidine, pyridine, pyrrolidinyl, thiophenyl and benzo[1,3]dioxol,

7) 1,2,3,4-tetrahydronaphthalenyl,

8) -(C0-C4)-alkylene-C(R11)(R12)-phenyl, where phenyl is unsubstituted or substituted independently of one another once, twice or three times by phenyl or fluorine,

9) -CH(R11)-C(O)-NH2,

10) -CH(R11)-C(O)-NH-CH(R12)-CH2-OH,

11) -(C1-C6)-alkylene-phenyl, where phenyl or alkylene are unsubstituted or substituted independently of one another once or twice by chlorine, fluorine, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11, -O-(C1-C4)-alkyl, phenyl or -(C1-C4)-alkyl,

12) -CH(R11)-C(O)-NH-(C1-C4)-alkyl,

13) -(C0-C4)-alkylene-C(R11)(R12)-bicyclo[3.1.1]heptanyl, where bicyclo[3.1.1]heptanyl is unsubstituted or substituted once to four times by -(C1-C4)-alkyl,

14) -(C1-C6)-alkylene-C(O)-O-R11, where alkylene is unsubstituted or substituted independently of one another once or twice by chlorine, fluorine, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11, -O-(C1-C4)-alkyl, phenyl or -(C1-C4)-alkyl,

15) -(C0-C4)-alkylene-C(R11)(R12)-C(O)-O-R11, or

16) -CH2-CF2-CF3,

or the two R6 radicals form together with the N atom to which they are bonded a mono- or bicyclic ring selected from the group of pyrrolidines, 2-azabicyclo[3.2.2]nonane and 7-aza-bicyclo[2.2.1]heptane, where the ring is unsubstituted or substituted once or twice by -(C1-C4)-alkyl, -C(O)-O-R11, -(C1-C4)-alkyl-O-R11 or phenyl,

R7 is hydrogen atom or -(C1-C4)-alkyl,

R9 is hydrogen atom or -(C1-C4)-alkyl,

R11 and R12 are identical or different and are independently of one another

1) hydrogen atom,

2) -(C1-C4)-alkyl,

3) -(C0-C4)-alkylene-phenyl, where phenyl is unsubstituted or substituted independently of one another once, twice or three times by -OH, halogen or -O-(C1-C4)-alkyl,

4) -(C0-C4)-alkylene-(C3-C12)-cycloalkyl, where cycloalkyl

is selected from the group of cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethylbicyclo[3.1.1]heptanyl, decahydronaphthalenyl, octahydro-4,7-methanoindenyl or bicyclo[2.2.1]heptanyl and in which cycloalkyl is unsubstituted or substituted independently of one another once, twice, three or four times by -(C1-C4)-alkyl, -C(O)-O-R13 or phenyl or

5) -(C0-C4)-alkylene-indolyl,

R13 is 1) hydrogen atom,

2) -(C1-C4)-alkyl,

3) -(C0-C4)-alkylene-C(O)-O-R14,

4) -(C0-C4)-alkylene-C(O)-R14 or

5) -(C0-C4)-alkylene-O-R14,

R14 is hydrogen atom, -(C1-C4)-alkyl, -NH2 or -OH and R15 is hydrogen atom, -(C1-C4)-alkyl, -O-CF3, -NH2, -OH, -CF3 or halogen.

The invention also relates to the use of the compound of the formula I for the manufacture of a medicament for the prophylaxis, secondary prevention and therapy of one or more disorders associated with thromboses, embolisms, hypercoagulability or fibrotic changes selected from the series myocardial infarction, angina pectoris and other forms of acute coronary syndrome, stroke, peripherally vascular disorders, deep vein thrombosis, pulmonary embolism, embolic or thrombotic events caused by cardiac arrhythmias, cardiovascular events such as restenosis following revascularization and angioplasty and similar procedures such as stent implantations and bypass operations, or reducing the risk of thrombosis following surgical procedures such as operations on the knee and hip, or disseminated intravascular coagulation, sepsis and other intravascular events associated with inflammation, or atherosclerosis, diabetes and the metabolic syndrome and the sequelae thereof, tumor growth and tumor metastasis, inflammatory and degenerative articular disorders such as rheumatoid arthritis and arthrosis, impairments of the hemostatic system such as fibrin deposits, fibrotic changes of the lung such as chronic obstructive

pulmonary disease, adult respiratory distress syndrome or fibrin deposits in the eye following eye operations or prevention or treatment of scarring.

The term "(C1-C6)-alkyl" means hydrocarbon radicals whose carbon chain is straight-chain or branched and comprises 1 to 6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, 2,3-dimethylbutane or neohexyl.

The term "-(C0-C4)-alkylene" means hydrocarbon radicals whose carbon chain is straight-chain or branched and comprises 1 to 4 carbon atoms, for example methylene, ethylene, propylene, isopropylene, isobutylene, butylene or tertiary butylene. "-C0-Alkylene" is a covalent bond.

The term "-(CH2)n- in which n is the integer zero or 1" means the methylene radical in the case where n equals 1, and the radical has the meaning of a covalent bond in the case where n is the integer zero.

The term "-(C1-C4)-alkylene" means hydrocarbon radicals whose carbon chain is straight-chain or branched and comprises 1 to 4 carbon atoms, for example methylene (-CH2-), ethylene (-CH2-CH2-), propylene (-CH2-CH2-CH2-), isopropylene, isobutylene, butylene or tertiary butylene.

The term "-(CH2)n- in which n is the integer zero, 1, 2 or 3" means radicals such as methylene, ethylene or propylene. In the case where n is the integer zero, the radical has the meaning of a covalent bond.

The term "(C3-C12)-cycloalkyl" means radicals such as compounds derived from 3- to 12-membered mono-, bi- or tricycles or bridged rings such as the monocycles cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane or cyclooctane, derived from the bicycles bicyclo[4.2.0]octane, octahydroindene, decahydronaphthalene, decahydroazulene, decahydrobenzocycloheptene or dodecahydroheptalene, or from tricycles such as adamantane, or derived from the bridged rings such as spiro[2.5]octane, spiro[3.4]octane, spiro[3.5]nonane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane or octahydro-4,7-

methanindene.

The term "R6 form together with the N atom to which they are bonded a mono- or bicyclic ring having 4 to 9 ring atoms" means radicals such as compounds derived from 4- to 8-membered monocycles which may be saturated or wholly or partly aromatic, for example azetidine, dihydroazete, azete, diazetidine, diazete, pyrrolidine, dihydropyrrole, pyrrole, imidazolidine, dihydroimidazole, imidazole, pyrazoline, pyrazolidine, piperidine, dihydropyridine, tetrahydropyridine, pyridine, piperazine, dihydropyrazine, pyrazine, pyridazine, pyrimidine, oxazine, azepane, tetrahydroazepine, azepine, azocan, dihydroazocine, hexohydroazocine or azocine or bicyclic rings such as 2-azabicyclo[3.2.2]nonane or, 7-azabicyclo[2.2.1]heptane.

The term "-(C6-C14)-aryl" means aromatic carbon radicals having 6 to 14 carbon atoms in the ring. Examples of -(C6-C14)-aryl radicals are phenyl, naphthyl, for example 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydronaphthalenyl, anthryl or fluorenyl. Naphthyl radicals and especially phenyl radicals are preferred aryl radicals.

The term "4- to 15-membered Het ring" or "Het" means ring systems having 4 to 15 carbon atoms which are present in one, two or three ring systems connected together and which comprise one, two, three or four identical or different heteratoms from the series oxygen, nitrogen or sulfur. Examples of these ring systems are the radicals acridinyl, azepinyl, azetidinyl, aziridinyl, benzimidazalinyl, benzimidazolyl, benzo[1,3]dioxol, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dibenzofuranyl, dibenzothiophenyl, dihydrofuran[2,3-b]-tetrahydrofuranyl, dihydrofuranyl, dioxolyl, dioxanyl, 2H,6H-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl,

isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolidinyl, 2-isothiazolinyl, isothiazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, oxothiolanyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridothiophenyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydropyridinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienoimidazolyl, thienooxazolyl, thienopyridine, thienothiazolyl, thiomorpholinyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

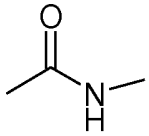
Preferred Het rings are the radicals isoxazolyl, benzo[1,3]dioxole and thiophenyl.

The term "halogen" means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, especially chlorine or bromine.

The term "amino acid" means compounds such as naturally occurring α-amino acids glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid. Histidine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, arginine, glutamic acid and aspartic acid are particularly preferred. Also included therewith are non-naturally occurring amino acids such as 2-aminoadipic acid, 2-aminobutyric acid, 2-aminoisobutyric acid, 2,3-diaminopropionic acid, 2,4-

diaminobutyric acid, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 2-aminopimelic acid, phenylglycine, 3-(2-thienyl)alanine, 3-(3-thienyl)alanine, sarcosine, 2-(2-thienyl)glycine, 2-aminoheptanoic acid, pipecolic acid, hydroxylysine, N-methylisoleucine, 6-N-methyllysine, N-methylvaline, norvaline, norleucine, ornithine, allo-isoleucine, 4-hydroxyproline, allo-hydroxylysine, allo-threonine, 3-hydroxyproline, 3-(2-naphtyl)alanine, 3-(1-naphtylalanine), homophenylalanine, homocysteine, 2-amino-3-phenylaminoethylpropionic acid, homocysteic acid, homotryptophan, cysteic acid, 3-(2-pyridyl)alanine, 3-(3-pyridyl)alanine, 3-(4-pyridyl)alanine, phosphinothricin, 4-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, 3-fluorophenylalanine, 3-fluorophenylalanine, 2-fluorophenylalanine, 4-chlorophenylalanine, 4-nitrophenylalanine, 4-aminophenylalanine, cyclohexylalanine, citrulline, 5-fluorotryptophan, 5-methoxytryptophan or 2-amino-3-phenylaminopropionic acid.

The term "peptide linkage" means structures such as



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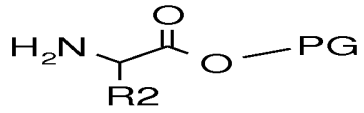
The term "protective group for the amino, carboxyl or for the hydroxy function" means protective groups such as suitable protective groups for amino functions, for example the t-butoxycarbonyl, the benzyloxycarbonyl or the phthalolyl group, and the trityl or tosyl protective group, suitable protective groups for the carboxyl function are for example, alkyl, aryl or arylalkyl esters and suitable protective groups for the hydroxy function are for example alkyl esters, t-butyl, benzyl or trityl groups. Protective groups can be introduced and removed by techniques which are well known or described herein (see Green, T.W., Wutz, P.G.M., Protective Groups in Organic Synthesis (1991), 2nd Ed., Wiley-Interscience, or Kocienski, P., Protecting Groups (1994), Thieme).

The term "-(C1-C3)-fluoroalkyl" means a partly or completely

fluorinated alkyl radical derived for example from the following radicals -CF3, -CHF2, -CH2F, -CHF-CF3, -CHF-CHF2, -CHF-CH2F, -CH2-CF3, -CH2-CHF2, -CH2-CH2F, -CF2-CF3, -CF2-CHF2, -CF2-CH2F, -CH2-CHF-CF3, -CH2-CHF-CHF2, -CH2-CHF-CH2F,
-CH2-CH2-CF3, -CH2-CH2-CHF2, -CH2-CH2-CH2F, -CH2-CF2-CF3, -CH2-CF2-CHF2, -CH2-CF2-CH2F, -CHF-CHF-CF3, -CHF-CHF-CHF2, -CHF-CHF-CH2F, -CHF-CH2-CF3, -CHF-CH2-CHF2, -CHF-CH2-CH2F, -CHF-CF2-CF3, -CHF-CF2-CHF2, -CHF-CF2-CH2F, -CF2-CHF-CF3, -CF2-CHF-CHF2, -CF2-CHF-CH2F, -CF2-CH2-CF3, -CF2-CH2-CHF2, -CF2-CH2-CH2F, -CF2-CF2-CF3, -CF2-CF2-CHF2 or -CF2-CF2-CH2F.
The term "-S(O)2-" means a sulfonyl radical.
The term "-C(O)-" means a carbonyl radical.

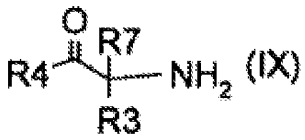
The invention further relates to a process for preparing the compound of the formula I, which comprises

a) reacting a compound of the formula II



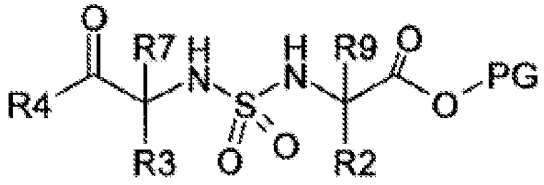
(II)

where R2 and PG have the meanings mentioned in the compound of the formula I, with a compound of the formula IX



(IX)

where R3, R4, R7 and PG have the meanings mentioned in the compound of the formula I, to give a compound of the formula X



(X)

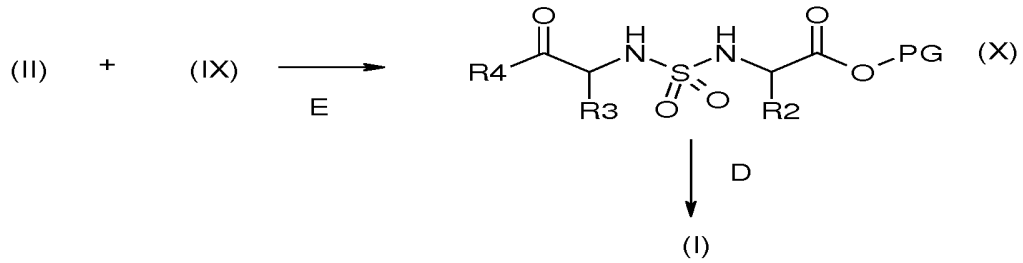
where R2, R3, R4, R7, R9 and PG have the meanings mentioned in the compound of the formula I, and then converting it into a compound of the formula I, or

b) fractionating a compound of the formula I prepared by processes a), or a suitable precursor of the formula I which occurs in enantiomeric forms owing to its chemical structure, by salt formation with enantiopure acids or bases,

chromatography on chiral stationary phases or derivatization by means of chiral enantiopure compounds such as amino acids, separation of the diastereomers obtained in this way, and elimination of the chiral auxiliary groups into the pure enantiomers, or

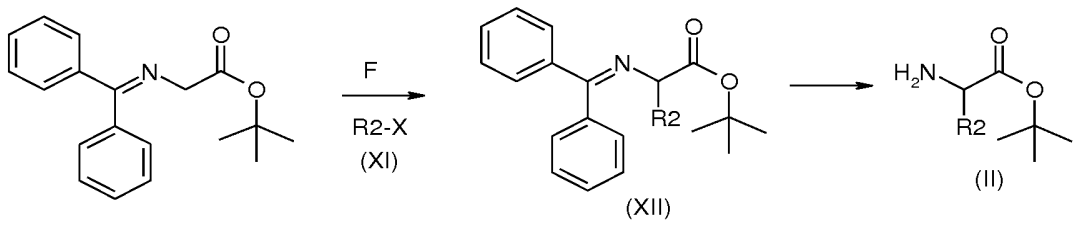
c) either isolating in free form the compound of the formula I prepared by processes a) or b), or converting into physiologically tolerated salts in the case where acidic or basic groups are present.

