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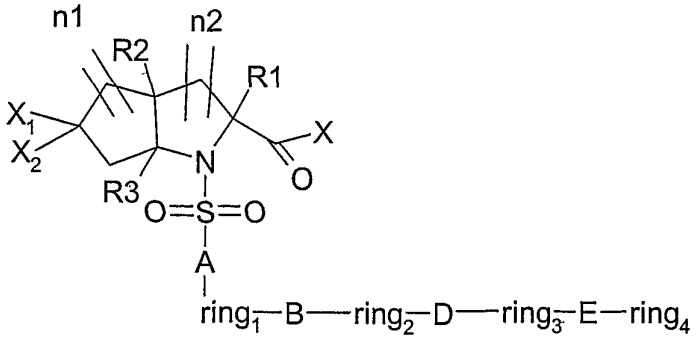
[Fortsetzung auf der nächsten Seite]

(54) Title: IMINO ACID DERIVATIVES FOR USE AS INHIBITORS OF MATRIX METALLOPROTEINASES

(54) Bezeichnung: IMINOSÄUREDERIVATE ALS INHIBITOREN VON MATRIX-METALLOPROTEINASEN



(I)

(57) Abstract: The compounds of formula (I) are useful for preparing drugs used in the prophylaxis and therapy of diseases which are associated with an increased matrix metalloproteinase activity. Examples of such diseases are degenerative articular diseases such as osteoarthroses, spondyloses, chondroporosis after articular trauma or prolonged joint immobilization after meniscus or patella injuries or rupture of a ligament, or a disease of the connective tissue such as collagenoses, periodontal diseases, defective wound healing, or a chronic diseases of the locomotor system such as inflammatory, immunologically or metabolically mediated acute or chronic arthritides, arthropathies, myalgias or disorders of the bone metabolism or an ulceration, atherosclerosis or stenosis or an inflammatory disease or a tumor disease, tumor metastatic spread, cachexia, anorexia or septicaemic shock.

(57) Zusammenfassung: Verbindungen der Formel (I) eignen sich zur Herstellung von Arzneimitteln zur Prophylaxe und Therapie von Erkrankungen, an deren Verlauf eine verstärkte Aktivität von Matrix-Metalloproteinasen beteiligt sind. Dazu gehören Erkrankungen wie eine degenerative Gelenkerkrankung beispielsweise Osteoarthrosen, Spondylosen, Knorpelschwund nach Gelenktrauma oder längerer Gelenksruhigstellung nach Meniskus-oder Patellaverletzungen oder Bänderrissen, oder eine Erkrankung des Bindegewebes wie Kollagenosen, Periodontalerkrankungen, Wundheilungsstörungen, oder eine chronische Erkrankung des Bewegungsapparates wie entzündliche, immunologisch oder stoffwechselbedingte akute oder chronische Arthritiden, Arthropathien, Myalgien oder Störungen des Knochenstoffwechsels oder eine Ulceration Atherosklerose oder Stenose oder eine entzündliche Erkrankung oder eine Krebserkrankung, Tumormetastasenbildung, Kachexie, Anorexie oder spetischer Schock.

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PT, RO, SE, SI, SK, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

— *mit internationalem Recherchenbericht*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Imino acid derivatives for use as inhibitors of matrix metalloproteinases

The invention relates to novel derivatives of octahydroindolecarboxylic acid and octahydrocyclopenta[b]pyrrolo-2-carboxylic acid, to processes for preparing them and to their use as pharmaceuticals.

In diseases such as osteoarthritis and rheumatism, the joint is destroyed, with this destruction being due, in particular, to the proteolytic breakdown of collagen by collagenases. Collagenases belong to the superfamily of the metalloproteinases (MPs) or matrix metalloproteinases (MMPs). The MMPs form a group of Zn-dependent enzymes which are involved in the biological breakdown of the extracellular matrix (D. Yip et al. in Investigational New Drugs 17 (1999), 387-399 and Michaelides et al. in Current Pharmaceutical Design 5 (1999) 787-819). These MMPs are able, in particular to break down fibrillar and nonfibrillar collagen and proteoglycans, both of which are important matrix constituents. MMPs are involved in processes of wound healing, tumor invasion, metastasis migration and in angiogenesis, multiple sclerosis and heart failure (Michaelides page 788; see above). In particular, they play an important role in the breakdown of the joint matrix in arthrosis and arthritis, whether this be osteoarthrosis, osteoarthritis or rheumatoid arthritis.

The activity of the MMPs is furthermore essential for many of the processes which play a role in the formation of atherosclerotic plaques, such as the infiltration of inflammatory cells, the migration of smooth muscle cells, and proliferation and angiogenesis (S.J. George, Exp. Opin. Invest. Drugs (2000), 9 (5), 993-1007). In addition, degradation of the matrix by MMPs can cause anything from plaque instabilities through to ruptures, with this being able to lead to the clinical symptoms of atherosclerosis, unstable angina pectoris, myocardial infarction or stroke (E.J.M. Creemers et al., Circulation Res. 89, 201-210 (2001)). All in all, the complete MMP family is able to break down all the components of the blood vessel extracellular matrix; for this reason, their activity is to a high degree subject to regulatory mechanisms in normal blood vessels. The increase in MMP activity during plaque formation and plaque instability is caused by an increase in cytokine-stimulated and growth factor-stimulated gene transcription, an increase in zymogen activation and an imbalance in the MMP/TIMP (tissue inhibitors of metalloproteases) ratio. It therefore seems plausible that MMP

inhibition or the reattainment of the MMP/TIMP equilibrium would be of assistance in treating the atherosclerotic diseases. It is also becoming ever clearer that aside from atherosclerosis, an increase in MMP activity is also at least a contributory cause of other cardiovascular diseases such as restenosis, dilated cardiomyopathy and the already mentioned myocardial infarction. It has been shown that administering synthetic inhibitors in experimental animal models can achieve marked improvements in these diseases as regards, for example, formation of atherosclerotic lesions, neointima formation, left-ventricular remodeling, pumping output malfunction or infarction healing. In a variety of preclinical studies using MMP inhibitors, detailed tissue analysis indicated a reduction in collagen damage, an improvement in extracellular matrix remodeling and an improvement in the structure and function of cardiac muscle and blood vessels. Of these processes, matrix remodeling processes and MMP-regulated fibroses are regarded, in particular, as being important components in the progress of cardiac diseases (infarction) (Drugs 61, 1239-1252 (2001)).

MMPs cleave matrix proteins, such as collagen, laminin, proteoglycans, elastin or gelatin, and also process (i.e. activate or deactivate), by means of a cleavage, a large number of other proteins and enzymes under physiological conditions, which means that they play an important role in the entire organism, with this role being of particular importance in connective tissue and bone.

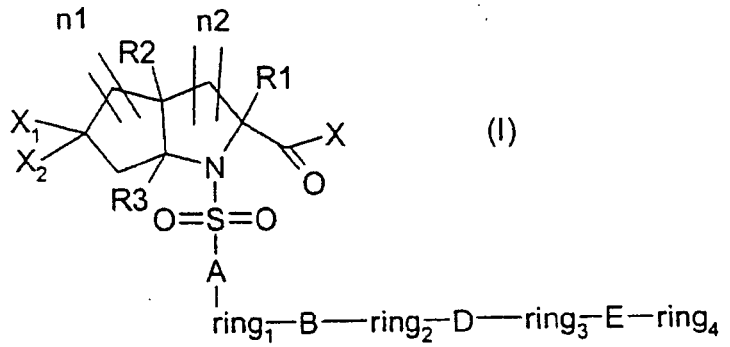
A large number of different inhibitors of the MMPs are known (EP 0 606 046; WO 94/28889; WO 96/27583; or also overviews such as Current Medicinal Chemistry **8**, 425-74 (2001)). Following the first clinical studies in humans, it has now been found that MMPs give rise to side effects. The side effects which are principally mentioned are musculoskeletal pains or anthralgias. The prior art states unambiguously that it is expected that more selective inhibitors will be able to reduce these said side effects (Yip, page 387, see above). Particular emphasis should be placed in this case on specificity in respect to MMP-1, as these undesirable side effects obviously occur to a greater extent with inhibition of MMP-1.

The known MMP inhibitors therefore frequently suffer from the disadvantage of lacking specificity. Most MMP inhibitors inhibit many MMPs simultaneously because the structure of the catalytic domain in the MMPs

is similar. As a consequence, the inhibitors have the undesirable property of acting on the enzymes including those which have a vital function (Massova I., et al., The FASEB Journal (1998) 12, 1075-1095).

In the endeavor to find effective compounds for treating connective tissue diseases, it has now been found that the derivatives used in accordance with the invention are powerful inhibitors of the matrix metalloproteinases MMP-2, MMP-3, MMP-8, MMP-9 and MMP-13 whereas they have only a weak inhibitory effect on MMP-1.

The invention therefore relates to a compound of formula I



(I)

and/or all the stereoisomeric forms 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

A is -(C_0-C_4)-alkylene,

B, D and E are identical or different and are, independently of each other,

1. -(C_0-C_4)-alkylene,
2. -(C_2-C_4)-alkenylene,
3. -$S(O)_o$-, where o is the integers zero, 1 or 2,
4. -NH-,
5. -NH-C(O)-,
6. -C(O)-NH-,
7. -NH-SO_2-,
8. -NH-C(O)-NH-,
9. -NH-C(S)-,
10. -NH-C(O)-O-,
11. -O-,
12. -O-C(O)-NH-,
13. -C(O)-,

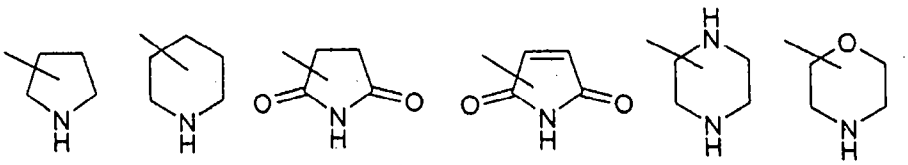
14. -O-$(CH_2)_n$-O-, in which n is the integer 2 or 3, or
15. -O-$(CH_2)_m$-NH-, in which m is the integer 2 or 3,

ring 1, ring 2 or ring 3 are identical or different and are, independently of each other,

1. covalent bond,
2. -(C_6-C_{14})-aryl, in which aryl is unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
3. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is unsubstituted or substituted, independently of each other, once, twice or three times, by G,

ring 4 is

1. -(C_6-C_{14})-aryl, in which aryl is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
2. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
3. heteroaryl, in which heteroaryl is unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
4. one of the following radicals



and these radicals are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

G is
1. hydrogen atom,
2. halogen,
3. R4 and R4 is
   a) hydrogen atom,
   b) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once, twice or three times, by

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halogen, -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl or heteroaryl,

c) -(C_6-C_{14})-aryl,

d) heteroaryl,

e) -C(O)-O-R5, in which R5 is

e)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl, or heteroaryl, or

e)2) -(C_6-C_{14})-aryl or heteroaryl,

f) -C(S)-O-R5, in which R5 is defined as above,

g) -C(O)-NH-R6, in which R6 is

g)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl or heteroaryl, or

g)2) -(C_6-C_{14})-aryl or heteroaryl, or

h) -C(S)-NH-R6, in which R6 is defined as above,

4. -O-R4, in which R4 is defined as above,

5. -C(O)-R5, in which R5 is defined as above,

6. -$S(O)_p$-R4, in which R4 is defined as above and p is the integers zero, 1 or 2,

7. -NO_2,

8. -CN or

9. -N(R3)-R4, in which R3 is

9.1) hydrogen atom, or

9.2) -(C_1-C_6)-alkyl and R4 is defined as above,

X is -OH or -NH-OH,

X_1 and X_2 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl, or together form the radical =O,

n1 and n2 are identical or different and are, independently of each other, zero, 1 or 2,

R1 is 1. hydrogen atom, or

2. -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl or heteroaryl,

R2 and R3 are identical or different and are, independently of each

other, hydrogen atom or -(C_1-C_6)-alkyl,

wherein each of the compounds 1-(toluene-4-sulfonyl)-octahydroindole-2-carboxylic acid and (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid are excluded.

