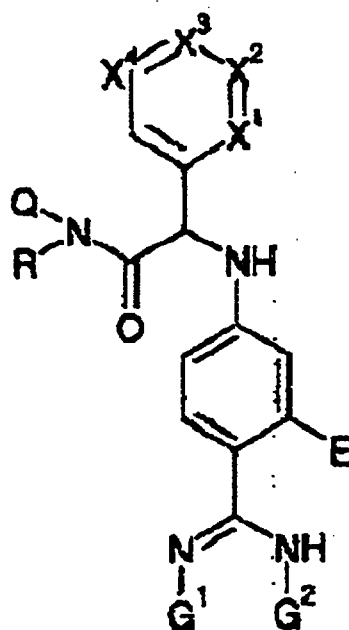




The invention relates to novel N-(4-carb-
5 amidophenyl)glycineamide derivatives, in particular to
those of the formula



10 in which

E is hydrogen or OH,

Q is hydrogen or alkyl,

R is aryl, cycloalkyl or alkyl which is substituted by R¹,
R² and R³,

15 R¹ is hydrogen, COOH, COO-alkyl or aryl,

R² is hydrogen, aryl, cycloalkyl or heteroaryl,

R³ is hydrogen, aryl or (in a position different from the
α-position to the nitrogen atom to which the alkyl group
R is attached) OH, alkoxy or optionally protected amino,

20 N(Q,R) is COOH- or COO-alkyl-substituted pyrrolidino,
piperidino or 1,2,3,4-tetrahydroisoquinolin-3-yl,

three of the radicals X¹ to X⁴ independently of one another

are a group $C(R^a)$, $C(R^b)$ or $C(R^c)$ and the fourth radical is a group $C(R^d)$ or N,

R^a to R^d independently of one another are H, OH, NO_2 , dialkylamino, halogen, alkyl, alkoxy, aryloxy, aralkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy, COOH, COO-alkyl, NH-SO₂-alkyl, NHSO₂-aryl, NHCO-alkyl, NHCO-aryl, NHCOO-alkyl, NHCO-alkyl-NH₂, NHCO-alkyl-NH-G, aralkyl-CONH, alkyl-O-alkyl-CONH, aryl-O-alkyl-CONH, alkyl-COOH, alkyl-COO-alkyl, O-alkyl-COOH or O-alkyl-COO-alkyl, or

two adjacent groups R^a to R^d together are alkylenedioxy, where not more than three of the radicals R^a to R^d shall have the same meaning and X^1 shall not be CCOOH or CCOO-alkyl, G is an amino protective group and one of the radicals G^1 and G^2 is hydrogen and the other radical is hydrogen, alkyl, OH, alkoxy, aroyl, alkanoyl-OCH₂, aroyl-OCH₂ or a group COO- R^g or OCO- R^g , R^g is optionally halogen-, OH-, alkoxy-, COOH- or COO-alkyl-substituted alkyl, and hydrates or solvates and physiologically acceptable salts thereof.

Furthermore, the invention relates to processes for preparing the above compounds, to pharmaceutical preparations comprising such compounds, and to the use of these compounds in the preparation of pharmaceutical preparations.

Examples of physiologically acceptable salts of these compounds of the formula I are salts with physiologically tolerable mineral acids, such as hydrochloric acid, sulphuric acid, sulphurous acid or phosphoric acid; or with organic acids, such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid.

The compounds of the formula I can be solvated, in particular hydrated. The hydration can occur during the preparation process or slowly as a consequence of hygroscopic

properties of an initially anhydrous compound of the formula I.

The compounds of the formula I contain at least one asymmetric carbon atom and can therefore be present as a
5 mixture of enantiomers or as optically pure compounds.

In the context of the present invention, "alkyl", on its own or in combination, such as in COO-alkyl, alkoxy, dialkylamino, aralkyloxy, heteroarylalkyloxy, heterocyclalkyloxy, NHSO₂-alkyl, NHCO-alkyl, aralkyl-CONH,
10 alkyl-O-alkyl-CONH, alkyl-COOH, CCOO-alkyl, alkanoyl and the like denotes a straight-chain or branched group containing up to 6, preferably up to 4, carbon atoms. Examples include methyl, ethyl and butyl. "Aryl", on its own or in combination, such as in aryloxy, aralkyl, NHSO₂-aryl,
15 NHCO-aryl, aralkyl-CONH, aryl-O-alkyl-CONH, aroyl and the like, denotes groups such as phenyl or naphthyl which can be substituted, for example by halogen, such as bromine, fluorine or chlorine; alkoxy, such as methoxy, ethoxy or propoxy; alkylenedioxy, such as methylenedioxy; hydroxyl,
20 nitro, amino, amidino, sulphamoyl, phenyl, phenoxy, COOH or COO-alkyl, such as COOCH₃ or COOC₂H₅. Examples of aryl groups include phenyl and amidinophenyl, of aralkyl groups: benzyl, phenethyl, naphthylmethyl, mono- or dimethoxybenzyl, aminobenzyl or nitrobenzyl, of aryloxy groups: phenoxy or
25 methoxycarbonylphenoxy, of aralkyloxy groups: benzyloxy, nitrobenzyloxy, bromobenzyloxy, dichlorobenzyloxy, methoxybenzyloxy, phenoxybenzyloxy, phenethoxy or biphenylmethoxy. "Cycloalkylalkyl" denotes saturated groups having 3 to 7 carbon atoms which are attached via an alkyl
30 group. An example of these is cyclopropylmethyl.

"Heteroarylalkyl", on its own or in "heteroarylalkoxy", denotes a 5- to 10-membered aromatic group which is attached via an alkyl and alkoxy group, respectively, and which consists of one or two rings and contains one or more
35 nitrogen atoms. Examples of these are imidazolylethyl and indolylethyl and pyridinylmethoxy, indolylmethoxy,

quinolylmethoxy or isoquinolylmethoxy, respectively.

"Heterocyclylalkoxy" denotes a 5- to 10-membered saturated or unsaturated non-aromatic group which is attached via an alkoxy group and comprises one or two rings and contains one or more heteroatoms N, O and/or S. Examples of these are morpholinylethoxy, thiomorpholinylethoxy and tetrahydroquinolylmethoxy. Examples of the groups COO-alkyl, NHSO₂-alkyl and NHSO₂-aryl are COOCH₃, NHSO₂CH₃ and NHSO₂C₆H₅, respectively. An example of an alkylenedioxy group is methylenedioxy.

Preferred compounds of the formula I are those in which R¹ is aryl, in particular phenyl or amidinophenyl; aralkyl, in particular benzyl, phenethyl, naphthylmethyl, mono- or dimethoxybenzyl, aminobenzyl or nitrobenzyl; benzhydryl; cycloalkylalkyl, in particular cyclopropylmethyl; or heteroarylalkyl, in particular imidazolylethyl or indolylethyl.

Preferred compounds of the formula I are furthermore those in which Q is hydrogen or methyl, and/or in which R is aryl, such as phenyl, amidinophenyl or carboxyphenyl, or in which R is alkyl which is substituted by R¹, R² and R³ and in which R¹ is a group COOH or COO-alkyl, R² is aryl or H, and R³ is aryl, H, amino or protected amino, or in which R¹ is H, R² is aryl or heteroaryl and R³ is H or OH.

Preferred R¹-, R²- and R³-substituted alkyl groups R are methyl, ethyl, propyl and isopropyl.

Preferred aryl groups R, R¹, R² or R³ are phenyl groups which are substituted by COOH or COO-alkyl, such as COOCH₃ or COOC₂H₅; NO₂, NH₂, SO₂NH₂ or by one or two groups OH or alkoxy, such as OCH₃ or OC₂H₅.

Preferred cycloalkyl groups R or R² are optionally COOH- or COO-alkyl-substituted cyclopentyl groups.

Preferred heteroaryl groups R² are imidazolyl, indolyl and pyridinyl.

Preferred COO-alkyl groups R^1 are COOCH_3 and COOC_2H_5 .

A preferred protected amino group R^3 is NH-Boc (t-butoxycarbonylamino).

Preferred compounds of the formula I are furthermore
5 those in which one of the radicals G^1 or G^2 is a group OH or COO-alkyl, such as COOCH_3 or COOC_2H_5 .

Preferred compounds of the formula I are furthermore those

in which X^1 is a group $\text{C}(\text{R}^a)$ in which R^a is H, OH, NO_2 ,
10 halogen, in particular fluorine; alkoxy, in particular methoxy; NHSO_2 -alkyl or NHSO_2 -aryl, in particular methanesulphonylamino or phenylsulphonylamino and/or in which X^2 is a group $\text{C}(\text{R}^b)$ in which R^b is H, OH, NO_2 , alkyl, in particular methyl; alkoxy, in particular methoxy, ethoxy
15 or butoxy; aryloxy, in particular phenoxy; aralkyloxy, in particular benzyloxy, and/or in which X^3 is a group $\text{C}(\text{R}^c)$ in which R^c is H, OH, NO_2 , dialkylamino, in particular dimethylamino; halogen, in particular bromine; alkyl, in particular methyl; alkoxy, in
20 particular methoxy, ethoxy or propoxy; aryloxy, in particular methoxycarbonylphenoxy; aralkyloxy, in particular benzyloxy, nitrobenzyloxy, bromobenzyloxy, dichlorobenzyloxy, methoxybenzyloxy, phenoxybenzyloxy, phenethoxy or biphenylylmethoxy; heteroarylalkyloxy, in particular
25 pyridinylmethoxy, indolylmethoxy, quinolylmethoxy or isoquinolylmethoxy; or heterocyclylalkyloxy, in particular morpholinylethoxy, thiomorpholinylethoxy or tetrahydroquinolinylmethoxy, or in which R^b and R^c together form an alkylenedioxy group, in
30 particular the methylenedioxy group, and/or in which X^4 is a group $\text{C}(\text{R}^d)$ in which R^d is H, NO_2 , alkoxy, in particular methoxy; or aralkoxy, in particular benzyloxy.

Preferred compounds of the formula I are furthermore those in which X^1 to X^4 independently of one another are a
35 group $\text{C}(\text{R}^a)$ to $\text{C}(\text{R}^d)$ in which R^a to R^d are NHCO -alkyl, such as NH-acetyl, NHCO -aryl, such as NH-benzoyl, NHCOO -alkyl, such

as NHCOOCH_3 , NHCO-alkyl- (optionally protected amino), such as $\text{NHCOCH}_2\text{NH}_2$, $\text{NHCOCH}_2\text{CH}_2\text{NH}_2$ and $\text{NHCOCH}_2\text{NH-Boc}$; aralkyl-CONH, such as benzyl-CONH, alkyl-O-alkyl-CONH, such as $\text{CH}_3\text{OCH}_2\text{CONH}$, alkyl-COOH, such as $\text{CH}_2\text{CH}_2\text{COOH}$, O-alkyl-COOH, such as

5 $\text{O}(\text{CH}_2)_1 \text{ or } 3\text{COOH}$ and $\text{OCH}(\text{CH}_3)\text{COOH}$, aryloxy, such as $\text{OC}_6\text{H}_4\text{COOH}$ and aralkyloxy, such as $\text{OCH}_2\text{C}_6\text{H}_4\text{COOH}$, where instead of a group COOH a group COO-alkyl, such as $\text{COO}(\text{CH}_3 \text{ or } \text{C}_2\text{H}_5)$ may be present.

Preferred compounds of the formula I are furthermore

10 those in which one of the radicals X^1 to X^4 is a nitrogen atom and the other three independently of one another are a group $\text{C}(\text{R}^a)$, $\text{C}(\text{R}^b)$ or $\text{C}(\text{R}^c)$, in particular in which one group of R^a , R^b and R^c denotes H and the other two denote lower alkoxy, such as methoxy or ethoxy.

Preferred compounds of the formula I are furthermore

15 those in which one of the groups G^1 and G^2 is hydrogen and the other group is aroyl, in particular optionally halogen-substituted benzoyl, such as fluorobenzoyl, alkyl-COOCH₂-benzoyl or phenyl-COOCH₂-benzoyl, or is haloalkyl-OCO, such

20 as trichloroethyl-OCO.

Particular preference is given to the compounds in which E, G^1 , G^2 and Q are each hydrogen, and/or in which R is R^1 -, R^2 - and R^3 -substituted alkyl, in particular methyl or ethyl, in particular where R^1 is aryl, specifically

25 phenyl, or COOH, R^2 is hydrogen or aryl, specifically phenyl, and R^3 is hydrogen, and/or in which X^1 to X^4 are a group $\text{C}(\text{R}^a)$ to $\text{C}(\text{R}^d)$, in particular a group in which R^a is H, aralkyloxy, specifically carboxy-benzyloxy; NHSO_2 -aryl, specifically phenylsulphonylamino;

30 aralkyl-CONH, specifically phenylacetyl amino, or O-alkyl-COOH, specifically carboxymethoxy, R^b is H or alkoxy, specifically methoxy or ethoxy, R^c is H, alkoxy, specifically methoxy, or aralkyloxy, specifically benzyloxy, and R^d is H or alkoxy, specifically methoxy.

35 Examples of such compounds are:

(R,S)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-car-

bamimidoylphenylamino)acetamide,
2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-N-
benzyl-2-(4-carbamimidoylphenylamino)acetamide and
furthermore

- 5 (RS)-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimid-
oylphenylamino)acetylaminodiphenylacetic acid,
(RS)- and (SR)-3-[(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-
carbamimidoylphenylamino)acetylaminodiphenylacetic acid,
(S)-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-car-
10 bamimidoylphenylamino)acetylaminodiphenylacetic acid,
(S)-[(S)-2-(4-carbamimidoylphenylamino)-2-(3,5-di-
methoxyphenyl)acetylaminodiphenylacetic acid,
(RS)-3-[2-[benzylcarbamoxy-(4-carbamimidoylphenyl-
amino)methyl]-4,5-dimethoxyphenoxy]benzoic acid,
15 (RS)-[2-[benzylcarbamoxy-(4-carbamimidoylphenylamino)methyl]-
4,5-dimethoxyphenoxy]acetic acid,
(S)-[(R)-2-(2-phenylsulphonylamino-4-benzyloxy-5-meth-
oxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminodiphenylacetic acid,
20 (S)-[(S)-2-(2-phenylsulphonylamino-4-benzyloxy-5-meth-
oxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminodiphenylacetic acid,
(S)-[(R)-2-(4-benzyloxy-5-methoxy-2-phenylacetylaminophenyl)-
2-(4-carbamimidoylphenylamino)acetylaminodiphenylacetic acid,
25 (S)-[(S)-2-(4-benzyloxy-5-methoxy-2-phenylacetylaminophenyl)-
2-(4-carbamimidoylphenylamino)acetylaminodiphenylacetic acid.