A further process for preparing the compounds of the invention according to (I) is reaction of compounds (IX) with compounds of the type (II) in analogy to A. In a process disclosed by Borghese et al. (*Org. Process Res. Dev.* 2006, 10, 770-775), compounds of the formula X are prepared and are subsequently deprotected and afford compounds of the formula I:



Scheme 3

Amines of the formula NH(R6)2 mean amines or dipeptide derivatives which are commercially available or prepared by processes disclosed in the literature. The compounds (II) are commercially available or can be obtained by alkylation of tert-butyl (benzhydrylideneamino)acetate in suitable solvents such as THF or DMF in the presence of bases such as lithiumhexamethyldisilazane, KOH, NaOH, CsOH, K2CO3 or NaH and subsequent deprotection under acidic conditions, for example in dilute hydrochloric acid or aqueous citric acid (Scheme 4, cf., for example, J. Ezquerra et al., *Tetrahedron Lett.* 1993, 34 (52), 8535-8538). The compounds (XI) are commercially available or disclosed in the literature, where X is a suitable leaving group such as bromine, iodine, chlorine, tosylate or mesylate.



Scheme 4

A compound of the formula I prepared as in Scheme 1 or 3, or a suitable precursor of the formula I which occurs in enantiomeric form owing to its chemical structure, can be fractionated by salt formation with enantiopure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiopure compounds such as amino acids, separation of the diastereomers obtained in this way, and elimination of the chiral auxiliary groups into the pure enantiomers (process b), or the compound of the formula I prepared as in Scheme 1 or 3 can either be isolated in free form or be converted into physiologically tolerated salts in the case where acetic or basic groups are present (process d).

In process step c), the compound of the formula I, if it occurs as mixture of diastereomers or enantiomers, or results as mixtures thereof in the chosen synthesis, is separated into the pure stereoisomers, either by chromatography on an optionally chiral support material or, if the racemic compound of the formula I is able to form salts, by fractional crystallization of the diastereomeric salts formed with an optically active base or acid as auxiliary. Examples of suitable chiral stationary phases for thin-layer or column chromatographic separation of enantiomers are modified silica gel supports (called Pirkle phases) and high molecular weight carbohydrates such as triacetylcellulose. For analytical purposes it is also possible to use gas chromatography methods, after appropriate derivatization known to the skilled worker, on chiral stationary phases. To separate enantiomers of the racemic carboxylic acids, diastereomeric salts differing in solubility are formed with an optically active, usually commercially available base such as (-)-nicotine, (+)-

and (-)-phenylethylamine, quinine bases, L-lysine or L- and D-arginine, the less soluble component is isolated as solid, the more soluble diastereomer is deposited from the mother liquor, and the pure enantiomers are obtained from the diastereomeric salts obtained in this way. It is possible in the same way in principle to convert the racemic compounds of the formula I comprising a basic group such as an amino group with optically active acids such as (+)-camphor-10-sulfonic acid, D- and L-tartaric acid, D- and L-lactic acid, and (+) and (-)-mandelic acid into the pure enantiomers. Chiral compounds comprising alcohol or amine functions can also be converted with appropriately activated or optionally N-protected enantiopure amino acids into the corresponding esters or amides, or conversely chiral carboxylic acids can be converted with carboxy-protected enantiopure amino acids into the amides, or with enantiopure hydroxy carboxylic acids such as lactic acid into the corresponding chiral esters. The chirality of the amino acid or alcohol residue introduced in enantiopure form can then be utilized for separating the isomers by carrying out a separation of the diastereomers now present by crystallization or chromatography on suitable stationary phases, and then eliminating the included chiral moiety again by suitable methods.

A further possibility with some of the compounds of the invention is to employ diastereomerically or enantiomerically pure starting materials to prepare the framework structures. It is thus possible where appropriate also to employ other or simplified processes for purifying the final products. These starting materials have previously been prepared enantiomerically or diastereomerically pure by processes known from the literature. This may mean in particular that either enantioselective processes are employed in the synthesis of the basic structures, or else a separation of enantiomers (or diastereomers) is carried out at an early stage of the synthesis and not at the stage of the final products. A simplification of these separations can likewise be achieved by proceeding in two or more stages.

Acidic or basic products of the compound of the formula I may be in the form of their salts or in free form. Pharmacologically acceptable salts are preferred, for example alkali metal or alkaline earth metal salts such as hydrochlorides, hydrobromides, sulfates, hemisulfates, all possible phosphates, and salts of amino acids, natural bases or carboxylic acids. Physiologically tolerated salts are prepared from compounds of the formula I able to form salts, including their stereoisomeric forms, in step c) of the process in a manner known per se. The compounds of the formula I form stable alkali metal, alkaline earth metal or, where appropriate, substituted ammonium salts with basic reagents such as hydroxides, carbonates, bicarbonates, alcoholates and ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine, diethanolamine or triethanolamine, trometamol or else basic amino acids, for example lysine, ornithine or arginine. If the compounds of the formula I have basic groups, it is also possible to prepare stable acid addition salts with strong acids. Suitable for this purpose are both inorganic and organic acids such as hydrochloric, hydrobromic, sulfuric, hemisulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexylamidosulfonic, trifluoromethylsulfonic, 2-hydroxyethanesulfonic, acetic, oxalic, tartaric, succinic, glycerolphosphoric, lactic, malic, adipic, citric, fumaric, maleic, gluconic, glucuronic, palmitic, or trifluoroacetic acid.

The invention also relates to medicaments characterized by an effective content of at least one compound of the formula I and/or of a physiologically tolerated salt of the compound of the formula I and/or an optionally stereoisomeric form of the compound of the formula I, together with a pharmaceutically suitable and physiologically tolerated carrier, additive and/or further active ingredients and excipients.

By reason of the pharmacological properties, the compounds of

the invention are suitable for the prophylaxis, secondary prevention and therapy of all disorders which can be treated by inhibition of TAFIa. Thus, TAFIa inhibitors are suitable both for a prophylactic and for a therapeutic use in humans. They are suitable both for an acute treatment and for a long-term therapy. TAFIa inhibitors can be employed in patients suffering from impairments of wellbeing or diseases associated with thromboses, embolisms, hypercoagulability or fibrotic changes.

These include myocardial infarction, angina pectoris and all other types of acute coronary syndrome, stroke, peripheral vascular disorders, deep vein thrombosis, pulmonary embolism, embolic or thrombotic events caused by cardiac arrhythmias, cardiovascular events such as restenosis following revascularization, angioplasty and similar procedures such as stent implantations and bypass operations. TAFIa inhibitors can additionally be employed in all procedures leading to contact of the blood with foreign surfaces such as, for example, for dialysis patients and patients with indwelling catheters. TAFIa inhibitors can be employed to reduce the risk of thrombosis after surgical procedures such as knee and hip joint operations.

TAFIa inhibitors are suitable for the treatment of patients with disseminated intravascular coagulation, sepsis and other intravascular events associated with an inflammation. TAFIa inhibitors are additionally suitable for the prophylaxis and treatment of patients with atherosclerosis, diabetes and the metabolic syndrome and the sequelae thereof. Impairments of the hemostatic system (e.g. fibrin deposits) have been implicated in mechanisms leading to tumor growth and tumor metastasis, and for inflammatory and degenerative articular disorders such as rheumatoid arthritis and arthrosis. TAFIa inhibitors are suitable for slowing down or preventing such processes.

Further indications for the use of TAFIa inhibitors are

fibrotic changes of the lung such as chronic obstructive lung disease, adult respiratory distress syndrome (ARDS) and of the eye such as fibrin deposits after eye operations. TAFIa inhibitors are also suitable for the prevention and/or treatment of scar formation.

The medicaments of the invention can be administered by oral, inhalational, rectal or transdermal administration or by subcutaneous, intraarticular, intraperitoneal or intravenous injection. Oral administration is preferred. It is possible for stents and other surfaces which come into contact with blood in the body to be coated with TAFIa inhibitors.

The invention also relates to a process for producing a medicament, which comprises making a suitable dosage form from at least one compound of the formula I with a pharmaceutically suitable and physiologically tolerated carrier and, where appropriate, further suitable active ingredients, additives or excipients.

Suitable solid or pharmaceutical formulations are, for example, granules, powder, coated tablets, tablets, (micro)capsules, suppositories, syrups, solutions, suspensions, emulsions, drops or injectable solutions, and products with protracted release of active ingredient, in the production of which conventional aids such as carriers, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavorings, sweeteners and solubilizers are used. Excipients which are frequently used and which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as fish liver oil, sunflower, peanut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and monohydric or polyhydric alcohols such as glycerol.

The pharmaceutical products are preferably produced and

administered in dosage units, where each unit comprises as active ingredient a particular dose of the compound of the invention of the formula I. In the case of solid dosage units such as tablets, capsules, coated tablets or suppositories, this dose can be up to 1000 mg, but preferably 50 to 300 mg and, in the case of injection solutions in ampoule form, up to 300 mg but preferably 10 to 100 mg.

The daily doses indicated for the treatment of an adult patient weighing about 70 kg are, depending on the activity of the compound of formula I, from 2 mg to 1000 mg of active ingredient, preferably 50 mg to 500 mg. However, in some circumstances, higher or lower daily doses may also be appropriate. The daily dose can be administered either by a single administration in the form of a single dosage unit or else a plurality of smaller dosage units or by multiple administration of divided doses at particular intervals.

TAFIa inhibitors can be administered both as monotherapy and in combination or together with all antithrombotics (anticoagulants and platelet aggregation inhibitors), thrombolytics (plasminogen activators of every type), other substances having profibrinolytic activity, antihypertensives, regulators of blood glucose, lipid-lowering agents and antiarrhythmics.

Examples

Final products are normally determined by mass spectroscopic methods (FAB-, ESI-MS) and ^{1}H-NMR; the main peak or two main peaks are indicated in each case. Temperatures are stated in degrees Celsius, RT means room temperature (21°C to 24°C). Abbreviations used are either explained or correspond to usual conventions. Unless stated otherwise, the LC/MS analyses were carried out under the following conditions:

Method A: = method column: YMC Jsphere H80 20x2 mm, packing material 4 µm, mobile phase: CH3CN: H2O + 0.05% trifluoroacetic acid (TFA), gradient: 4:96 (0 min.) to 95:5 (2.0 min.) to 95:5 (2.4 min.) to 4:96 (2.45 min.) flow rate:

1.0 ml/min., temperature: 30°C.
Method B: column: YMC Jsphere 33x2.1 mm, packing material 4 µm, mobile phase: CH3CN + 0.05% TFA: H2O + 0.05% TFA, gradient: 5:95 (0 min.) to 95:5 (2.5 min.) to 95:5 (3.0 min.), flow rate: 1.3 ml/min., temperature: 30°C.
Method C: column: YMC Jsphere 33x2.1 mm, packing material 4 µm, mobile phase: CH3CN + 0.08% formic acid: H2O + 0.1% formic acid, gradient: 5:95 (0 min.) to 95:5 (2.5 min.) to 95:5 (3.0 min.), flow rate: 1.3 ml/min., temperature: 30°C.
Method D: column: YMC Jsphere 33x2.1 mm, packing material 4 µm, mobile phase: CH3CN + 0.05% TFA: H2O + 0.05% TFA, gradient: 5:95 (0-0.5 min.) to 95:5 (3.5 min.) to 95:5 (4.0 min.), flow rate: 1.3 ml/min., temperature: 30°C.
Method E: column: YMC Jsphere 33x2.1 mm, packing material 4 µm, mobile phase: CH3CN + 0.05% TFA: H2O + 0.05% TFA, gradient: 2:98 (0-1.0 min.) to 95:5 (5.0 min.) to 95:5 (6.2 min.), flow rate: 1.0 ml/min., temperature: 30°C.
Method F: column: YMC Jsphere 33x2.1 mm, packing material 4 µm, mobile phase: CH3CN + 0.05% TFA: H2O + 0.05% TFA, gradient: 5:95 (0 min.) to 95:5 (3.4 min.) to 95:5 (4.4 min.), flow rate: 1.0 ml/min., temperature: 30°C.

Unless indicated otherwise, chromatographic separations were carried out on silica gel with ethyl acetate/heptane mixtures as mobile phase. Preparative separations on reversed phase (RP) silica gel (HPLC) were, unless indicated otherwise, carried out under the following conditions: column Merck Hibar RT 250-25 LiChrospher 100 RP-18e 5µm, mobile phase A: H2O + 0.1% TFA, phase B: 80% acetonitrile + 0.1% TFA, flow rate 25 ml/min., 0-7 min. 100% A , 7-22 min. to 100% B, 22-30 min. 100% B, 30-33 min. to 100% A, 33-35 min. 100% A.

Evaporation of solvents normally took place under reduced pressure in a rotary evaporator at 35°C to 45°C.