The invention furthermore relates to the compound of formula I, where

A is -(C_0-C_4)-alkylene,

B, D and E are identical or different and are, independently of each other,

1. -(C_0-C_4)-alkylene,
2. -(C_2-C_4)-alkenylene,
3. -$S(O)_o$-, where o is the integers zero, 1 or 2,
4. -NH-,
5. -NH-C(O)-,
6. -C(O)-NH-,
7. -NH-SO_2-,
8. -NH-C(O)-NH-,
9. -NH-C(S)-,
10. -NH-C(O)-O-,
11. -O-,
12. -O-C(O)-NH-,
13. -C(O)-,
14. -O-$(CH_2)_n$-O-, in which n is the integer 2 or 3, or
15. -O-$(CH_2)_m$-NH-, in which m is the integer 2 or 3,

ring 1, ring 2 or ring 3 are identical or different and are, independently of each other,

1. covalent bond,
2. -(C_6-C_{14})-aryl, in which aryl is a radical from the series phenyl, naphthyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, anthryl or fluorenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
3. 5- or 6-membered aromatic heteroaryl ring in which the heteroaryl ring is a radical from the series dihydrofuranyl, dioxolyl, dioxanyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, isothiazolyl, isothiazolidinyl,

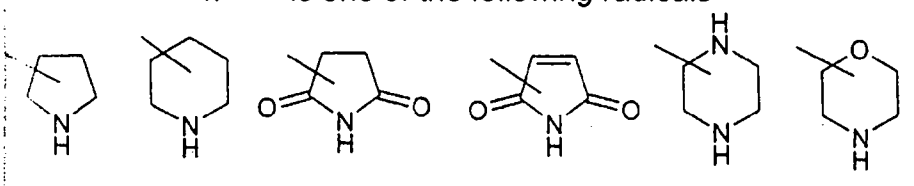
2-isothiazolinyl, morpholinyl, oxazolyl, oxothiolanyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyridinyl, thiazolyl, thiomorpholinyl, thiophenyl or thiopyranyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

ring 4 is

1. -(C_6-C_{14})-aryl, in which aryl is a radical from the series phenyl, naphthyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, anthryl or fluorenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
2. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is a radical from the series dihydrofuranyl, dioxolyl, dioxanyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, isothiazolyl, isothiazolidinyl, 2-isothiazolinyl, morpholinyl, oxazolyl, oxothiolanyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyridinyl, thiazolyl, thiomorpholinyl, thiophenyl or thiopyranyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G,
3. heteroaryl, in which heteroaryl is a radical from the series acridinyl, azetidinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, deca-hydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuran[2,3-b]tetrahydrofuran, fuaranyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl,

isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, 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, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl, and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or

4. is one of the following radicals



and these radicals are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

G is
1. hydrogen atom,
2. halogen,
3. R4, and R4 is
   a) hydrogen atom,
   b) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once, twice or three times, by halogen, -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl defined as above,
   c) phenyl or naphthyl,

d) heteroaryl, where heteroaryl is defined as above,

e) -C(O)-O-R5, in which R5 is

e)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is as defined above,

e)2) phenyl or naphthyl, or

e)3) heteroaryl, where heteroaryl as defined above, is substituted,

f) -C(S)-O-R5, in which R5 is defined as above,

g) -C(O)-NH-R6, in which R6 is

g)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is defined as above,

g)2) phenyl or naphthyl, or

g)3) heteroaryl, where heteroaryl as defined above, is substituted, or

h) -C(S)-NH-R6, in which R6 is defined as above,

4. -O-R4, in which R4 is defined as above,

5. -C(O)-R5, in which R5 is defined as above,

6. -$S(O)_p$-R4, in which R4 is defined as above and p is the integers zero, 1 or 2,

7. -NO_2,

8. -CN, or

9. -N(R3)-R4, in which R3 is

9.1) hydrogen atom, or

9.2) -(C_1-C_6)-alkyl and R4 is defined as above,

X is -OH or -NH-OH,

X_1 and X_2 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl, or together form the radical =O,

n1 and n2 are identical or different and are, independently of each other, zero, 1 or 2,

R1 is 1. hydrogen atom, or

2. -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or

substituted, once or twice, by -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is defined as above,

R2 and R3 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl.

The invention furthermore relates to the compound of formula I where

A is -(C_0-C_4)-alkylene,

B, D and E are identical or different and are, independently of each other,

1. -(C_0-C_2)-alkylene,
2. -C_2-alkenylene,
3. -$S(O)_o$-, where o is the integer 2,
4. -NH-,
5. -NH-C(O)-,
6. -C(O)-NH-,
7. -NH-C(O)-NH-,
8. -O-, or
9. -C(O)-,

ring 1, ring 2 or ring 3 are identical or different and are, independently of each other,

1. covalent bond,
2. phenyl or naphthyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
3. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is a radical from the series dihydrofuranyl, furanyl, morpholinyl, piperazinyl, piperidinyl, pyridinyl, pyrimidinyl, pyrrolyl, thiazolyl or thiophenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

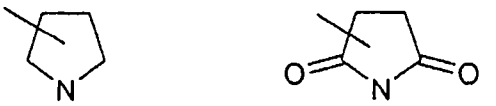
ring 4 is

1. phenyl or naphthyl and is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
2. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is and is a radical from the series

dihydrofuranyl, furanyl, morpholinyl, piperazinyl, piperidinyl, pyridinyl, pyrimidinyl, pyrrolyl, thiazolyl or thiophenyl and is unsubstituted or substituted, independently of each other, once, twice or three times, by G,

3. heteroaryl, in which heteroaryl is a radical from the series benzofuranyl, benzothiophenyl, dihydrofuranyl, furanyl, morpholinyl, piperazinyl, piperidinyl, pyridinyl, pyridothiophenyl, pyrimidinyl, pyrrolyl, thiazolyl or thiophenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or

4. is one of the following radicals



and these radicals are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

G is
1. hydrogen atom,
2. Br; Cl, I or F,
3. R4, and R4 is
   a) hydrogen atom,
   b) -(C_1-C_4)-alkyl, in which alkyl is unsubstituted or substituted, once, twice or three times, by Br, Cl, F, -C_3-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl defined as above,
   c) phenyl or naphthyl,
   d) heteroaryl, where heteroaryl defined as above,
   e) -C(O)-O-R5, in which R5 is
      e)1) -(C_1-C_4)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -C_3-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is as defined above,
      e)2) phenyl or naphthyl, or
      e)3) heteroaryl, where heteroaryl as defined above, is substituted, or
   f) -C(O)-NH-R6, in which R6 is
      f)1) -(C_1-C_4)-alkyl, in which alkyl is

unsubstituted or substituted, once or twice, by -C_3-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is defined as above,

f)2) phenyl or naphthyl, or

f)3) heteroaryl, where heteroaryl as defined above, is substituted,

4. -O-R4, in which R4 is defined as above,

5. -C(O)-R5, in which R5 is defined as above,

6. -$S(O)_p$-R4, in which R4 is defined as above and p is the integer 2,

7. -NO_2,

8. -CN, or

9. -N(R3)-R4, in which R3 is

9.1) hydrogen atom, or

9.2) -(C_1-C_6)-alkyl and R4 is defined as above,

X is -OH or -NH-OH,

X_1 and X_2 are identical and are hydrogen atom,

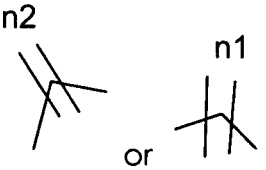
n1 and n2 are identical and are 1 or are nonidentical and n1 is 2 and n2 is 1,

R1 is hydrogen atom, and

R2 and R3 are identical and are hydrogen atom.

The term "(C_1-C_6)-alkyl" is understood as meaning hydrocarbon radicals whose carbon chain is straight or branched and contains from 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 "-(C_0-C_4)-alkylene" is understood as meaning hydrocarbon radicals whose carbon chain is straight or branched and contains from 1 to 4 carbon atoms, for example methylene, ethylene, propylene, isopropylene, isobutylene, butylene or tertiary butylene. "-C_0-alkylene" is a covalent bond.
The term "-$(CH_2)_n$-, in which n is the integer zero, 1 or 2" is understood as meaning, for n equal to zero, a covalent bond, for n equal to 1, the methylene radical and for n equal to 2, the ethylene radical.
The term "-(C_2-C_4)-alkenylene" is understood as meaning hydrocarbon radicals whose carbon chain is straight or branched and contains from 2 to 4 carbon atoms and, depending on the chain length, possesses one or two double bonds, for example ethenylene, propenylene, isopropenylene, isobutenylene or butenylene; provided the possibility exists in principle, the substituents on the double bond can be arranged in the E configuration or the Z configuration.
The term "-(C_2-C_6)-alkynylene" is understood as meaning hydrocarbon radicals whose carbon chain is straight or branched and contains from 2 to 6 carbon atoms and, depending on the chain length, possess 1 or 2 double bonds, for example ethynylene, propenylene, isopropynylene, isobuthylynylene, butynylene, pentynylene or isomes of pentynylene or hexynylene or isomers of hexynylene.
The term "(C_3-C_6)-cycloalkyl" is understood as meaning radicals such as compounds which are derived from 3- to 6-membered monocycles such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
The radicals



or

are in each case understood as being -CH_2 radicals in the ring of the formula I, where the variables n1 or n2 in each case indicate the number of the -CH_2 radicals in the ring of the formula I. When n1 has the value zero, a covalent bond is formed and the resulting part ring has a total of 4 ring atoms. When n2 has the value zero, a covalent bond is formed and the resulting part ring has a total of 3 ring atoms. When n1 has the value 1, a -CH_2 radical is formed and the resulting part ring has a total of 5 ring atoms. When n1 has the value 2, a -CH_2-CH_2 radical is formed and the resulting part ring has a total of 6 ring atoms. When n1 has the value 3, a -CH_2-CH_2-CH_2 radical is formed and the resulting part ring has a total of 7 ring atoms. Corresponding part rings are formed in the case of n2.

The term "-(C_6-C_{14})-aryl" is understood as meaning aromatic carbon radicals having from 6 to 14 carbon atoms in the ring. -(C_6-C_{14})-aryl radicals are, for example, phenyl, naphthyl, for example 1-naphthyl or 2-naphthyl, anthryl or fluorenyl. Naphthyl radicals and, in particular, phenyl radicals are preferred aryl radicals.

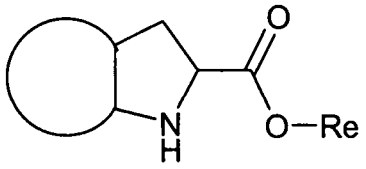
The term "5- or 6-membered aromatic heteroaryl ring" is understood as meaning aromatic ring systems which contain one or two heteroatoms from the series oxygen, nitrogen and sulfur and which can be derived from dihydrofuran, dioxole, dioxane, furan, imidazolidine, imidazoline, imidazole, isoxazole, isoxazolidine, 2-isoxazoline, isothiazole, isothiazolidine, 2-isothiazoline, morpholine, oxazole, oxothiolane, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazolidine, pyrazoline, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrahydrofuran, tetrahydropyridine, thiazole, thiomorpholine, thiophenyl or thiopyran.

The term "heteroaryl" is understood as meaning radicals such as acridinyl, azepinyl, azetidinyl, aziridinyl, benzimidazalinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, 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, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, 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, thienothiazolyl, thienooxazolyl,

thienoimidazolyl, 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. Preference is given to pyridyl; such as 2-pyridyl, 3-pyridyl or 4-pyridyl; pyrrolyl; such as 2-pyrrolyl and 3-pyrrolyl; furyl; such as 2-furyl and 3-furyl; thiophenyl, thienyl; such as 2-thienyl and 3-thienyl; imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, 1,3-benzodioxolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, chromanyl, isochromanyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyridoimidazolyl, pyridopyridinyl, pyridopyrimidinyl, purinyl and pteridinyl.

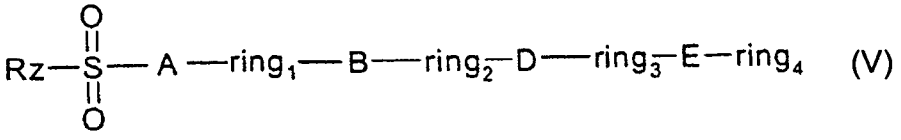
The invention furthermore relates to a process for preparing the compound of formula I and/or a stereoisomeric form of the compound of formula I and/or a physiologically tolerated salt of the compound of formula I, which comprises

a) reacting a compound of formula IV,



(IV)

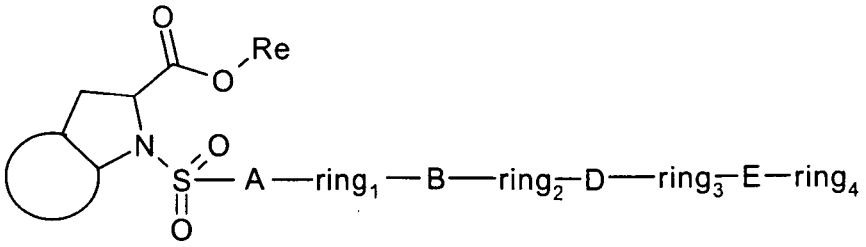
in which Re is a hydrogen atom or an ester protecting group, with a compound of formula V,



(V)

in which A, B, D, E and ring 1, ring 2, ring 3 and ring 4 are defined as in formula I, and in which Rz is chlorine atom, imidazolyl or OH,

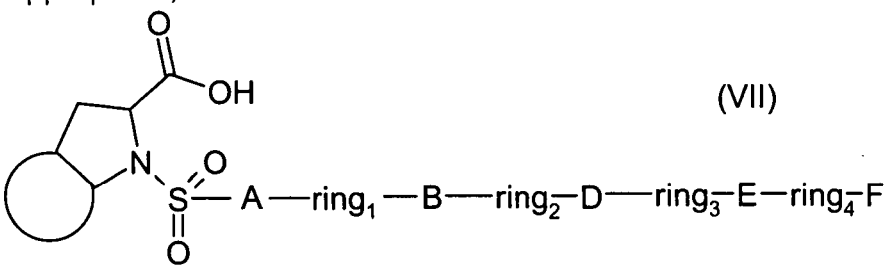
in the presence of a base, or after silylation with a suitable silylating agent, to give a compound of formula VI,



(VI)

in which A, B, D, E, Re and ring 1, ring 2, ring 3 and ring 4 are defined as above, and

b) where Re = ester, reacting a compound of formula VI, which has been prepared in accordance with a), with a solution of an alkali such as NaOH or LiOH, and then treating with acid, to give the carboxylic acid of formula I, in which X = OH (corresponds to formula VII), with modifications in one of the side chains of the rings ring 1-ring 4 also having previously been carried out, where appropriate,



(VII)

and then converting this compound into the novel hydroxamic acid X = NH-OH of formula I,

c) separating a compound of formula I, which has been prepared in accordance with process a) or b) and which arises in enantiomeric forms on account of its chemical structure, into the pure enantiomers by means of salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization using chiral, enantiomerically pure compounds, such as amino acids, separation of the resulting diastereomers and elimination of the chiral auxiliary groups, or

d) either isolating the compound of formula I, which has been prepared in accordance with processes b) or c), in free form or, when acidic or basic groups are present, converting it into physiologically tolerated salts.

Compounds such as those of formulae IV to VII are only exemplary

compounds; in accordance with formula I it is also possible to configure four-ring, six-ring and seven-ring compounds instead of the five-ring compound.

The groups which are used in Protective Groups in Organic Synthesis, T.H. Greene, P.G.M. Wuts, Wiley-Interscience, 1991, as groups for protecting esters can be employed as the ester protecting group Re. Examples of preferred ester protecting groups are methyl, ethyl, isopropyl, tert-butyl or benzyl.
The starting compounds and reagents which are used can either be prepared using known methods or are commercially available.