Further examples of compounds of the formula I are
the compounds below:

- (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
30 amimidoylphenylamino)acetylaminopropionic acid,
(S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminopropionic acid,
(S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminopropionic acid,
35 (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminopropionic acid,

- (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-(4-hydroxyphenyl)-propionic acid,
- (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-(4-hydroxyphenyl)-propionic acid,
- 5 (S)-1-[(R)- and -[(S)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]pyrrolidine-2-carboxylic acid,
- 10 (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-2-methylpropionic acid,
- (S)-[[(R)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]methylamino]phenylacetic acid,
- (S)-[[(S)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]methylamino]phenylacetic acid,
- 15 (RS)- and (SR)-1-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]pyrrolidine-3-carboxylic acid,
- (RS)- or (SR)-2-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,
- 20 (RS)-1-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]cyclopentanecarboxylic acid,
- (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-4-tert-butoxycarbonylaminobutyric acid,
- 25 (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-4-tert-butoxycarbonylaminobutyric acid,
- 30 (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-tert-butoxycarbonylaminopropionic acid,
- (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-tert-butoxycarbonylaminopropionic acid,
- 35 (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-tert-butoxycarbonylaminopropionic acid,

- amimidoylphenylamino)acetyl amino]benzoic acid,
(RS)-3-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetyl amino]benzoic acid,
(RS)-4-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
5 amimidoylphenylamino)acetyl amino]benzoic acid,
(E)- and/or (Z)-(S)-2-[(R)- and -[(S)-2-(4-benzyloxy-
3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetyl amino]-propionic acid,
(E)- and/or (Z)-(S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-
10 [4-(N-hydroxycarbamimidoyl)phenylamino]acetyl amino]-
3-phenylpropionic acid,
(E)- and/or (Z)-(S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-
[4-(N-hydroxycarbamimidoyl)phenylamino]acetyl amino]-
3-phenylpropionic acid,
15 (E)- and/or (Z)-(S)-2-[(R)- and -[(S)-2-(4-benzyloxy-
3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetyl amino]-3-(4-hydroxyphenylpropionic acid,
(E)- and/or (Z)-(S)-1-[(R)- and -[(S)-(4-benzyloxy-
3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenyl-
20 amino]acetyl]pyrrolidine-2-carboxylic acid,
(E)- and/or (Z)-(RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-
[4-(N-hydroxycarbamimidoyl)phenylamino]acetyl amino]-
2-methylpropionic acid,
(E)- and/or (Z)-(S)-1-[(R)- and -[(S)-(4-benzyloxy-
25 3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetyl]methylamino]phenylacetic acid,
(E)- and/or (Z)-(RS)- and -(SR)-1-[(RS)-(4-benzyloxy-
3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetyl]pyrrolidine-3-carboxylic acid,
30 (E)- and/or (Z)-(RS)- and -(SR)-2-[(RS)-(4-benzyloxy-
3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic
acid,
(E)- and/or (Z)-(RS)-1-[2-(4-benzyloxy-3-methoxy-phenyl)-
35 2-[4-(N-hydroxycarbamimidoyl)phenylamino]-acetyl amino]-
cyclopentanecarboxylic acid,

- (E)- and/or (Z)-(RS)-[2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetylaminol-
diphenylacetic acid,
- (S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-
5 2-[4-[(E)- and/or -[(Z)-N-hydroxycarbamimidoyl]phenyl-
amino]acetylaminol-4-tert-butoxycarbonylaminobutyric acid,
(S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-[(E)- and/or -[(Z)-N-hydroxycarbamimidoyl]phenyl-
amino]acetylaminol-3-tert-butoxycarbonylaminopropionic acid,
- 10 (E)- and/or (Z)-(RS)-3-[2-(4-benzyloxy-3-methoxy-phenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-acetylaminol-3-tert-
butoxycarbonylaminopropionic acid,
(E)- and/or (Z)-(RS)-4-[2-(4-benzyloxy-3-methoxy-phenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-acetylaminol]benzoic
15 acid,
- (E)- and/or (Z)-(RS)- and -(SR)-3-[(RS)-2-(4-benzyloxy-
3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetylaminol-3-phenylpropionic acid,
- (S)-4-amino-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxy-
20 phenyl)-2-(4-carbamimidoylphenylamino)acetylaminol]butyric
acid,
- (S)-3-amino-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxy-
phenyl)-2-(4-carbamimidoylphenylamino)acetylaminol]propionic
acid,
- 25 (E)- and/or (Z)-(S)[(R)- or -[(S)-2-(4-benzyloxy-
3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenyl-
amino]acetylaminol-phenylacetic acid,
(S)[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminol]phenylacetic acid,
- 30 (R)[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminol]phenylacetic acid,
(R)[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminol]phenylacetic acid,
ethyl (E)- and/or (Z)-(S)-3-(4-aminophenyl)-2-[(R)- and
35 -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxy-
carbamimidoyl)phenylamino]acetylaminol]propionate,

- ethyl (S)-3-(4-aminophenyl)-2-[(R)- and
-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)acetylaminopropionate,
(S)-3-(4-aminophenyl)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-
5 2-(4-carbamimidoylphenylamino)acetylaminopropionic acid,
(S)-3-(4-aminophenyl)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-(4-carbamimidoylphenylamino)acetylaminopropionic acid,
(S)-[(R)-2-(4-carbamimidoylphenylamino)-2-(3,5-di-
methoxyphenyl)acetylaminophenylacetic acid,
10 (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)-N-[2-(3,4-dihydroxyphenyl)-
ethyl]acetamide,
(RS)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-car-
bamimidoylphenylamino)-N-methylacetamide,
15 (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-car-
bamimidoylphenylamino)-N-[2-(4-sulphamoylphenyl)-
ethyl]acetamide,
(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carb-
amimidoylphenylamino)-N-(2-pyridin-2-ylethyl)acetamide,
20 (RS)-N-[2-(4-aminophenyl)ethyl]-2-(4-benzyloxy-
3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide,
(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
phenylamino)-N-[(R)-2-hydroxy-1-phenylethyl]acetamide,
(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
25 phenylamino)-N-[(R)-2-hydroxy-1-phenylethyl]acetamide,
(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
phenylamino)-N-[(S)-2-hydroxy-1-phenylethyl]acetamide,
(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
phenylamino)-N-[(S)-2-hydroxy-1-phenylethyl]acetamide,
30 (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
phenylamino)-N-[(R)-1-phenylethyl]acetamide,
(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
phenylamino)-N-[(R)-1-phenylethyl]acetamide,
(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-
35 phenylamino)-N-[(S)-1-phenylethyl]acetamide,
(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-

- phenylamino)-N-[(S)-1-phenylethyl]acetamide,
(E)- and/or (Z)-(RS)-N-benzyl-2-(4-benzyloxy-3-methoxy-
phenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-
N-methylacetamide,
- 5 (E)- and/or (Z)-(RS)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[2-(4-sul-
phamoylphenyl)ethyl]acetamide,
(E)- and/or (Z)-(RS)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-(2-pyridin-
- 10 2-ylethyl)acetamide,
(E)- and/or (Z)-(RS)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-
N-[2-(4-nitrophenyl)ethyl]acetamide,
(E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-
- 15 2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[(R)-(2-hydroxy-
1-phenylethyl)acetamide,
(E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[(R)-(2-hydroxy-
1-phenylethyl)acetamide,
- 20 (E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[(S)-2-hydroxy-1-
phenylethyl]acetamide,
(E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[(S)-2-hydroxy-1-
- 25 phenylethyl]acetamide,
(E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-
N-[(R)-1-phenylethyl]acetamide,
(E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-
- 30 2-[4-(N-hydroxycarbamimidoyl)phenylamino]-
N-[(R)-1-phenylethyl]acetamide,
(E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-
N-[(S)-1-phenylethyl]acetamide,
- 35 (E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-[4-(N-hydroxycarbamimidoyl)phenylamino]-

- N-[(S)-1-phenylethyl]acetamide,
(RS)-N-[2-[benzylcarbamoyl-(4-carbamimidoylphenyl-
amino)methyl]-5-benzyloxy-4-methoxyphenyl]benzamide acetate,
methyl (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenyl-
5 amino)methyl]-5-benzyloxy-4-methoxyphenyl]carbamate acetate,
(RS)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-
2-(4-carbamimidoylphenylamino)acetamide,
(RS)-N-benzyl-2-(4-benzyloxy-5-methoxy-2-phenylacetyl-
aminophenyl)-2-(4-carbamimidoylphenylamino)acetamide,
10 (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4,5-di-
methoxy-2-phenylacetylaminophenyl)acetamide,
methyl (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenyl-
amino)methyl]-4,5-dimethoxyphenyl]carbamate,
(RS)-N-[2-[benzylcarbamoyl-(4-carbamimidoylphenyl-
15 amino)methyl]-4,5-dimethoxyphenyl]benzamide,
(RS)-N-[2-[benzylcarbamoyl-(4-carbamimidoylphenyl-
amino)methyl]-4-methoxyphenyl]benzamide,
(RS)-2-(2-benzenesulphonylamino-5-methoxyphenyl)-N-benzyl-
2-(4-carbamimidoylphenylamino)acetamide,
20 (RS)-N-(2-[benzylcarbamoyl-[4-(N-hydroxycarbamidoyl)-
phenylamino]methyl]-5-benzyloxy-4-methoxyphenyl)benzamide,
methyl (RS)-(2-[benzylcarbamoyl-[4-(N-hydroxy-
carbamimidoyl)phenylamino]methyl]-5-benzyloxy-4-meth-
oxyphenyl)carbamate,
25 (E)- and/or (Z)-(RS)-2-(2-acetylamino-4-benzyloxy-
5-methoxyphenyl)-N-benzyl-2-[4-(N-hydroxy-
carbamimidoyl)phenylamino]acetamide,
(E)- and/or (Z)-(RS)-N-benzyl-2-(4-benzyloxy-5-methoxy-
2-phenylacetylaminophenyl)-2-[4-(N-hydroxy-
30 carbamidoyl)phenylamino]acetamide,
(E)- and/or (Z)-(RS)-N-benzyl-2-(4,5-dimethoxy-
2-phenylacetylaminophenyl)-2-[4-(N-hydroxy-
carbamimidoyl)phenylamino]acetamide,
methyl (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-
35 [4-(N-hydroxycarbamidoyl)phenylamino]methyl]-4,5-di-
methoxyphenyl]carbamate,

- (E)- and/or (Z)-(RS)-N-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenyl]benzamide,
- (E)- and/or (Z)-(RS)-N-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4-methoxyphenyl]benzamide,
- 5 (E)- and/or (Z)-(RS)-2-(2-phenylsulphonylamino-5-methoxyphenyl)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide,
- 10 (RS)-N-benzyl-2-[4-benzyloxy-5-methoxy-2-(2-methoxyacetylaminophenyl)]-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide,
- (RS)-N-benzyl-2-[4-benzyloxy-5-methoxy-2-(2-methoxyacetylaminophenyl)]-2-(4-carbamimidoylphenylamino)acetamide,
- 15 tert-butyl (RS)-[(2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-5-benzyloxy-4-methoxyphenylcarbamoyl)methyl]carbamate,
- (RS)-2-[2-(2-aminoacetylaminophenyl)-4-benzyloxy-5-methoxyphenyl]-N-benzyl-2-(4-carbamimidoylphenylamino)acetamide,
- 20 (RS)-4-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]benzoic acid,
- (RS)-4-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]butyric acid,
- (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4-methoxyphenoxy]acetic acid,
- 25 (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,6-dimethylphenoxy]acetic acid,
- (E)- and/or (Z)-(RS)-3-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]benzoic acid,
- 30 (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]acetic acid,
- (E)- and/or (Z)-(RS)-4-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]benzoic acid,
- 35

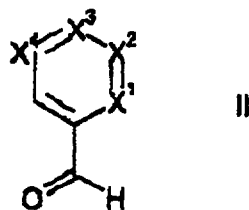
- (E)- and/or (Z)-(RS)-4-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]butyric acid,
- (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4-methoxyphenoxy]acetic acid,
- 5 (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,6-dimethylphenoxy]acetic acid,
- 10 (E)- and/or (Z)-(R)-2-[2-[(R)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]propionic acid,
- (E)- and/or (Z)-(R)-2-[2-[(S)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]propionic acid,
- 15 (R)-2-[2-[(R)-benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid,
- (R)-2-[2-[(S)-benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid,
- 20 (E)- and/or (Z)-(S)-2-[2-[(R)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]propionic acid,
- (E)- and/or (Z)-(S)-2-[2-[(S)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]propionic acid,
- 25 (S)-2-[2-[(R)-benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid,
- (S)-2-[2-[(S)-benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid,
- 30 (RS)-3-[4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy]benzoic acid,
- (RS)-2-[4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy]benzoic acid,
- (RS)-4-[4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy]benzoic acid,
- 35 (RS)-3-(4-[benzylcarbamoyl-[4-(N-hydroxy-

- carbamimidoyl)phenylamino]methyl]-2-methoxyphenoxy)benzoic acid,
- (RS)-4-(4-[benzylcarbamoyl-[4-(N-hydroxy-carbamimidoyl)phenylamino]methyl]-2-methoxyphenoxy)benzoic acid,
- 5 methyl (RS)-5-[benzylcarbamoyl-[4-(N-hydroxy-carbamimidoyl)phenylamino]methyl]-2,3-dimethoxybenzoate, methyl (RS)-5-[benzylcarbamoyl-(4-carbamimidoylphenyl-amino)methyl]-2,3-dimethoxybenzoate,
- 10 (RS)-5-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2,3-dimethoxybenzoic acid, (RS)-2-(4-[benzylcarbamoyl-[4-(N-hydroxy-carbamimidoyl)phenylamino]methyl]-2-methoxyphenoxy)benzoic acid,
- 15 (E)- and/or (Z)-(RS)-3-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamidoyl)phenylamino]methyl]-4,5-dimethoxyphenyl]propionic acid, (RS)-3-[2-[benzylcarbamoyl-(4-carbamimidoylphenyl-amino)methyl]-4,5-dimethoxyphenyl]propionic acid,
- 20 (E)- and/or (Z)-(RS)-2-(3-acetylaminophenyl)-N-benzyl-2-[4-(N-hydroxycarbamidoyl)phenylamino]acetamide, (RS)-2-(3-acetylaminophenyl)-N-benzyl-2-(4-carbamimidoylphenylamino)acetamide, (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-
- 25 2-(3-nitrophenyl)acetamide, (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,6-dimethoxypyridin-4-yl)acetamide, (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4,6-dimethoxypyridin-2-yl)acetamide,
- 30 (RS)-N-benzyl-2-(4-benzyloxy-3,5-dimethylphenyl)-2-(4-carbamimidoylphenylamino)acetamide, (RS)-N-benzyl-2-(3-benzyloxy-5-propoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride, (RS)-N-benzyl-2-(3,5-bisbenzyloxyphenyl)-2-(4-car-
- 35 bamimidoylphenylamino)acetamide hydrochloride, (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,6-di-

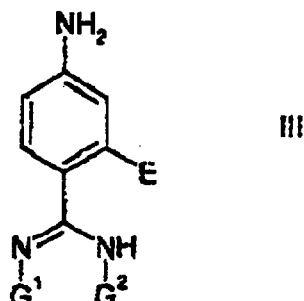
- ethoxypyridin-4-yl)acetamide,
 (RS)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-[3-hydroxy-4-(N-hydroxycarbamimidoyl)phenylamino]acetamide,
 (RS)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-
 5 2-(4-carbamimidoyl-3-hydroxyphenylamino)acetamide,
 (S)[(R)- and -[(S)-2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-[4-[(E)- and/or -[(Z)-N-hydroxy-carbamimidoyl]phenylamino]acetylaminophenylacetic acid,
 (S)[(R)- and -[(S)-2-(4-benzyloxy-5-methoxy-2-phenyl-
 10 acetylaminophenyl)-2-[4-[(E)- and/or -[(Z)-N-hydroxy-carbamimidoyl]phenylamino]acetylaminophenylacetic acid,
 (S)-[(R)-2-(2-acetylaminophenyl)-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid acetate,
 15 (S)-[(S)-2-(2-acetylaminophenyl)-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid,
 (RS)-N-[amino-(4-[[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino]phenyl)methylene]-4-fluorobenzamide,
 20 (RS)-2-[[amino-(4-[[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino]phenyl)methylene]carbamoyl]benzyl benzoate,
 2,2,2-trichloroethyl (RS)-[amino-(4-[[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino]phenyl)-
 25 methylene]carbamate,
 methyl (RS)-[amino-(4-[[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino]phenyl)methylene]carbamate.

The compounds of the formula I according to the invention can be prepared by

- 30 a) reacting an aldehyde of the formula



with an isonitrile of the formula R^1NC and a 4-amino-benzamidine of the formula

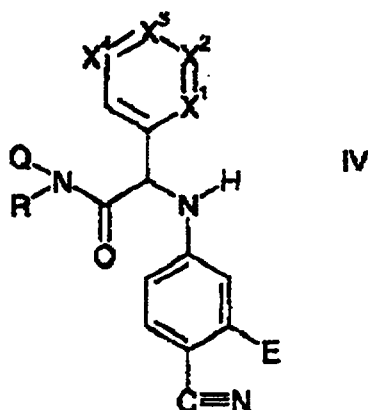


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or

b) by converting the cyano group CN contained in an appropriate nitrile of the formula below

10



into an amidino group $C(N-G^1)NH-G^2$,

c) functionally derivatizing, if desired, a reactive group
15 contained in a compound I, and

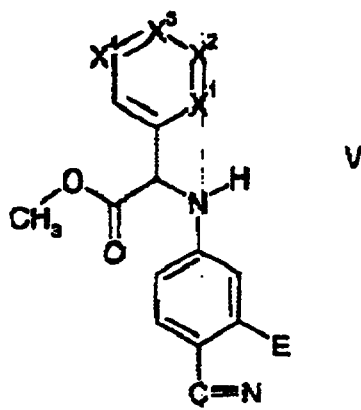
d) converting, if desired, a compound of the formula I into a physiologically acceptable salt or converting a salt of a compound I into the free acid or base.

The reaction of a substituted benzaldehyde of the
20 formula II, an isonitrile of the formula RNC and a 4-aminobenzamidine of the formula III is advantageously carried out in a solvent, such as methanol, isopropanol,

ethanol, dioxane, tetrahydrofuran, or in a solvent mixture, such as tetrahydrofuran and water or isopropanol and water, advantageously by using an inorganic acid, such as hydrochloric acid, sulphuric acid or boron trifluoride etherate, or an organic acid, such as toluenesulphonic acid, or in acidic ion exchanger, such as Amberlyst K10 as catalyst, at a temperature between 0°C and 100°C, giving compounds of the formula I. The reaction of a substituted aldehyde of the formula II, of an isonitrile of the formula R^1NC and 4-aminobenzonitrile under similar reaction conditions leads to compounds of the formula IV in which Q is hydrogen.