Example 1
(S)-6-Amino-2-{3-[(R)-1-(3-methyl-butylcarbamoyl)-2-phenyl-ethyl]-ureido}-hexanoic acid hydrochloride

Example 1a)

tert-Butyl (R)-1-(3-methyl-butylcarbamoyl)-2-phenyl-ethyl]-carbamate

1-Hydroxybenzotriazole hydrate (1.685 g, 11 mmol) and N,N'-dicyclohexylcarbodiimide (DCC, 2.270 g, 11 mmol) were successively added to a solution of N-Boc-D-phenylalanine (2.653 g, 10 mmol) in tetrahydrofuran (THF) (80 ml) and stirred at RT for 2 h. Subsequently, isoamylamine (1.162 ml, 10 mmol) was added, and stirring was continued at RT. Leaving to stand overnight was followed by filtration, concentration of the filtrate, taking up in ethyl acetate, renewed filtration, successive washing with saturated $NaHCO_3$ solution and 1N HCl, and the organic phase was dried over $MgSO_4$, filtered and concentrated.

LC/MS data: R_t(min.) 1.568; calculated (calc.): $[M+H]^+$ = 335.47, found (found): 235.15 (- tert-butyloxycarbonyl during the measurement) (Method A)

Example 1b)

(R)-2-Amino-N-(3-methyl-butyl)-3-phenyl-propionamide

A solution of the crude product from Example 1a) (2.710 g, 8.103 mmol) in dichloromethane/trifluoroacetic acid (TFA) (60 ml, 1:1 v/v) was stirred at RT for 30 min. The solution was concentrated, taken up in ethyl acetate and washed with 1N HCl. The aqueous phase was made weakly alkaline with potassium hydroxide and extracted three times with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and concentrated.

LC/MS data: R_t(min) 0.978; calc.: $[M+H]^+$ = 235.35 found: 235.15 (method A)

Example 1c)

tert-Butyl (S)-6-tert-butoxycarbonylamino-2-{3-[(R)-1-(3-methyl-butylcarbamoyl)-2-phenyl-ethyl]-ureido}-hexanoate

The crude product from Example 1b) (1.380 g, 5.889 mmol) was added to a solution of 1,1'-carbonyldiimidazole (0.955 g, 5.889 mmol) in dimethylformamide (DMF) (21 ml) and stirred at RT for 1h. Then triethylamine (1.633 ml, 11.780 mmol) and tert-butyl (S)-2-amino-6-tert-butoxycarbonylaminohexanoate hydrochloride (1.996 g, 5.889 mmol) were added, and the

mixture was left to stand at RT overnight. The solution was concentrated and partitioned between water and ethyl acetate, and the organic phase was dried over $MgSO_4$, filtered and concentrated. The resulting crude product was purified by preparative HPLC.

LC/MS data: R_t(min) 1.757; calc.: $[M+H]^+$ = 563.76 found: 563.35 (method A)

Example 1d)

(S)-6-Amino-2-{3-[(R)-1-(3-methyl-butylcarbamoyl)-2-phenyl-ethyl]-ureido}-hexanoic acid hydrochloride

The product from Example 1c) (0.500 g, 0.889 mmol) was dissolved in dichloromethane/TFA (10 ml,1:1, v/v) and stirred at RT for 2 h. The solution was concentrated and purified by preparative HPLC. The combined product fractions were mixed with 2N HCl, concentrated and freeze dried.

LC/MS data: R_t(min) 0.971; calc.: $[M+H]^+$ = 407.54 found: 407.30 (method A)

Example 11

(S)-6-Amino-2-{3-[(R)-2-cyclohexyl-1-(2,4-difluoro-benzylcarbamoyl)-ethyl]-ureido}-hexanoic acid

Example 11a)

(R)-2-Amino-3-cyclohexylpropanoic acid trifluoroacetate

5 ml of TFA were added to a solution of (R)-N-Boc-2-amino-3-cyclohexylpropanoic acid (3.0 g, 11.1 mmol) in 20 ml of CH_2Cl_2, and the mixture was stirred at RT overnight. After deprotection was complete, the CH_2Cl_2 was evaporated off, and the remaining solid was mixed with 50 ml of H_2O and lyophilized. Yield: 2.84 g (90%) of (R)-2-amino-3-cyclohexylpropanoic acid trifluoroacetate as colorless solid.

Example 11b)

tert-Butyl (S)-6-tert-butoxycarbonylamino-2-[3-((R)-1-carboxy-2-cyclohexyl-ethyl)-ureido]-hexanoate

Commercial tert-butyl (S)-2-amino-6-tert-butoxycarbonylaminohexanoate hydrochloride (1.95 g, 5.75 mmol) was mixed in 30 ml of DMF with NEt_3 (0.8 ml, 5.754 mmol) and 1,1'-carbonyldiimidazole (0.933 g, 5.754 mmol) and stirred at RT for 30 min. Then (R)-2-amino-3-cyclohexylpropanoic acid

trifluoroacetate (1.64 g, 5.754 mmol) and NEt_3 (1.6 ml, 11.5 mmol) were added, and the mixture was heated at 80°C until the imidazolide formed as intermediate was completely converted. The product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH gradient). Yield: 2.1 g (73%) of tert-butyl (S)-6-tert-butoxycarbonylamino-2-[3-((R)-1-carboxy-2-cyclohexylethyl)-ureido]-hexanoate.

Example 11c)

(S)-6-Amino-2-{3-[(R)-2-cyclohexyl-1-(2,4-difluoro-benzylcarbamoyl)-ethyl]-ureido}-hexanoic acid trifluoroacetate

N-Methylmorpholine (53 µl, 0.48 mmol), 1-hydroxybenzotriazole (28 mg, 0.208 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (36.8 mg, 0.192 mmol) were added in the stated sequence to a solution of tert-butyl (S)-6-tert-butoxycarbonylamino-2-[3-((R)-1-carboxy-2-cyclohexyl-ethyl)-ureido]-hexanoate (80 mg, 0.16 mmol) and 2,4-difluorobenzylamine (22.9 mg, 0.16 mmol) in 3 ml of CH_2Cl_2 and 1 ml of DMF, and the mixture was stirred at RT for about 14 h. Extraction with CH_2Cl_2/H_2O, drying of the organic phase with $MgSO_4$ and evaporation afforded tert-butyl (S)-6-tert-butoxycarbonylamino-2-{3-[(R)-2-cyclohexyl-1-(2,4-difluorobenzylcarbamoyl)-ethyl]-ureido}-hexanoate as crude product. The entire crude product was dissolved in 4 ml of CH_2Cl_2, 1 ml of TFA was added and, after 4 h, a further 0.5 ml of TFA was added, and deprotection was carried out at RT for about 10 h. Purification of the deprotected crude product by preparative HPLC afforded 25 mg (27%) of (S)-6-amino-2-{3-[(R)-2-cyclohexyl-1-(2,4-difluorobenzylcarbamoyl)-ethyl]-ureido}-hexanoic acid trifluoroacetate.

Example 130:

(S)-6-Amino-2-{3-[(R)-5-benzyloxycarbonylamino-1-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-ureido}-hexanoic acid

Example 130a)

Benzyl [(R)-5-tert-butoxycarbonylamino-5-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-carbamate

N-Methylmorpholine (0.87 ml, 7.9 mmol), 1-hydroxybenzotriazole

(0.46 g, 3.41 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.65 g, 3.41 mmol) were added in this sequence to a solution of commercially available (R)-6-benzyloxycarbonylamino-2-tert-butoxycarbonylamino-hexanoic acid (1 g, 2.63 mmol) and commercially available (S)-2-amino-3-methylbutyramide hydrochloride (0.40 g, 2.63 mmol) in 12 ml of CH_2Cl_2 and 4 ml of DMF, and the mixture was stirred at RT for about 14 h. Flash chromatography (gradient heptane/AcOEt to CH_2Cl_2/MeOH) afforded 1 g of the product (79%).

Example 130b)

Benzyl [(R)-5-amino-5-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-carbamate hydrochloride

A solution of benzyl [(R)-5-tert-butoxycarbonylamino-5-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-carbamate (1 g, 2.09 mmol) in 30 ml of CH_2Cl_2 was mixed with 5 ml of H_2O and 5 ml of conc. HCl/H_2O and heated at 40°C until the Boc protective group was completely eliminated. Extraction with H_2O/ CH_2Cl_2, drying of the organic phase over $MgSO_4$ and evaporation afforded 230 mg (27%) of the product.

Example 130c)

tert-Butyl (S)-2-{3-[(R)-5-benzyloxycarbonylamino-1-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-ureido}-6-tert-butoxycarbonylamino-hexanoate trifluoroacetate

Commercially available tert-butyl (S)-2-amino-6-tert-butoxycarbonylaminohexanoate hydrochloride (89 mg, 0.26 mmol) was mixed in 4 ml of DMF with NEt_3 (0.12 ml, 0.53 mmol) and 1,1´-carbonyldiimidazole (43 mg, 0.26 mmol) and stirred at RT for 1 h. Then benzyl [(R)-5-amino-5-((S)-1-carbamoyl-2-methylpropylcarbamoyl)-pentyl]-carbamate hydrochloride (100 mg, 0.24 mmol) was added and the mixture was heated at 80°C until the imidazolide formed as intermediate was completely converted. Preparative HPLC afforded 76 mg (39%) of tert-butyl (S)-2-{3-[(R)-5-benzyloxycarbonylamino-1-((S)-1-carbamoyl-2-methylpropylcarbamoyl)-pentyl]-ureido}-6-tert-butoxycarbonylaminohexanoate trifluoroacetate.

Example 130d)

(S)-6-Amino-2-{3-[(R)-5-benzyloxycarbonylamino-1-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-ureido}-hexanoic

acid trifluoroacetate

tert-Butyl (S)-2-{3-[(R)-5-benzyloxycarbonylamino-1-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-ureido}-6-tert-butoxycarbonylaminohexanoate trifluoroacetate (37 mg, 0.045 mmol) was dissolved in 5 ml of CH_2Cl_2 and 1 ml of TFA and stirred at RT for 14 h. Preparative HPLC afforded 21 mg (70%) of (S)-6-amino-2-{3-[(R)-5-benzyloxycarbonylamino-1-((S)-1-carbamoyl-2-methyl-propylcarbamoyl)-pentyl]-ureido}-hexanoic acid trifluoroacetate.

LC/MS: R_t (min) = 1.17 calc.: $[M+H]^+$ = 551.32, found: 551.31 (method B).

Example 143

(S)-6-Amino-2-(3-{(S)-1-[(S)-1-((S)-1-methoxycarbonyl-2-methyl-propylcarbamoyl)-2-methyl-propylcarbamoyl]-2-phenyl-ethyl}-sulfamidyl)-hexanoic acid

Example 143a)

Methyl (S)-2-((S)-2-amino-3-methylbutyrylamino)-3-methylbutyrate

600 mg (1.65 mmol) of commercially available methyl (S)-2-((S)-2-benzyloxycarbonylamino-3-methylbutyrylamino)-3-methylbutyrate (Z-Val-Val-OMe) was dissolved in 10 ml of methanol, mixed with 20 mg of palladium on carbon (10%) and stirred under a hydrogen atmosphere (1 bar) at RT for 2 h. The reaction mixture was filtered and concentrated and afforded the title compound quantitatively.

LC/MS: R_t(min) 0.85; calc.: $[M+H]^+$ 231.17 found: 231.16 (method B).

Example 143b)

Methyl (S)-2-[(S)-2-((S)-2-benzyloxycarbonylamino-3-phenyl-propionylamino)-3-methylbutyrylamino]-3-methylbutyrate

247mg of Z-Phe-OH (0.825 mmol, 1 eq) were dissolved in 10 ml of dry DMF at 0°C under argon. Then 56 mg of 1-hydroxybenzotriazole (0.5 eq), 221 mg of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (1.4 eq) and 346 µl of Hünig's base (2.4 eq) were added, and the mixture was stirred for 30 min. 190 mg of the compound from Example 143a) were then added, and the mixture was stirred at RT for

20 h. The reaction mixture was mixed with 50 ml of saturated $NaHCO_3$ solution and extracted with ethyl acetatet (2 x 30 ml). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was chromatographed on silica gel with heptane/ethyl acetate mixtures. 314 mg of the desired compound were obtained.

LC/MS: R_t(min) 1.85; calc.: $[M+H]^+$ 512.28 found 512.36 (method B).

Example 143c)

Methyl (S)-2-[(S)-2-((S)-2-amino-3-phenyl-propionylamino)-3-methyl-butyrylamino]-3-methylbutyrate

Z deprotection of Z-Phe-Val-Val-OMe to give Phe-Val-Val-OMe was carried out as described in 143a) and afforded 247 mg of the title compound.

LC/MS: R_t(min) 1.09; calc.: $[M+H]^+$ 378.24 found 378.33 (method B).

Example 143d)

2-Oxooxazolidine-3-sulfonyl chloride

A solution of 1.13 ml of 2-bromoethanol (15.9 mmol, 1.0 eq) in dichloromethane (20 ml) was slowly added to a solution of 2.25 g of chlorosulfonyl isocyanate (15.9 mmol, 1.0 eq) in dichloromethane (100 ml) under argon at 0°C in such a way that the temperature did not exceed 10°C. After the addition was complete, stirring was continued at 0°C for 30 min. The product obtained in this way was directly reacted further in the next step.

Example 143e)

tert-Butyl (S)-6-tert-butoxycarbonylamino-2-(2-oxo-oxazolidine-3-sulfonylamino)-hexanoate

A suspension of 5.39 g of H-Lys(Boc)-OtBu hydrochloride (15.9 mmol, 1.0 eq) and 7.1 ml of triethylamine (50.9 mmol, 3.2 eq) in dichloromethane (70 ml) was added to the solution obtained in Example 143d), in such a way that the temperatures did not exceed 10°C. After the addition was complete, the mixture was allowed to reach RT and was stirred for a further 2 h. The reaction mixture was then mixed with 200 ml of 0.2 M hydrochloride acid, and the organic phase was separated off and washed with 100 ml of 0.2 M hydrochloric acid and

concentrated. 5.5 g of the desired material were obtained as a colorless oil, which crystallized on standing.
LC/MS: R_t(min) 1.76; calc.: $[M+H]^+$ 452.14 found 452.18 (method B).