The reactions take place as depicted, for example, in WO 97/18194. The reaction in accordance with process step a) takes place in the presence of a base such as KOH, NaOH, LiOH, N,O-bis(trimethylsilyl)acetamide (BSA), N-methylmorpholine (NMM), N-ethylmorpholine (NEM), triethylamine (TEA), diisopropylethylamine (DIPEA), pyridine, collidine, imidazole or sodium carbonate in solvents such as tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide, dioxane, acetonitrile, toluene, chloroform or methylene chloride, or else in the presence of water.

Modifications in the side chain F means that, for example, a nitro group is hydrogenated using the metal catalyst Pd/C or reacted with $SnCl_2$ or Zn under standard conditions and the resulting amino group can then be subjected to further modification, for example by reacting it with carbonyl chlorides, sulfonyl chlorides, chloroformic esters, isocyanates, isothiocyanates, or other reactive or activatable reagents, in order to arrive at the precursors of the novel compounds of formula I. For this case, it is frequently advantageous if Re is an ester in compound VI since side reactions are to be expected when the carboxylic acid is unprotected.

Provided it arises as a mixture of diastereomers or enantiomers, or accrues in the chosen synthesis as their mixtures, the compound of formula I is separated, in process step c), into the pure stereoisomers either by means of chromatography on an optionally chiral support material or, provided the racemic compound of formula I is capable of salt formation, by means of fractional crystallization of the diastereomeric salts which have been formed using an optically active base or acid as auxiliary substance. Examples of suitable chiral stationary phases for the thin-layer or column

chromatographic separation of enantiomers are modified silica gel supports (what are termed Pirkle phases) and also high molecular weight carbohydrates, such as triacetyl cellulose. Following appropriate derivatization, which is known to the skilled person, gas-chromatographic methods on chiral stationary phases can also be used for analytical purposes. In order to separate the enantiomers of the racemic carboxylic acids, the diastereomeric salts, which differ in solubility, are formed using an optically active, as a rule commercially available, base such as (-)-nicotine, (+)- and (-)-phenylethylamine, quinine bases, L-lysine or L- and D-arginine, the more sparingly soluble component is isolated as a solid, the more readily soluble diastereomer is separated out from the mother liquor, and the pure enantiomers are isolated from the diastereomer salts which have been obtained in this way. The racemic compounds of the formula I which contain a basic group, such as amino group, can, in what is in principle the same manner, be converted into the pure enantiomers using optically active acids, such as (+)-camphor-10-sulfonic acid, D- and L-tartaric acid, D- and L-lactic acid and (+) and (-)-mandelic acid. Chiral compounds which contain alcohol or amine functions can also be converted into the corresponding esters or amides using appropriately activated or optionally N-protected enantiomerically pure amino acids or, conversely, chiral carboxylic acids can be converted into the amides using carboxyl-protected enatiomerically pure amino acids or into the corresponding chiral esters using enantiomerically pure hydroxyl carboxylic acids such as lactic acid. The chirality of the amino acid or alcohol radical which has been introduced in enantiomerically pure form can then be used for separating the isomers by the diastereomers, which are now present, being separated by means of crystallization or chromatography on suitable stationary phases and, after that, using suitable methods to once again eliminate the entrained chiral molecule moiety.

Acidic or basic products of the compound of the formula I may be present in the form of their salts or in free form. Preference is given to pharmacologically tolerated salts, e.g. alkali metal salts or alkaline earth metal salts or hydrochorides, hydrobromides, sulfates, hemisulfates, all possible phosphates and also salts of the amino acids, natural bases or carboxylic acids.

Physiologically tolerated salts are prepared according to process step d) in a manner known per se from compounds of the formula I, including their

stereoisomeric forms, which are capable of salt formation. The compounds of formula I form stable alkali metal salts, alkaline earth metal salts or optionally substituted ammonium salts with basic reagents such as hydroxides, carbonates, hydrogen carbonates, alkoxides and ammonia or organic bases, for example trimethylamine or triethylamine, ethanolamine, diethanolanine or triethanolamine, trometamol or else basic amino acids, for example lysine, ornithine or arginine. Insofar as the compounds of formula I possess basic groups, stable acid addition salts can also be prepared using strong acids. Both inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, 4-bromobenzenesulfonic acid, cyclohexylamidosulfonic acid, trifluoromethylsulfonic acid, acetic acid, oxalic acid, tartaric acid, succinic acid glycerol phosphoric acid, lactic acid, malic acid, adipic acid, citric acid, fumaric acid, maleic acid, gluconic acid, glucuronic acid and trifluoroacetic acid are suitable for this purpose.

The invention also relates to pharmaceuticals which are characterized by an effective content of at least one compound of formula I and/or of a physiologically tolerated salt of the compound of formula I and/or an optionally stereoisomeric form of the compound of formula I, together with a pharmaceutically suitable and physiologically tolerated carrier substance, additive and/or other active compounds and auxiliary substances.

On account of their pharmacological properties, the compounds according to the invention are suitable for the selective prophylaxis and therapy of all those diseases whose course involves an increase in the activity of the metalloproteinases. These diseases include degenerative joint diseases, such as osteoarthroses, spondyloses, cartilage loss following joint trauma or a relatively long period of joint immobilization following meniscus injuries or patella injuries or ligament rupture. They also include diseases of the connective tissue such as collagenoses, periodontal diseases, wound healing disturbances and chronic diseases of the locomotory apparatus, such as inflammatory, immunologically-determined or metabolism-determined acute and chronic arthritides, arthropathies, myalgias and disturbances in bone metabolism. In addition, the compounds of formula I are suitable for treating ulceration, atherosclerosis and stenoses. The compounds of formula I are furthermore suitable for treating inflammations, cancer diseases, tumor metastasis formation, cachexia, anorexia, heart

failure and septic shock. The compounds are also suitable for the prophylaxis of myocardial and cerebral infarcts.

The pharmaceuticals according to the invention can be administered by means of oral, inhalative, rectal or transdermal administration or by means of subcutaneous, intraarticular, intraperitoneal or intravenous injection. Oral administration is preferred.

The invention also relates to a process for producing a pharmaceutical, in which process at least one compound of formula I is brought, together with a pharmaceutically suitable and physiologically tolerated excipient and, where appropriate, other suitable active compounds, additives or auxiliary substances, into a suitable form for administration.

Examples of suitable solid or galenic preparation forms are granules, powders, sugar-coated tablets, tablets, (micro)capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions, and also preparations involving a protracted release of active compound, in the production of which customary adjuvants such as carrier substances, disintegrants, binders, coating agents, swelling agents, glidants, lubricants, flavorings, sweeteners and solubilizers are used. Frequently employed auxiliary substances 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 cod liver oil, sunflower oil, peanut oil or sesame oil, polyethylene glycol and solvents, such as sterile water and monohydric or polyhydric alcohols such as glycerol.

The pharmaceutical preparations are preferably produced and administered in dosage units, with each unit containing, as the active constituent, a defined dose of the novel compound of formula I. In the case of solid dose units, such as tablets, capsules, sugar-coated tablets or suppositories, this dose can be up to about 1 000 mg, preferably, however, from about 50 to 300 mg, while it can be up to about 300 mg, preferably, however, from about 10 to 100 mg, in the case of injection solutions in ampoule form.

Depending on the activity of the compound of formula I, daily doses of from about 20 mg to 1 000 mg of active compound, preferably of from about

100 mg to 500 mg, are indicated for treating an adult patient of about 70 kg in weight. However, higher or lower daily doses may also possibly be appropriate. The daily dose may be administered either by means of a once-only administration in the form of a single dosage unit or of several smaller dosage units or else by means of the multiple administration of subdivided doses at defined intervals.

As a rule, end products are determined by means of mass-spectroscopic methods (FAB MS, ESI MS) and ^{1}H NMR (400 MHz, in DMSO-D6); the main peak or the two main peaks is/are given in each case. Temperatures are given in degrees centigrade; RT denotes room temperature (from 22°C to 26°C). Abbreviations which are used are either explained or conform to the customary conventions.

The invention is explained in more detail below with the aid of examples.

1-Arylsulfonyloctahydrocyclopenta[b]pyrrole-2-carboxylic acid

General directions 1:
The carboxylic acid (6.45 mmol) is dissolved in 20 ml of dimethylformamide (DMF), after which 3 equivalents of a 3N solution of NaOH (6.45 ml) are added at 0°C. After 10 min, a solution of the arylsulfonyl chloride (1.1 equivalents, 7.1 mmol) in from 10 to 15 ml of DMF was slowly added dropwise; after the mixture had reached room temperature, it was stirred for at most a further 12 hours (h) at temperatures of between 20°C and 80°C and the solvent was removed under reduced pressure. The crude product was purified chromatographically.

Examples:

Compound No. 4: 1-[4-(1,1-Dimethylpropyl)benzenesulfonyl]octahydro-cyclopenta[b]pyrrole-2-carboxylic acid
1 g of octahydrocyclopenta[b]pyrrole-2-carboxylic acid (6.45 mmol) was dissolved in 20 ml of DMF, after which 3 equivalents of a 3N solution of NaOH (6.45 ml) were added at 0°C. After 10 minutes (min), a solution of 1.75 g of 4-(1,1-dimethylpropylbenzenesulfonyl chloride (1.1 equivalents, 7.1 mmol) in 12 ml of DMF was slowly added dropwise; after it had reached room temperature (RT), the mixture was stirred at 40°C for a further 6 h and, after that, the solvent was removed under reduced pressure. The

crude product was purified chromatographically.

Compound No. 20: 1-(4-Acetylbenzenesulfonyl)octahydrocyclopenta-[b]pyrrole-2-carboxylic acid

1 g of octahydrocyclopenta[b]pyrrole-2-carboxylic acid (6.45 mmol) was dissolved in 20 ml of DMF, after which 3 equivalents of a 3N solution of NaOH (6.45 ml) were added at 0°C. After 10 min, a solution of 1.55 g of 4-acetylbenzenesulfonyl chloride (1.1 equivalents, 7.1 mmol) in 8 ml of DMF was slowly added dropwise; after it had reached RT, the mixture was stirred at 40°C for a further 6 h and, after that, the solvent was removed under reduced pressure. The crude product was purified chromatographically.

1-Arylsulfonyloctahydrocyclopenta[b]pyrrole-2-carboxylic acid hydroxyamide

General directions 2:
The sulfonated carboxylic acid was dissolved in 10 ml of DMF, after which 1.1 equivalents of ethyl chloroformate, 2.2 equivalents of N-ethylmorpholine and 3 equivalents of trimethylsilylhydroxylamine were added. After the mixture had been heated at 80°C for at least 4 h, the solvent was removed under reduced pressure and the crude product was purified using chromatographic methods.

Examples

Compound No. 50: 1-(Naphthaline-1-sulfonyl)octahydrocyclopenta[b]-pyrrole-2-carboxylic acid hydroxyamide
200 mg (0.56 mmol) of 1-(naphthaline-1-sulfonyl)octahydrocyclopenta-[b]pyrrole-2-carboxylic acid were dissolved in 10 ml of DMF, after which 0.61 mmol of ethyl chloroformate, 1.23 mmol of N-ethylmorpholine and 1.68 mmol of trimethylsilylhydroxylamine were added. After the mixture had been heated at 80°C for 6 h, the solvent was removed under reduced pressure and the crude product was purified using chromatographic methods.

Compound No. 52: 1-(4-Methanesulfonylbenzenesulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid hydroxyamide

200 mg (0.55 mmol) of 1-(4-methanesulfonylbenzenesulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid were dissolved in 10 ml of DMF, after which 0.60 mmol of ethyl chloroformate, 1.22 mmol of N-ethylmorpholine and 1.67 mmol of trimethylsilylhydroxylamine were added. After the mixture had been heated at 80°C for 4 h, the solvent was removed under reduced pressure and the crude product was purified using chromatographic methods.

Special directions:

Compound No. 27: 1-(4'-Aminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]-pyrrole-2-carboxylic acid

1 g of 1-(4'-nitrobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (27) was dissolved in 15 ml of DMF, after which 0.1 g of hydrogenation catalyst (10% Pd on active charcoal) was added and the starting compound was quantitatively hydrogenated within 2 h. After the solvent had been removed, the crude product was purified chromatographically.

Compound No. 37: 1-(4-Aminobenzenesulfonyl)octahydrocyclopenta[b]-pyrrole-2-carboxylic acid

1 g of 1-(4-nitrobenzenesulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid (14) was dissolved in 15 ml of DMF, after which 0.1 g of hydrogenation catalyst (10% Pd on active charcoal) was added and the starting compound was quantitatively hydrogenated within 2h. After the solvent had been removed, the crude product was purified chromatographically.

Compound No. 22: 1-(4'-Isopropoxycarbonylaminobiphenyl-4-sulfonyl)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

500 mg (1.30 mmol) of 1-(4'-aminobiphenyl-4-sulfonyl)octahydrocyclo-penta[b]pyrrole-2-carboxylic acid were dissolved in 3 ml of DMF, after which the solution was cooled down to 0°C in an ice bath and 2.6 mmol of pyridine were added. After the mixture had been stirred at 0°C for 15 min, 2 mmol of isopropyl chloroformate in 3 ml of DMF were added. The reaction solution was then stirred at RT for a further 2 h. The crude product was purified using chromatographic methods.

Compound No. 32: 1-(4'-Cyclopropylmethoxycarbonylaminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid

500 mg (1.30 mmol) of 1-(4'-aminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid were dissolved in 3 ml of DMF, after which the solution was cooled down to 0°C in an ice bath and 2.6 mmol of pyridine were added. After the mixture had been stirred at 0°C for 15 min, 2 mmol of cyclopropylmethyl chloroformate in 3 ml of DMF were added. The reaction solution was then stirred at RT for a further 6 h. The crude product was purified using chromatographic methods.

Compound No. 23: 1-(4'-Methanesulfonylaminobiphenyl-4-sulfonyl)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid
500 mg (1.30 mmol) of 1-(4'-aminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid were dissolved in 3 ml of DMF, after which the solution was cooled down to 0°C in an ice bath and 2.6 mmol of pyridine were added. After the mixture had been stirred at 0°C for 15 min, 1.40 mmol of methanesulfonyl chloride in 3 ml of DMF were added. The reaction solution was then stirred at room temperature for a further 6 h. The crude product was purified using chromatographic methods.