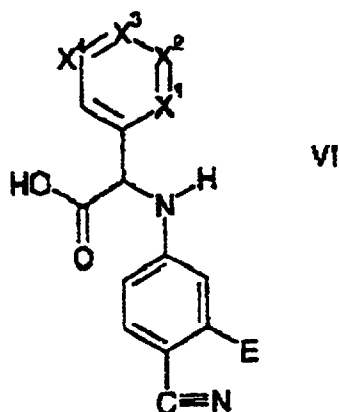
Compounds of the formula IV are also obtained a) by reaction of an aldehyde of the formula II, the benzylisonitrile and an optionally 2-hydroxylated 4-aminobenzonitrile in anhydrous methanol and boron trifluoride etherate, b) subsequent treatment with water, c) hydrolysis of the resulting compound of the formula

20



for example advantageously in THF using lithium hydroxide, and then

25 d) conversion of the resulting acid of the formula



into a corresponding nitrile of the formula IV by reaction with an amine of the formula $\text{HN}(\text{R}, \text{Q})$ in a solvent, such as DMF or dichloromethane, with addition of a coupling reagent, such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) in the presence of a carbodiimide, such as diisopropylcarbodiimide or dicyclohexylcarbodiimide, and, if appropriate, a tertiary amine, such as diisopropylamine.

Compounds of the formula IV can also be obtained by converting a compound IV in which one of the groups X^2 , X^3 and X^4 is C-O-allyl or C-O-benzyl into the corresponding phenol, followed, if desired, by alkylation. The allyl group is preferably removed in an aprotic solvent, such as tetrahydrofuran (THF), using a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium in THF, in the presence of a reducing agent, such as sodium borohydride. The benzyl group is preferably removed by catalytic hydrogenation (Pd/C) in a solvent, for example ethanol and dioxane. The resulting phenol can then, if desired, be alkylated in a solvent, such as THF, using triphenylphosphine and diethyl azodicarboxylate as catalyst, and in an appropriate alcohol. The alkylation can also be carried out using a suitable alkyl bromide in acetone or DMF in the presence of K_2CO_3 .

Reactive groups which are present in the compounds of the formulae I and IV to VI can be functionally derivatized for example as follows:

A C- NO_2 group X^1 , X^2 , X^3 or X^4 can be reduced by

catalytic hydrogenation (Pd, Pt or Ni) in a solvent, for example ethyl acetate and ethanol, to give the group C-NH₂.

A C-NH₂ group X¹, X², X³ or X⁴ can be acylated, for example, in THF in the presence of diisopropylethylamine
5 using an acyl chloride, such as benzoyl chloride, to give the group C-NH-acyl. It is possible to employ the corresponding acid instead of the acyl chloride. In this case, the procedure is as described above for the reaction of an amine HN(R,Q) with an acid of the formula VI.

10 A C-Br group X¹, X², X³ or X⁴ can be converted into a C-alkyl group or a group X¹, X², X³ or X⁴ which is attached via alkyl. In a first step, for example, a bromide IV is converted in dimethylacetamide using a terminally unsaturated compound, such as CH₂=CH-alkyl-COOH, triethylamine, Pd
15 acetate and tri-*o*-tolyl phosphine into the corresponding compound IV in which X¹, X², X³ or X⁴ denotes CCH=CH-alkyl-COOH. The resulting unsaturated acid IV is hydrogenated, for example, in ethanol and THF using hydrochloric acid and Pd/C to give the corresponding acid IV in which X¹, X², X³ or X⁴ is
20 CCH₂CH₂-alkyl-COOH.

A group COO-alkyl present in a group R can be hydrolysed in THF using LiOH to give COOH.

To convert CN into a group C(N-G¹)NH-G² in which one of the groups G¹ and G² is H and the other is OH, the nitrile
25 starting material of the formula IV is dissolved in a solvent such as DMF, ethanol or methanol and added to a reaction solution comprising a base, such as diisopropylethylamine or triethylamine, sodium hydride, sodium methoxide or sodium hydroxide, and hydroxylamine or a salt of hydroxylamine with
30 an inorganic acid, such as hydroxylamine hydrochloride, advantageously at a temperature of up to 80°C.

To convert CN into C(NH)NH₂, the nitrile starting material can be gassed in a solvent, such as ethanol or methanol, or a solvent mixture, such as chloroform and
35 methanol or chloroform and ethanol, using a dry stream of hydrogen chloride, advantageously at a temperature of below

10°C. The reaction solution is admixed with a solvent, such as diethyl ether, and the intermediate which is precipitated in this way is filtered off. The intermediate can then be dissolved in water, neutralized with a base such as sodium carbonate or sodium hydroxide and extracted from the aqueous phase using a solvent, such as dichloromethane, chloroform or ethyl acetate. The resulting material is treated in a solvent such as methanol or ethanol either with gaseous ammonia or an ammonium salt, such as ammonium chloride, advantageously at a temperature of up to 80°C. Alternatively, the intermediate is filtered off and immediately treated with gaseous ammonia or an ammonium salt in methanol or ethanol.

To convert CN into C(NH)NH₂, it is also possible to hydrogenate the amidoximes of the formula I which are obtained after conversion of CN into a group C(N-G¹)NH-G², in which one of the groups G¹ and G² is H and the other is OH, in a solvent, such as ethanol, methanol, dioxane, THF or glacial acetic acid, or in a solvent mixture, such as ethanol and glacial acetic acid, using hydrogen and a catalyst, such as palladium, platinum or nickel. A nitro group R^a, R^b, R^c or R^d which is contained in a compound of the formula I is reduced to the amino group. If the hydrogenation is carried out using palladium, a benzyloxy group R^a, R^b, R^c or R^d which is contained in an amidoxime of the formula I is converted into the hydroxyl group.

Reacting a compound of the formula I, in which G¹ and G² are hydrogen, in a solvent such as dichloromethane, dioxane or DMF, or a solvent mixture such as dichloromethane and water or ethyl acetate and water in the presence of an organic base such as pyridine or triethylamine, or an inorganic base such as sodium hydroxide, sodium carbonate or potassium bicarbonate, with a chloroformate of the formula ClC(O)O-A or a 2,4-dinitrophenyl formate of the formula [2,4(NO₂)₂-C₆H₃]OC(O)O-A gives the corresponding compound in which G¹ or G² is the group C(O)O-A and A denotes alkyl.

Reacting a compound I in which G¹ and G² are hydrogen

with an acyl chloride such as an aroyl chloride gives the corresponding compound I in which one of the groups G^1 and G^2 is hydrogen and the other group is acyl. Analogously, it is possible to convert a compound I in which G^1 and G^2 are
5 hydrogen with a p-nitrophenyl carbonate of the formula $p\text{-NO}_3\text{C}_6\text{H}_4\text{OCOO-R}$ [illegible] into the corresponding compound I in which one of the groups G^1 and G^2 denotes COO-R [illegible]. To carry out the reaction, the acyl chloride or the p-nitrophenyl carbonate in THF and DMF is admixed first
10 with N,N-diisopropylethylamine and then with the unsubstituted amidine of the formula I.

A protected amino group which is contained in a group R can be converted into the free amino group. Thus, a compound I which contains a Boc-protected amino group can be
15 converted in methylene chloride with trifluoroacetic acid into the free amine I.

Moreover, some of the examples below contain details with respect to the preparation of certain starting materials and intermediates.

20 The compounds of the formulae IV, V and VI are novel and therefore also form part of the subject-matter of the present invention. The compounds of the formulae II and III are known or can be prepared analogously to the known compounds. Thus, the optionally 2-substituted
25 4-aminobenzamidines III are obtained from the corresponding 4-aminobenzonitriles via the 4-nitrobenzonitriles.

The compounds of the formula I and their solvates and salts inhibit the formation of the coagulation factors Xa, IXa and thrombin induced by the factor VIIa and the tissue
30 factor. The compounds in question consequently influence both the platelet aggregation which is induced by these factors and plasmatic blood coagulation. They therefore inhibit the formation of thrombi and can be used for controlling or preventing diseases, such as thrombosis, apoplexy, cardiac
35 infarction, inflammation and arteriosclerosis. Furthermore, these compounds have an effect on tumour cells and prevent

metastases. They can therefore also be employed as antitumour agents.

The inhibition of the amidolytic activity of the factor VIIa/tissue factor complex by the compounds according to the invention was demonstrated with the aid of a chromogenic peptide substrate, as described below.

The measurements were carried out on microtitre plates at room temperature. To this end, per well of the plate, 100 µl of a solution of 26 nM of tissue factor, 9 nM of soluble factor VIIa and 8 mM of calcium chloride were added to 25 µl of a solution of the inhibitor in a buffer [pH 7.5, 100 mM, comprising 0.14 M NaCl, 0.1 M N(2-hydroxyethyl)piperazine-N'-(2-ethanesulphonic acid) (HEPES), 0.5 mg/l of fatty-acid-free BSA (bovine serum albumin) and 0.05% NaN₃]. After an incubation time of 15 minutes, the reaction was started by addition of 50 µl of chromogenic substrate Chromozym-tPA (3.5 mM, MeSO₂-D-Phe-Gly-Arg-paranitroanilide), and the hydrolysis of the substrate was followed spectrophotometrically on a kinetic microtitre plate reader over 10 minutes. Using the plot of the inhibition curves, the K_i values were determined according to the method described in Biochem. J. 55, 1953, 170-171. The results are shown in the table below (K_i in microM):

Example	1	2a	5a	5b	5c	5d	5g	6	7a
Ki	0.057	0.283	0.281	0.195	0.169	0.116	0.044	0.22	0.19

Example	7e	7f	7h	7n	7s	8	10
Ki	0.11	0.26	0.21	0.17	0.171	0.159	0.112

25

As mentioned at the outset, medicaments comprising a compound of the formula I, a solvate or a salt thereof also form part of the subject-matter of the present invention, and furthermore also a process for preparing such medicaments which is characterized in that one or more of such compounds,

30

solvates or salts and, if desired, other therapeutically useful substances are prepared as pharmaceutical formulations. These medicaments can be administered orally, for example in the form of sugar-coated tablets, hard and
5 soft gelatin capsules, solutions, emulsions or suspensions, or rectally, for example in the form of suppositories, or as a spray. However, administration can also be carried out parenterally, for example in the form of solutions for injection.

10 To prepare tablets, film tablets, sugar-coated tablets and hard gelatin capsules, the active ingredient can be mixed with pharmaceutically inert inorganic or organic excipients. Excipients which are suitable for tablets, film tablets, sugar-coated tablets and hard gelatin capsules are,
15 for example, lactose, maize starch or derivatives thereof, talc, stearic acid or salts thereof. Excipients which are suitable for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols; however, depending on the properties of the active
20 ingredient, some soft gelatin capsules may not require any excipients at all. Excipients which are suitable for preparing the solutions and syrups are, for example, water, polyols, sucrose, inverted sugar and glucose; suitable for use in solutions for injection are, for example, water,
25 alcohols, polyols, glycerol and vegetable oils; and suitable for use in suppositories are natural and hardened oils, waxes, fats, semi-liquid or liquid polyols. In addition, the pharmaceutical preparations may also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers,
30 sweeteners, colorants, aromas, salts to modify the osmotic pressure, buffers, coatings or antioxidants.

 The dosage of the active ingredient for the control and/or prevention of the diseases mentioned above can vary within wide limits and must of course be adapted to the
35 individual circumstances in each individual case. In general, for oral or parenteral, for example intravenous or

subcutaneous administration, a dose of about 0.1 to 20 mg/kg, preferably about 0.6 to 4 mg/kg, per day should be adequate for adults, but the upper limit which has just been mentioned may be exceeded or the dose may be lower, should this be
5 appropriate.

Example 1

At room temperature, 1 mmol of 4-aminobenzamidine
10 dihydrochloride (208 mg), 1 mmol of triethylamine (101 mg),
1 mmol of benzylisonitrile (117 mg) and 1 mmol of
4-benzyloxy-3-methoxybenzaldehyde (260 mg) are stirred in a
solvent mixture of 1.2 ml of isopropanol and 0.8 ml of water
for 5 days. The mixture is then admixed with 0.5 ml of 25%
15 strength hydrochloric acid and stirred at room temperature
for 1 hour, and the precipitated crystals are filtered off
and washed with 5 ml of water. This gives 218 mg (41%) of
(R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-
2-(4-carbamimidoylphenylamino)acetamide hydrochloride as
20 colourless crystals. ISP-MS: 495.5 ($[M+H]^+$, 100).

Example 2

By the method of Example 1, the following compounds
25 are prepared:

2.a) 4-aminobenzamidine dihydrochloride,
triethylamine, benzylisonitrile and 3,4-dimethoxybenzaldehyde
give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-
2-(3,4-dimethoxyphenyl)acetamide hydrochloride as colourless
30 crystals. ISP-MS: 455 ($[M+H]^+$, 100).

2.b) 4-aminobenzamidine dihydrochloride,
triethylamine, benzylisonitrile and piperonylbenzaldehyde
give (R,S)-2-benzo[1,3]dioxol-5-yl-N-benzyl-2-(4-
carbamimidoylphenylamino)acetamide hydrochloride as
35 colourless crystals. ISP-MS: 439 ($[M+H]^+$, 100).

2.c) 4-aminobenzamidine dihydrochloride,

triethylamine, benzylisonitrile and 2-hydroxy-4-methoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2-hydroxy-4-methoxyphenyl)acetamide hydrochloride as colourless crystals. ISP-
5 MS: 405 ($[M+H]^+$, 100).

2.d) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 4-hydroxy-3-methoxy-5-nitrobenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4-hydroxy-3-methoxy-5-
10 nitrophenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 450 ($[M+H]^+$, 100).

2.e) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 4-hydroxy-3,5-dimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4-hydroxy-3,5-dimethoxy-
15 phenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 435 ($[M+H]^+$, 100).

2.f) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and methyl 4-formylbenzoate
20 give methyl (R,S)-4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]benzoate hydrochloride as colourless crystals. ISP-MS: 417 ($[M+H]^+$, 100).

2.g) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 2,3,4-trimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,3,4-trimethoxyphenyl)acetamide
25 hydrochloride as colourless crystals. ISP-MS: 449 ($[M+H]^+$, 100).

2.h) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 3,4-dimethylbenzaldehyde
30 give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,4-dimethylphenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 387 ($[M+H]^+$, 100).

2.i) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 4-methoxy-3-methylbenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoyl-

phenylamino)-2-(4-methoxy-3-methylphenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 403 ($[M+H]^+$, 100).

2.j) 4-aminobenzamidinium dihydrochloride, triethylamine, benzylisonitrile and 4,5-dimethoxy-2-nitrobenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4,5-dimethoxy-2-nitrophenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 464 ($[M+H]^+$, 100).

10 2.k) 4-aminobenzamidinium dihydrochloride, triethylamine, benzylisonitrile and 2,3-dimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,3-dimethoxyphenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 419 ($[M+H]^+$, 100).

15 2.l) 4-aminobenzamidinium dihydrochloride, triethylamine, benzylisonitrile and 2,4,5-trimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,4,5-trimethoxyphenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 449 ($[M+H]^+$, 20 100).

2.m) 4-aminobenzamidinium dihydrochloride, triethylamine, benzylisonitrile and 3-hydroxy-4-methoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3-hydroxy-4-methoxyphenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 405 ($[M+H]^+$, 25 100).

2.n) 4-aminobenzamidinium dihydrochloride, triethylamine, benzylisonitrile and 2,4-dimethoxybenzaldehyde give N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,4-dimethoxyphenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 419 ($[M+H]^+$, 100). 30

2.o) 4-aminobenzamidinium dihydrochloride, triethylamine, benzylisonitrile and 2-fluoro-4,5-dimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2-fluoro-4,5-dimethoxyphenyl)acetamide hydrochloride as colourless crystals. ISP- 35

MS: 437 ($[M+H]^+$, 100).

2.p) 4-aminobenzamidine dihydrochloride, triethylamine, cyclopropylmethylisonitrile and 3,4,5-trimethoxybenzaldehyde give (R,S)-2-(4-carbamimidoyl-phenylamino)-N-cyclopropylmethyl-2-(3,4,5-trimethoxy-phenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 413 ($[M+H]^+$, 100).

2.q) 4-aminobenzamidine dihydrochloride, triethylamine, 3,4-dimethoxybenzylisonitrile and 3,4,5-trimethoxybenzaldehyde give (R,S)-2-(4-carbamimidoyl-phenylamino)-N-(3,4-dimethoxybenzyl)-2-(3,4,5-trimethoxy-phenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 509 ($[M+H]^+$, 100).

2.r) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and methyl 2-(formyl-2-methoxyphenoxy)benzoate give methyl (R,S)-2-{4-[benzyl-carbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy}benzoate hydrochloride as colourless crystals. ISP-MS: 539.4 ($[M+H]^+$, 100).

2.s) 4-aminobenzamidine dihydrochloride, triethylamine, 2-phenylethylisonitrile and 4-dimethylamino-3-nitrobenzaldehyde give (R,S)-N-(2-phenylethyl)-2-(4-carbamimidoylphenylamino)-2-(4-dimethylamino-3-nitrophenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 461.7 ($[M+H]^+$, 100).

2.t) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 3,5-dimethoxy-4-methylbenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,5-dimethoxy-4-methyl-phenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 433 ($[M+H]^+$, 100).