Example 143f)
tert-Butyl (S)-6-tert-butoxycarbonylamino-2-(3-{(S)-1-[(S)-1-((S)-1-methoxycarbonyl-2-methyl-propylcarbamoyl)-2-methyl-propylcarbamoyl]-2-phenyl-ethyl}-sulfamidyl)-hexanoate
240 mg of Phe-Val-Val-OMe (compound from Example 143c), 0.636 mmol, 1 eq) were dissolved with 345 mg of the compound from Example 143e) in 7 ml of acetonitrile, and 106 µl of triethylamine were added. The reaction mixture was stirred at 80°C for 20 h and, after cooling, evaporated. The crude product was purified by chromatography on silica gel with heptane/ethyl acetate mixtures as mobile phase. 275 mg of the title compound were obtained.
LC/MS: R_t(min) 1.733; calc.: $[M+H]^+$ 742.41 found 742.35 (method A).

Example 143g)
(S)-6-Amino-2-(3-{(S)-1-[(S)-1-((S)-1-methoxycarbonyl-2-methyl-propylcarbamoyl)-2-methyl-propylcarbamoyl]-2-phenyl-ethyl}-sulfamidyl)-hexanoic acid
A solution of 270 mg of the compound from Example 143f) in 4 ml of dichloromethane/TFA (1:1, v/v) was stirred at RT for 2 h and then evaporated. The residue was purified by preparative HPLC and afforded 131 mg of the title compound as trifluoroacetate.
LC-MS: R_t(min) 1.16; calc.: $[M+H]^+$ 586.29 found 586.39 (method B).

Example 144
(S)-6-Amino-2-{3-[(R)-1-(bicyclo[2.2.1]hept-2-ylcarbamoyl)-2-cyclohexyl-ethyl]-sulfamidyl}-hexanoic acid
The title compound was in analogy to Example 143 employing a commercially available endo-norborbonylamine instead of the dipeptide in Example 143c).
LC-MS: R_t(min) 1.34; calc.: $[M+H]^+$ 473.28 found 473.36 (method B).

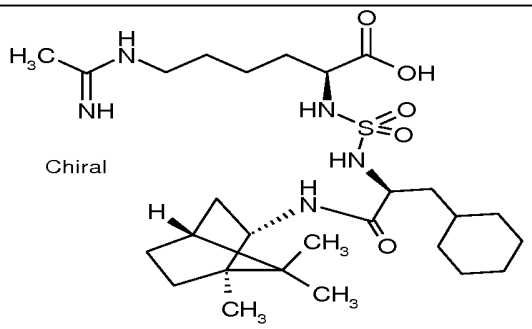
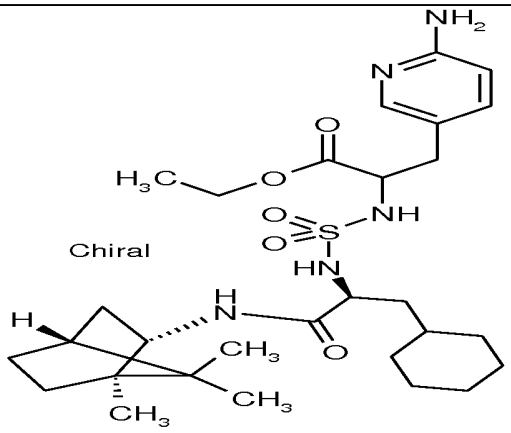
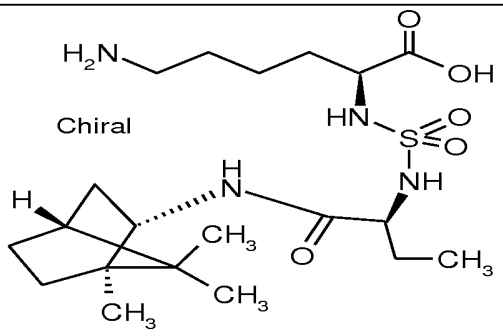
Example 145

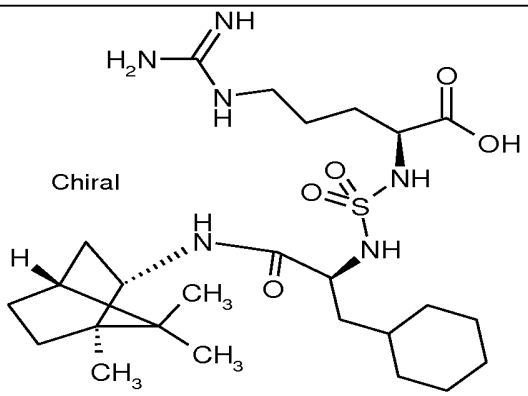
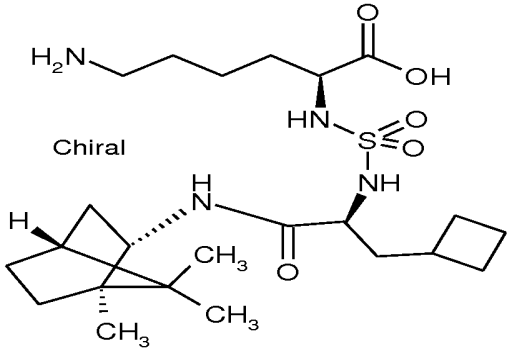
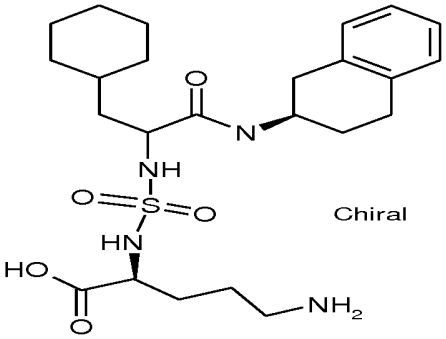
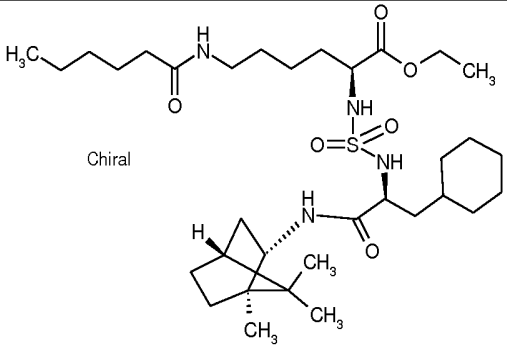
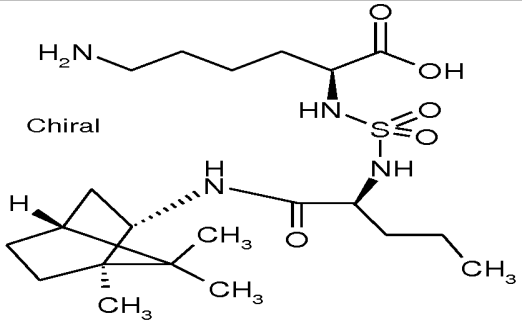
(S)-6-Amino-2-[3-((S)-1-cyclohexylcarbamoyl-2-phenyl-ethyl)-sulfamidyl]-hexanoic acid

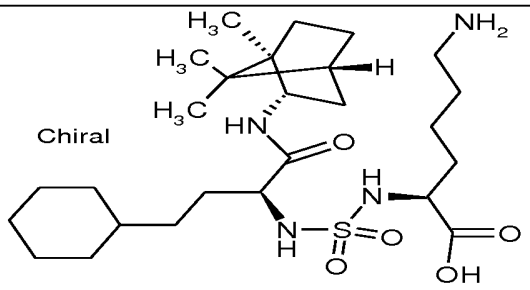
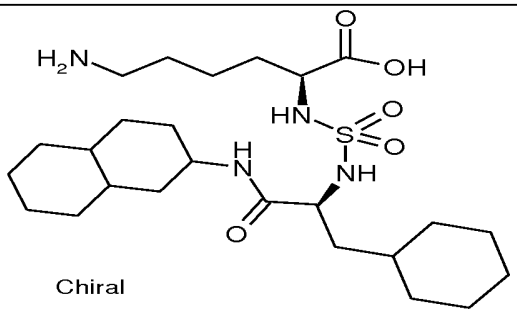
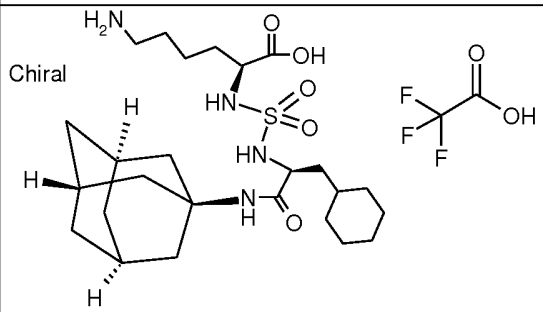
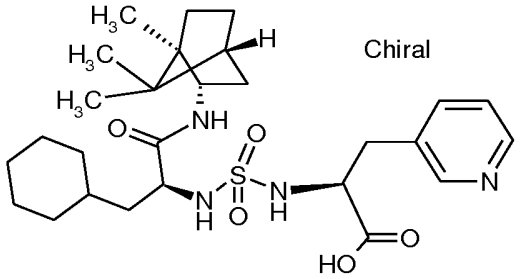
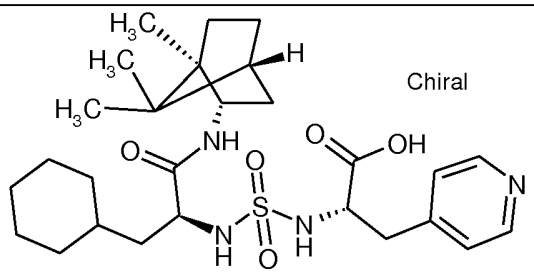
The title compound was in analogy to Example 143 employing a commercially available cyclohexylamine instead of the dipeptide in Example 143c).

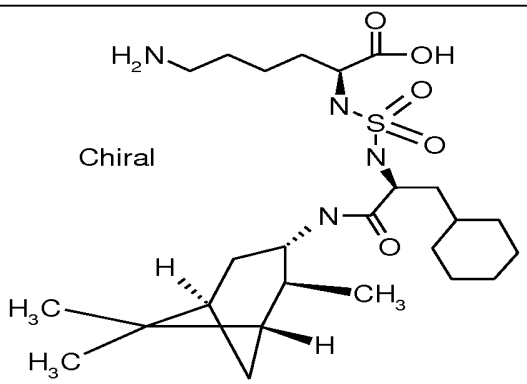
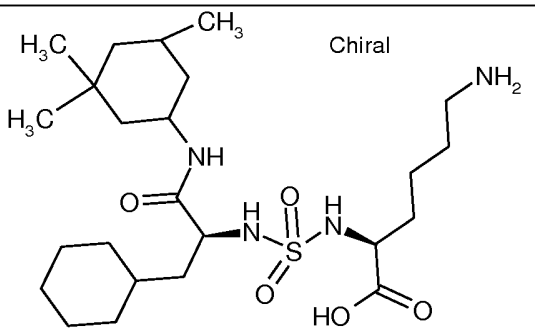
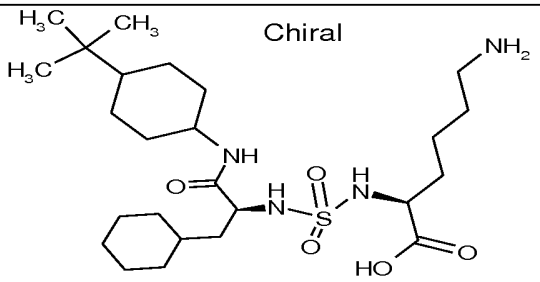
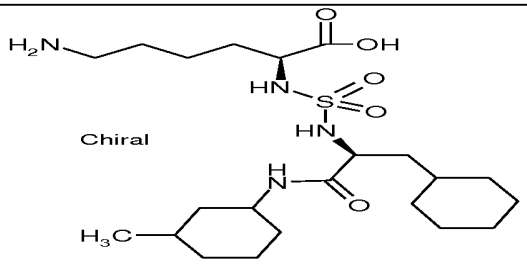
LC-MS: R_t(min) 1.20; calc.: $[M+H]^+$ 455.24 found 455.33 (method B).

The following examples were prepared in analogy to Example 143:

Example	Formula	LC/MS method	R_t	$[M+H]^+$ calc.	$[M+H]^+$ found
146		D	2.20	556.35	556.36
147		D	2.40	578.34	578.41
148		D	1.80	447.26	447.28

149		D	2.21	543.33	543.38
150		C	1.58	485.28	485.39
151		A	1.14	496.67	495.35
152		D	3.21	641.43	641.34
153		D	1.96	461.28	461.23

154		D	2.29	529.34	529.34
155		B	1.51	515.33	515.34
156		F	1.63	513.31	513.33
157		C	1.91	533.28	533.17
158		C	1.84	533.28	533.23

159		B	1.51	515.33	515.56
160		B	1.50	503.33	503.49
161		B	1.58	517.34	517.49
162		B	1.38	475.30	475.45

Example 163

(S)-6-Amino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoic acid

1) Benzyl (S)-6-benzyloxycarbonylamino-2(2-oxo-oxazolidine-sulfonylamino)-hexanoate

A solution of 2.61 ml of 2-bromoethanol (36.9 mmol, 1.0 equiv.) in dichloromethane (20 ml) was slowly added to a solution of 5.21 g of chlorosulfonyl isocyanate (36.9 mmol,

1.0 equiv.) in dichloromethane (300 ml) at 0°C under argon in such a way that the internal temperature remained below 10°C. Stirring was then continued at 0°C for 30 min. A solution of 15.0 g of H-Lys(Z)-OBzL•HCl (36.9 mmol, 1.0 equiv.) and 16.5 ml of triethylamine (118.0 mmol, 3.2 equivalents (equiv.)) in 120 ml of CH_2Cl_2 was added dropwise to the solution in such a way that the temperature of the reaction mixture did not go above 10°C. After the addition, the ice bath was removed and the mixture was stirred at RT for 4 h. The organic solution was then washed three times with 100 ml of 0.2M HCl (aq.), dried over Na_2SO_4 and concentrated. 18.4 g of the crude title compound were obtained as a colorless oil which was directly employed further in step 3..
LC-MS: R_t(min) 1.82; calc.: $[M+H]^+$ 520.17 found: 520.30 (method B).