Compound No. 25: 1-(4'-Benzenesulfonylaminobiphenyl-4-sulfonyl)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid
500 mg (1.30 mmol) of 1-(4'-aminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid were dissolved in 3 ml of DMF, after which the solution was cooled down to 0°C in an ice bath and 2.6 mmol of pyridine were added. After the mixture had been stirred at 0°C for 15 min, 1.5 mmol of benzenesulfonyl chloride in 6 ml of DMF were added. The reaction solution was then stirred at RT for a further 12 h. The crude product was purified using chromatographic methods.

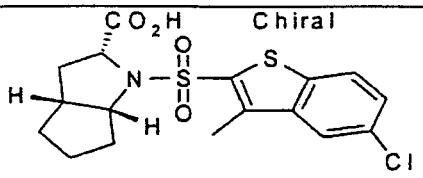
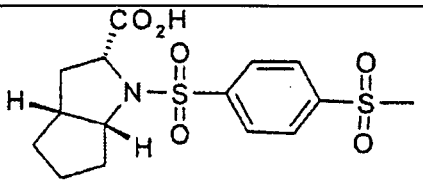
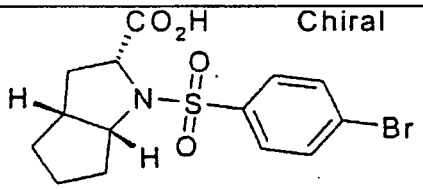
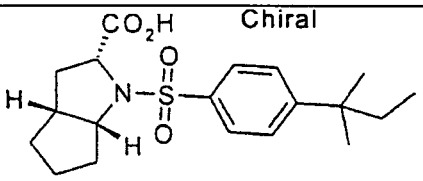
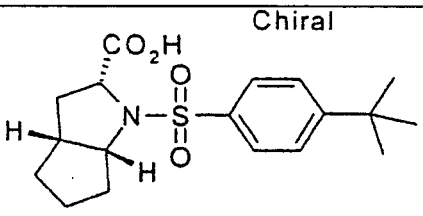
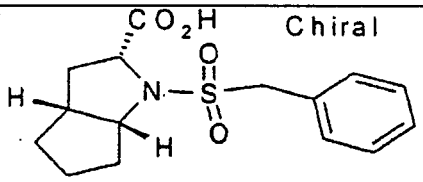
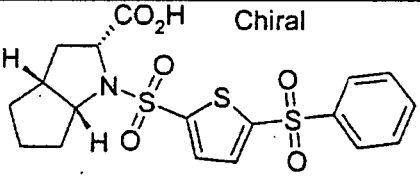
Compound No. 24: 1-(4'-Benzoylaminobiphenyl-4-sulfonyl)octahydro-cyclopenta[b]pyrrole-2-carboxylic acid
500 mg (1.30 mmol) of 1-(4'-aminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid were dissolved in 3 ml of DMF, after which the solution was cooled down to 0°C in an ice bath and 2.6 mmol of pyridine were added. After the mixture had been stirred at 0°C for 15 min, 1.8 mmol of benzoyl chloride in 3 ml of DMF were added. The reaction solution was then stirred at RT for a further 20 h. The crude product was purified using chromatographic methods.

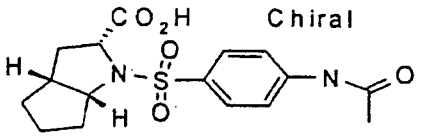
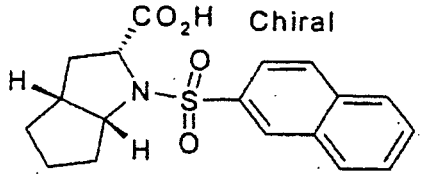
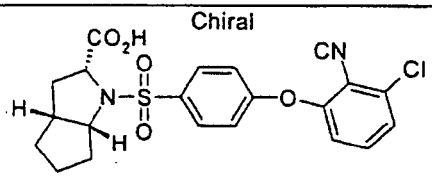
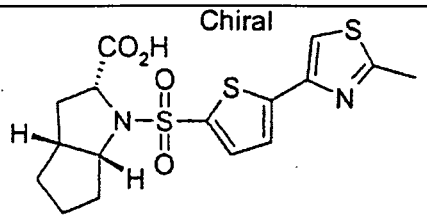
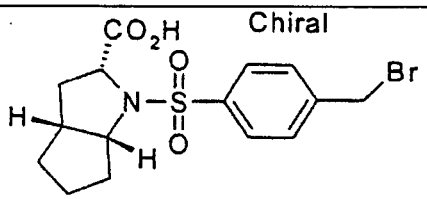
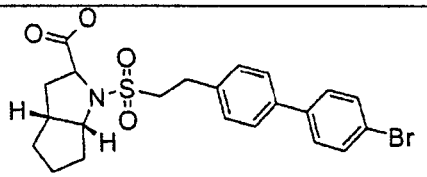
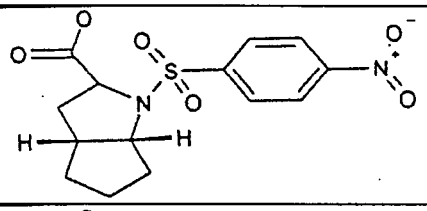
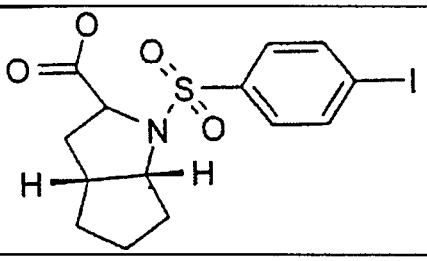
Compound No. 26: 1-[4'-(3-Phenylureido)biphenyl-4-sulfonyl]octahydro-

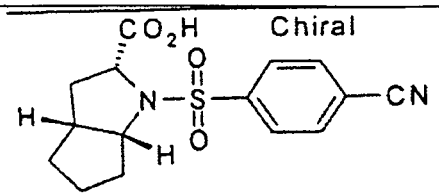
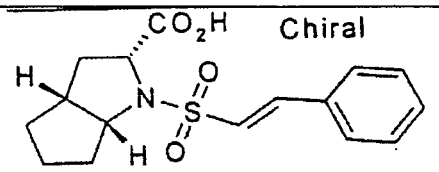
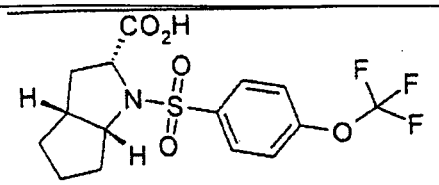
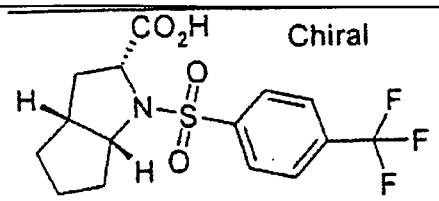
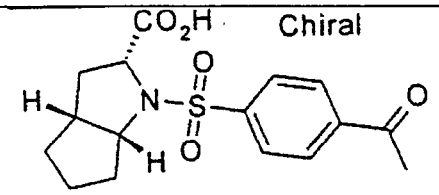
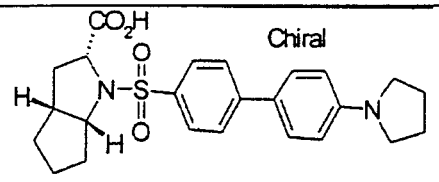
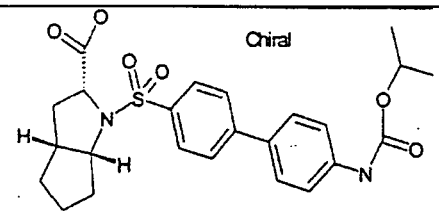
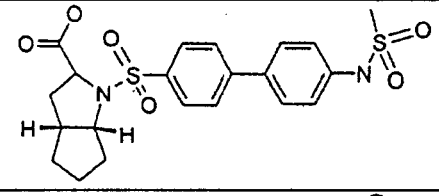
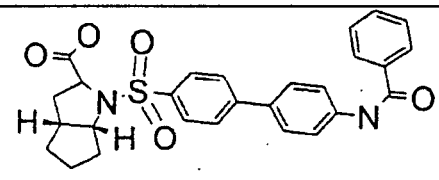
cyclopenta[b]pyrrole-2-carboxylic acid

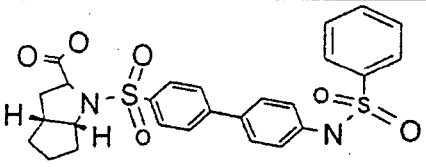
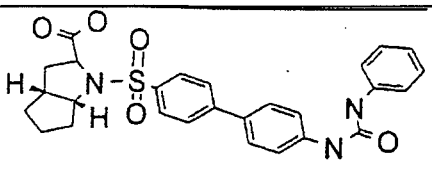
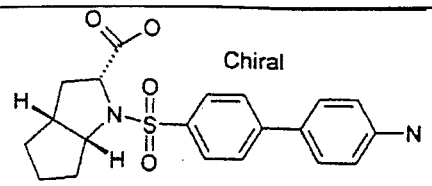
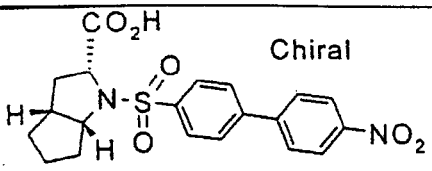
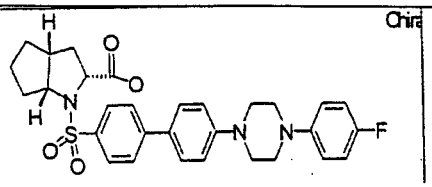
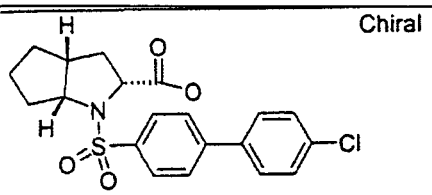
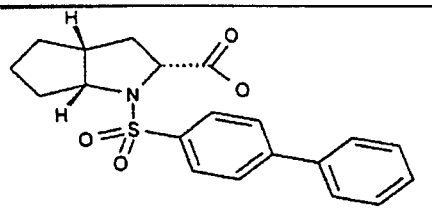
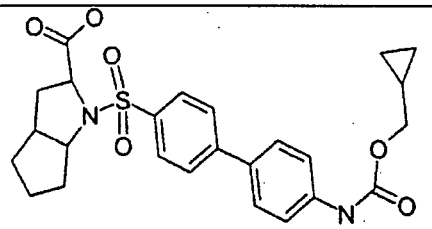
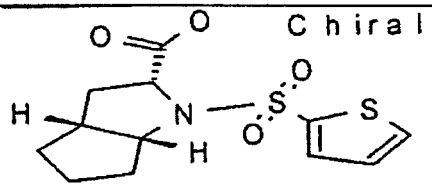
500 mg (1.30 mmol) of 1-(4'-aminobiphenyl-4-sulfonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid were dissolved in 3 ml of DMF, after which the solution was cooled down to 0°C in an ice bath and 1.4 mmol of phenylisocyanate were added. The reaction solution was then stirred at RT for a further 4 h. The crude product was purified using chromatographic methods.

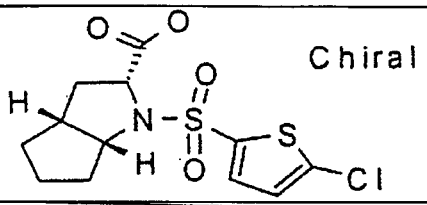
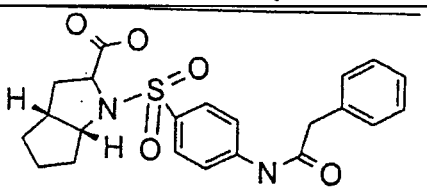
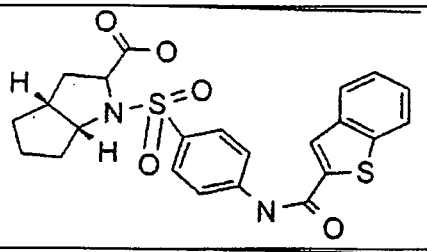
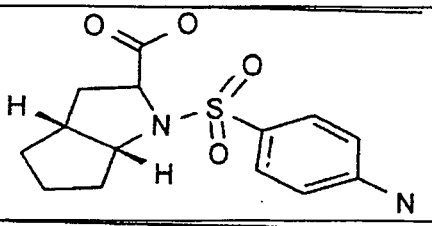
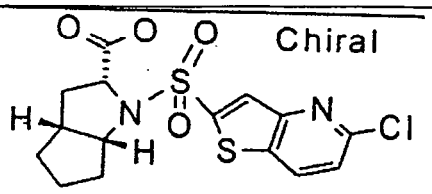
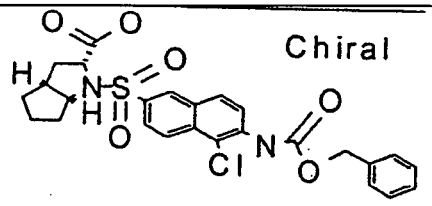
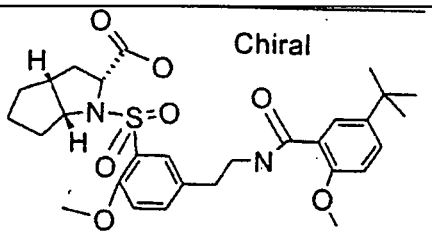
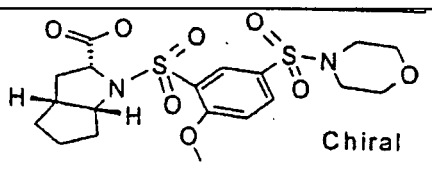
Preparation examples