2.u) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 3-phenoxybenzaldehyde give (R,S)-N-benzyl-2-(3-phenoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as colourless crystals. ISP-MS: 451.6 ($[M+H]^+$, 100).

2.v) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 3,5-bis-benzyloxy-benzaldehyde give (R,S)-N-benzyl-2-(3,5-bis-benzyloxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as
5 colourless crystals. ISP-MS: 571 ($[M+H]^+$, 100).

2.w) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 3-benzyloxy-4-hydroxybenzaldehyde give (R,S)-N-benzyl-2-(3-benzyloxy-4-hydroxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide
10 hydrochloride as colourless crystals. ISP-MS: 481 ($[M+H]^+$, 100).

2.x) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 4-bromo-3,5-dimethoxy-benzaldehyde give (R,S)-N-benzyl-2-(4-bromo-3,5-dimethoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide
15 hydrochloride as colourless crystals. ISP-MS: 498 ($[M+H]^+$, 100).

2.y) 4-aminobenzamidine dihydrochloride, triethylamine, benzylisonitrile and 3,5-dimethoxy-4-nitrobenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,5-dimethoxy-4-nitrophenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 464 ($[M+H]^+$, 100).

25 Example 3

10 mmol of 4-aminobenzamidine dihydrochloride (2.8 g), 10 mmol of triethylamine (1.01 g), 0.5 ml of water, 10 mmol of 4-benzyloxy-3-methoxybenzaldehyde (2.6 g) and 10
30 mmol of benzylisonitrile (1.2 ml) are initially charged in 40 ml of methanol, and 3.8 ml of boron trifluoride etherate (30 mmol) are then added dropwise with ice-bath cooling over a period of 2 hours. The mixture is stirred at room temperature for a further hour, the solvent is then removed
35 under reduced pressure and the crude product is chromatographed over an RP-18 column using water/methanol as

mobile phase. Alternatively, the crude product is, with ice-cooling, admixed with 5 ml of 25% strength hydrochloric acid, 10 ml of dichloromethane and 10 ml of water are added and the precipitated crystals are filtered off with suction after 5 hours. This gives 1.6 g (30%) of (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as colourless crystals. ISP-MS: 495.5 ($[M+H]^+$, 100). Chromatography of the crude product over an RP-18 column using a mobile phase of methanol/water with 0.1% of trifluoroacetic acid gives 0.8 g (15%) of (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide trifluoroacetate as colourless crystals. ISP-MS: 495.2 ($[M+H]^+$, 100).

15

Example 4

10 mmol of 4-aminobenzonitrile (1.2 g), 0.5 ml of water, 10 mmol of 4-benzyloxy-3-methoxybenzaldehyde (2.6 g) are initially charged in 40 ml of methanol and stirred at room temperature for one hour, and 10 mmol of benzylisonitrile (1.2 ml) are then added dropwise and, with ice-bath cooling and stirring, 3.8 ml of boron trifluoride etherate are added over a period of 2 hours. The mixture is stirred at room temperature for a further hour, the solvent is then removed under reduced pressure and the crude product is filtered over a silica gel column using hexane/ethyl acetate 1/1 as mobile phase. The main fraction is concentrated and the resulting crude (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetamide is dissolved in a solvent mixture of 20 ml of chloroform and 4 ml of methanol and, with stirring and at a temperature of below 5°C, gassed with dry hydrogen chloride for 20 minutes. The reaction mixture is then allowed to stand at 5°C for 24 hours, 20 ml of diethyl ether are then added and the precipitated crystals are filtered off with suction and washed with diethyl ether and the residue is taken up in

methanol which is saturated with ammonia. The ammoniacal solution is boiled under reflux for 2 hours and the solvent is then removed using a water pump vacuum. 5 ml of a 1 N solution of hydrochloric acid are then added to the residue, 5 and the solvent is once more removed using a water pump vacuum. The resulting crude product is chromatographed over an RP-18 column using water/methanol as mobile phase. This gives 228 mg (43%) of (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide 10 hydrochloride as colourless crystals. ISP-MS: 495.5 ($[M+H]^+$, 100).

Example 5

15 By the method of Example 4, the following compounds are prepared:

5.a) 4-aminobenzonitrile, benzylisonitrile and 3,4,5-trimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,4,5-trimethoxy- 20 phenyl)acetamide hydrochloride as colourless crystals. ISP-MS: 449.2 ($[M+H]^+$, 100).

5.b) 4-aminobenzonitrile, benzylisonitrile and 3,5-dimethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,5-dimethoxyphenyl)acetamide 25 hydrochloride as colourless crystals. ISP-MS: 419 ($[M+H]^+$, 100).

5.c) 4-aminobenzonitrile, benzhydrylisonitrile and 3,4-dimethoxybenzaldehyde give (R,S)-N-benzhydryl-2-(4-carbamimidoylphenylamino)-2-(3,4-dimethoxyphenyl)acetamide 30 hydrochloride as colourless crystals. ISP-MS: 495 ($[M+H]^+$, 100).

5.d) 4-aminobenzonitrile, benzylisonitrile and 3,4-diethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,4-diethoxyphenyl)acetamide 35 hydrochloride as colourless crystals. ISP-MS: 447.2 ($[M+H]^+$, 100).

5.e) 4-aminobenzonitrile, benzhydrylisonitrile and 4-benzyloxy-3-methoxybenzaldehyde give (R,S)-N-benzhydryl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as
5 colourless crystals. ISP-MS: 571.4 ($[M+H]^+$, 100).

5.f) 4-aminobenzonitrile, benzhydryliso-nitrile and 4-benzyloxy-3-ethoxybenzaldehyde give (R,S)-N-benzhydryl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as
10 colourless crystals. ISP-MS: 585.4 ($[M+H]^+$, 100).

5.g) 4-aminobenzonitrile, benzylisonitrile and 4-benzyloxy-3-ethoxybenzaldehyde give (R,S)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as
15 colourless crystals. ISP-MS: 509.4 ($[M+H]^+$, 100).

5.h) 4-aminobenzonitrile, 4-methoxybenzylisonitrile and 4-benzyloxy-3-methoxybenzaldehyde give (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-(4-methoxybenzyl)acetamide hydrochloride as
20 colourless crystals. ISP-MS: 525.2 ($[M+H]^+$, 100).

5.i) 4-aminobenzonitrile, naphthyl-1-yl-methylisonitrile and 4-benzyloxy-3-methoxybenzaldehyde give (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-naphthalen-1-yl-methylacetamide
25 hydrochloride as colourless crystals. ISP-MS: 545.3 ($[M+H]^+$, 100).

5.j) 4-aminobenzonitrile, benzylisonitrile and 3-butoxy-5-methoxybenzaldehyde give (R,S)-N-benzyl-2-(3-butoxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as colourless crystals.
30 ISP-MS: 461.3 ($[M+H]^+$, 100).

5.k) 4-aminobenzonitrile, benzylisonitrile and 3-benzyloxy-5-ethoxybenzaldehyde give (R,S)-N-benzyl-2-(3-benzyloxy-5-ethoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide hydrochloride as
35 colourless crystals. ISP-MS: 509.4 ($[M+H]^+$, 100).

5.1) 4-aminobenzonitrile, benzyisonitrile and 3-benzyloxy-5-methoxybenzaldehyde give (R,S)-N-benzyl-2-(3-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-acetamide hydrochloride as colourless crystals. ISP-MS: 495.3
5 ([M+H]⁺, 100).

Example 6

Under an atmosphere of argon, an NaOMe solution was
10 freshly prepared from 130 mg (5.6 mmol) of sodium and 10 ml of MeOH, and the solution was admixed with 474 mg (6.8 mmol) of hydroxylamine hydrochloride. The suspension was stirred at room temperature for 30 min. 286 mg (0.6 mmol) of (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-
15 4-(3-methoxybenzyloxy)phenyl]acetamide (Example 18) were added and the reaction mixture was heated under reflux overnight. The solvent was subsequently distilled off under reduced pressure. The residue was taken up in water and extracted with EtOAc. The organic phase was washed with
20 saturated NaCl solution, dried over MgSO₄, filtered and concentrated under reduced pressure.

The residue was taken up in 10 ml of ethanol, 1 ml of THF and 1 ml of HOAc and admixed with a spatula tip of Raney nickel. The reaction mixture was hydrogenated for 5 h. The
25 catalyst was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/acetone/H₂O/HOAc 6:2:1:1). This gave 191 mg (53%) of (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[3-methoxy-
30 4-(3-methoxybenzyloxy)phenyl]acetamide acetate as colourless crystals. ISP-MS: 525.2 ([M+H]).

Example 7

35 By the method of Example 6, the following compounds were obtained:

7.a) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
2-[3-methoxy-4-(pyridin-4-ylmethoxy)phenyl]acetamide (Example
19.a) gave N-benzyl-2-(4-carbamimidoylphenylamino)-
2-[3-methoxy-4-(pyridin-4-ylmethoxy)phenyl]acetamide acetate
5 in a yield of 18%. Colourless solid. ISP-MS: 496.2 ([M+H]).

7.b) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
2-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]acetamide
(Example 19.b) gave (R,S)-N-benzyl-2-(4-carbamimidoyl-
phenylamino)-2-[3-methoxy-4-(2-morpholin-4-ylethoxy)-
10 phenyl]acetamide acetate in a yield of 15%. Colourless solid.
ISP-MS: 518.3 ([M+H]).

7.c) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
2-[3-methoxy-4-(2-thiomorpholin-4-ylethoxy)phenyl]acetamide
(Example 19.c) gave (R,S)-N-benzyl-2-(4-carbamimidoyl-
15 phenylamino)-2-[3-methoxy-4-(2-thiomorpholin-4-ylethoxy)-
phenyl]acetamide acetate in a yield of 22%. Yellow-green
solid. ISP-MS: 534.3 ([M+H]).

7.d) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
2-[3-methoxy-4-(3-phenoxybenzyloxy)phenyl]acetamide (Example
20 19.d) gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-
2-[3-methoxy-4-(3-phenoxybenzyloxy)phenyl]acetamide acetate
in a yield of 28%. Colourless solid. ISP-MS: 587.4 ([M+H]).

7.e) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(1H-
indol-5-ylmethoxy)-3-methoxyphenyl]acetamide (Example 19.e)
25 gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[4-(1H-
indol-5-ylmethoxy)-3-methoxyphenyl]acetamide acetate in a
yield of 23%. Colourless solid. ISP-MS: 534.3 ([M+H]).

7.f) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
2-[3-methoxy-4-(quinolin-7-ylmethoxy)phenyl]acetamide
30 (Example 19.f) gave (R,S)-N-benzyl-2-(4-carbamimidoyl-
phenylamino)-2-[3-methoxy-4-(1,2,3,4-tetrahydroquinolin-7-
ylmethoxy)phenyl]acetamide acetate in a yield of 13%.
Colourless solid. ISP-MS: 550.2 ([M+H]).

7.g) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
35 2-[3-methoxy-4-(quinolin-7-ylmethoxy)phenyl]acetamide
(Example 19.f) gave (R,S)-N-benzyl-2-(4-carbamimidoyl-

phenylamino)-2-[3-methoxy-4-(quinolin-7-ylmethoxy)-phenyl]acetamide acetate in a yield of 16%. Slightly pink solid. ISP-MS: 546.3 ([M+H]).

7.h) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-phenethyloxyphenyl] acetamide (Example 19.g) gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[3-methoxy-4-phenethyloxyphenyl]acetamide acetate in a yield of 21%. Colourless solid. ISP-MS: 509.4 ([M+H]).

7.i) (R,S)-N-benzyl-2-[4-(biphenyl-4-ylmethoxy)-3-methoxyphenyl]-2-(4-cyanophenylamino)acetamide (Example 19.h) gave (R,S)-N-benzyl-2-[4-(biphenyl-4-ylmethoxy)-3-methoxyphenyl]-2-(4-carbamimidoylphenylamino)acetamide acetate in a yield of 58%. Colourless solid. ISP-MS: 571.3 ([M+H]).

7.j) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(2,6-dichlorobenzoyloxy)-3-methoxyphenyl]acetamide (Example 19.i) gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[4-(2,6-dichlorobenzoyloxy)-3-methoxyphenyl]acetamide acetate in a yield of 58%. Colourless solid. ISP-MS: 563.3 ([M+H]).

7.k) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(3,5-dichlorobenzoyloxy)-3-methoxyphenyl]acetamide (Example 19.j) gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[4-(3,5-dichlorobenzoyloxy)-3-methoxyphenyl]acetamide acetate in a yield of 47%. Colourless solid. ISP-MS: 563.3 ([M+H]).

7.l) (R,S)-N-benzyl-2-[4-(3-bromobenzoyloxy)-3-methoxyphenyl]-2-(4-cyanophenylamino)acetamide (Example 19.k) gave (R,S)-N-benzyl-2-[4-(3-bromobenzoyloxy)-3-methoxyphenyl]-2-(4-carbamimidoylphenylamino)acetamide acetate in a yield of 35%. Colourless solid. ISP-MS: 573 ([M+H]).

7.m) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(pyridin-2-ylmethoxy)phenyl]acetamide (Example 19.l) gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[3-methoxy-4-(pyridin-2-ylmethoxy)phenyl]acetamide acetate in a yield of 34%. Colourless solid. ISP-MS: 496.3 ([M+H]).

7.n) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-

(isoquinolin-6-ylmethoxy)-3-methoxyphenyl]acetamide (Example 19.m) gave (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-[4-(isoquinolin-6-ylmethoxyphenyl]acetamide acetate in a yield of 11%. Colourless solid. ISP-MS: 546.3 ([M+H]).

5 7.o) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-(3,4-dimethoxybenzyl)acetamide (Example 24.a) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[3,4-dimethoxybenzyl]-acetamide acetate in a yield of 5%. Colourless solid. ISP-MS:
10 555.3 ([M+H]).

 7.p) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-phenethylacetamide (Example 23) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-phenethylacetamide acetate in a yield of 30%.
15 Colourless solid. ISP-MS: 555.3 ([M+H]).

 7.q) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-(4-nitrobenzyl)acetamide (Example 24.b) gave (R,S)-N-(4-aminobenzyl)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide
20 acetate in a yield of 52%. Light-yellow solid. ISP-MS: 510.4 ([M+H]).

 7.r) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-N-(4-cyanophenyl)-2-(4-cyanophenylamino)acetamide (Example 24.d) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-N-(4-carbamimidoylphenyl)-2-(4-carbamimidoylphenylamino)acetamide
25 acetate in a yield of 30%. Colourless solid. ISP-MS: 523.3 ([M+H]).

 7.s) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-phenylacetamide (Example 24.c) gave
30 (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-phenylacetamide acetate in a yield of 12%. Colourless solid. ISP-MS: 481.4 ([M+H]).

 7.t) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(3H-imidazol-4-yl)ethyl]acetamide
35 (Example 24.e) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[2-(3H-imidazol-4-

yl)ethyl]acetamide acetate in a yield of 9%. Colourless solid. ISP-MS: 482.4 ([M+H]).

7.u) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-(4-cyanophenylamino)-N-[2-(1H-indol-3-yl)ethyl]acetamide
5 (Example 24.f) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-(4-carbamimidoylphenylamino)-N-[2-(1H-indol-3-
yl)ethyl]acetamide acetate in a yield of 68%. Colourless solid. ISP-MS: 553.3 ([M+Na]), 548.3 ([M+NH₄]), 531.3 ([M+H]).

10

Example 8

440 mg of N-benzyl-2-(4-benzyloxy-2-phenylsulphonyl-
amino-5-methoxyphenyl)-2-[4-(N-hydroxycarbam-
15 imidoyl)phenylamino]acetamide (0.66 mmol) (Example 14) were
dissolved in 10 ml of MeOH, admixed with a drop of AcOH and
admixed with 200 mg of 5% Pt/C. The reaction mixture was
hydrogenated overnight. The catalyst was filtered off. The
filtrate was concentrated under reduced pressure. The residue
20 was purified by silica gel chromatography
(EtOAc/acetone/H₂O/HOAc). This gave 263 mg of
2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-
N-benzyl-2-(4-carbamimidoylphenylamino)acetamide acetate as a
colourless solid. ISP-MS: 650 (M+H).

25

Example 9

By the method of Example 8, N-benzyl-2-(4-benzyloxy-
2-methanesulphonylamino-5-methoxyphenyl)-2-[4-(N-hydroxy-
30 carbamidoyl)phenylamino]acetamide (Example 15) gave, after
purification by HPLC over an RP-18 column using a mobile
phase of CH₃CN/water with 0.1% of trifluoroacetic acid,
N-benzyl-2-(4-benzyloxy-2-methanesulphonylamino-5-
methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide
35 trifluoroacetate as a colourless solid. ISP-MS: 588 (M+H).

Example 10

350 mg of N-benzyl-2-(4-benzyloxy-2-phenyl-sulphonylamino-5-methoxyphenyl)-2-[4-(N-hydroxy-carbamimidoyl)phenylamino]acetamide (0.53 mmol) (Example 14) were dissolved in 3 ml of AcOH, admixed with 100 ml of Ac₂O and hydrogenated in the presence of 150 mg of 5% Pd/C overnight. The catalyst was filtered off. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/acetone/H₂O/HOAc). This gave 188 mg (64%) of 2-(2-phenylsulphonylamino-4-hydroxy-5-methoxyphenyl)-N-benzyl-2-(4-carbamimidoylphenylamino)-acetamide acetate as a colourless solid. ISP-MS: 560 (M+H).