2) tert-Butyl [(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethyl]-carbamate
3.53 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (18.4 mmol, 1.0 equiv.), 1.25 g of 1-hydroxybenzotriazole (9.2 mmol, 0.5 equiv.) and 7.3 ml of Hünig's base were added to a solution of 5.0 g of (S)-2-tert-butoxycarbonylamino-3-cyclohexylpropionic acid (Boc-Cha-OH, 18.4 mmol, 1.0 equiv.) in DMF (60 ml) at 0°C under argon, and the mixture was stirred for 30 min. Then 2.83 g of (R)-(+)-bornylamine (18.4 mmol, 1.0 equiv.) and 3.7 ml of Hünig's base were added, and the mixture was stirred at RT for 16 h. The reaction mixture was quenched with $NaHCO_3$ (saturated, aq.) and extracted three times with ethyl acetate. The combined organic phases were washed twice with water and dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel with heptane/ethyl acetate mixtures as eluent afforded 6.58 g (88% yield) of the title compound as a colorless oil.
LC-MS: R_t(min) 2.42; calc.: $[M+H]^+$ 407.33 found: 407.32 (method B).

3) (S)-2-Amino-3-cyclohexyl-N-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-propionamide trifluoroacetate

50 ml of TFA were slowly added to a solution of 6.5 g of tert-butyl [(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethyl]-carbamate (16.0 mmol) in 50 ml of CH_2Cl_2 at 0°C under argon. The mixture was allowed to reach RT. After 3 h, the reaction mixture was concentrated. The title compound was obtained as a pale yellow oil which was employed directly in the next step. LC-MS R_t(min) 1.60; calc.: $[M+H]^+$ 307.27 found: 307.39 (method C).

4) Benzyl (S)-6-benzyloxycarbonylamino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoate

11.63 g of benzyl (S)-6-benzyloxycarbonylamino-2(2-oxo-oxazolidine-sulfonylamino)-hexanoate (22.4 mmol, 1.4 equiv.) and 4.9 g of (S)-2-amino-3-cyclohexyl-N-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-propionamide trifluoroacetate (16.0 mmol, 1.0 equiv.) were suspended in 80 ml of MeCN and, after addition of 8.9 ml of Et_3N, the mixture was heated under reflux for 20 h. After cooling, the volatile constituents were removed in a rotary evaporator and the residue was purified by flash chromatography on silica gel with heptane/ethyl acetate mixtures as eluent. 9.0 g (76% yield) of the title compound were obtained as a colorless foam.

LC-MS: R_t(min) 2.61; calc.: $[M+H]^+$ 739.41 found: 739.43 (method B).

5) (S)-6-Amino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoic acid

9.0 g of benzyl (S)-6-benzyloxycarbonylamino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexanoate (12.2 mmol) were dissolved in 90 ml of methanol and, after addition of 600 mg of 10% Pd/C, hydrogenated at RT under atmospheric pressure for 3.5 h. The reaction mixture was filtered through Celite and concentrated. 6.1 g (97%) of the title compound were obtained as a colorless oil. 100 mg of the compound were dissolved in 5

ml of MeCN. Addition of 50 ml of water resulted in a suspension. Freeze drying resulted in a colorless solid.
LC-MS: R_t(min) 1.70; calc.: $[M+H]^+$ 515.33 found: 515.35 (method F).
^{1}H-NMR (DMSO-d_6) δ 0.68 (s, 3H), 0.82 (s, 3H), 0.83-0.91 (m, 2H), 0.89 (s, 3H), 0.97 (dd, 1H, J = 4.8, 13.0 Hz), 1.08-1.34 (m, 7H), 1.35-1.55 (m, 5H), 1.56-1.72 (m, 9H), 1.78 (d, 1H, J = 13.0 Hz), 2.04-2.13 (m, 1H), 2.75 (t, 2H, J = 7.1 Hz), 3.51 (t, 1H, J = 5.5 Hz), 3.83 (t, 1H, J = 7.0 Hz), 4.03-4.10 (m, 1H), 6.91-7.05 (br, 1H), 7.77 (d, 1H, J = 8.8 Hz), 7.5-8.2 (br, 2H).

Example 164
3-(6-Amino-pyridin-3-ylmethyl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-carbamoyl)-ethylsulfamidyl]-propionic acid

1) tert-Butyl 2-amino-3-(6-tert-butoxycarbonylamino-pyridin-3-yl)-propionate
660 mg of N-(diphenylmethylene)glycine tert-butyl ester (2.23 mmol, 1.0 equiv.) were dissolved in 15 ml of dry THF and cooled to 0°C under argon. Then 2.23 ml of 1 M lithium hexamethyldisilazane (LiHMDS) solution in THF were added dropwise, and the mixture was stirred at 0°C for 15 min. Subsequently, 642 mg of tert-butyl (5-bromomethylpyridin-2-yl)-carbamate (2.23 mmol, 1.0 equiv.) were added, and the mixture was stirred at 0°C for 2 h. The mixture was quenched with 18 ml of sat. citric acid and stirred at RT for 1 h. The mixture was extracted with ethyl acetate (2x 30 ml), and the organic phases were washed with 50 ml of 1M HCl. The aqueous phases were combined and adjusted to pH 10 with 2M NaOH and then extracted 3x with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel with heptane/ethyl acetate mixtures as eluent. 600 mg (80% yield) of the title compound were obtained as a colorless solid.
LC-MS: R_t(min) 1.06; calc.: $[M+H]^+$ 338.21 found: 338.27 (method B).

2) tert-Butyl 3-(6-tert-butoxycarbonylamino-pyridin-3-yl)-2-(2-oxo-oxazolidine-3-sulfonylamino)-propionate

A solution of 0.126 ml of 2-bromoethanol (1.78 mmol, 1.0 equiv.) in dichloromethane (10 ml) was slowly added dropwise to a solution of 251 mg of chlorosulfonyl isocyanate (1.78 mmol, 1.0 equiv.) in dichloromethane (10 ml) under argon at 0°C in such a way that the temperature did not exceed 10°C. After the addition, the mixture was stirred at 0°C for a further 30 min. A mixture of 600 mg of tert-butyl 2-amino-3-(6-tert-butoxycarbonylamino-pyridin-3-yl)-propionate (1.78 mmol, 1.0 equiv.) and 0.545 ml of triethylamine (3.91 mmol, 2.2 equiv.) in 5 ml of CH_2Cl_2 was added dropwise to this solution in such a way that the temperature did not rise above 10°C. After the addition, the ice bath was removed and the mixture was stirred at RT for a further 3 h. The residue after concentration was chromatographed on silica gel with heptane/ethyl acetate mixtures as eluent. 320 mg (37% yield) of the title compound were obtained as a colorless solid.

LC-MS: R_t(min) 1.40; calc.: $[M+H]^+$ 487.19 found: 487.26 (method B).

3) tert-Butyl 3-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-carbamoyl)-ethylsulfamidyl] propionate

320 mg of tert-butyl 3-(6-tert-butoxycarbonylamino-pyridin-3-yl)-2-(2-oxo-oxazolidine-3-sulfonylamino)-propionate (0.66 mmol, 1.0 equiv.) and 277 mg of (S)-2-amino-3-cyclohexyl-N-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-propionamide trifluoroacetate (0.66 mmol, 1.0 equiv.), prepared as described above, were suspended in 12 ml of MeCN and, after addition of 0.37 ml of Et_3N, heated under reflux for 20 h. After cooling, the volatile constituents were evaporated off, and the residue was purified by flash chromatography on silica gel with heptane/ethyl acetate mixtures as eluent. 139 mg (30% yield) of the title compound were obtained as a colorless solid.

LC-MS: R_t(min) 2.19; calc.: $[M+H]^+$ 706.42 found: 706.54 (method

B).

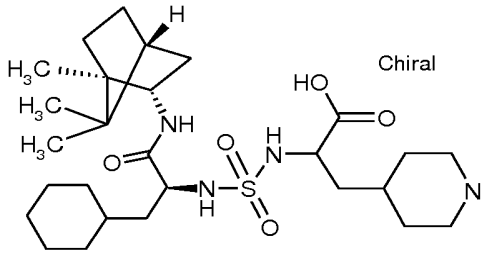
4) 3-(6-Amino-pyridin-3-ylmethyl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-carbamoyl)-ethylsulfamidyl]-propionic acid trifluoroacetate

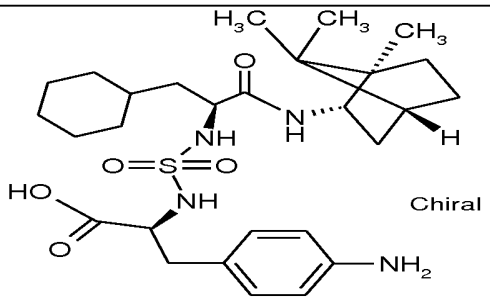
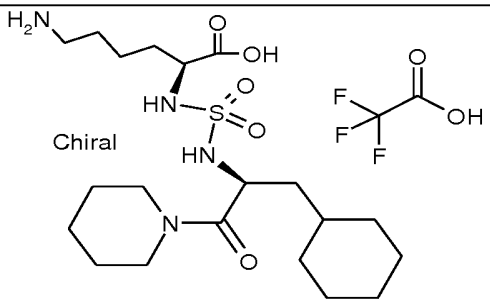
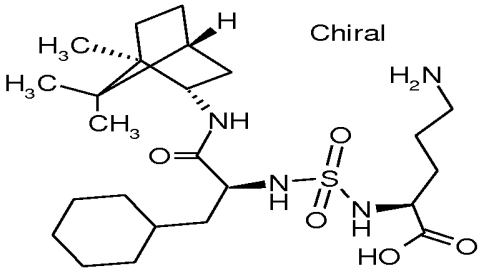
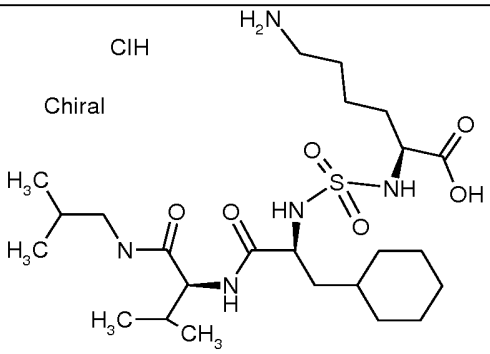
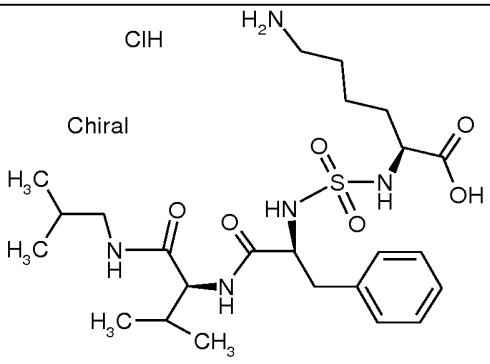
135 mg of tert-butyl 3-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-carbamoyl)-ethylsulfamidyl] propionate (0.19 mmol) were dissolved in 1.0 ml of CH_2Cl_2 and cooled to 0°C. Then 0.8 ml of TFA was added, and the mixture was stirred at RT. After 1 h, the volatile constituents were evaporated and the residue was purified by RP-HPLC. 70 mg (55% yield) of the title compound were obtained as a colorless solid.

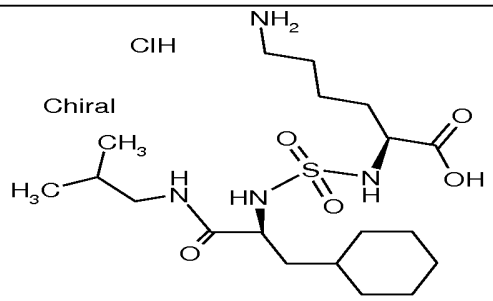
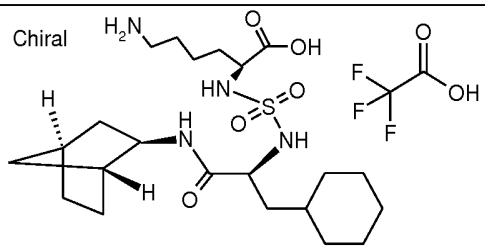
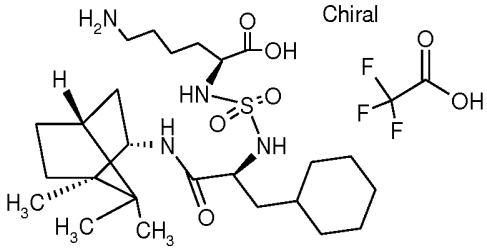
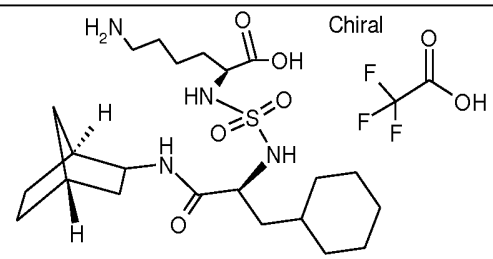
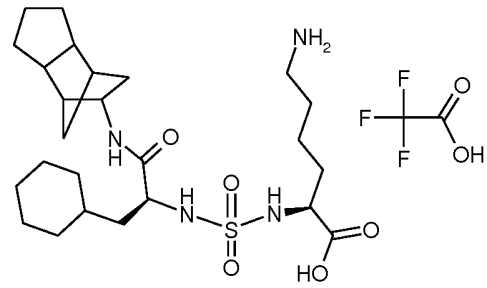
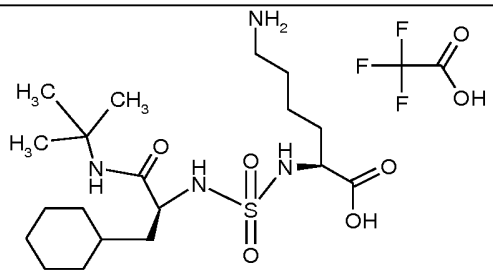
LC-MS: R_t(min) 1.61; calc.: $[M+H]^+$ 550.31 found: 550.39 (method B), 1:1 mixture of the diastereomers.