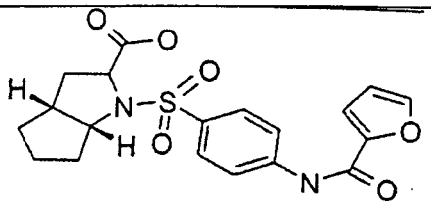
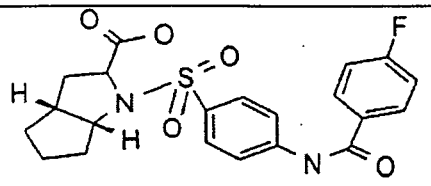
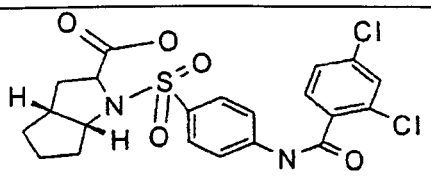
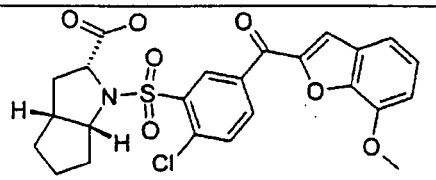
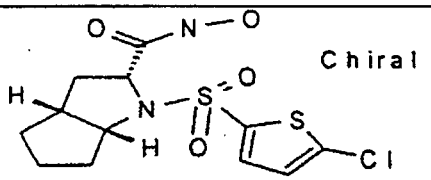
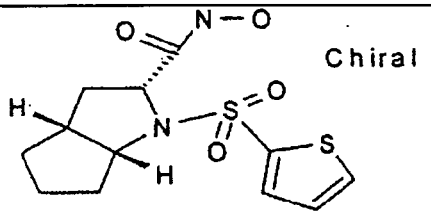
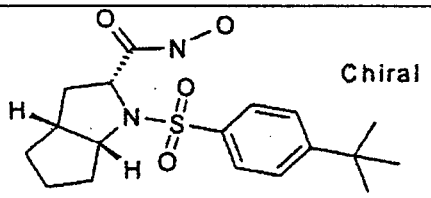
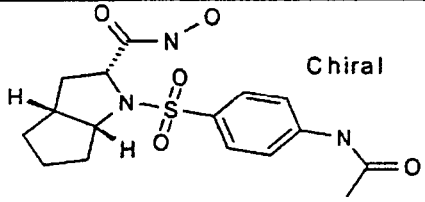
No.	Structure	MS (ESI+)	NMR
1		399.92 400.10	1.4-1.85: m, 6H; 1.9: m, 1H; 2.35: m, 1H; 2.55: m, 1H; 2.7: s, 3H; 4.0: m, 1H; 4.2: m, 1H; 7.6: d, 1H; (.1: m, 2H; 12.1, bs, 1H
2		373.45 374.08	1.3-1.9: m, 8H; 2.15: m, 1H; 3.95: m, 1H; 3.3: s, 3H; 4.2: m, 1H; 8.1: d, 2H; 8.2: d, 2H; 12.5: bs, 1H
3		374.26 374.06	1.4-1.9: m, 7H; 2.15: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.75: d, 2H; 7.85: d, 2H 13.0: bs, 1H
4		365.9 366.19	0.6: t, 3H; 1.3: s, 6H; 1.35-1.8: m, 8H; 1.9: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 3.85: m, 1H; 4.0: m, 1H; 7.55: d, 2H; 7.75: d, 2H; 12.8: bs, 1H
5		351.47 352.15	1.45: s, 9H; 1.5-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 3.85: m, 1H; 4.05: m, 1H; 7.6: d, 2H; 7.85: d, 2H; 12.5: s, 1H
6		309.39 310.22	1.35: m, 2H; 1.7: m, 5H; 2.3: m, 1H; 2.65: m, 1H; 4.15: m, 2H; 4.5: m, 2H; 7.4: m, 5H
7		441.55 442.11	1.3-1.9: m, 7H; 2.2: m, 1H; 2.55: m, 1H; 4.0: m, 1H; 4.2: m, 1H; 7.6: m, 2H; 7.8: m, 2H; 7.95: m, 1H; 8.05: m, 2H; 13.0: bs,

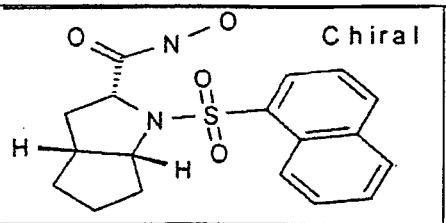
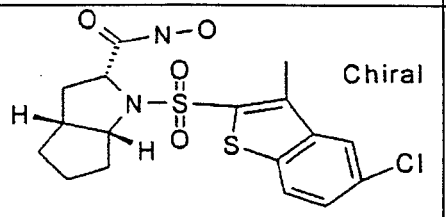
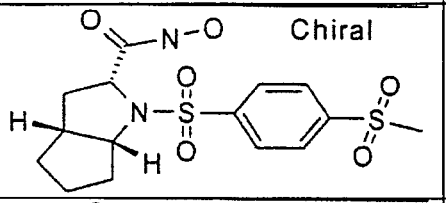
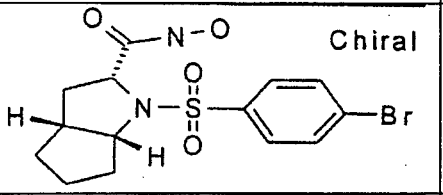
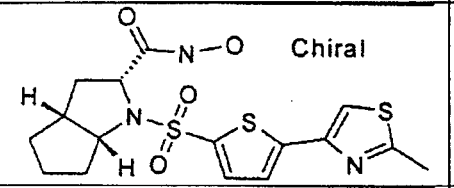
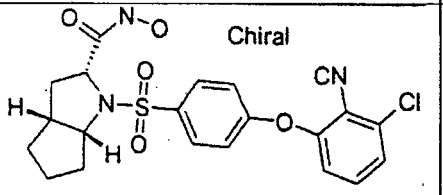
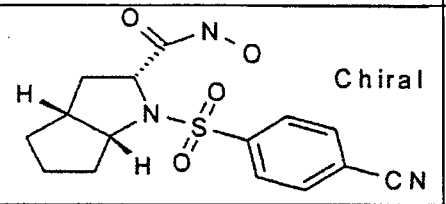
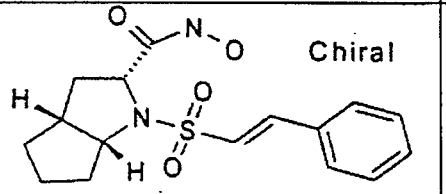
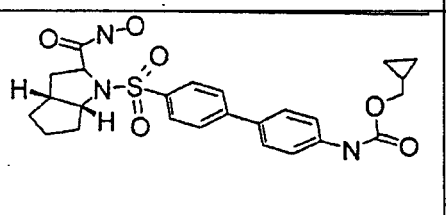
			1H
8		352.01 353.14	1.3-1.8: m, 6H; 1.9: m, 1H; 2.1: s, 3H; 2.15: m, 1H; 2.45: m, 1H; 3.85: m, 1H; 4.0: m, 1H; 7.8: m, 4H; 10.9: s, 1H
9		345.42 346.10	1.3-1.8: m, 6H; 1.9: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 3.95: m, 1H; 4.2: m, 1H; 7.7: m, 2H; 7.9: d, 1H; 8.05: d, 1H; 8.15: d, 1H; 8.2: d, 1H; 8.5: s, 1H; 12.8: bs, 1H
10		446.91 447.11	1.3-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.2: d, 1H; 7.4: d, 2H; 7.6: d, 1H; 7.75: m, 2H; 7.9: d, 2H
11		398.52 399.02	1.3-1.8: m, 6H; 1.95: m, 1H; 2.2: m, 1H; 2.5: m, 1H; 2.7: s, 3H; 3.95: m, 1H; 4.05: m, 1H; 7.65: s, 2H; 8.1: s, 1H
12		388.28 388.04	1.3-1.8: m, 6H; 1.9: m, 1H; 2.1: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 4.4: s, 2H; 7.7: d, 2H; 7.85: d, 2H
13		478.41 480.04	1.3-1.9: m, 7H; 2.4: m, 1H; 2.7: m, 1H; 3.05: t, 2H; 3.45: m, 2H; 4.25: m, 1H; 4.35: m, 1H; 7.35: m, 2H; 7.65: m, 6H
14		340.36 341.04	1.3-1.9: m, 7H; 2.1: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.2: m, 1H; 8.1: d, 2H; 8.4: d, 2H
15		421.26 421.97	1.3-1.8: m, 6H; 1.9: m, 1H; 2.1: m, 1H; 2.45: m, 1H; 3.8: m, 1H; 4.05: m, 1H; 7.55: d, 1H; 8.05: d, 1H

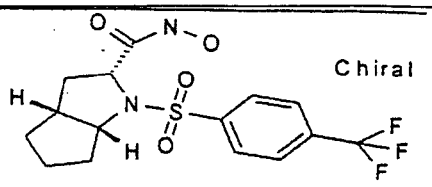
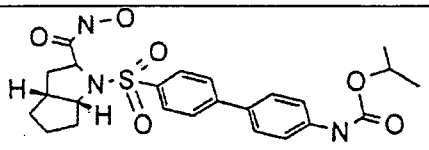
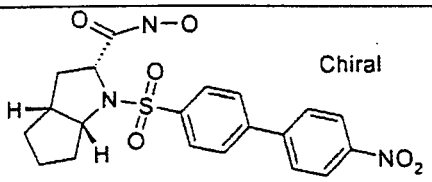
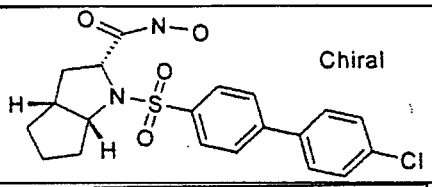
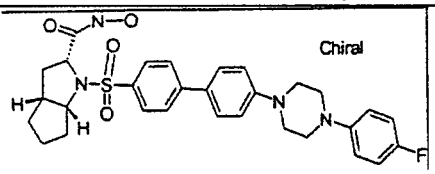
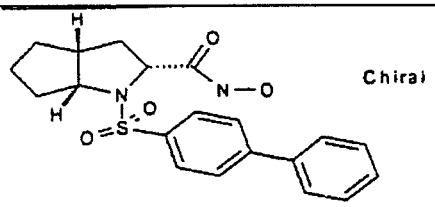
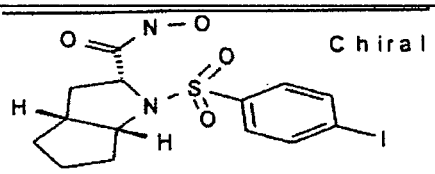
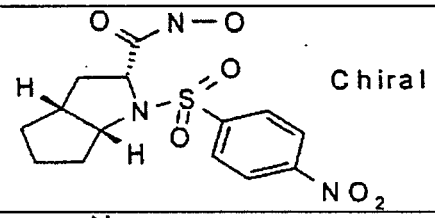
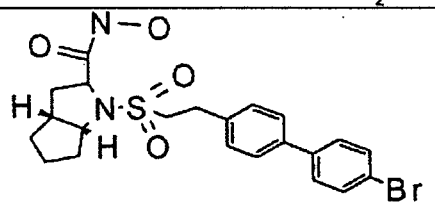
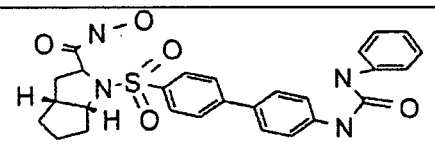
16		320.37 321.10	1.3-1.9: m, 7H; 2.2: m, 1H; 2.45: m, 1H; 3.95: m, 1H; 4.2: m, 1H; 8.0: d, 2H; 8.1: d, 2H; 12.8: s, 1H
17		321.39 322.02	1.35-1.8: m, 6H; 1.95: m, 1H; 2.4: m, 1H; 2.65: m, 1H; 4.05: m, 1H; 4.2: m, 1H; 7.4: s, 2H; 7.45: m, 3H; 7.7: m, 2H
18		379.36 379.97	1.3-1.9: m, 7H; 2.15: m, 1H; 2.5: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.6: d, 2H; 8.0: d, 2H; 12.8: s, 1H
19		363.36 364.00	1.3-1.9: m, 7H; 2.2: m, 1H; 2.5: m, 1H; 4.0: m, 1H; 4.2: m, 1H; 8.1: d, 2H; 8.15: d, 2H; 12.95: s, 1H
20		337.39 338.05	1.3-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 2.65: s, 3H; 3.9: m, 1H; 4.15: m, 1H; 7.95: d, 2H; 8.15: d, 2H; 12.8: s, 1H
21		440.56 441.09	1.3-1.8: m, 6H; 1.9: m, 1H; 2.0: m, 4H; 2.15: m, 1H; 2.45: m, 1H; 3.3: m, 4H; 3.9: m, 1H; 4.05: m, 1H; 6.6: d, 2H; 7.6: d, 2H; 7.8: m, 4H
22		472.56 473.16	11.3-1.8: m, 6H; 1.35: d, 6H; 1.9: m, 1H; 2.2: m, 1H; 2.45: m, 1H; 3.9: s, 1H; 4.0: s, 1H; 4.9: s, 1H; 7.6: d, 2H; 7.8: d, 2H; 7.8: m, 4H; 10.0: s, 1H
23		464.56 465.20	1.3-1.9: m, 7H; 2.1: m, 1H; 2.4: m, 1H; 3.0: s, 3H; 3.9: s, 1H; 4.05: s, 1H; 7.35: d, 2H; 7.8: d, 2H; 7.9: m, 4H; 9.9: s, 1H
24		490.58 491.34	1.3-1.9: m, 7H; 2.1: m, 1H; 2.4: m, 1H; 3.95: m, 1H; 4.1: m, 1H; 7.55: m, 2H; 7.8-8.1: m, 8H; 8.4: m, 2H