Example 11

By the method of Example 10, N-benzyl-2-(4-benzyloxy-2-methanesulphonylamino-5-methoxyphenyl)-2-[4-(N-hydroxy-carbamimidoyl)phenylamino]acetamide (Example 15) gave, after purification by HPLC over an RP-18 column using a mobile phase of CH₃CN/water with 0.1% of trifluoroacetic acid, N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4-hydroxy-2-methanesulphonylamino-5-methoxyphenyl)acetamide trifluoroacetate as a colourless solid. ISP-MS: 498 (M+H).

Example 12

Under an atmosphere of argon, an NaOMe solution was freshly prepared from 115 mg (5 mmol) of sodium and 15 ml of MeOH, and this solution was admixed with 420 mg (6 mmol) of hydroxylamine hydrochloride. The suspension was stirred at room temperature for 30 min. 261 mg (0.5 mmol) of (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(4-nitrobenzyloxy)phenyl]acetamide (Example 19.n) were added and the reaction mixture was then heated under reflux overnight. The solvent was subsequently distilled off under

reduced pressure. The residue was taken up in water and extracted with EtOAc. The organic phase was washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified
5 by silica gel chromatography (EtOAc). This gave 166 mg (60%) of (R,S)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-2-[3-methoxy-4-(4-nitrobenzyloxy)phenyl]acetamide as a colourless solid foam. ISP-MS: 556.3 [M+H].

10

Example 13

By the method of Example 12,

13.a) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(pyridin-4-ylmethoxy)phenyl]acetamide (Example
15 19.a) gave (R,S)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-2-[3-methoxy-4-(pyridin-4-ylmethoxy)phenyl]-acetamide in a yield of 35%. Colourless solid foam. ISP-MS: 512.4 ([M+H]).

13.b) (R,S)-N-benzyl-2-(4-cyanophenylamino)-
20 2-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]acetamide (Example 19.b) gave (R,S)-N-benzyl-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-2-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]acetamide in a yield of 28%. Colourless solid foam. ISP-MS: 534.4 ([M+H]).

25 13.c) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(3-phenoxybenzyloxy)phenyl]acetamide (Example 19.d) gave (R,S)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-2-[3-methoxy-4-(4-phenoxybenzyloxy)phenyl]-acetamide in a yield of 40%. Slightly greyish solid foam.
30 ISP-MS: 603.2 ([M+H]).

13.d) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-(4-nitrobenzyl)acetamide (Example 24.b) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-(4-nitrobenzyl)acetamide
35 in a yield of 98%. Yellow oil. ISP-MS: 545.2 ([M+Na]), 540.3 ([M+NH₄]), 523.3 ([M+H]).

13.e) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(3H-imidazol-4-yl)ethyl]acetamide (Example 24.e) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[2-(3H-imidazol-4-yl)ethyl]acetamide in a yield of 85%. A greyish-green solid foam. ISP-MS: 515.3 ([M+H]).

13.f) (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(1H-indol-3-yl)ethyl]acetamide (Example 24.f) gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[1H-indol-3-yl)ethyl]acetamide in a yield of 85%. A greyish-green solid foam. ISP-MS: 564.4 ([M+H]).

13.g) (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-(3,4,5-trimethoxyphenyl)acetamide (Example 17.a) gave (R,S)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-2-(3,4,5-trimethoxyphenyl)acetamide as a colourless solid. ISP-MS: 465.6 ([M+H]⁺, 100).

13.h) (R,S)-N-benzyl-2-(3,5-dimethoxyphenyl)-2-(4-cyanophenylamino)acetamide (Example 17.b) gave (R,S)-N-benzyl-2-(3,5-dimethoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide as a colourless solid. ISP-MS: 435.5 ([M+H]⁺, 100).

13.i) (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetamide (Example 17.c) gave (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide as a colourless solid. ISP-MS: 511.6 ([M+H]⁺, 100).

13.j) (R,S)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-cyanophenylamino)acetamide (Example 17.d) gave (R,S)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide as a colourless solid. ISP-MS: 525.5 ([M+H]⁺, 100).

Example 14

35

995 mg of 2-(2-phenylsulphonylamino-4-benzyl-oxy-

5-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide (1.57 mmol) (Example 28), 547 mg of hydroxylamine hydrochloride (7.87 mmol) and 2.2 ml of triethylamine (15.7 mmol) were initially charged in 5 ml of EtOH. The reaction mixture was heated under reflux for 5 hours. The solvent was subsequently distilled off under reduced pressure. The residue was taken up in water and extracted with EtOAc. The organic phase was washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated under reduced pressure. This gave 885 mg (85%) of 2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide as an oily yellow solid. ISP-MS: 666 (M+H).

15 Example 15

By the method of Example 14, N-benzyl-2-(4-benzyloxy-2-methanesulphonylamino-5-methoxyphenyl)-2-(4-cyanophenylamino)acetamide (Example 29) gave N-benzyl-2-(4-benzyloxy-2-methanesulphonylamino-5-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide as a yellow oil in a yield of 95%. ISP-MS: 604 (M+H).

25 Example 16

10 g of 4-benzyloxy-5-methoxy-2-nitrobenz-aldehyde (34.8 mmol) and 4.11 g of 4-aminobenzonitrile (34.8 mmol) were dissolved in 140 ml of methanol and stirred at room temperature for one hour. The mixture was then admixed with 4.25 ml of benzylisonitrile (34.8 mol). 12.9 ml of boron trifluoride etherate (104.4 mmol) were subsequently added to this mixture, dropwise and with ice-bath cooling, over a period of half an hour. After 30 min, the ice bath was removed. The reaction mixture was stirred at room temperature for another 2 days. The solvent was subsequently distilled off under reduced pressure. The residue was taken up in EtOAc and

washed with water. The organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using acetone/toluene (3/97). This gave 8.9 g (48%) of N-benzyl-2-(4-benzyloxy-5-methoxy-2-nitrophenyl)-2-(4-cyanophenyl-amino)acetamide as an oily orange solid. ISP-MS: 523 (M+H).

Example 17

10 By the method of Example 16:

17.a) 4-aminobenzonitrile, 3,4,5-trimethoxybenzaldehyde and benzylisonitrile gave (R,S)-N-benzyl-2-(4-cyanophenylamino-2-(3,4,5-trimethoxyphenyl)acetamide as colourless crystals. ^1H NMR ($\text{DMSO}-d_6$): 8.80 (t;NH;1H), 5.02 (d;CH;1H), 4.28 (d;CH₂;2H), 3.75 (s;CH₃;6H), 2.61 (s; CH₃;3H).

17.b) 4-aminobenzonitrile, 3,5-dimethoxybenzaldehyde and benzylisonitrile gave (R,S)-N-benzyl-2-(3,5-dimethoxyphenyl)-2-(4-cyanophenylamino)acetamide as colourless crystals. ^1H NMR ($\text{DMSO}-d_6$): 8.82 (t;NH;1H), 5.15 (d;CH;1H), 4.28 (d;CH₂;2H), 3.72 (s;CH₃;6H).

17.c) 4-aminobenzonitrile, 4-benzyloxy-3-methoxybenzaldehyde and benzylisonitrile gave (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetamide as colourless crystals. ^1H NMR ($\text{DMSO}-d_6$): 8.80 (t;NH;1H), 5.07 (d;CH;2H), 4.99 (d;CH;2H), 4.28 (s;CH₂;2H), 3.73 (s;CH₃;3H).

17.d) 4-aminobenzonitrile, 4-benzyloxy-3-ethoxybenzaldehyde and benzylisonitrile gave (R,S)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-cyanophenylamino)acetamide as colourless crystals. ^1H NMR ($\text{DMSO}-d_6$): 8.75 (t;NH;1H), 5.10 (s;CH₂;2H), 4.95 (d;CH;1H), 4.28 (d;CH₂;2H), 4.05 (q;CH₂;2H), 1.32 (t;CH₃;3H).

Example 18

35 Under an atmosphere of argon, a solution of 290 mg (0.75 mmol) of (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-

(4-hydroxy-3-methoxyphenyl)acetamide (Example 20), 110 ml (0.9 mmol) of 3-methoxybenzyl alcohol and 236 mg (0.9 mmol) of triphenylphosphine in 15 ml of THF were admixed with 140 ml (0.9 mmol) of diethyl azodicarboxylate, and the mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 9:1). This gave 326 mg (86%) of (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(3-methoxybenzyloxy)-phenyl]acetamide as a colourless solid. ISP-MS: 530.2 ($[\text{M}+\text{Na}]$), 525.2 ($[\text{M}+\text{NH}_4]$), 508.4 ($[\text{M}+\text{H}]$), 390.2.

Example 19

By the method of Example 18, (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-(4-hydroxy-3-methoxyphenyl)acetamide 19.a) and 4-hydroxymethylpyridine gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(pyridin-4-ylmethoxy)phenyl]acetamide in a yield of 72%. ISP-MS: 479.3 $[\text{M}+\text{H}]$.

19.b) and N-(2-hydroxyethyl)morpholine gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]acetamide in a yield of 66%. Colourless resin. ISP-MS: 501.3 $[\text{M}+\text{H}]$.

19.c) and N-(2-hydroxyethyl)thiomorpholine (L.A. Burrows, E.E. Reid, Journal of American Chemical Society (1934) 56, 1720) gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(2-thiomorpholin-4-ylethoxy)phenyl]acetamide in a yield of 84%. Colourless solid foam. ISP-MS: 517.3 $[\text{M}+\text{H}]$.

19.d) and 3-phenoxybenzylalcohol gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(3-phenoxybenzyloxy)phenyl]acetamide in a yield of 44%. Colourless solid foam. ISN-MS: 628.3 ($[\text{M}+\text{AcOH}-\text{H}]$), 568.3 $[\text{M}-\text{H}]$.

19.e) and 5-hydroxymethylindole (M. Somei, Y. Saida,

N. Komura, Chem. Pharm. Bull. (1986) 34, 4116) gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(1H-indol-5-ylmethoxy)-3-methoxyphenyl]acetamide in a yield of 67%. Light-yellow solid foam. ISP-MS: 539.3 ([M+Na]), 534.3 ([M+NH₄]), 517.2
5 ([M+H]), 399.3.

19.f) and 7-hydroxymethylquinoline (C.E. Kaslow, W.R. Clark, Journal of Organic Chemistry (1953) 18, 55) gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(quinolin-7-ylmethoxy)phenyl]acetamide in a yield of 100%.
10 Colourless solid. ISP-MS: 529.2 [M+H].

19.g) and 2-phenylethyl alcohol gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-phenethyloxyphenyl]acetamide in a yield of 90%. Light-green resin. ISP-MS: 492.2 [M+H].

15 19.h) and 4-hydroxymethylbiphenyl gave (R,S)-N-benzyl-2-[4-(biphenyl-4-ylmethoxy)-3-methoxyphenyl]-2-(4-cyanophenylamino)acetamide in a yield of 25%. Colourless solid. ISN-MS: 612.3 ([M+AcOH-H]), 552.2 [M-H].

19.i) and 2,6-dichlorobenzyl alcohol gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(2,6-dichlorobenzyloxy)-3-methoxyphenyl]acetamide in a yield of 70%. Colourless
20 crystals. ISN-MS: 604.1 ([M+AcOH-H]), 544.1 [M-H].

19.j) and 3,5-dichlorobenzyl alcohol gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(3,5-dichlorobenzyloxy)-3-methoxyphenyl]acetamide in a yield of 74%. Colourless
25 crystals. ISN-MS: 604.1 ([M+AcOH-H]), 544.1 [M-H].

19.k) and 3-bromobenzyl alcohol gave (R,S)-N-benzyl-2-[4-(3-bromobenzyloxy)-3-methoxyphenyl]-2-(4-cyanophenylamino)acetamide in a yield of 51%. Colourless
30 crystals. ISN-MS: 614.2 ([M+AcOH-H]), 556.0 [M-H].

19.l) and 2-hydroxymethylpyridine gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(pyridin-2-ylmethoxy)phenyl]acetamide in a yield of 89%. Colourless resin. ISP-MS: 479.3 [M+H].

35 19.m) and 6-hydroxymethylisoquinoline (EP 385 662) gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[4-(isoquinolin-

6-ylmethoxy)-3-methoxyphenyl]acetamide in a yield of 100%. Colourless solid. ISP-MS: 529.3 [M+H].

19.n) and 4-nitrobenzyl alcohol gave (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-[3-methoxy-4-(4-nitro-benzyloxy)phenyl]acetamide in a yield of 71%. Light-yellow, solid foam. ISN-MS: 581.2 ([M+AcOH-H]), 521.2 [M+H].

Example 20

10 460 mg (0.4 mmol) of tetrakis(triphenyl-phosphine)palladium were added to a solution of 8.5 g (20 mmol) of (R,S)-2-(4-allyloxy-3-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide (Example 21) in 250 ml of THF. The solution was stirred at room temperature for 10 min and
15 then admixed with 1.13 g (30 mmol) of NaBH₄. The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was taken up in CH₂Cl₂/EtOAc 9:1 and stirred in the presence of activated carbon for 30 min. The suspension was filtered through
20 Dicalite. The filtrate was concentrated under reduced pressure and the residue was recrystallized from EtOAc/hexane. This gave 6.81 g (88%) of (R,S)-N-benzyl-2-(4-cyanophenylamino)-2-(4-hydroxy-3-methoxyphenyl)acetamide as colourless crystals. ISN-MS: 386.1 ([M-H]), 268.3.

25

Example 21

 A solution of 17.8 g (35 mmol) of methyl (R,S)-2-(4-allyloxy-3-methoxyphenyl)-N-benzyl-2-(4-cyanophenyl-
30 amino)acetamidate (Example 22) in 35 ml of DMSO was stirred at room temperature overnight. The solvent was evaporated off under high vacuum. The residue was purified by silica gel chromatography (CH₂Cl₂/EtOAc 19:1). This gave 10.6 g (71%) of
35 (R,S)-2-(4-allyloxy-3-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide as a colourless solid. ISN-MS: 486.1 ([M+AcOH-H]), 426.1 [M-H].

Example 22

Under an atmosphere of argon, a solution of 17.72 g
5 (150 mmol) of 4-aminobenzonitrile and 28.8 g of 4-allyloxy-
3-methoxybenzaldehyde (W.A. Ayer, P.A. Craw, Can. J. Chem.
(1991) 69, 1909) was stirred at room temperature for 1 h.
18.3 ml (150 mmol) of benzylisonitrile were added. At 0°C,
56 ml (450 mmol) of boron trifluoride ethyl etherate were
10 subsequently slowly added dropwise. After a short period of
time, crystals formed, which were filtered off under an
atmosphere of argon and dried under high vacuum. This gave
74.1 g (87%) of methyl (R,S)-2-(4-allyloxy-3-methoxyphenyl)-
N-benzyl-2-(4-cyanophenylamino)acetimidate as a light-yellow
15 solid. ISP-MS: 442.3 [M+H].

Example 23

Under an atmosphere of argon, 144 mg (0.75 mmol) of
20 N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
were added to a solution of 194 mg (0.5 mmol) of (R,S)-(4-
benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetic acid
(Example 25), 75 ml (0.6 mmol) of phenethylamine, 115 mg
(0.75 mmol) of 1-hydroxybenzotriazole and 128 ml (0.75 mmol)
25 of N,N-diisopropylethylamine in 2.5 ml of THF. The reaction
mixture was stirred at room temperature for 5 h and then
concentrated under reduced pressure. The residue was taken up
in EtOAc and washed with saturated KHCO₃ solution, with 2%
strength citric acid solution, with H₂O and then with
30 saturated NaCl solution. The organic phase was dried over
MgSO₄, filtered and concentrated under reduced pressure. The
crude product was purified by silica gel chromatography
(cyclohexane/ EtOAc 2:1). This gave 210 mg (86%) of
(R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyano-
35 phenylamino)-N-phenethylacetamide as a colourless solid foam.
ISP-MS: 492.3 ([M+Na]), 509.4 ([M+NH₄]), 523.3 ([M+H]).

Example 24

By the method of Example 23, (R,S)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetic acid

24 a) and veratrylamine gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-(3,4-dimethoxybenzyl)acetamide in a yield of 80%. Light-yellow, solid foam. ISP-MS: 560.4 ([M+Na]), 555.3 ([M+NH₄]), 538.4 ([M+H]).

24 b) and 4-nitrobenzylamine hydrochloride gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-(4-nitrobenzyl)acetamide in a yield of 43%. Colourless solid. ISP-MS: 545.2 ([M+Na]), 540.3 ([M+NH₄]), 523.2 ([M+H]).

24 c) and aniline gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-phenylacetamide in a yield of 52%. Colourless solid. ISP-MS: 486.2 ([M+Na]), 464.2 ([M+H]).