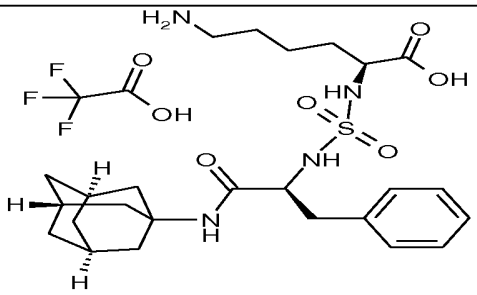
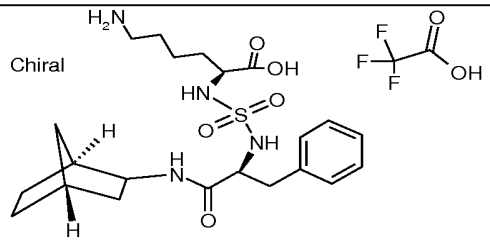
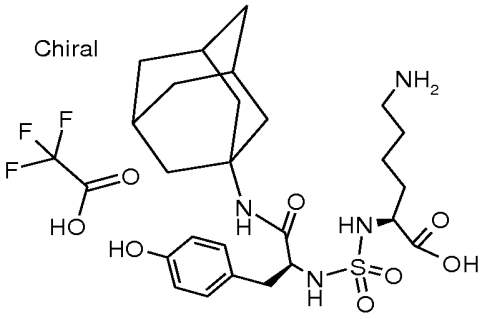
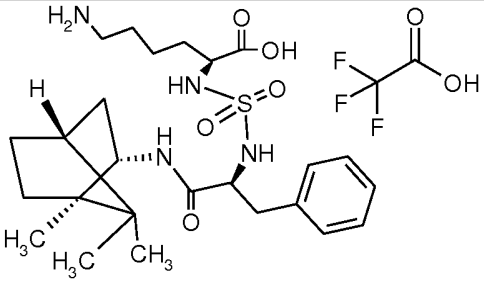
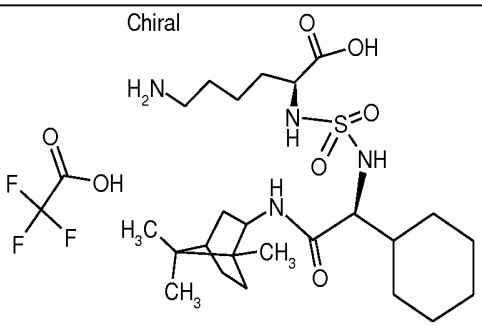
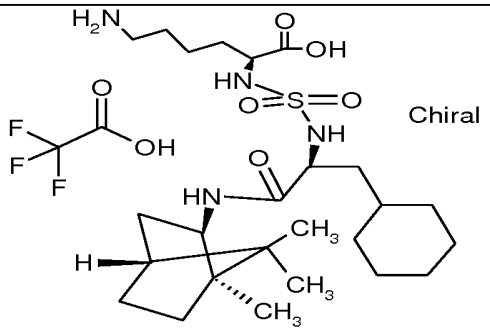
^{1}H-NMR (DMSO-d_6) δ 0.67 (s, 3H), 0.69 (s, 3H), 0.82 (s, 6H), 0.79-0.92 (m, 4H), 1.08-1.39 (m, 16H), 1.56-1.78 (m, 16H), 2.01 (t, 1H, J = 12.0 Hz), 2.11 (t, 1H, J = 12.0 Hz), 2.70 (dd, 1H, J = 6.4, 13.9 Hz), 2.79 (dd, 2H, J = 7.0, 13.9 Hz), 2.94 (dd, 1H, J = 5.5, 14.1 Hz), 3.73-3.90 (m, 2H), 4.01-4.13 (m, 1H), 6.80 (d, 0.5H, J = 8.0 Hz), 6.94 (dd, 2H, J = 5.3, 8.6 Hz), 7.01 (d, 1H, J = 9.1 Hz), 7.11 (d, 1H, J = 8.7 Hz), 7.18 (d, 1H, J = 9.1 Hz), 7.69-7.74 (m, 3H), 7.79 (d, 2H, J = 9.4 Hz), 7.85 (dd, 1H, J = 1.9, 9.1 Hz), 7.88-7.99 (br, 4H)

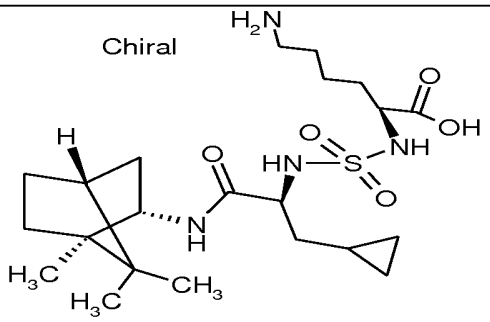
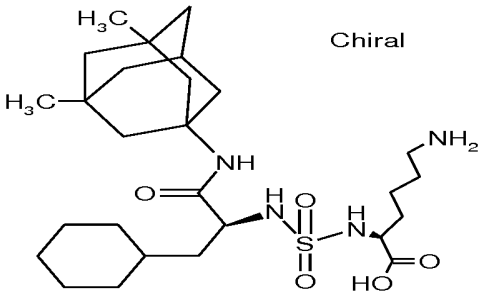
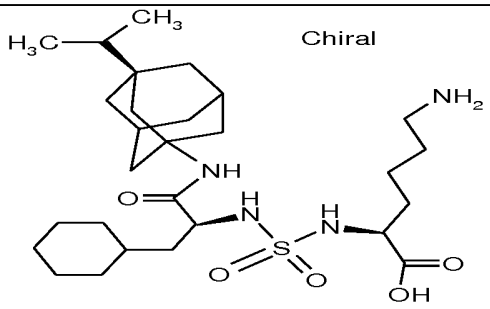
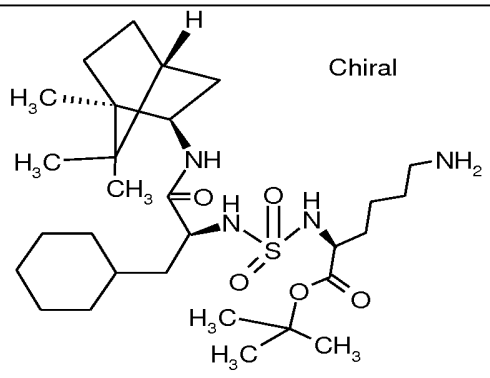
The following examples were prepared in analogy to Example 163:

165		B	1.55	541.34	541.39

166		B	1.50	549.31	549.35
167		B	1.28	447.26	447.25
168		A	1.20	501.71	501.25
169		A	1.00	534.74	534.35
170		A	0.94	528.70	528.25

171		A	0.96	435.61	435.25
172		B	1.32	473.28	473.30
173		B	1.51	515.33	515.33
174		B	1.33	473.30	473.28
175		B	1.45	513.31	513.34
176		B	1.26	435.26	435.28

177		B	1.35	507.26	507.24
178		F	1.30	467.23	467.35
179		F	1.36	523.23	523.41
180		F	1.53	509.28	509.40
181		C	1.60	501.31	501.29
182		F	1.69	515.33	515.51

183		B	1.31	473.28	473.39
184		B	1.61	541.34	541.39
185		B	1.66	555.36	555.36
186		B	1.67	571.39	571.50

Pharmacological examples

The prepared substances were tested for TAFIa inhibition using the Actichrome plasma TAFI activity kit from American Diagnostica (Pr. No. 874). This entailed adding 28 µl of assay buffer (20 mM Hepes, 150 mM NaCl, pH 7.4) and 10 µl of TAFIa (American Diagnostica Pr. No. 874TAFIA; 2.5 /ml) to 2 µl of 2.5 mM DMSO solution of the substance and incubating in a 96 half-well microtiter plate at room temperature for 15 minutes. The enzymic reaction was started by adding 10 µl of TAFIa developer (prediluted 1:2 with assay buffer). The time course

of the reaction was followed at 420 nm in a microtiter plate reader (SpectraMax plus 384; Molecular Devices) for 15 minutes.

The IC50 values were calculated from the averaged values (duplicate determination) of serial dilutions of the substance with the aid of the Softmax Pro software (version 4.8; Molecular Devices).

Table 1 shows the results.

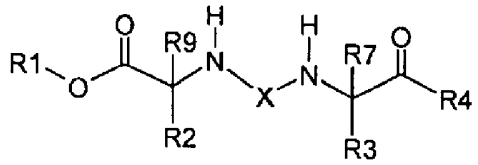
Table 1:

Example No.	IC_{50} [µM]
143	9.756
145	10.601
146	0.071
149	0.049
150	0.357
153	1.087
154	0.220
155	0.669
156	0.492
157	0.2
159	0.131
163	0.012
164	0.026
165	0.882
169	0.770
172	0.420
173	0.012
174	0.326
175	0.168
177	2.117
180	0.168
182	0.069
183	0.805
184	1.069
185	0.4

Example No.	IC_{50} [µM]
186	22.943
187	10.176

Patentkrav

1. Forbindelse med formel I



(I)

og/eller en stereoisomer form af forbindelsen med formel I og/eller blandinger af disse former i ethvert forhold og/eller et fysiologisk forligeligt salt af forbindelsen med formel I, idet

X står for $-SO_2-$,

R1 står for

1) hydrogenatom,

2) $-(C_1-C_6)$-alkyl,

3) $-(C_0-C_4)$-alkylen-(C_3-C_{12})-cycloalkyl eller

4) $-(C_1-C_6)$-alkylen-(C_6-C_{14})-aryl,

R2 står for gruppen med formel II

$-(A1)_m-A2$ (II)

hvor

m betegner det hele tal nul eller 1,

A1 står for

1) $-(CH_2)_n-$, hvor n betegner det hele tal nul, 1, 2 eller 3,

2) $-NH-(CH_2)_n-$, hvor n betegner det hele tal nul, 1, 2 eller 3,

3) $-NH(C_1-C_6)$-alkyl$)-(CH_2)_n-$, hvor n betegner det hele tal nul, 1, 2 eller 3,

4) $-NH((C_3-C_6)$-cycloalkyl$)-(CH_2)_n-$, hvor n betegner det hele tal nul, 1, 2 eller 3,

5) $-O-(CH_2)_n-$, hvor n betegner det hele tal nul, 1, 2 eller 3, eller

6) $-(CH_2)_n-SO_x-$, hvor n betegner det hele tal nul, 1, 2 eller 3, og x betegner det hele tal nul, 1 eller 2,

A2 står for

1) Het, idet der ved Het forstås et 4- til 15-leddet heterocyklisk ringsystem med 4 til 15 ringatomer, som foreligger i et, to eller tre med hinanden forbundne ringsystemer, og som indeholder en, to, tre eller fire ens eller forskellige heteroatomer fra rækken oxygen, nitrogen eller svovl og er usubstitueret eller uafhængigt af hinanden

er substitueret en, to eller tre gange med et -(C_1-C_3)-alkyl, halogen, -NH_2, -CF_3 eller -O-CF_3,
2) -(C_0-C_6)-alkylen-NH_2,
3) -(C_1-C_6)-alkylen-NH-C(=NH)-NH_2,
4) -(C_1-C_6)-alkylen-NH-C(=NH)-(C_1-C_4)-alkyl,
5) -(C_0-C_4)-alkylen-O-NH-C(=NH)-NH_2,
6) -(C_0-C_4)-alkylen-NH-C(O)-(C_1-C_6)-alkyl,
7) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-aryl, idet aryl er usubstitueret eller er substitueret med -NH_2 eller er substitueret med -NH_2 og en, to eller tre gange med R15,
8) -(C_3-C_8)-cycloalkyl-NH_2 eller
9) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl, idet aryl er usubstitueret eller er substitueret med -NH_2 eller er substitueret med -NH_2 og en, to eller tre gange med R15,
R3 står for
1) -(C_1-C_6)-alkyl,
2) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl,
3) -(C_1-C_6)-alkylen-(C_6-C_{14})-aryl, idet aryl uafhængigt af hinanden er substitueret en, to eller tre gange med R15,
4) -(C_0-C_8)-alkylen-N(R5)-PG,
5) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-aryl, idet aryl uafhængigt af hinanden er substitueret en, to eller tre gange med R15,
6) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl-(C_0-C_4)-alkylen-N(R5)-PG,
7) -(C_0-C_8)-alkylen-O-PG,
8) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl-(C_0-C_4)-alkylen-O-PG,
9) -(C_0-C_8)-alkylen-C(O)-O-PG,
10) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl-(C_0-C_4)-alkylen-C(O)-O-PG eller
11) hydrogenatom,
R4 står for -N(R6)$_2$,
idet R6 er ens eller forskellige og uafhængigt af hinanden står for
1) hydrogenatom,
2) -(C_1-C_6)-alkyl,
3) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med R11, halogen, -C(O)-O-R11, -(C_1-

C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl,

4) -(C_0-C_6)-alkylen-(C_6-C_{14})-aryl, idet aryl og alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med R11, halogen, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11, -C(O)-N(R8)$_2$ eller -O-(C_1-C_4)-alkyl,

5) -(C_0-C_8)-alkylen-N(R5)-PG,

6) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl-(C_0-C_4)-alkyl-N(R5)-PG,

7) -(C_0-C_8)-alkylen-O-PG,

8) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl-(C_0-C_4)-alkyl-O-PG,

9) -(C_0-C_8)-alkylen-C(O)-O-R11,

10) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl-(C_0-C_4)-alkyl-C(O)-O-PG,

11) -(C_0-C_4)-alkylen-Het, idet der ved Het forstås et 4- til 15-leddet heterocyklisk ringsystem med 4 til 15 ringatomer, som foreligger i et, to eller tre med hinanden forbundne ringsystemer, og som indeholder et, to, tre eller fire ens eller forskellige heteroatomer fra rækken oxygen, nitrogen eller svovl, idet Het eller alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med R11, halogen, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller -O-(C1-C4)-alkyl,

12) -(C_1-C_3)-fluoralkyl,

13) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH$_2$,

14) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH-(C_1-C_4)-alkyl eller

15) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH-CH(R12)-R13,

eller de to grupper R6 sammen med det N-atom, som de er bundet til, danner en mono- eller bicyklisk ring med 4 til 9 ringatomer, som er mættet, delvist mættet eller aromatisk, idet ringen er usubstitueret eller er substitueret en eller to gange med -(C_1-C_4)-alkyl, -C(O)-O-R11, halogen, -(C_1-C_4)-alkyl-O-R11 eller phenyl,

R5 står for hydrogenatom eller -(C_1-C_6)-alkyl,

PG står for en beskyttelsesgruppe for amino-, carboxyl- eller for hydroxyfunktionen,

R7 står for hydrogenatom eller -(C_1-C_6)-alkyl,

R8 står for hydrogenatom eller -(C_1-C_6)-alkyl,

R9 står for hydrogenatom eller -(C_1-C_6)-alkyl,

R11 og R12 er ens eller forskellige og uafhængigt af hinanden står for

1) hydrogenatom,
2) -(C_1-C_6)-alkyl,
3) -(C_0-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med halogen, -OH eller -O-(C_1-C_4)-alkyl,
4) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med R13, halogen, -C(O)-O-R13, -(C_1-C_4)-alkyl-O-R13, -O-(C_1-C_4)-alkyl eller -(C_0-C_4)-alkylen-phenyl,
5) -(C_0-C_4)-alkylen-C(O)-N(R13)$_2$ eller
6) -(C_0-C_4)-alkylen-indolyl,
R13 står for
1) hydrogenatom,
2) -(C_1-C_4)-alkyl,
3) -(C_0-C_4)-alkylen-C(O)-O-R14,
4) -(C_0-C_4)-alkylen-C(O)-R14 eller
5) -(C_0-C_4)-alkylen-O-R14,
R14står for hydrogenatom, -(C_1-C_4)-alkyl, -NH_2 eller -OH, og
R15 står for hydrogenatom, -(C_1-C_4)-alkyl, -O-CF_3, -NH_2, -OH, -CF_3 eller halogen.