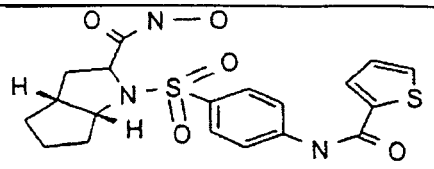
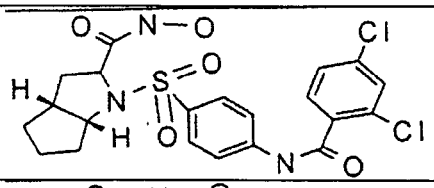
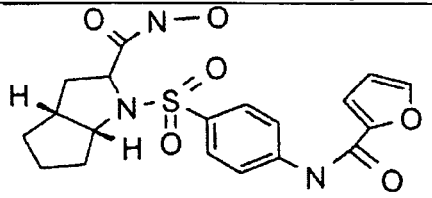
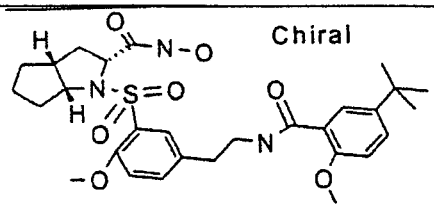
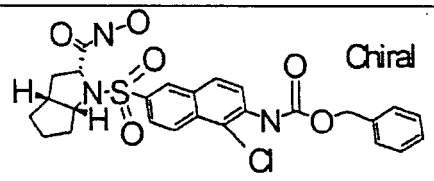
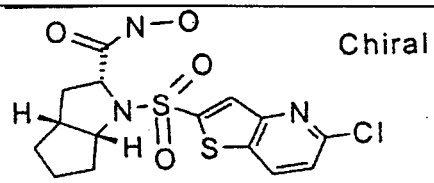
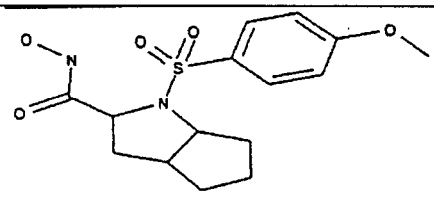
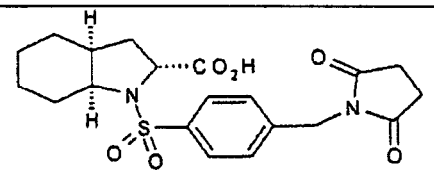
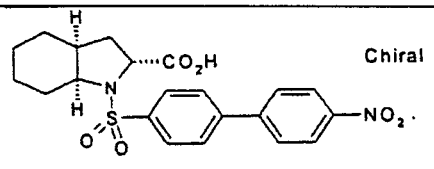
25		526.63 527.12	1.3-1.8: m, 6H; 1.8: m, 1H; 2.0: m, 1H; 2.1: m, 1H; 3.85: m, 1H; 4.05: m, 1H; 7.2: m, 1H; 7.6: m, 6H; 7.9: m, 6H
26		505.59 506.28	1.3-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.0-8.5: m, 13H; 12.8: s, 1H
27		386.47 387.14	1.3-1.8: m, 6H; 1.85: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 3.85: m, 1H; 4.1: m, 1H; 8.1: d, 2H; 8.3: d, 2H
28		416.46 417.23	1.3-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 3.95: m, 1H; 4.10: m, 1H; 8.0: m, 4H; 8.1: d, 2H; 8.3:d,2H
29		549.67 550.37	1.3-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 3.25: m, 4H; 3.4: m, 4H; 3.9: m, 1H; 4.05: m, 1H; 7.1: m, 6H; 7.7: d, 2H; 7.9: m, 4H;
30		405.90 406.21	1.3-1.8: m, 6H; 1.9: m, 1H; 2.2: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.6: d, 2H; 7.8: d, 2H; 7.95: m, 4H
31		371.46 372.16	1.3-1.8: m, 6H; 1.9: m, 1H; 2.2: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.5: m, 3H; 7.75: m, 2H; 7.95: m, 4H
32		484.58 485.12	0.35: m, 2H; 0.55: m, 2H; 1.3-1.8: m, 8H; 1.95: m, 1H; 2.3: m, 1H; 3.95: 1H; 4.2: m, 1H; 7.6: m, 3H; 7.85: m, 3H; 8.05: m, 2H
33		301.39 302.06	1.3-1.8: m, 6H; 1.9: m, 1H; 2.2: m, 1H; 2.4: m, 1H; 3.9: m, 1H; 4.05: m, 1H; 7.3: m, 1H; 7.7: m, 1H; 8.0: m, 1H

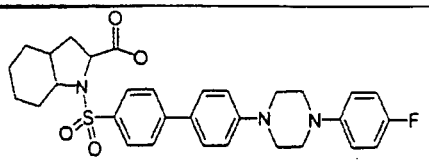
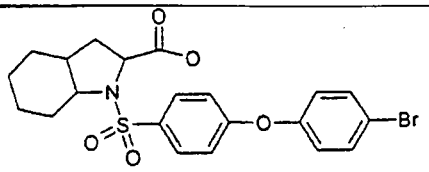
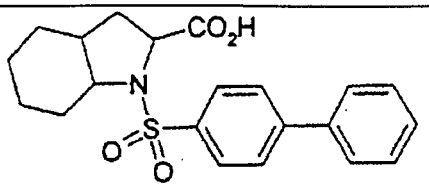
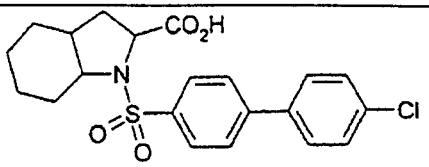
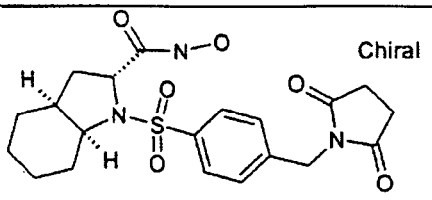
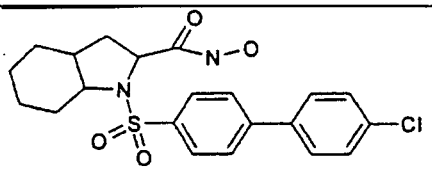
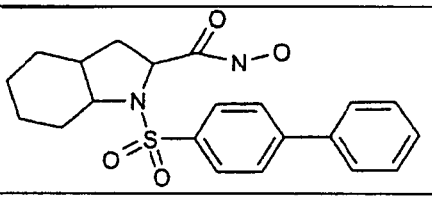
34	 Chiral	335.83 336.01	1.3-1.8: m, 6H; 1.9: m, 1H; 2.15: m, 1H; 2.5: m, 1H; 3.95: m, 1H; 4,: m, 1H; 7.35: m, 1H; 7.35: d, 1H; 7.65: d, 1H
35		428.51 429.24	1.3-1.7: m, 6H; 1.9: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 3.8: m, 1H; 4.0: m, 1H; 7.3: m, 5H; 7.8: d, 2H; 7.85: d, 2H, 10.8: s, 1H
36		470.57 471.22	1.3-1.7: m, 6H; 1.85: m, 1H; 2.1: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.5: m, 2H; 7.9: d, 2H; 8.05: m, 4H; 8.45: s, 1H; 10.9: s, 1H
37		310.09 311.13	1.3-1.7: m, 6H; 1.85: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 3.8: m, 1H; 3.9: m, 1H; 6.6: d, 2H; 7.45: d, 2H;
38	 Chiral	386.88 387.14	1.3-2.0: m, 7H; 2.2: m, 1H; 2.55: m, 1H; 4.2: m, 1H; 4.25: m, 1H; 7.65: d, 1H; 8.2: s, 1H; 8.7: d, 2H
39	 Chiral	529.02 529.25	1.3-1.8: m, 6H; 1.8: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 3.95: m, 1H; 4.2: m, 1H; 5.2: s, 2H; 7.4: m, 5H; 8.0: m, 2H; 8.2: d, 1H; 8.4: d, 1H; 8.55: s, 1H
40	 Chiral	558.69 559.32	1.2: s, 9H; 1.3-1.7: m, 6H; 1.9: m, 1H; 2.25: m, 1H; 2.45: m, 1H; 2.85: m, 2H; 3.5: m, 2H; 3.65: m, 1H; 3.8: s, 3H; 3.9: s, 3H; 4.5: m, 1H; 7.0: d, 1H; 7.2: d, 1H; 7.45: m, 2H; 7.7: m, 2H; 8.15: m, 1H
41	 Chiral	474.56 475.21	1.3-1.8: m, 6H; 2.0: m, 1H; 2.3: m, 1H; 2.6: m, 1H; 2.9: m, 4H; 3.6: m, 4H; 3.8: m, 1H; 4.1: s, 3H; 4.5: m, 1H; 7.5: d, 1H; 7.95: d, 1H; 8.05: d, 1H

42		404.45 405.22	1.3-1.8: m, 6H; 1.85: m, 1H; 2.1: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.05: m, 1H; 6.7: d, 1H; 7.4: d, 1H; 7.8: d, 2H; 8.0: m, 3H; 10.4: s, 1H
43		432.47 433.23	1.3-1.7: m, 6H; 1.85: m, 1H; 2.1: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.05: m, 1H; 7.4: m, 2H; 7.8: m, 2H; 8.05: m, 4H; 10.6: s, 1H
44		483.37 483.19	1.3-1.8: m, 6H; 1.85: m, 1H; 2.15: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.05: m, 1H; 7.5: d, 1H; 7.65: d, 1H; 7.75: s, 1H; 7.8: d, 2H; 7.9: d, 2H; 10.9: s, 1H
45		503.96 504.25	1.3-1.85: m, 6H; 2.05: m, 1H; 2.4: m, 1H; 2.65: m, 1H; 3.95: s, 3H; 4.0: m, 1H; 4.6: m, 1H; 7.2: d, 2H; 7.3: m, 1H; 7.4: d, 1H; 7.85: s, 1H; 7.9: d, 1H; 8.2: d, 1H; 8.45: s, 1H
46		350.85 351.14	1.4-2.0: m, 8H; 2.4: m, 1H; 3.8: m, 1H; 3.95: m, 1H; 7.35: d, 1H; 7.65: d, 1H; 10.4: s, 1H;
47		316.40 317.17	1.8-2.4: m, 8H; 2.85: m, 1H; 3.8: m, 1H; 3.9: m, 1H; 7.25: m, 1H; 7.8: m, 1H; 8.05: m, 1H; 10.4: s, 1H
48		366.48 367.22	1.35: s, 9H; 1.4-1.95: m, 8H; 2.35: m, 1H; 3.8-4.0: m, 2H; 7.6: d, 2H; 7.8: d, 2H; 10.55: s, 1H
49		367.43 368.19	1.4-1.95: m, 8H; 2.1: s, 3H; 2.35: m, 1H; 3.8-4.0: m, 2H; 7.8: m, 4H; 10.4: s, 1H; 10.6: s, 1H

50	 Chiral	360.44 361.77	1.4-2.0: m, 8H; 2.35: m, 1H; 3.8-4.1: m, 2H; 7.65: m, 2H; 7.95: d, 1H; 8.10: d, 1H; 8.15: m, 2H; 8.5: s, 1H, 10.6: s, 1H
51	 Chiral	414.93 415.12	1.4-1.9: m, 7H; 1.95-2.2: m, 2H; 2.7: s, 3H; 4.1: m, 2H; 7.6: m, 1H; 8.1: m, 2H; 10.6: s, 1H
52	 Chiral	388.46 389.14	1.4-1.8: m, 8H; 1.90: m, 1H; 3.4: s, 3H; 3.9: m, 2H; 8.15: m, 4H; 10.6: s, 1H
53	 Chiral	389.27 389.07	1.4-2.0: m, 8H; 2.40: m, 1H; 3.9: m, 2H; 7.8: m, 4H; 10.6: s, 1H
54	 Chiral	413.54 414.05	N.A.
55	 Chiral	461.93 462.07	1.4-2.1: m, 8H; 2.4: m, 1H; 3.95: m, 2H; 7.65: d, 1H; 7.40: d, 1H; 7.50: d, 1H; 7.60: d, 1H; 7.75: m, 1H; 7.95: d, 2H; 10.6: s, 1H
56	 Chiral	335.38 336.14	1.4-2.1: m, 8H; 2.4: m, 1H; 2.4: m, 1H; 3.95: m, 2H; 8.0: d, 2H; 8.1: d, 2H; 10.6: s, 1H;
57	 Chiral	336.41 337.11	1.4-1.8: m, 6H; 2.0: m, 1H; 2.2: m, 1H; 2.6: m, 1H; 3.95: m, 1H; 4.05: m, 1H; 7.9: m, 4H; 7.7: m, 2H; 10.5: s, 1H
58		499.59 500.09	0.35: m, 2H; 0.55: m, 2H; 1.1-1.85: m, 9H; 1.95: m, 2H; 2.35: m, 1H; 3.85: m, 1H; 3.95: m, 1H; 7.60: d, 2H; 7.7: d, 2H; 7.9: m, 4H; 9.8: s, 1H; 10.6: s, 1H