24 d) and 4-aminobenzonitrile gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-N-(4-cyanophenyl)-2-(4-cyanophenylamino)acetamide in a yield of 10%. Colourless solid, ISN-MS: 547.2 ([M+AcOH-H]), 487.2 ([M-H]).

24 e) and histamine dihydrochloride gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(3H-imidazole-4-yl)ethyl]acetamide in a yield of 74%. Colourless solid foam. ISP-MS: 482.4 ([M+H]).

24 f) and tryptamine gave (R,S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(1H-indol-3-yl)ethyl]acetamide in a yield of 92%. Orange solid foam. ISP-MS: 553.3 ([M+Na]), 548.3 ([M+NH₄]), 531.3 [M+H].

Example 25

A solution of 1.17 g (2.9 mol) of methyl (R,S)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetate in

6 ml of THF was cooled to 0°C and admixed with 14.5 ml (14.5 mmol) of 1N LiOH solution. The mixture was stirred at 0°C for 30 min and at room temperature for 2 h. The THF was distilled off under reduced pressure. The solution that remained was adjusted to pH 3 using 1N HCl. A colourless precipitate formed, which was filtered off and washed with water. The solid was recrystallized in EtOH/H₂O. This gave 788 mg (70%) of (R,S)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetic acid as a colourless solid. ISN-MS: 387.1 ([M-H]).

Example 26

Under an atmosphere of argon, a solution of 970 mg (4 mmol) of 4-benzyloxy-3-methoxybenzaldehyde and 473 mg (4 mmol) of 4-aminobenzonitrile in 16 ml of MeOH was stirred at room temperature for 1 h. A light-yellow precipitate formed. The suspension was admixed with 488 ml (4 mmol) of benzyllisonitrile and cooled to 0°C. 1.52 ml (12 mmol) of boron trifluoride ethyl etherate were then slowly added dropwise. After 2 h, the mixture was allowed to warm to room temperature and concentrated under reduced pressure. The residue was taken up in MeOH. The solution was slowly admixed with water until crystallization set in. The mixture was allowed to stand at 4°C overnight. The solid was filtered off and dried under high vacuum. The residue was recrystallized from cyclohexane/EtOAc. This gave 1.17 g (73%) of methyl (R,S)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetate as a colourless solid. ISP-MS: 425 ([M+Na]), 420.2 ([M+NH₄]).

Example 27

2.0 g of N-benzyl-2-(4-benzyloxy-5-methoxy-2-nitrophenyl)-2-(4-cyanophenylamino)acetamide (3.8 mmol) (Example 16) were dissolved in 50 ml of EtOAc and 50 ml of

EtOH, admixed with 1.2 g of 5% Pt/C and hydrogenated for 3 h. The catalyst was filtered off. The filtrate was concentrated under reduced pressure. This gave 1.42 g (76%) of 2-(2-amino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide as an oily yellow solid. ISP-MS: 493 (M+H).

Example 28

1.7 g of 2-(2-amino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide (3.4 mmol) (Example 27) were dissolved in 60 ml of CH₂Cl₂ and 20 ml of DMF and admixed with 0.7 ml of Hünig base. At 0°C, 0.7 ml of phenylsulphonyl chloride (3.8 mmol) were subsequently added dropwise. The reaction mixture was stirred at room temperature for 4 hours and subsequently diluted with 100 ml of CH₂Cl₂ and washed with 5% NaHCO₃ solution. The organic phase was washed with saturated NaCl solution, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using acetone/toluene (10/90). This gave 995 mg (46%) of 2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide as an oily orange solid. ISN-MS: 631 (M-H).

Example 29

By the method of Example 28, 2-(2-amino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide (Example 27) and methanesulphonyl chloride gave N-benzyl-2-(4-benzyloxy-2-methane-sulphonylamino-5-methoxyphenyl)-2-(4-cyanophenylamino)-acetamide as an orange solid in a yield of 36%. ISN-MS: 569 (M-H).

Example 30

Under argon and at 0°C, 0.2 mmol of (R,S)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide trifluoroacetate (Example 3) (120 mg) in 1.3 ml of tetrahydrofuran are admixed with 0.335 mmol of O-methyl O'-(4-nitrophenyl) carbonate (66 mg). The reaction mixture is then allowed to warm to room temperature overnight, the solvent is removed under reduced pressure and the residue is extracted with ethyl acetate and water. The combined organic phases are dried over sodium sulphate. The mixture is filtered and the solvent is removed, and the residue is then suspended in diethyl ether and filtered off. This gives 88 mg (82%) of methyl [amino-(4-
15 {[benzylcarbamoyl-(4-benzyloxy-3-methoxyphenyl)-methyl]amino}phenyl)methylene]carbamate as a colourless solid. ISP-MS: 553.3 ([M+H]⁺, 100).

Example 31

20

By the method of Example 30, the following compounds are prepared:

31 a) (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-1-(3,4-dimethoxyphenyl)acetamide hydrochloride (Example 2)
25 gives methyl [amino-(4-{[benzylcarbamoyl-(3,4-dimethoxyphenyl)methyl]-amino}phenyl)methylene]carbamate as a colourless solid. ISP-MS: 477.5 ([M+H]⁺, 100).

31 b) (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,5-dimethoxyphenyl)acetamide hydrochloride (Example 5b)
30 gives methyl [amino-(4-{[benzylcarbamoyl-(3,5-dimethoxyphenyl)methyl]-amino}phenyl)methylene]carbamate as a colourless solid. ISP-MS: 477.5 ([M+H]⁺, 100).

31 c) (R,S)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3,4,5-trimethoxyphenyl)acetamide hydrochloride (Example 5a)
35 5a) gives methyl [amino-(4-{[benzylcarbamoyl-(3,4,5-trimethoxyphenyl)methyl]amino}phenyl)methylene]carbamate as a

colourless solid. ISP-MS: 507.6 ($[M+H]^+$, 100).

A compound of the formula I, a hydrate, a solvate or a salt thereof can be used as an active ingredient for preparing pharmaceutical preparations, like those below.

5

Example 32

A degassed solution of 369 mg of the material prepared according to the Example 36.3 in 5 ml of EtOH, 5 ml
10 of THF, 2 ml of H₂O and 1 ml of HOAc was admixed with a spatula tip of Raney nickel and hydrogenated for 5 hours. The catalyst was filtered off. The filtrate was concentrated. The residue was purified by silica gel chromatography (EtOAc/acetone/H₂O/HOAc 6:2:1:1). This gave the two epimers:
15 1. (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminopropionic acid acetate (1:1) and
2. (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminopropionic acid acetate
20 (1:1) both as colourless lyophilizates, ISP-MS: 477.3 $[M+H]$.

Example 33

By the method of Example 32,

25

33.a

The mixture of epimers from Example 37.a.1 gave:

1. (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminopropionic acid
30 acetate (1:1) and the mixture of epimers from Example 37.a gave
2. (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminopropionic acid acetate (1:1), ISP-MS: 553.3 $[M+H]$,

35

33.b

the product from Example 37.b gave, after chromatographic separation, the two epimers:

1. (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-(4-hydroxyphenyl)propionic acid acetate (1:2) and
2. (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-3-(4-hydroxyphenyl)propionic acid acetate (1:1), ISP-MS: 569.3 [M+H],

10

33.c

the product from Example 37.c gave a mixture of (S)-1-[(R)- and -[(S)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]pyrrolidine 2-carboxylic acid acetate, ISP-MS: 503.3 [M+H],

15

33.d

the product from Example 37.d gave (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl]amino]-2-methylpropionic acid acetate (1:0.5), ISP-MS: 491.5 [M+H], 513.5 [M+Na],

20

33.e

the product from Example 37.e gave, after chromatographic separation, the two epimers:

1. (S)-[[[(R)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]methylamino]phenyl]acetic acid acetate (1:2) and
2. (S)-[[[(S)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]methylamino]phenyl]acetic acid acetate (1:1), ISP-MS: 553.3 [M+H], 575.1 [M+Na],

30

33.f

the product from Example 37.f gave the mixture of (RS)- and (SR)-1-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-carbamimidoylphenylamino)acetyl]pyrrolidine-3-carboxylic

35

acid, ISP-MS: 503.3 [M+H],

33.g

the product from Example 37.g gave, after
5 chromatographic separation, the two diastereomeric racemates
of (RS)- or (SR)-2-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-
carbamimidoylphenylamino)acetyl]-1,2,3,4-tetrahydroiso-
quinoline-3-carboxylic acid acetate (1:1), ISP-MS: 565.3
[M+H], 587.2 [M+Na],

10

33.h

the product from Example 37.h gave (RS)-1-[2-(4-
benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoyl-phenylamino)-
acetylaminocyclopentanecarboxylic acid acetate (1:2),
15 ISP-MS: 517.2 [M+H], 539.3 [M+Na],

33.i

the product from Example 37.i gave (RS)-[2-(4-
benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenyl-
20 amino)acetylaminodiphenylacetic acid acetate (1:1),
ISP-MS: 615.3 [M+H],

33.j

the product from Example 37.j gave, after
25 chromatographic separation, the two epimers:
1. (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-
carbamimidoylphenylamino)acetylaminocyclopentanecarboxylic acid acetate (1:3) and
2. (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-
30 carbamidoylphenylamino)acetylaminocyclopentanecarboxylic acid acetate (1:3), ISP-MS: 606.1 [M+H], 628.2
[M+H],

33.k

35 the product from Example 37.k gave, after
chromatographic separation, the two epimers:

1. (S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]-3-tert-butoxycarbonylaminopropionic acid acetate (1:1) and
2. (S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]-3-tert-butoxycarbonylaminopropionic acid acetate (1:1), ISP-MS: 592.2 [M+H].

Example 34

10

By the method of Example 32,

34.a

the product from Example 38.a gave (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]benzoic acid acetate (1:1), ISP-MS: 525.1 [M+H],

34.b

the product from Example 38.b gave (RS)-3-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]benzoic acid acetate (1:1), ISP-MS: 525.1 [M+H],

25 34.c

the product from Example 38.c gave (RS)-4-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]benzoic acid acetate (1:1), ISP-MS: 525.1 [M+H].

30

Example 35

By the method of Example 32, the product from Example 39 gave a mixture of (RS)- and (SR)-3-[(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]-3-phenylpropionic acid.

Example 36

36.1

5 335 mg of methyl L-alaninate hydrochloride, 1.03 ml
of diisopropylethylamine and 1.06 g of (benzotriazol-1-
yloxy)tris(dimethylamino)phosphonium hexafluorophosphate were
added to a solution of 777 mg of the material prepared in
Example 25 in 10 ml of DMF. The reaction solution was stirred
10 at RT for 2 hours and subsequently concentrated under high
vacuum. The residue was taken up in ethyl acetate and then
washed with 10% strength KHCO_3 solution, with 2% strength
citric acid, water and saturated NaCl solution. The organic
phase was dried over MgSO_4 and concentrated under reduced
15 pressure. The residue was purified by silica gel
chromatography. This gave 823 mg (87%) of a 1:1 mixture of
methyl (S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-
2-(4-cyanophenylamino)acetylaminopropionate as a solid
colourless foam. ISP-MS: 474.3 [M+H], 496.1 [M+Na], 512.2
20 [M+K].

36.2

8.4 ml of 1N LiOH solution were added to a solution,
coded to 0°C, of 792 mg of the material which had been
25 prepared according to Example 36.1 in 10 ml of THF. The
mixture was stirred at 0°C for 30 min and at RT for 2 hours.
The THF was distilled off under reduced pressure. The aqueous
solution that remained was acidified using 1N HCl, and a
colourless precipitate formed. This was filtered off and
30 dried under high vacuum. This gave 712 mg (91%) of a 1:1
mixture of (S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-
methoxyphenyl)-2-(4-cyanophenylamino)acetylaminopropionic
acid as a colourless solid. ISN-MS: 458.3 [M-H].

35 36.3.

4.1 ml of triethylamine and then 683 mg of the

material prepared according to Example 36.2 were added to a suspension of 1.04 g of hydroxylamine hydrochloride in 25 ml of EtOH. The reaction mixture was heated under reflux overnight and subsequently concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/acetone/H₂O/HOAc 6:2:1:1). This gave 625 mg (86%) of a 1:1 mixture of (E)- and/or (Z)-(S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetylaminopropionic acid as a slightly pink lyophilizate. ISP-MS: 493.3 [M+H], 515.3 [M+Na].

Example 37

By the method of Example 36, the material prepared in Example 25

37.a

and methyl L-phenylalaninate hydrochloride gave a 1:1 mixture of methyl (S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetylaminopropionate which gave a 1:1 mixture of (S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetylaminopropionic acid and from this, after chromatographic separation, the two products:

1. (E)- and/or (Z)-(S)-2-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetylaminopropionic acid and
2. (E)- and/or (Z)-(S)-2-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetylaminopropionic acid,

37.b

and ethyl L-tyrosinate hydrochloride gave a 1:1 mixture of ethyl (S)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetylaminopropionic acid,

hydroxyphenyl)propionate which gave a 1:1 mixture of (S)-2-
[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-
cyanophenylamino)acetyl]amino]-3-(4-hydroxyphenyl)propionic
acid which gave a 1:1 mixture of (E)- and/or (Z)-(S)-2-[(R)-
5 and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-
hydroxycarbamimidoyl)phenylamino]acetyl]amino]-3-(4-
hydroxyphenyl)propionic acid,

37.c

10 and methyl L-prolinate gave a 1:1 mixture of methyl
(S)-1-[(R)- and -[(S)-(4-benzyloxy-3-methoxyphenyl)-(4-
cyanophenylamino)acetyl]pyrrolidine-2-carboxylate which gave
a mixture of (S)-1-[(R)- and [(S)-(4-benzyloxy-3-
methoxyphenyl)-(4-cyanophenylamino)acetyl]pyrrolidine-2-
15 carboxylic acid which gave a 1:1 mixture of (E)- and/or (Z)-
(S)-1-[(R)- and -[(S)-(4-benzyloxy-3-methoxyphenyl)-[4-(N-
hydroxycarbamimi-doyl)phenylamino]acetyl]pyrrolidine-2-
carboxylic acid,

20 37.d

and methyl 2-aminoisobutyrate hydrochloride gave
methyl (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-
cyanophenylamino)acetyl]amino]-2-methylpropionate which gave
(RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenyl-
25 amino)acetyl]amino]-2-methylpropionic acid which gave (E)-
and/or (Z)-(RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-
hydroxycarbamimidoyl)phenylamino]acetyl]amino]-2-
methylpropionic acid,

30 37.e

and ethyl N-methyl-L-phenylglycinate hydrochloride
gave a 1:1 mixture of ethyl (S)-[[[(R)- and -[[[(S)-(4-
benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetyl]methyl-
amino]phenyl acetate which gave a 1:1 mixture of (S)-[[[(R)-
35 and [[[(S)-(4-benzyloxy-3-methoxyphenyl)-(4-
cyanophenylamino)acetyl]methylamino]phenylacetic acid which

gave a mixture of (E)- and/or (Z)-(S)-[[(R)- and -[[(S)-(4-benzyloxy-3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenyl-amino]acetyl]methylamino]phenylacetic acid,

5 37.f

and ethyl beta-D,L-prolinate hydrochloride gave a mixture of ethyl (RS)- and (SR)-1-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetyl]pyrrolidine-3-carboxylate which gave a mixture of (RS)- and (SR)-1-[(RS)-
10 (4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetyl]-pyrrolidine-3-carboxylic acid which gave a mixture of (E)- and/or (Z)-(RS)- and -(SR)-1-[(RS)-(4-benzyloxy-3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenylamino]-acetyl]pyrrolidine-3-carboxylic acid,

15

37.g

and ethyl 1,2,3,4-tetrahydro-3-isoquinoline-carboxylate hydrochloride gave a mixture of ethyl (RS)- and (SR)-2-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenyl-amino)acetyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate
20 which gave a mixture of (RS)- and (SR)-2-[(RS)-(4-benzyloxy-3-methoxyphenyl)-(4-cyanophenylamino)acetyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid which gave a mixture of (E)- and/or (Z)-(RS)- and -(SR)-2-[(RS)-(4-benzyloxy-3-methoxyphenyl)-[4-(N-hydroxycarbamimidoyl)phenylamino]-acetyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid,

25

37.h

and ethyl 1-amino-1-cyclopentanecarboxylate
30 hydrochloride gave ethyl (RS)-1-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetyl]amino]cyclopentanecarboxylate which gave (RS)-1-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetyl]amino]cyclopentanecarboxylic acid which gave (E)- and/or (Z)-(RS)-1-[2-
35 (4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetyl]amino]cyclopentanecarboxylic

acid,

37.i

and methyl α,α -diphenylglycinate hydrochloride gave
5 methyl (RS)-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-
cyanophenylamino)acetyl-amino]diphenylacetate which gave (RS)-
[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenyl-
amino)acetyl-amino]diphenylacetic acid which gave (E)- and/or
(Z)-(RS)-[2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-
10 hydroxycarbamimidoyl)phenylamino]acetyl-amino]diphenylacetic
acid,

37.j

and methyl N- γ -Boc-L- α,γ -diaminobutyrate
15 hydrochloride gave a 1:1 mixture of methyl (S)-2-[(R)- and
-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyano-
phenylamino)acetyl-amino]-4-tert-butoxycarbonylamino]butyrate
which gave a 1:1 mixture of (S)-2-[(R)- and -[(S)-2-(4-
benzyloxy-3-methoxyphenyl)-2-(4-cyanophenyl-
20 amino)acetyl-amino]-4-tert-butoxycarbonylamino]butyric acid
which gave a 1:1 mixture of (S)-2-[(R)- and -[(S)-2-(4-
benzyloxy-3-methoxyphenyl)-2-[4-[(E)- and/or -[(Z)-N-
hydroxycarbamimidoyl]phenylamino]acetyl-amino]-4-tert-
butoxycarbonylamino]butyric acid,

25

37.k

and methyl N- β -Boc-L- α,β -diaminopropionate
hydrochloride gave a 1:1 mixture of methyl (S)-2-[(R)- and
-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyano-
30 phenylamino)acetyl-amino]-3-tert-butoxycarbonylamino]propionate
which gave a 1:1 mixture of (S)-2-[(R)- and -[(S)-2-(4-
benzyloxy-3-methoxyphenyl)-2-(4-cyanophenyl-
amino)acetyl-amino]-3-tert-butoxycarbonylamino]propionic acid
which gave a 1:1 mixture of (S)-2-[(R)- and -[(S)-2-(4-
35 benzyloxy-3-methoxyphenyl)-2-[4-[(E)- and/or -[(Z)-N-

hydroxycarbamimidoyl]phenylamino]acetyl amino]-3-tert-butoxycarbonylaminopropionic acid.