2. Forbindelse med formel I ifølge krav 1, idet
R1 står for
1) hydrogenatom eller
2) -(C_1-C_4)-alkyl,
R2 står for
1) -(C_1-C_6)-alkylen-NH_2,
2) -(C_0-C_4)-alkylen-pyridyl-NH_2,
3) -(C_0-C_4)-alkylen-piperidinyl-NH_2,
4) -(C_0-C_4)-alkylen-thiazolyl-NH2,
5) -(C_1-C_6)-alkylen-NH-C(=NH)-NH_2,
6) -(C_0-C_4)-alkylen-(C_3-C_8)-cycloalkyl-NH_2,
7) -(C_1-C_6)-alkylen-NH-C(=NH)-(C_1-C_4)-alkyl,
8) -(C_0-C_4)-alkylen-O-NH-C(=NH)-NH_2,
9) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-aryl, idet aryl er usubstitueret eller er substitueret med -NH_2 eller er substitueret med -NH_2 og en, to eller tre gange med R15,
10) -(C_0-C_4)-alkylen-NH-C(O)-(C_1-C_4)-alkyl,

11) -(C_0-C_4)-alkylen-(C_6-C_{14})-aryl, idet aryl er usubstitueret eller er substitueret med -NH_2 eller er substitueret med -NH_2 og en, to eller tre gange med R15, eller

12) -(C_1-C_4)-alkylen-SO_x-(C_1-C_4)-alkylen-NH_2, idet x betegner det hele tal nul, 1 eller 2,

R3 står for

1) -(C_1-C_4)-alkyl,

2) -(C_0-C_4)-alkylen-(C_3-C_8)-cycloalkyl,

3) -(C_1-C_6)-alkylen-aryl, idet aryl uafhængigt af hinanden er substitueret en, to eller tre gange med R15,

4) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-aryl, idet aryl uafhængigt af hinanden er substitueret en, to eller tre gange med R15,

5) -(C_1-C_6)-alkylen-NH-PG,

6) -(C_1-C_6)-alkylen-O-PG,

7) -(C_1-C_6)-alkyl, eller

8) hydrogenatom,

idet PG står for t-butyl-, t-butyloxycarbonyl eller benzyloxycarbonyl,

R4 står for -N(R6)$_2$,

idet R6 er ens eller forskellige og uafhængigt af hinanden står for

1) hydrogenatom,

2) -(C_1-C_6)-alkyl,

3) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med R11, halogen, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl

4) -(C_0-C_4)-alkylen-C(R11)(R12)-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med R11, halogen, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl,

5) -(C_0-C_4)-alkylen-Het, idet der ved Het forstås et 4- til 15-leddet heterocyklisk ringsystem med 4 til 15 ringatomer, som foreligger i et, to eller tre med hinanden forbundne ringsystemer, og som indeholder et, to, tre eller fire ens eller forskellige heteroatomer fra rækken oxygen, nitrogen eller svovl, idet Het eller alkylen er usubstitueret eller

uafhængigt af hinanden er substitueret en, to eller tre gange med R11, halogen, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl,

6) -(C_0-C_6)-alkylen-aryl, idet aryl eller alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med R11, halogen, -C(O)-O-R11, -(C_0-C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl,

7) -(C_0-C_4)-alkylen-C(R11)(R12)-aryl, idet aryl eller alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med R11, halogen, -C(O)-O-R11, -(C_0-C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl,

8) 1,2,3,4-tetrahydro-naphthalenyl,

9) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH_2,

10) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH-(C_1-C_4)-alkyl,

11) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH-CH(R12)-R13,

12) -(C_0-C_6)-alkylen-C(O)-O-R11, idet alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en eller to gange med R11, halogen, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller -O-(C_1-C_4)-alkyl,

13) -(C_0-C_4)-alkylen-C(R11)(R12)-C(O)-O-R11, eller

14) -(C_1-C_3)-fluoralkyl,

eller de to grupper R6 sammen med det N-atom, som de er bundet til, danner en mono- eller bicyklisk ring med 4 til 9 ringatomer, som er mættet, delvist mættet eller aromatisk, idet ringen er usubstitueret eller er substitueret en eller to gange med -(C_1-C_4)-alkyl, -C(O)-O-R11, halogen, -(C_1-C_4)-alkyl-O-R11 eller phenyl,

R7 står for hydrogenatom eller -(C_1-C_4)-alkyl,

R9 står for hydrogenatom eller -(C_1-C_4)-alkyl,

R11 og R12 er ens eller forskellige og uafhængigt af hinanden står for

1) hydrogenatom,

2) -(C_1-C_4)-alkyl,

3) -(C_0-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med halogen, -OH eller -O-(C_1-C_4)-alkyl,

4) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en,

to, tre eller fire gange med R13, halogen, -C(O)-O-R13, -(C_1-C_4)-alkyl-O-R13, -O-(C_1-C_4)-alkyl eller -(C_0-C_4)-alkylen-phenyl,
5) -(C_0-C_4)-alkylen-C(O)-N(R13)$_2$ eller
6) -(C_0-C_4)-alkylen-indolyl,
R13 står for
1) hydrogenatom,
2) -(C_1-C_4)-alkyl,
3) -(C_0-C_4)-alkylen-C(O)-O-R14,
4) -(C_0-C_4)-alkylen-C(O)-R14 eller
5) -(C_0-C_4)-alkylen-O-R14,
R14 står for hydrogenatom, -(C_1-C_4)-alkyl, -NH_2 eller -OH, og
R15 står for hydrogenatom, -(C_1-C_4)-alkyl, -O-CF_3, -NH_2, -OH, -CF_3 eller halogen.

3. Forbindelse med formel I ifølge krav 1 eller 2, idet
R1 står for
1) hydrogenatom eller
2) -(C_1-C_4)-alkyl,
R2 står for
1) -(C_1-C_6)-alkylen-NH_2,
2) -(C_1-C_4)-alkylen-pyridyl-NH_2,
3) -(C_1-C_4)-alkylen-piperidinyl-NH_2,
4) -(C_1-C_6)-alkylen-NH-C(=NH)-NH_2,
5) -(C_0-C_4)-alkylen-(C_3-C_6)-cycloalkyl-NH_2,
6) -(C_1-C_6)-alkylen-NH-C(=NH)-(C_1-C_4)-alkyl,
7) -(C_1-C_4)-alkylen-O-NH-C(=NH)-NH_2,
8) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller er substitueret med -NH_2 eller er substitueret med -NH_2 og en, to eller tre gange med R15,
9) -(C_1-C_4)-alkylen-NH-C(O)-(C_1-C_6)-alkyl,
10) -(C_1-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller er substitueret med -NH_2 eller er substitueret med -NH_2 og en, to eller tre gange med R15,
11) -(C_1-C_4)-alkylen-SO_2-(C_1-C_4)-alkylen-NH_2 eller
12) -(C_1-C_4)-alkylen-S-(C_1-C_4)-alkylen-NH_2,
R3 står for
1) -(C_1-C_4)-alkyl,
2) -(C_1-C_4)-alkylen-(C_3-C_6)-cycloalkyl,

3) -(C_1-C_4)-alkylen-phenyl, idet phenyl uafhængigt af hinanden er substitueret en, to eller tre gange med R15,

4) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-phenyl, idet phenyl uafhængigt af hinanden er substitueret en, to eller tre gange med R15,

5) hydrogenatom,

R4 står for -N(R6)$_2$,

idet R6 er ens eller forskellige og uafhængigt af hinanden står for

1) hydrogenatom,

2) -(C_1-C_4)-alkyl,

3) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er udvalgt af gruppen cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethyl-bicyclo[3.1.1]heptanyl, decahydro-naphthalenyl, tetrahydronaphthalenyl, octahydro-4,7-methano-indenyl eller bicyclo[2.2.1]heptanyl, og hvor cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med -(C_1-C_4)-alkyl, -C(O)-O-R11 eller -(C_1-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller er substitueret med halogen,

4) -(C_0-C_4)-alkylen-C(R11)(R12)-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er udvalgt af gruppen cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethyl-bicyclo[3.1.1]heptanyl, decahydronaphthalen, tetrahydronaphthalenyl, octahydro-4,7-methano-indenyl eller bicyclo[2.2.1]heptanyl, og hvor cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med -(C_1-C_4)-alkyl, -C(O)-O-R11 eller -(C_1-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller er substitueret med halogen,

5) -(C_0-C_4)-alkylen-Het, idet Het er udvalgt fra gruppen acridinyl, azepinyl, azetidinyl, aziridinyl, benzimidazalinyl, benzimidazolyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl,

quinuclidinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dibenzofuranyl, dibenzothiophenyl, dihydrofuran[2,3-b]-tetrahydrofuranyl, dihydrofuranyl, dioxolyl, dioxanyl, 2H, 6H-1,5,2-dithiazinyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolidinyl, 2-isothiazolinyl, isothiazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, oxothiolanyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxatiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridothiophenyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrahydropyridinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienoimidazolyl, thienooxazolyl, thienopyridin, thienothiazolyl, thiomorpholinyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl og xanthenyl, idet Het eller alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en eller to gange med -(C_1-C_4)-alkyl,

6) -(C_1-C_6)-alkylen-phenyl, idet phenyl eller alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en eller to gange med halogen, phenyl, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11, -O-(C_1-C_4)-alkyl eller -(C_1-C_4)-alkyl,

7) -(C_0-C_4)-alkylen-C(R11)(R12)-phenyl, idet phenyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med phenyl eller fluor,

8) 1,2,3,4-tetrahydro-naphthalenyl,

9) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH2,
10) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH-(C1-C4)-alkyl,
11) -(C_0-C_4)-alkylen-CH(R11)-C(O)-NH-CH(R12)-R13,
12) -(C_1-C_6)-alkylen-C(O)-O-R11, idet alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en eller to gange med halogen, phenyl, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11, -O-(C_1-C_4)-alkyl eller-(C_1-C_4)-alkyl,
13) -(C_0-C_4)-alkylen-C(R11)(R12)-C(O)-O-R11 eller
14) -(C_1-C_3)-fluoralkyl,
eller de to grupper R6 sammen med det N-atom, som de er bundet til, danner en mono- eller bicyklisk ring udvalgt af gruppen pyrrolidin, piperidin, 2-aza-bicyclo[3.2.2]nonan og 7-aza-bicyclo[2.2.1]heptan, idet ringen er usubstitueret eller er substitueret en eller to gange med -(C_1-C_4)-alkyl, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller phenyl,
R7 står for hydrogenatom eller -(C_1-C_4)-alkyl,
R9 står for hydrogenatom eller -(C_1-C_4)-alkyl,
R11 og R12 er ens eller forskellige og uafhængigt af hinanden står for
1) hydrogenatom,
2) -(C_1-C_4)-alkyl,
3) -(C_0-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med -OH, halogen eller -O-(C_1-C_4)-alkyl,
4) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er udvalgt af gruppen cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethyl-bicyclo[3.1.1]heptanyl, decahydro-naphthalenyl, tetrahydronaphthalenyl, octahydro-4,7-methano-indenyl eller bicyclo[2.2.1]heptanyl, og hvor cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med -(C_1-C_4)-alkyl, -C(O)-O-R13 eller phenyl, eller
5) -(C_0-C_4)-alkylen-indolyl,
R13 står for
1) hydrogenatom,
2) -(C_1-C_4)-alkyl,
3) -(C_0-C_4)-alkylen-C(O)-O-R14,
4) -(C_0-C_4)-alkylen-C(O)-R14 eller

5) -(C_0-C_4)-alkylen-O-R14, og
R14 står for hydrogenatom, -(C_1-C_4)-alkyl, -NH_2 eller -OH, og
R15 står for hydrogenatom, -(C_1-C_4)-alkyl, -O-CF_3, -NH_2, -OH, -CF_3 eller halogen.