59		378.38 379.02	1.4-2.1: m, 8H; 2.4: m, 1H; 3.9: m, 2H; 8.0: d, 2H; 8.1: d, 2H; 10.65: s, 1H
60		487.58 488.36	1.26: d, 6H; 1.4-2.0: m, 8H; 2.35: m, 1H; 3.85: m, 2H; 4.95: m, 1H; 7.6: d, 2H; 7.7: d, 2H; 7.85: m, 4H; 9.8: s, 1H; 10.6: s, 1H
61		431.12 432.01	1.4-1.8: m, 8H; 2.45: m, 1H; 3.9: m, 2H; 8.05: m, 6H; 8.35: m, 2H; 10.65: s, 1H
62		420.92 421.24	1.4-1.8: m, 6H; 2.0: m, 2H; 2.4: m, 1H; 3.95: m, 2H; 7.6: d, 2H; 7.8: d, 2H; 8.0: m, 4H; 10.6: s, 1H
63		564.68 565.39	1.4-2.05: m, 8H; 2.35: m, 1H; 3.35: m, 4H; 3.40: m, 4H; 3.9: m, 2H; 7.1: m, 6H; 7.6: d, 2H; 7.9: m, 4H; 10.6: s, 1H
64		386.47 387.19	1.4-2.0: m, 8H; 2.45: m, 1H; 3.95: m, 2H; 7.45: m, 3H; 7.75: m, 2H; 7.95: m, 4H; 10.6: s, 1H
65		435.99 437.02	1.4-20: m, 8H; 2.35: m, 1H; 3.85: m, 2H; 7.6: d, 2H; 8.0: d, 2H; 10.6: s, 1H
66		355.08 356.09	1.4-2.0: m, 8H; 2.35: m, 1H; 3.95: m, 2H; 8.15: d, 2H; 8.4: d, 2H; 10.6: s, 1H
67		493.42 493.10	1.4-1.95: m, 8H; 2.35: m, 1H; 2.70: m, 2H; 3.0: m, 2H; 4.1: m, 1H; 4.3: m, 1H; 7.4: m, 2H; 7.6: m, 6H; 10.6: s, 1H
68		520.61 521.16	1.4-1.9: m, 8H; 2.4: m, 1H; 3.85: m, 2H; 7.0-8.0: m, 12H; 8.6: s, 1H; 8.8: s, 1H; 10.6: s, 1H

69		435.52 436.19	1.4-1.85: m, 6H; 1.9: m, 2H; 2.4: m, 1H; 3.95: m, 2H; 7.25: m, 1H; 7.8-8.1: m, 6H; 8.9: s, 1H; 10.5: s, 1H
70		498.39 498.17	1.4-1.85: m, 6H; 1.9: m, 2H; 2.4: m, 1H; 3.85: m, 2H; 7.6-7.9: m, 7H; 8.95: s, 1H; 11.0: s, 1H
71		419.59 420.21	1.4-1.85: m, 6H; 1.95: m, 2H; 2.3: m, 1H; 3.95: m, 2H; 3.85: m, 2H; 6.7: m, 1H; 7.4: m, 1H; 7.8: m, 2H; 8.0: m, 3H; 8.9: s, 1H; 10.8: s, 1H
72		573.71 574.38	1.25: s, 9H; 1.3-1.8: m, 6H; 1.9: m, 1H; 2.1: m, 1H; 2.4: m, 1H; 2.85: m, 2H; 3.5: m, 2H; 3.8: s, 3H; 3.9: s, 3H; 4.3: m, 2H; 7.0: d, 2H; 7.2: d, 2H; 7.5: m, 2H; 7.7: d, 2H; 8.1: m, 1H; 10.2: s, 1H
73		544.03 544.24	1.4-1.8: m, 6H; 1.95: m, 2H; 2.3: m, 1H; 3.95: m, 2H; 5.2: s, 2H; 7.4: m, 6H; 8.0: m, 2H; 8.2: d, 1H; 8.45: d, 1H; 8.55: s, 1H; 10.8: s, 1H
74		401.89 402.13	1.4-1.9: m, 6H; 2.05: m, 2H; 2.4: m, 1H; 3.95: m, 1H; 4.1: m, 1H; 7.6: d, 1H; 8.25: s, 1H; 8.7: d, 1H
75		340.11	1.4-2.0: m, 8H; 2.3: m, 1H; 3.8: m, 2H; 3.85: s, 3H; 7.17: d, 2H; 7.82: d, 2H; 8.9: s, 1H; 10.6: s, 1H
76		420.49 421.02	N.A.
77		430.48 431.17	1.0-1.9: m, 9H; 1.85: m, 1H; 2.45: m, 1H; 3.75: m, 1H; 4.3: m, 1H; 8.0: m, 6H; 8.4: m, 2H

78		563.70 564.35	1.0-1.95: m, 10H; 2.4: m, 1H; 3.25: m, 4H; 3.45: m, 4H; 3.75: m, 1H; 4.3: m, 1H; 7.1: m, 6H; 7.7: m, 2H; 7.85: m, 4H
79		480.38 482.16	1.0-1.9: m, 9H; 2.35: m, 1H; 2.4: m, 1H; 3.7: m, 1H; 4.2: m, 1H; 7.1: m, 4H; 7.6: m, 2H; 7.8: m, 2H
80		371.46 372.16	1.3-1.9: m, 9H; 2.2: m, 1H; 2.45: m, 1H; 3.9: m, 1H; 4.1: m, 1H; 7.5: m, 3H; 7.8: m, 3H; 7.95: m, 4H
81		419.93 420.34	1.1-1.8: m, 9H; 1.9: m, 1H; 2.1: m, 1H; 3.65: m, 1H; 4.05: pt, 1H; 7.6: d, 2H; 7.8: d, 2H; 7.9: m, 4H
82		435.50 436.19	1.0-1.6: m, 8H; 1.9: m, 1H; 2.25: m, 1H; 2.6: m, 1H; 2.75: m, 4H; 3.6: m, 1H; 4.1: m, 1H; 7.4: d, 2H; 7.8: d, 2H
83		434.95 435.20	1.1-2.0: 11H; 3.6: m, 1H; 3.9: m, 1H; 7.6: d, 2H; 7.8: d, 2H; 7.95: d, 2H; 8.0: d, 2H
84		400.50 401.25	1.0-1.6: m, 8H; 1.9: m, 1H; 2.2: m, 1H; 2.7: m, 1H; 3.7: m, 1H; 4.15: m, 1H; 7.8: m, 4H; 8.0: m, 2H, 8.1: m, 2H

Pharmacological examples

Preparing, and determining the enzymic activity of the catalytic domain of human stromelysin (MMP-3) and neutrophilic collagenase (MMP-8).

The two enzymes, i.e. stromelysin (MMP-3) and neutrophilic collagenase (MMP-8), were prepared as described in Ye et al. (Biochemistry; 31 (1992) pages 11231-11235). For measuring enzymic activity or the effect of an enzyme inhibitor, 70 µl of buffer solution and 10 µl of enzyme solution are incubated, for 15 minutes and at a physiological pH, with 10 µl of a 10% (v/v) aqueous solution of dimethyl sulfoxide containing the enzyme

inhibitor, where appropriate. After 10 µl of a 10% (v/v) aqueous solution of dimethyl sulfoxide containing 1 mmol of the substrate/l have been added, the enzyme reaction is monitored by fluorescence spectroscopy (328 nm (ex)/393 nm(em)).

The enzyme activity is recorded as increase in extinction/minute. The IC_{50} values listed in table 2 are determined as the inhibitor concentrations which in each case lead to 50% inhibition of the enzyme.
The buffer solution contains 0.05% Brij (Sigma, Deisenhofen, Germany) and also 0.1 mol of Tris/HCl/l, 0.1 mol of NaCl/l, 0.01 mol of $CaCl_2$/l and 0.1 mol of piperazine-N,N'-bis[2-ethanesulfonic acid]/l (pH = 7.5). The enzyme solution contains 5 µg/ml of one of the enzyme domains prepared as described in Ye et al. The substrate solution contains 1 mmol of the fluorogenic substrate (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-3-(2',4'-dinitrophenyl)-L-2,3-diaminopropionyl-Ala-Arg-NH_2/l (Bachem, Heidelberg, Germany).

Determining the enzymic activity of the catalytic domain of human collagenase 3 (MMP-13).

This protein is obtained from INVITEK, Berlin, as an inactive proenzyme (catalogue No. 30 100 803). Activating the proenzyme:
2 parts by volume of the proenzyme are incubated with 1 part by volume of APMA solution at 37°C for 1.5 hours. The APMA solution is prepared from a 10 mmol/l solution of p-aminophenylmercuric acetate in 0.1 mmol/l NaOH by diluting with 3 parts by volume of Tris/HCl buffer, pH 7.5 (see below). The pH is adjusted to between 7.0 and 7.5 by adding 1 mmol of HCl/l. After the enzyme has been activated, it is diluted with the Tris/HCl buffer to a concentration of 1.67 µg/ml.

In order to measure the enzyme activity, 10 µl of enzyme solution are incubated for 15 minutes with 10 µl of a 3% (v/v) buffer solution of dimethyl sulfoxide (reaction 1). In order to measure enzyme inhibitor activity, 10 µl of enzyme solution are incubated with 10 µl of a 3% (v/v) buffer solution of dimethyl sulfoxide which contains the enzyme inhibitor (reaction 2).

Both in the case of reaction 1 and in the case of reaction 2, the enzyme reaction is monitored by fluorescence spectroscopy (328 nm

(extinction)/393 nm (emission)) after 10 µl of a 3% (v/v) aqueous solution of dimethyl sulfoxide containing 0.75 mmol of the substrate/l have been added. The enzyme activity is recorded as increase in extinction/minute.
The inhibitory effect is calculated as a percentage inhibition in accordance with the following formula:
% inhibition = 100 - [(increase in extinction/minute in reaction 2)/(increase in extinction/minute in reaction 1) × 100].
The IC_{50}, i.e. the inhibitor concentration which is required for 50% inhibition of the enzyme activity, is determined graphically by plotting the percentage inhibitions at different inhibitor concentrations.

The buffer solution contains 0.05% Brij (Sigma, Deisenhofen, Germany) and also 0.1 mol of Tris/HCl/l, 0.1 mol of NaCl/l and 0.01 mol of $CaCl_2$/l (pH = 7.5).
The enzyme solution contains 1.67 µg/ml of the enzyme domain.
The substrate solution contains 0.75 mmol of the fluorogenic substrate (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-3-(2',4'-dinitrophenyl)-L-2,3-diaminopropionyl-Ala-Arg-NH_2/l (Bachem, Heidelberg, Germany).

The following table 2 shows the results.

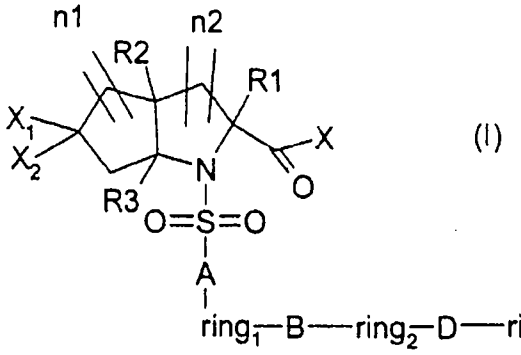
Table 2

Example No.	MMP-3 IC_{50} (nM)	MMP-8 IC_{50} (nM)	MMP-13 IC_{50} (nM)
13	200	200	700
21	160	4	100
29	>10 000	10 000	260
57	330	320	200
61	22	3	2
63	200	3 700	4.2
64	100	20	3
65	300	100	220

Comprises/comprising and grammatical variations thereof when used in this specification are to be taken to specify the presence of stated features, integers, steps or components or groups thereof, but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula I



(I)

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

A is -(C_0-C_4)-alkylene,

B, D and E are identical or different and are, independently of each other,

1. -(C_0-C_4)-alkylene,
2. -(C_2-C_4)-alkenylene,
3. -$S(O)_o$-, where o is the integers zero, 1 or 2,
4. -NH-,
5. -NH-C(O)-,
6. -C(O)-NH-,
7. -NH-SO_2-,
8. -NH-C(O)-NH-,
9. -NH-C(S)-,
10. -NH-C(O)-O-,
11. -O-,
12. -O-C(O)-NH-,
13. -C(O)-,
14. -O-$(CH_2)_n$-O-, in which n is the integer 2 or 3, or
15. -O-$(CH_2)_m$-NH-, in which m is the integer 2 or 3,

ring 1, ring 2 or ring 3 are identical or different and are, independently of each other,

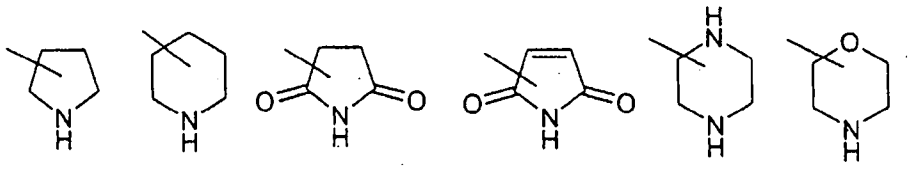
1. covalent bond,
2. -(C_6-C_{14})-aryl, in which aryl is unsubstituted or substituted, independently of each other, once, twice or

three times, by G, or

3. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is unsubstituted or substituted, independently of each other, once, twice or three times, by G,

ring 4 is

1. -(C_6-C_{14})-aryl, in which aryl is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
2. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
3. heteroaryl, in which heteroaryl is unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
4. one of the following radicals



and these radicals are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

G is
1. hydrogen atom,
2. halogen,
3. R4 and R4 is
   a) hydrogen atom,
   b) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once, twice or three times, by halogen, -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl or heteroaryl,
   c) -(C_6-C_{14})-aryl,
   d) heteroaryl,
   e) -C(O)-O-R5, in which R5 is
      e)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl, or

heteroaryl, or

e)2) -(C_6-C_{14})-aryl or heteroaryl,

f) -C(S)-O-R5, in which R5 is defined as above,

g) -C(O)-NH-R6, in which R6 is

g)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl or heteroaryl, or

g)2) -(C_6-C_{14})-aryl or heteroaryl, or

h) -C(S)-NH-R6, in which R6 is defined as above,

4. -O-R4, in which R4 is defined as above,

5. -C(O)-R5, in which R5 is defined as above,

6. -$S(O)_p$-R4, in which R4 is defined as above and p is the integers zero, 1 or 2,

7. -NO_2,

8. -CN or

9. -N(R3)-R4, in which R3 is

9.1) hydrogen atom, or

9.2) -(C_1-C_6)-alkyl and R4 is defined as above,

X is -OH or -NH-OH,

X_1 and X_2 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl, or together form the radical =O,

n1 and n2 are identical or different and are, independently of each other, zero, 1 or 2,

R1 is 1. hydrogen atom, or

2. -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, -(C_6-C_{14})-aryl or heteroaryl,

R2 and R3 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl,

wherein each of the compounds 1-(toluene-4-sulfonyl)-octahydroindole-2-carboxylic acid and (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid are excluded.