Example 38

5

By the method of Example 36, the material prepared in Example 25

38.a

10 and ethyl 2-aminobenzoate gave ethyl (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-acetyl amino]benzoate which gave (RS)-2-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetyl amino]benzoic acid which gave (E)- and/or (Z)-(RS)-2-[2-(4-benzyloxy-3-
15 methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetyl amino]benzoic acid,

38.b

and ethyl 3-aminobenzoate gave ethyl (RS)-3-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-acetyl amino]benzoate which gave (RS)-3-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetyl amino]benzoic acid which gave (E)- and/or (Z)-(RS)-3-[2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-
25 acetyl amino]benzoic acid,

38.c

and ethyl 4-aminobenzoate gave ethyl (RS)-4-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-acetyl amino]benzoate which gave (RS)-4-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetyl amino]benzoic acid which gave (E)- and/or (Z)-(RS)-4-[2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-acetyl amino]benzoic acid.

35

Example 39

By the method of Example 36, the material prepared in Example 25 and methyl D,L-3-amino-3-phenylpropionate
5 hydrochloride gave the mixtures of the diastereomers of the corresponding nitrile esters which gave the corresponding nitrile acids and finally a mixture of (E)- and/or (Z)-(RS)- and -(SR)-3-[(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarb-amimidoyl)phenylamino]acetylamino]-3-
10 phenylpropionic acid.

Example 40

40.a

15 A suspension of 107 mg of the mixture of epimers obtained according to Example 33.j in 3 ml of CH₂Cl₂ was admixed with 0.5 ml of trifluoroacetic acid and stirred at RT for 1 hour. The reaction mixture was concentrated. The residue was purified by silica gel chromatography
20 (EtOAc/acetone/H₂O/HOAc 6:2:2:4). This gave 79 mg (85%) of a mixture of (S)-4-amino-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]-butyric acid acetate (1:1) as a beige lyophilizate.

25 40.b

By the method of Example 40.a, the mixture of epimers obtained according to Example 33.k gave a 1:1 mixture of (S)-3-amino-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]propionic acid
30 acetate (1:1) in a yield of 44% as a beige lyophilizate.

Example 41

41.a

35 By the method of Example 32 and via (E)- and/or (Z)-(S)-[(R)- or -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-

hydroxycarbamimidoyl)phenylamino]acetylaminophenylacetic acid, the following compounds were obtained:

- a) (S)-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid and
5 b) (S)-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid.

41.b

The amidoxime used in 41.a was prepared by the method
10 of Example 37 starting from material obtained according to Example 25 and methyl (S)-phenylglycinate via the corresponding nitrile esters and the corresponding nitrile acids prepared therefrom.

15

Example 42

42.a

By the method of Example 41, but using methyl (R)-phenylglycinate hydrochloride instead of methyl (S)-
20 phenylglycinate hydrochloride, the two epimers
1. (R)-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid and
2. (R)-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid are
25 obtained.

42.b

By the method of Example 41, but using ethyl p-amino-L-phenylalaninate dihydrochloride instead of methyl (S)-
30 phenylglycinate hydrochloride, a 1:1 mixture of ethyl (S)-3-(4-aminophenyl)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)acetylaminopropionate are obtained, which gives
1. a 1:1 mixture of ethyl (E)- and/or (Z)-(S)-3-(4-aminophenyl)-2-[(R)- and -[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenyl-

amino]acetyl-amino]propionate which gives

2. a 1:1 mixture of ethyl (S)-3-(4-aminophenyl)-2-[(R)- and
-[(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbam-

5 finally gives, after chromatographic separation,

3. (S)-3-(4-aminophenyl)-2-[(R)-2-(4-benzyloxy-3-
methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl-
amino]propionic acid acetate (1:3) and

4. (S)-3-(4-aminophenyl)-2-[(S)-2-(4-benzyloxy-3-
10 methoxyphenyl)-2-(4-carbamimidoylphenylamino)-
acetyl-amino]propionic acid acetate (1:3), ISP-MS: 568.3
[M+H], 590.3 [M+Na].

Example 43

15

43.1

By the method of Example 26, 3,5-dimethoxybenz-
aldehyde, 4-aminobenzonitrile and benzylisonitrile gave
methyl (RS)-(4-cyanophenylamino)-(3,5-dimethoxyphenyl)-

20 acetate.

43.2

By the method of Example 25, the product prepared
under 43.1 gave (RS)-(4-cyanophenylamino)-(3,5-
25 dimethoxyphenyl)acetic acid.

43.3

By the method of Example 41, the acid prepared under
43.2 and methyl (S)-phenylglycinate hydrochloride gave, after
30 chromatographic separation of the mixture of epimers, the two
products

a) (S)-[(R)-2-(4-carbamimidoylphenylamino)-2-(3,5-
dimethoxyphenyl)acetyl-amino]phenylacetic acid acetate (1:1.6)
and

35 b) (S)-[(S)-2-(4-carbamimidoylphenylamino)-2-(3,5-
dimethoxyphenyl)acetyl-amino]phenylacetic acid acetate

(1:1.75), ISP-MS: 463.2 [M+H].

Example 44

5 By the method of Example 26, 3,4-diethoxybenzaldehyde, 4-aminobenzonitrile and benzylisonitrile gave (RS)-(4-cyanophenylamino)-(3,4-diethoxyphenyl)acetic acid.

Example 45

10

A degassed solution of 147 mg of the product from Example 47.b in 5 ml of EtOH, 5 ml of THF, 2 ml of H₂O and 1 ml of HOAc was admixed with a spatula tip of Raney nickel and hydrogenated for 5 hours. The catalyst was filtered off.
15 The filtrate was concentrated. The residue was purified by silica gel chromatography (EtOAc/acetone/H₂O/HOAc 6:2:1:1). This gave 80 mg (56%) of (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[2-(3,4-dihydroxyphenyl)ethyl]acetamide acetate (1:1) as a colourless
20 lyophilizate. ISP-MS: 541.2 [M+H].

Example 46

Using the method of Example 45

25 46.a

the product from Example 48.a gave (RS)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-methylacetamide, ISP-MS: 509.5 [M+H],

30 46.b

the product from Example 48.b gave (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[2-(4-sulphamoylphenyl)ethyl]acetamide, ISP-MS: 588.4 [M+H],

35 46.c

the product from Example 48.c gave (RS)-2-(4-

benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-(2-pyridin-2-ylethyl)acetamide acetate (1:1), ISP-MS: 510.3 [M+H],

5 46.d

the product from Example 48.d gave (RS)-N-[2-(4-aminophenyl)ethyl]-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetamide acetate (1:1),
ISP-MS: 523.4 [M+H],

10

46.e

1. the diastereomer from Example 48.e.1 gave the corresponding (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(R)-2-hydroxy-1-phenyl-ethyl]acetamide acetate (1:1) and

15

2. the diastereomer from Example 48.e.2 gave the corresponding (S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(R)-2-hydroxy-1-phenyl-ethyl]acetamide acetate (1:1), ISP-MS: 525.2 [M+H],

20

46.f

1. the diastereomer from Example 48.f.1 gave the corresponding (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(S)-2-hydroxy-1-phenyl-ethyl]acetamide acetate (1:1) and

25

2. the diastereomer from Example 48.f.2 gave the corresponding (S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(S)-2-hydroxy-1-phenyl-ethyl]acetamide acetate (1:1), ISP-MS: 525.4 [M+H],

30

46.g

1. the diastereomer from Example 48.g.1 gave the corresponding (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(R)-1-phenylethyl]acetamide acetate (1:1) and

35

2. the diastereomer from Example 48.g.2 gave the

corresponding (S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(R)-1-phenylethyl]acetamide acetate (1:1), ISP-MS: 509.4 [M+H],

5 46.h

1. the diastereomer from Example 48.h.1 gave the corresponding (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(S)-1-phenylethyl]acetamide acetate (1:1) and

10 3. the diastereomer from Example 48.h.2 gave the corresponding (S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)-N-[(S)-1-phenylethyl]acetamide acetate (1:1), ISP-MS: 509.4 [M+H].

15

Example 47

47.a

By the method of Example 36.1, 388 mg of the product from Example 25 and 184 mg of 3-hydroxythyramine gave 323 mg
20 (62%) of (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(3,4-dihydroxyphenyl)ethyl]acetamide as a solid colourless foam. ISN-MS: 522.1 [M-H].

47.b

25 By the method of Example 36.3, 258 mg of the product obtained according to Example 47.a gave 222 mg (81%) of (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(3,4-dihydroxyphenyl)ethyl]-acetamide as a colourless powder. ISP-MS: 557.2 [M+H].

30

Example 48

By the method of the process described in Examples 36.1 and 36.3, the following compounds were prepared:

35

From the product of Example 25:

48.a

and N-benzylmethylaniline, via the intermediate (RS)-N-benzyl-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenyl-amino)-N-methylacetamide, (E)- and/or (Z)-(RS)-N-benzyl-2-(4-
5 benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-methylacetamide,

48.b

and 4-(2-aminoethyl)benzenesulphonamide, via the
10 intermediate (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(4-sulphamoylphenyl)ethyl]acetamide, (E)- and/or (Z)-(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[2-(4-sulphamoylphenyl)-ethyl]acetamide,

15

48.c

and 2-(2-aminoethyl)pyridine, via the intermediate (RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-(2-pyridin-2-ylethyl)acetamide, (E)- and/or (Z)-(RS)-2-(4-
20 benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-(2-pyridin-2-ylethyl)acetamide,

48.d

and 4-nitrophenethylamine, via the intermediate (RS)-
25 2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[2-(4-nitrophenyl)ethyl]acetamide, (E)- and/or (Z)-(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[2-(4-nitrophenyl)ethyl]acetamide,

30 48.e

and (R)-phenylglycinol, after chromatographic separation, the two diastereomers (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[(R)-2-hydroxy-1-phenylethyl]acetamide and (S)-2-(4-benzyloxy-3-
35 methoxyphenyl)-2-(4-cyanophenylamino)-N-[(R)-2-hydroxy-1-phenylethyl]acetamide;

1. the first diastereomer gave (E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[(R)-2-hydroxy-1-phenylethyl]acetamide, and

2. the second diastereomer gave (E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[(R)-2-hydroxy-1-phenylethyl]acetamide,

48.f

and (S)-phenylglycinol, after chromatographic separation, the two diastereomers (R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[(S)-2-hydroxy-1-phenylethyl]acetamide and (S)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-cyanophenylamino)-N-[(S)-2-hydroxy-1-phenylethyl]acetamide;

1. the first diastereomer gave (E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[(S)-2-hydroxy-1-phenylethyl]acetamide and

2. the second diastereomer gave (E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[(S)-2-hydroxy-1-phenylethyl]acetamide,

48.g

and (R)-1-phenylethylamine, after chromatographic separation, the two diastereomers

1. (E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[(R)-1-phenylethyl]acetamide and

2. (E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]-N-[(R)-1-phenylethyl]acetamide,

48.h

and (S)-1-phenylethylamine, after chromatographic separation, the two diastereomers (R)-2-(4-benzyloxy-3-

methoxyphenyl)-2-(4-cyanophenylamino)-N-[(S)-1-phenylethyl]acetamide and (S)-2-(4-benzyloxy-3-

methoxyphenyl)-2-(4-cyanophenylamino)-N-[(S)-1-phenylethyl]acetamide;

1. the first diastereomer gave (E)- and/or (Z)-(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[(S)-1-phenylethyl]acetamide,
2. the second diastereomer gave (E)- and/or (Z)-(S)-2-(4-benzyloxy-3-methoxyphenyl)-2-[4-(N-hydroxycarbamimidoyl)-phenylamino]-N-[(S)-1-phenylethyl]acetamide.

10

Example 49

By the method of Example 45

49.a

- the product from Example 50.2 gave (RS)-N-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-5-benzyloxy-4-methoxyphenyl]benzamide acetate (1:1.5) as a colourless solid,

49.b

- the product from Example 51.a gave methyl (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-5-benzyloxy-4-methoxyphenyl]carbamate acetate (1:1.3) as a colourless solid,

25 49.c

the product from Example 51.b gave (RS)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-(4-carbamimidoylphenylamino)acetamide acetate (1:1) as a colourless solid,

30

49.d

- the product from Example 51.c gave (RS)-N-benzyl-2-(4-benzyloxy-5-methoxy-2-phenylacetylaminophenyl)-2-(4-carbamimidoylphenylamino)acetamide acetate (1:1) as a slightly brown solid,

35

49.e

the product from Example 52.3 gave (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4,5-dimethoxy-2-phenylacetylaminophenyl)acetamide acetate (1:1) as a
5 colourless solid,

49.f

the product from Example 53.a gave methyl (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-
10 dimethoxyphenyl]carbamate acetate (1:1) as a slightly brown solid,

49.g

the product from Example 53.b gave (RS)-N-[2-
15 [benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenyl]benzamide acetate (1:1) as a colourless solid, ISP-MS: 588.3 [M+H],

49.h

20 the product from Example 54.3 gave (RS)-N-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4-methoxyphenyl]benzamide acetate (1:1) as a colourless lyophilizate, ISP-MS: 508.3 [M+H],

25 49.i

the product from Example 55 gave (RS)-2-(2-benzenesulphonylamino-5-methoxyphenyl)-N-benzyl-2-(4-carbamimidoylphenylamino)acetamide acetate (1:1) as a
30 colourless lyophilizate, ISP-MS: 544.1 [M+H].

Example 50

50.1

0.26 ml of diisopropylethylamine and 0.08 ml of
35 benzoyl chloride were added to a solution of 300 mg of the nitrile obtained according to Example 27 in 10 ml of THF. The

reaction solution was stirred at RT for 3 hours. The THF was subsequently distilled off under reduced pressure. The residue was taken up in CH₂Cl₂ and washed with saturated NaCl solution. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was crystallized from cyclohexane/toluene/acetone. This gave 288 mg (79%) of (RS)-N-{2-[benzylcarbamoyl-(4-cyanophenyl-amino)methyl]-5-benzyloxy-4-methoxyphenyl}benzamide as a slightly brown solid.

10

50.2

By the method of Example 36.3, 280 mg of the material prepared above gave 254 mg (86%) of (RS)-N-(2-{benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl}-5-benzyloxy-4-methoxyphenyl)benzamide as a slightly brown solid.

15

Example 51

20

By the method of Example 50.1, the product from Example 27 and

51.a

25

methyl chloroformate give methyl (RS)-(2-{benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl}-5-benzyloxy-4-methoxyphenyl)carbamate,

51.b

30

acetyl chloride give (E)- and/or (Z)-(RS)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide,

51.c

35

phenylacetyl chloride give (E)- and/or (Z)-(RS)-N-benzyl-2-(4-benzyloxy-5-methoxy-2-phenylacetylaminophenyl)-2-

[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide.

Example 52

5 52.1

By the method of Example 16 and starting from 6-nitroveratraldehyde, 4-aminobenzonitrile and benzylisonitrile, (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(4,5-dimethoxy-2-nitrophenyl)acetamide was obtained in a
10 yield of 10% as yellow crystals.

52.2

By the method of Example 27, the nitro compound prepared in 52.1 gave (RS)-2-(2-amino-4,5-dimethoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide in a yield of 25%.
15 Slightly grey crystals.