4. Forbindelse med formel I ifølge krav 1 til 3, idet
R1 står for
1) hydrogenatom eller
2) -(C_1-C_4)-alkyl,
R2 står for
1) -(C_1-C_6)-alkylen-NH_2,
2) -(C_1-C_4)-alkylen-pyridyl-NH_2,
3) -(C_1-C_4)-alkylen-piperidinyl-NH_2,
4) -(C_1-C_4)-alkylen-NH-C(=NH)-NH_2,
5) -(C_1-C_6)-alkylen-NH-C(=NH)-(C_1-C_4)-alkyl,
6) -(C_1-C_4)-alkylen-(C_3-C_6)-cycloalkyl-NH_2,
7) -(C_1-C_4)-alkylen-O-NH-C(=NH)-NH_2,
8) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-phenyl,
9) -(C_1-C_4)-alkylen-NH-C(O)-(C_1-C_6)-alkyl,
10) -(C_1-C_4)-alkylen-phenyl-NH_2,
11) -(C_1-C_4)-alkylen-SO_2-(C_1-C_4)-alkylen-NH_2 eller
12) -(C_1-C_4)-alkylen-S-(C_1-C_4)-alkylen-NH_2,
R3 står for
1) -(C_1-C_4)-alkyl,
2) -(C_1-C_4)-alkylen-(C_3-C_6)-cycloalkyl,
3) -(C_1-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller er substitueret med -OH,
4) -(C_1-C_6)-alkylen-NH-C(O)-O-(C_1-C_4)-alkylen-phenyl,
5) hydrogenatom,
R4 står for -N(R6)$_2$,
idet R6 er ens eller forskellige og uafhængigt af hinanden står for
1) hydrogenatom,
2) -(C_1-C_6)-alkyl,
3) -(C_0-C_4)-alkylen-(C_3-C_8)-cycloalkyl, idet cycloalkyl er udvalgt af gruppen cyclohexyl, cyclopentyl, cyclopropyl, adamantanyl, 1,7,7-trimethyl-bicyclo[3.1.1]heptanyl, decahydro-naphthalen, octahydro-4,7-methano-indenyl eller

bicyclo[2.2.1]heptanyl, og hvor cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med -(C_1-C_4)-alkyl eller phenyl,

4) -C(R11)(R12)-adamantanyl,

5) -CH(R11)-C(O)-NH-CH(R12)-R13,

6) -(C_0-C_4)-alkylen-Het, idet Het er udvalgt af gruppen benzimidazolyl, isoxazolyl, piperidin, pyridin, pyrrolidinyl, thiophenyl og benzo[1,3]dioxol,

7) 1,2,3,4-tetrahydro-naphthalenyl,

8) -(C_0-C_4)-alkylen-C(R11)(R12)-phenyl, idet phenyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med phenyl eller fluor,

9) -CH(R11)-C(O)-NH_2,

10) -CH(R11)-C(O)-NH-CH(R12)-CH_2-OH,

11) -(C_1-C_6)-alkylen-phenyl, idet phenyl eller alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en eller to gange med chlor, fluor, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11, -O-(C_1-C_4)-alkyl, phenyl eller -(C_1-C_4)-alkyl,

12) -CH(R11)-C(O)-NH-(C_1-C_4)-alkyl,

13) -(C_0-C_4)-alkylen-C(R11)(R12)-bicyclo[3.1.1]heptanyl, idet bicyclo[3.1.1]heptanyl er usubstitueret eller er substitueret en til fire gange med -(C_1-C_4)-alkyl,

14) -(C_1-C_6)-alkylen-C(O)-O-R11, idet alkylen er usubstitueret eller uafhængigt af hinanden er substitueret en eller to gange med chlor, fluor, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11, -O-(C_1-C_4)-alkyl, phenyl eller -(C_1-C_4)-alkyl,

15) -(C_0-C_4)-alkylen-C(R11)(R12)-C(O)-O-R11 eller

16) -CH_2-CF_2-CF_3,

eller de to grupper R6 sammen med det N-atom, som de er bundet til, danner en mono- eller bicyklisk ring udvalgt af gruppen pyrrolidin, 2-aza-bicyclo[3.2.2]nonan og 7-aza-bicyclo[2.2.1]heptan, idet ringen er usubstitueret eller er substitueret en eller to gange med -(C_1-C_4)-alkyl, -C(O)-O-R11, -(C_1-C_4)-alkyl-O-R11 eller phenyl,

R7 står for hydrogenatom eller -(C_1-C_4)-alkyl,

R9 står for hydrogenatom eller -(C_1-C_4)-alkyl,

R11 og R12 er ens eller forskellige og uafhængigt af hinanden står for

1) hydrogenatom,
2) -(C_1-C_4)-alkyl,
3) -(C_0-C_4)-alkylen-phenyl, idet phenyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to eller tre gange med -OH, halogen eller -O-(C_1-C_4)-alkyl,
4) -(C_0-C_4)-alkylen-(C_3-C_{12})-cycloalkyl, idet cycloalkyl er udvalgt af gruppen cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, adamantanyl, 1,7,7-trimethyl-bicyclo[3.1.1]heptanyl, decahydro-naphthalenyl, octahydro-4,7-methano-indenyl eller bicyclo[2.2.1]heptanyl, og hvor cycloalkyl er usubstitueret eller uafhængigt af hinanden er substitueret en, to, tre eller fire gange med -(C_1-C_4)-alkyl, -C(O)-O-R13 eller phenyl, eller
5) -(C_0-C_4)-alkylen-indolyl,
R13 står for
1) hydrogenatom,
2) -(C_1-C_4)-alkyl,
3) -(C_0-C_4)-alkylen-C(O)-O-R14,
4) -(C_0-C_4)-alkylen-C(O)-R14 eller
5) -(C_0-C_4)-alkylen-O-R14,
R14 står for hydrogenatom, -(C_1-C_4)-alkyl, -NH_2 eller -OH, og
R15 står for hydrogenatom, -(C_1-C_4)-alkyl, -O-CF_3, -NH_2, -OH, -CF_3 eller halogen.

5. Forbindelse med formel I ifølge et eller flere af kravene 1 til 4, kendetegnet ved, at det er forbindelsen med formel I (S)-6-amino-2-(3-{(S)-1-[(S)-1-((S)-1-methoxycarbonyl-2-methyl-propylcarbamoyl)-2-methyl-propylcarbamoyl]-2-phenyl-ethyl}-sulfamidyl)-hexansyre, (S)-6-amino-2-{3-[(R)-1-(bicyclo[2.2.1]hept-2-ylcarbamoyl)-2-cyclohexyl-ethyl]-sulamidyl}-hexansyre, (S)-6-amino-2-[3-((S)-1-cyclohexylcarbamoyl-2-phenyl-ethyl)-sulfamidyl]-hexansyre, (S)-6-acetimidoylamino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, 3-(6-amino-pyridin-3-yl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamid-yl]-propionsyreethylester, (S)-6-amino-2-{[(S)-1-((1R,2S,4R)-1,7,7-trimethyl-

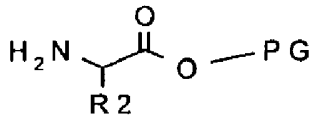
bicyclo[2.2.1]hept-2-ylcarbamoyl)-propylsulfamidyl]-}-hexansyre, (S)-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]-}-5-guanidino-pentansyre, (S)-6-amino-2-{[(S)-2-cyclobutyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulf-amidyl]}-hexansyre, (S)-5-amino-2-({2-cyclohexyl-1-[(R)-(1,2,3,4-tetrahydronaphthalen-2-yl)carbamoyl]-ethylsulfamidyl})-pentanyre, (S)-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-6-hexanoylamino-hexansyre-ethylester, (S)-6-amino-2-{[(S)-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-butylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-3-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-propylsulf-amidyl]-methyl}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-(decahydro-naphthalen-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-2-{[(S)-1-(adamantan-1-ylcarbamoyl)-2-cyclohexyl-ethylsulfamidyl]}-6-amino-hexansyre, (S)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]-hept-2-ylcarbamoyl)-ethylsulfamidyl]-3-pyridin-3-yl-propionsyre, (S)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]-3-pyridin-4-yl-propionsyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-((1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-(3,3,5-trimethyl-cyclohexylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-1-(4-tert-butyl-cyclohexylcarbamoyl)-2-cyclohexyl-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-(3-methyl-cyclohexylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, 3-(6-amino-pyridin-3-ylmethyl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-carbamoyl)-ethylsulfamidyl]-propionsyre, 2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]-3-piperidin-4-yl-propionsyre, (S)-3-(4-amino-phenyl)-2-[(S)-2-cyclohexyl-1-((1R,2S,4R)-

1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]-propionsyre, (S)-6-amino-2-[((S)-1-cyclohexylmethyl-2-oxo-2-piperidin-1-yl-ethylsulfamidyl)]-hexansyre, (S)-5-amino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-pentansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-((S)-1-isobutylcarbamoyl-2-methyl-propylcarbamoyl)-ethylsulfamidyl]}-hexansyre (S)-6-amino-2-{[(S)-1-((S)-1-isobutylcarbamoyl-2-methyl-propylcarbamoyl)-2-phenyl-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-[((S)-2-cyclohexyl-1-isobutylcarbamoyl-ethylsulfamidyl)]-hexansyre, (S)-6-amino-2-{[(S)-1-((1R,2R,4S)-bicyclo[2.2.1]hept-2-ylcarbamoyl)-2-cyclohexyl-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-1-((1S,4R)-bicyclo[2.2.1]hept-2-ylcarbamoyl)-2-cyclohexyl-ethylsulf-amidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-(octahydro-4,7-methano-inden-5-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-[((S)-1-tert-butylcarbamoyl-2-cyclohexyl-ethylsulfamidyl)]-hexansyre, (S)-2-{[(S)-1-(adamantan-1-ylcarbamoyl)-2-phenyl-ethylsulfamidyl]}-6-amino-hexansyre, (S)-6-amino-2-{[(S)-1-((1S,4R)-bicyclo[2.2.1]hept-2-ylcarbamoyl)-2-phenyl-ethylsulfamidyl]}-hexansyre, (S)-2-{[(S)-1-(adamantan-1-ylcarbamoyl)-2-(4-hydroxy-phenyl)-ethylsulfamidyl]}-6-amino-hexansyre, (S)-6-amino-2-{[(S)-2-phenyl-1-((1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-({[(S)-cyclohexyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-methyl]-sulfamidyl})-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-((1R,2R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclopropyl-1-((1R,2R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-(3,5-dimethyl-adamantan-1-ylcarbamoyl)-ethylsulf-amidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-1-(3-isopropyl-adamantan-1-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre, (S)-6-amino-2-{[(S)-2-cyclohexyl-

1 -((1R,2R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-ethylsulfamidyl]}-hexansyre-tert-butylester eller (S)-2-{[(S)-1-(adamantan-1-ylcarbamoyl)-3-methylbutylsulfamidyl]}-6-amino-hexansyre.

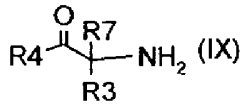
6. Fremgangsmåde til fremstilling af forbindelsen med formel I ifølge et eller flere af kravene 1 til 5, kendetegnet ved, at man omsætter

a) en forbindelse med formel II



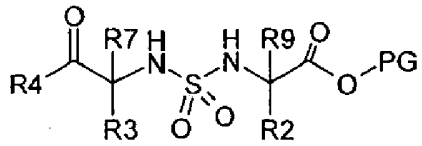
(II)

idet R2 og PG har de i forbindelsen med formel I nævnte betegnelser, med en forbindelse med formel IX,



(IX)

idet R3, R4, R7 og PG har de i forbindelsen med formel I nævnte betegnelser, til en forbindelse med formel X,



(X)

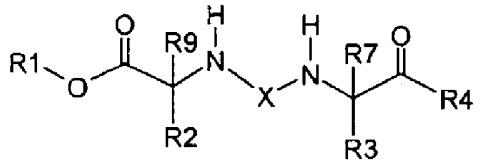
idet R2, R3, R4, R7, R9 og PG har de i forbindelsen med formel I nævnte betegnelser, og så omdanner den til en forbindelse med formel I, eller fraskiller

b) en ifølge fremgangsmåde a) fremstillet forbindelse med formel I, eller et egnet forstadie med formel I, som på grund af dens kemiske struktur optræder i enantiomere former, ved hjælp af saltdannelse med enantiomerrene syrer eller baser, kromatografi på chirale stationærfaser eller derivatisering ved hjælp af chirale enantiomerrene forbindelser såsom aminosyrer, separation af de således opnåede diastereomerer og fraspaltning af de chirale hjælpegrupper til de rene enantiomerer, eller isolerer

c) den ifølge fremgangsmåde a) eller b) fremstillede forbindelse med formel I enten i fri form, eller i det tilfælde at der foreligger sure eller basiske grupper, omdanner den til fysiologisk forligelige salte.

7. Lægemiddel, kendetegnet ved et virksomt indhold af i det mindste en forbindelse med formel I ifølge et eller flere af kravene 1 til 5 sammen med et farmaceutisk egnet og fysiologisk forligeligt bærestof, tilsætningsstof og/eller andre aktiv- og hjælpestoffer.

8. Anvendelse af forbindelsen med formel I



(I)

og/eller en stereoisomer form af forbindelsen med formel I og/eller blandinger af disse former i ethvert forhold og/eller et fysiologisk forligeligt salt af forbindelsen med formel I ifølge krav 1 til 5 til fremstilling at et lægemiddel til profylakse, sekundærprævention og terapi af en eller flere sygdomme, som er forbundet med tromboser, embolier, hyperkoagulabilitet eller fibrotiske forandringer, udvalgt af rækken myokardinfarkt, angina pectoris og andre former for akut koronarsyndrom, slagtilfælde, de perifært vaskulære sygdomme, dyb venetrombose, lungeemboli, emboliske eller trombotiske hændelser betinget af kardiale arytmier, kardiovaskulære hændelser såsom restenose efter revaskularisering og angioplastik og lignende indgreb såsom stentimplantationer og bypass-operationer eller reduktion af tromboserisikoen efter kirurgiske indgreb som ved knæ- og hofteledsoperationer eller dissemineret intravaskulær koagulation, sepsis og andre intravaskulære hændelser, som er forbundet med en betændelse, aterosklerose, diabetes og det metaboliske syndrom og følgerne heraf, tumorvækst og tumormetastasering, betændelses- og degenerative ledsygdomme såsom reumatoid arthritis og arthrose, forstyrrelser i det hæmostatiske system såsom fibrinaflejringer, fibrotiske forandringer i lungerne såsom kronisk obstruktiv lungesygdom, adult respiratory distress syndromet eller fibrinaflejringer i øjet efter øjenoperationer eller hindring af eller behandling af ardannelse.