2. A compound of formula I as claimed in claim 1, wherein

A is -(C_0-C_4)-alkylene,

B, D and E are identical or different and are, independently of each

other,

1. -(C_0-C_4)-alkylene,
2. -(C_2-C_4)-alkenylene,
3. -$S(O)_o$-, where o is the integers zero, 1 or 2,
4. -NH-,
5. -NH-C(O)-,
6. -C(O)-NH-,
7. -NH-SO_2-,
8. -NH-C(O)-NH-,
9. -NH-C(S)-,
10. -NH-C(O)-O-,
11. -O-,
12. -O-C(O)-NH-,
13. -C(O)-,
14. -O-$(CH_2)_n$-O-, in which n is the integer 2 or 3, or
15. -O-$(CH_2)_m$-NH-, in which m is the integer 2 or 3,

ring 1, ring 2 or ring 3 are identical or different and are, independently of each other,

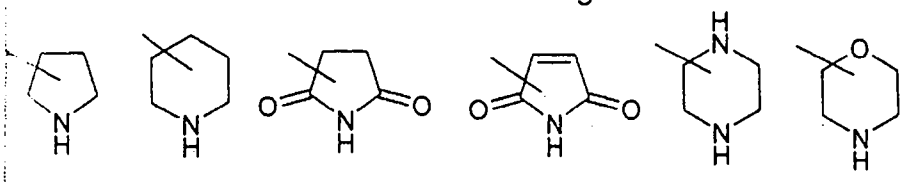
1. covalent bond,
2. -(C_6-C_{14})-aryl, in which aryl is a radical from the series phenyl, naphthyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, anthryl or fluorenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
3. 5- or 6-membered aromatic heteroaryl ring in which the heteroaryl ring is a radical from the series dihydrofuranyl, dioxolyl, dioxanyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, isothiazolyl, isothiazolidinyl, 2-isothiazolinyl, morpholinyl, oxazolyl, oxothiolanyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyridinyl, thiazolyl, thiomorpholinyl, thiophenyl or thiopyranyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

ring 4 is

1. -(C_6-C_{14})-aryl, in which aryl is a radical from the series phenyl, naphthyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, anthryl or fluorenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
2. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is a radical from the series dihydrofuranyl, dioxolyl, dioxanyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, isoxazolyl, isoxazolidinyl, 2-isoxazolinyl, isothiazolyl, isothiazolidinyl, 2-isothiazolinyl, morpholinyl, oxazolyl, oxothiolanyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyridinyl, thiazolyl, thiomorpholinyl, thiophenyl or thiopyranyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G,
3. heteroaryl, in which heteroaryl is a radical from the series acridinyl, azetidinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzotetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, deca-hydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuran[2,3-b]tetrahydrofuran, fuaranyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, 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, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl, and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or

4. is one of the following radicals



and these radicals are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

G is

1. hydrogen atom,
2. halogen,
3. R4, and R4 is
   - a) hydrogen atom,
   - b) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once, twice or three times, by halogen, -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl defined as above,
   - c) phenyl or naphthyl,
   - d) heteroaryl, where heteroaryl is defined as above,
   - e) -C(O)-O-R5, in which R5 is
     - e)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is as defined above,
     - e)2) phenyl or naphthyl, or

e)3) heteroaryl, where heteroaryl as defined above, is substituted,

f) -C(S)-O-R5, in which R5 is defined as above,

g) -C(O)-NH-R6, in which R6 is

g)1) -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is defined as above,

g)2) phenyl or naphthyl, or

g)3) heteroaryl, where heteroaryl as defined above, is substituted, or

h) -C(S)-NH-R6, in which R6 is defined as above,

4. -O-R4, in which R4 is defined as above,

5. -C(O)-R5, in which R5 is defined as above,

6. -$S(O)_p$-R4, in which R4 is defined as above and p is the integers zero, 1 or 2,

7. -NO_2,

8. -CN, or

9. -N(R3)-R4, in which R3 is

9.1) hydrogen atom, or

9.2) -(C_1-C_6)-alkyl and R4 is defined as above,

X is -OH or -NH-OH,

X_1 and X_2 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl, or together form the radical =O,

n1 and n2 are identical or different and are, independently of each other, zero, 1 or 2,

R1 is 1. hydrogen atom, or

2. -(C_1-C_6)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -(C_3-C_6)-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is defined as above,

R2 and R3 are identical or different and are, independently of each other, hydrogen atom or -(C_1-C_6)-alkyl.

3. A compound of formula I as claimed in claim 1 or claim 2, wherein

A is -(C_0-C_4)-alkylene,

B, D and E are identical or different and are, independently of each other,

1. -(C_0-C_2)-alkylene,
2. -C_2-alkenylene,
3. -$S(O)_o$-, where o is the integer 2,
4. -NH-,
5. -NH-C(O)-,
6. -C(O)-NH-,
7. -NH-C(O)-NH-,
8. -O-, or
9. -C(O)-,

ring 1, ring 2 or ring 3 are identical or different and are, independently of each other,

1. covalent bond,
2. phenyl or naphthyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or
3. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is a radical from the series dihydrofuranyl, furanyl, morpholinyl, piperazinyl, piperidinyl, pyridinyl, pyrimidinyl, pyrrolyl, thiazolyl or thiophenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

ring 4 is

1. phenyl or naphthyl and is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
2. 5- or 6-membered aromatic heteroaryl ring, in which the heteroaryl ring is and is a radical from the series dihydrofuranyl, furanyl, morpholinyl, piperazinyl, piperidinyl, pyridinyl, pyrimidinyl, pyrrolyl, thiazolyl or thiophenyl and is unsubstituted or substituted, independently of each other, once, twice or three times, by G,
3. heteroaryl, in which heteroaryl is a radical from the series benzofuranyl, benzothiophenyl, dihydrofuranyl, furanyl, morpholinyl, piperazinyl, piperidinyl, pyridinyl,

pyridothiophenyl, pyrimidinyl, pyrrolyl, thiazolyl or thiophenyl and are unsubstituted or substituted, independently of each other, once, twice or three times, by G, or

4. is one of the following radicals

and these radicals are unsubstituted or substituted, independently of each other, once, twice or three times, by G,

G is 1. hydrogen atom,

2. Br; Cl, I or F,

3. R4, and R4 is

a) hydrogen atom,

b) -(C_1-C_4)-alkyl, in which alkyl is unsubstituted or substituted, once, twice or three times, by Br, Cl, F, -C_3-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl defined as above,

c) phenyl or naphthyl,

d) heteroaryl, where heteroaryl defined as above,

e) -C(O)-O-R5, in which R5 is

e)1) -(C_1-C_4)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -C_3-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is as defined above,

e)2) phenyl or naphthyl, or

e)3) heteroaryl, where heteroaryl as defined above, is substituted, or

f) -C(O)-NH-R6, in which R6 is

f)1) -(C_1-C_4)-alkyl, in which alkyl is unsubstituted or substituted, once or twice, by -C_3-cycloalkyl, phenyl, naphthyl or heteroaryl, where heteroaryl is defined as above,

f)2) phenyl or naphthyl, or

f)3) heteroaryl, where heteroaryl as defined above, is substituted,

4. -O-R4, in which R4 is defined as above,

5. -C(O)-R5, in which R5 is defined as above,
6. $-S(O)_p$-R4, in which R4 is defined as above and p is the integer 2,
7. $-NO_2$,
8. -CN, or
9. -N(R3)-R4, in which R3 is
   - 9.1) hydrogen atom, or
   - 9.2) $-(C_1-C_6)$-alkyl and R4 is defined as above,

X is -OH or -NH-OH,

X_1 and X_2 are identical and are hydrogen atom,

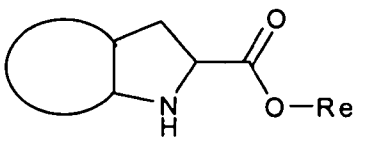
n1 and n2 are identical and are 1 or are nonidentical and n1 is 2 and n2 is 1,

R1 is hydrogen atom, and

R2 and R3 are identical and are hydrogen atom.

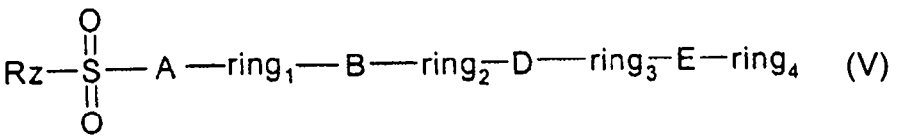
4. A process for preparing the compound of formula I as claimed in any one or more of claims 1 to 3 and/or a stereoisomeric form of the compound of formula I and/or a physiologically tolerated salt of the compound of formula I, which comprises

a) reacting a compound of formula IV,



(IV)

in which Re is a hydrogen atom or an ester protecting group, with a compound of formula V,



(V)

in which A, B, D, E and ring 1, ring 2, ring 3 and ring 4 are defined as in formula I, and in which Rz is chlorine atom, imidazolyl or OH,

in the presence of a base, or after silylation with a suitable silylating agent, to give a compound of formula VI,

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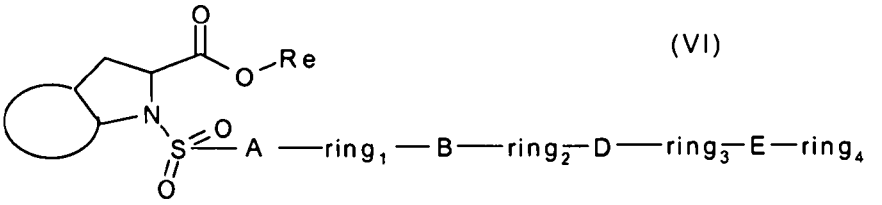
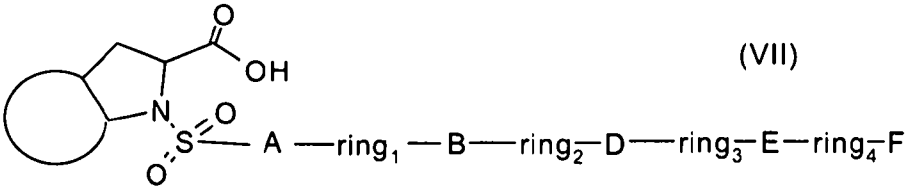


(VI)

in which A, B, D, E, Re and ring 1, ring 2, ring 3 and ring 4 are defined as above,

b) where Re = ester, reacting a compound of formula VI, which has been prepared in accordance with a), with a solution of an alkali such as NaOH or LiOH, and then treating with acid, to give the novel carboxylic acid of formula I, with modifications in one of the side chains of the rings ring 1-ring 4 also having been previously carried out, where appropriate,



(VII)

and then converting this compound into the novel hydroxamic acid, where X = NH-OH, of formula I,

c) separating a compound of formula I, which has been prepared in accordance with process a) or b) and which arises in enantiomeric forms on account of its chemical structure, into the pure enantiomers by means of salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization using chiral, enantiomerically pure compounds, such as amino acids, separation of the resulting diastereomers and elimination of the chiral auxiliary groups, or

d) either isolating the compound of formula I, which has been prepared in accordance with processes b) or c), in free form or, when acidic or basic groups are present, converting it into physiologically tolerated salts.

5. A pharmaceutical, which comprises an effective content of at least one compound of formula I as claimed in any one or more of claims 1 to 3 or the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid together with a pharmaceutically suitable and physiologically tolerated carrier substance, additive and/or other active compounds and auxiliary

substances.

6. The use of the compound of formula I as claimed in any one or more of claims 1 to 3 or the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid for producing a pharmaceutical for the prophylaxis and therapy of diseases.

7. The use according to claim 6 wherein the diseases are selected from osteoarthroses, spondyloses, cartilage loss following joint trauma or a relatively long period of joint immobilization following meniscus or patella injuries or ligament rupture, diseases of the connective tissue such as collagenoses, periodontal diseases, wound healing disturbances and chronic diseases of the locomotory apparatus, such as inflammatory, immunologically-determined or metabolism-determined acute and chronic arthritides, arthropathies, myalgias and disturbances in bone metabolism.

8. The use of the compound of formula I as claimed in any one or more of claims 1 to 3 or the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid for producing a pharmaceutical for treatment of conditions selected from ulceration, atherosclerosis and stenoses, treatment of inflammations, cancer diseases, tumor metastasis formation, cachexia, anorexia, heart failure and septic shock.

9. The use of the compound of formula I as claimed in any one or more of claims 1 to 3 or the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid for producing a pharmaceutical for prophylaxis of myocardial and cerebral infarcts.

10. A method for the prophylaxis and therapy of diseases in a patient, the method comprising administering to a patient a therapeutically effective amount of a compound of formula I as claimed in any one or more of claims 1 to 3, the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid or of a pharmaceutical as claimed in claim 5.

11. The method according to claim 10 wherein the diseases are selected from osteoarthroses, spondyloses, cartilage loss following joint trauma

or a relatively long period of joint immobilization following meniscus or patella injuries or ligament rupture, diseases of the connective tissue such as collagenoses, periodontal diseases, wound healing disturbances and chronic diseases of the locomotory apparatus, such as inflammatory, immunologically-determined or metabolism-determined acute and chronic arthritides, arthropathies, myalgias and disturbances in bone metabolism.

12. A method for the treatment of conditions selected from ulceration, atherosclerosis and stenoses, treatment of inflammations, cancer diseases, tumor metastasis formation, cachexia, anorexia, heart failure and septic shock, the method comprising administering to a patient a therapeutically effective amount of a compound of formula I as claimed in any one or more of claims 1 to 3, the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid or of a pharmaceutical as claimed in claim 5.

13. A method for the prophylaxis of myocardial and cerebral infarcts, which method comprises administering to a patient a therapeutically effective amount of a compound of formula I as claimed in any one or more of claims 1 to 3, the compound (2R, 3aR, 6aS)-octahydro-1-(phenylsulfonyl)-cyclopenta [b] pyrrole-2-carboxylic acid or of a pharmaceutical as claimed in claim 5.

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