52.3

By the method of Example 50, the aniline compound prepared above and phenylacetyl chloride gave (E)- and/or
20 (Z)-(RS)-N-benzyl-2-(4,5-dimethoxy-2-phenylacetylaminophenyl)-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide.

Example 53

25 By the method of Example 50, the aniline compound prepared in 52.2 and:

53.a

methyl chloroformate gave methyl (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenyl]carbamate,
30

53.b

benzoyl chloride gave (E)- and/or (Z)-(RS)-N-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenyl]benzamide.
35

Example 54

54.1

5 By the method of Example 16 and starting from 6-nitroveratraldehyde, 4-aminobenzonitrile and benzylisocyanitrile, (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(5-methoxy-2-nitrophenyl)acetamide is obtained in a yield of 24%. Yellow crystals.

10 54.2

By the method of Example 27, the nitro compound prepared above gives (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(2-amino-5-methoxyphenyl)acetamide in a yield of 79%.
ISP-MS: 387.1 [M+H], 409.2 [M+Na].

15

54.3

By the method of Example 50, the nitrile obtained in Example 54.2 and benzoyl chloride give (E)- and/or (Z)-(RS)-N-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenyl-amino]methyl]-4-methoxyphenyl]benzamide.

20

Example 55

By the method of Example 50, the nitrile obtained in Example 54.2 and phenylsulphonyl chloride gave (E)- and/or (Z)-(RS)-2-(2-benzenesulphonylamino-5-methoxyphenyl)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide.

25

Example 56

30

56.1

By the method of Example 36.1, the material obtained according to Example 27 and methoxyacetic acid gave (RS)-N-benzyl-2-[4-benzyloxy-5-methoxy-2-(2-methoxyacetyl-amino)-phenyl]-2-(4-cyanophenylamino)acetamide in a yield of 66%. Solid.

35

56.2

By the method of Example 36.3, the nitrile prepared in Example 56.1 was reacted in a yield of 81% to give (RS)-N-benzyl-2-[4-benzyloxy-5-methoxy-2-(2-methoxyacetyl-amino)-phenyl]-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide. Slightly brown solid.

56.3

By the method of Example 45, the amidoxime obtained in Example 56.2 was reduced to (RS)-N-benzyl-2-[4-benzyloxy-5-methoxy-2-(2-methoxyacetyl-amino)phenyl]-2-(4-carbamimidoylphenylamino)acetamide hydrochloride (1:2).

15

Example 57

57.1

By the method of Example 36.1, the product from Example 27 and N-Boc-glycine gave tert-butyl (RS)-({2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-5-benzyloxy-4-methoxyphenylcarbamoyl)methyl}carbamate in a yield of 65%.

57.2

The product obtained above was reacted by the method of Example 36.3 to give tert-butyl (RS)-[(2-{benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl}-5-benzyloxy-4-methoxyphenylcarbamoyl)methyl]carbamate in a yield of 65%. Slightly brown solid.

30 57.3

A solution of 170 mg of the amidoxime obtained according to Example 57.2 in 10 ml of EtOH was admixed with a spatula tip of Raney nickel and a few drops of acetic acid. The mixture was then hydrogenated for 2 hours and subsequently filtered off from the catalyst. The filtrate was concentrated. The residue was purified by silica gel

chromatography (EtOAc/acetone/H₂O/HOAc 6:2:1:1). The product fractions were concentrated. The residue was dissolved in CH₂Cl₂, admixed with 5 ml of trifluoroacetic acid and stirred at 0°C for 3 hours. The mixture was then concentrated under
5 reduced pressure. The residue was crystallized from Et₂O. This gave 107 mg (76%) of (RS)-2-[2-(2-aminoacetyl-amino)-4-benzyloxy-5-methoxyphenyl]-N-benzyl-2-(4-carbamimidoyl-phenylamino)acetamide trifluoroacetate (1:2) as a slightly brown solid.

10

Example 58

By the method of Example 45:

15 58.a

the product obtained in Example 59.5 gave (RS)-3-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]benzoic acid acetate (1:1),
ISP-MS: 569.3 [M+H],

20

58.b

the product obtained in Example 60.a gave (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]acetic acid acetate (1:1),

25

58.c

the product obtained in Example 60.b gave (RS)-4-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]benzoic acid acetate (1:1),

30 ISP-MS: 569.3 [M+H],

58.d

the product obtained in Example 60.c gave (RS)-4-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-
35 dimethoxyphenoxy]butyric acid,

58.e

the product obtained in Example 61 gave (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4-methoxyphenoxy]acetic acid, ISP-MS: M+H [463.2],

5

58.f

the product obtained in Example 62 gave (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,6-dimethylphenoxy]acetic acid acetate (1:0.5), ISP-MS: 461.3 [M+H], 483.4 [M+Na].

10

Example 59

59.1

1.18 g of 4-aminobenzonitrile and 1.22 ml of benzylisonitrile were added to a solution of 2.78 mg of 2-benzyloxy-4,5-dimethoxybenzaldehyde in 36 ml of THF and 4 ml of H₂O. The mixture was stirred at RT for 5 min and then admixed with 2.85 g of p-toluenesulphonic acid. The reaction solution was stirred at RT for 24 hours and then concentrated under reduced pressure. The residue was taken up in CH₂Cl₂ and then washed with saturated NaHCO₃ solution and saturated NaCl solution. The organic phase was dried over Na₂SO₄, filtered off and concentrated under reduced pressure. The residue was purified by silica gel chromatography (toluene/acetone 9:1). This gave 2.13 g (42%) of (RS)-N-benzyl-2-(2-benzyloxy-4,5-dimethoxyphenyl)-2-(4-cyanophenylamino)acetamide as a light-yellow solid.

25

59.2

A solution of 1.4 g of the material obtained in 59.1 in 140 ml of EtOH was admixed with 420 mg of Pd/C 10% and hydrogenated for 5 hours, during which a colourless precipitate formed. This was redissolved by addition of 75 ml of dioxane. The catalyst was subsequently removed by filtration. The filtrate was concentrated under reduced pressure. The residue was crystallized from EtOH. This gave

30

35

907 mg (79%) of (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(2-hydroxy-4,5-dimethoxyphenyl)acetamide as colourless crystals.

59.3

5 A solution of 418 mg of the material obtained in 59.2 in 30 ml of acetone was admixed with 415 mg of K₂CO₃ and 252 mg of methyl 3-bromomethylbenzoate. The reaction mixture was heated under reflux for 3 hours and subsequently filtered. The filtrate was concentrated. The residue was
10 taken up in CH₂Cl₂ and washed with H₂O. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexane 2:3). This gave 365 mg (65%) of
15 methyl (RS)-3-[2-[benzylcarbamoyl-(4-cyanophenylamino)-methyl]-4,5-dimethoxyphenoxy-methyl]benzoate as a colourless solid.

59.4

 By the method of Example 36.2, the material obtained
20 in 59.3 gave (RS)-3-[2-[benzylcarbamoyl-(4-cyanophenylamino)-methyl]-4,5-dimethoxyphenoxy-methyl]benzoic acid in quantitative yield. Colourless solid.

59.5

25 By the method of Example 36.3, the material obtained according to 59.4 gave (E)- and/or (Z)-(RS)-3-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenyl-amino]methyl]-4,5-dimethoxyphenoxy-methyl]benzoic acid in a
30 yield of 70%. Colourless solid.

Example 60

 By the methods of Examples 59.3 - 59.5, the material
obtained according to Example 59.2 and

35

60.a

ethyl bromoacetate gave, via the nitriles ethyl (RS)-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]acetate and (RS)-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]acetic acid, (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]acetic acid,

10 60.b

methyl 4-bromomethylbenzoate gave, via the nitriles methyl (RS)-4-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]methyl]benzoate and (RS)-4-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]methyl]benzoic acid, (E)- and/or (Z)-(RS)-4-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]methyl]benzoic acid,

60.c

20 ethyl 4-bromobutyrate gave, via the nitriles ethyl (RS)-4-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]butyrate and (RS)-4-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]butyric acid, (E)- and/or (Z)-(RS)-4-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]butyric acid.

Example 61

30 By the method of Example 60, (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(2-hydroxy-5-methoxyphenyl)acetamide and ethyl bromoacetate gave, via the nitriles ethyl (RS)-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4-methoxyphenoxy]acetate and (RS)-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4-methoxyphenoxy]acetic acid, (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxy-

carbamimidoyl)phenylamino]methyl]-4-methoxyphenoxy]acetic acid.

The starting material was prepared as follows:

5 61.1

A solution of 30 g of 2-hydroxy-5-methoxybenzaldehyde in 200 ml of acetone was admixed with 51.2 ml of allyl bromide and 81.75 g of K_2CO_3 and heated under reflux for 2 hours. The reaction mixture was subsequently filtered. The
10 filtrate was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with H_2O . The organic phases were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was distilled under high vacuum. This gave 24.5 g (65%) of 2-allyloxy-5-
15 methoxybenzaldehyde as a slightly green oil.

61.2

By the method of Example 59.1, the aldehyde obtained above, 4-aminobenzonitrile and benzylisonitrile gave (RS)-2-
20 (2-allyloxy-5-methoxyphenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide in a yield of 35%. ISP-MS: 428.3 [M+H], 450.1 [M+Na].

61.3

25 A solution of 4.6 g of the nitrile obtained above in 140 ml of THF was admixed with 249 mg of tetrakis(triphenylphosphine)palladium(0). The mixture was stirred at RT for 10 min, and 626 mg of $NaBH_4$ were then added a little at a time. The mixture was stirred at RT for 2 hours and
30 subsequently concentrated under reduced pressure. The residue was taken up in EtOAc and washed with H_2O . The organic phase was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 /EtOAc 9:1 and decolorized with activated carbon. The product was
35 subsequently crystallized from Et_2O/CH_2Cl_2 . This gave 3.22 g (77%) of (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(2-hydroxy-5-

methoxyphenyl)acetamide as a slightly brown crystalline solid. ISN-MS: 386.1 [M-H].

Example 62

5

By the method of Example 60, (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(2-hydroxy-3,5-dimethylphenyl)-acetamide and ethyl bromoacetate gave ethyl (RS)-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,6-dimethylphenoxy]acetate, 10 which gave (E)- and/or (Z)-(RS)-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimido)phenylamino]methyl]-4,6-dimethylphenoxy]acetic acid.

The starting material was prepared by the method of Example 16 from 3,5-dimethyl-2-hydroxybenzaldehyde 15 (G. Casiraghi et al., J. Chem. Soc. (1980), 1862), 4-aminobenzonitrile and benzylisonitrile.

Example 63

20 63.1

A solution of 1.04 g of the nitrile obtained in Example 59.2, 0.35 ml of methyl (S)-lactate and 785 mg of triphenylphosphine in 75 ml of THF was admixed with 0.475 ml of diethyl azodicarboxylate and stirred at RT for 4 hours. 25 The THF was subsequently distilled off under reduced pressure. The residue was taken up in EtOAc and washed with saturated NaCl solution. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography 30 (CH₂Cl₂/EtOAc 9:1). This gave 1.145 g (88%) of a 1:1 mixture of ethyl (R)-2-[2-[(R)- and -(S)-benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]propionate as a yellow foam. ISP-MS: 518.2 [M+H], 540.3 [M+Na].

35 63.2

By the method of Example 36.2, the ester prepared

above gave, after chromatographic separation over silica gel, the two diastereomers (R)-2-[2-[(R)-benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid and (R)-2-[2-[(S)-benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid in a yield of 49%, both as light-yellow resins. ISP-MS: 490.3 [M+H], 512.3 [M+Na].

63.3

- By the method of Example 36.3, the first of the diastereomers obtained above gave
- a) (E)- and/or (Z)-(R)-2-[2-[(R)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]propionic acid and the second of the diastereomers obtained above gave
- a) (E)- and/or (Z)-(R)-2-[2-[(S)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl]-4,5-dimethoxyphenoxy]propionic acid, both as colourless powders. ISP-MS: 523.2 [M+H], 545.2 [M+Na], 567.2 [M+2Na].

63.4

- By the method of Example 33, the respective diastereomeric amidoximes from Example 63.3 gave the amidines
- a) (R)-2-[2-[(R)-benzylcarbamoyl-(4-carbamimidoyl-phenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid acetate (1:1) and
- c) (R)-2-[2-[(S)-benzylcarbamoyl-(4-carbamimidoyl-phenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid acetate (1:1), ISP-MS: 507.4 [M+H].

Example 64

64.1

- By the method of Examples 63.1 - 63.3, the material obtained in Example 59.2 and ethyl (R)-lactate gave, via the

mixture of epimers of the corresponding nitrile ester, the two diastereomeric nitrile acids, which gave the respective epimers

- a) (E)- and/or (Z)-(S)-2-[2-[(R)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid and
- b) (E)- and/or (Z)-(S)-2-[2-[(S)-benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid, both as colourless lyophilizates.

10

64.2

By the method of Example 33, the amidoximes obtained above gave the respective amidines

- a) (S)-2-[2-[(R)-benzylcarbamoyl-(4-carbamimidoyl-phenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid and
- b) (S)-2-[2-[(S)-benzylcarbamoyl-(4-carbamimidoyl-phenylamino)methyl]-4,5-dimethoxyphenoxy]propionic acid, both as colourless lyophilizates. ISP-MS: 507.4 [M+H], 529.2 [M+Na].

20

Example 65

By the method of Example 45,

25 65.a

the product from Example 66.4 gave (RS)-3-{4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy}benzoic acid in a yield of 44%. Colourless solid, ISP-MS: 525.2 [M+H],

30

65.b

the product from Example 67.a gave (RS)-2-{4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy}benzoic acid, ISP-MS: 525.2 [M+H],

35

65.c

the product from Example 67.b gave (RS)-4-{4-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-2-methoxyphenoxy}benzoic acid. Slightly brown solid.
ISP-MS: 525.2 [M+H].

5

Example 66

66.1

A solution of 3 g of vanillin, 11 g of ethyl
10 3-iodobenzoate and 2.9 g of Cu₂O in 5 ml of dimethylacetamide
was heated at 165°C for 24 hours. The mixture was allowed to
cool to RT and filtered. The filtrate was concentrated under
high vacuum. The residue was purified by silica gel
chromatography (EtOAc/hexane 3:7). This gave 1.93 g (32%) of
15 ethyl 3-(4-formyl-2-methoxyphenoxy)benzoate as a slightly
brown oil.

66.2

By the method of Example 59.1, the aldehyde obtained
20 above gave ethyl (RS)-3-{4-[benzylcarbamoyl-(4-
cyanophenylamino)methyl]-2-methoxyphenoxy}benzoate in a yield
of 58%. Colourless solid.

66.3

25 By the method of Example 36.2, the nitrile ester
obtained above gave (RS)-3-{4-[benzylcarbamoyl-(4-
cyanophenylamino)methyl]-2-methoxyphenoxy}benzoic acid in a
yield of 51%. Colourless solid. ISN-MS: 506.2 [M-H].

30 66.4

By the method of Example 36.3, the nitrile acid
obtained above gave (RS)-3-(4-{benzylcarbamoyl-[4-(N-
hydroxycarbamimidoyl)phenylamino]methyl}-2-methoxy-
phenoxy)benzoic acid in a yield of 94%. Colourless solid.
35 ISP-MS: 541.2 [M+H], 563.3 [M+Na].

Example 67

By the method of Example 66

5 67.a

and using methyl 2-iodobenzoate instead of ethyl 3-iodobenzoate, (RS)-2-(4-{benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl}-2-methoxyphenoxy)benzoic acid was obtained via the corresponding intermediates 4-(2-carbomethoxy)phenoxy-3-methoxybenzaldehyde, methyl (RS)-2-[4-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-2-methoxyphenoxy]benzoate and (RS)-2-{4-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-2-methoxyphenoxy}benzoic acid,

15 67.b

and using methyl 4-iodobenzoate instead of ethyl 3-iodobenzoate, (RS)-4-(4-{benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl}-2-methoxyphenoxy)benzoic acid was obtained via the corresponding intermediates methyl 4-(4-formyl-2-methoxyphenoxy)benzoate, methyl (RS)-4-{4-[benzylcarbamoyl-(4-cyano-phenylamino)methyl]-2-methoxyphenoxy}benzoate and (RS)-4-{4-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-2-methoxyphenoxy}benzoic acid.

25

Example 68

By the method of Examples 66.2 - 66.4, methyl 5-formyl-2,3-dimethoxybenzoate (F.Y. Wu, D.L. Brink, J. Agric. Food Chem. (1977), 25, 692) gave, via the intermediate methyl (RS)-5-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-2,3-dimethoxybenzoate,

- a) methyl (RS)-5-{benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenylamino]methyl}-2,3-dimethoxybenzoate and
- b) methyl (RS)-5-[benzylcarbamoyl-(4-carbamimidoyl-phenylamino)methyl]-2,3-dimethoxybenzoate and
- c) (RS)-5-[benzylcarbamoyl-(4-carbamimidoylphenyl-

amino)methyl]-2,3-dimethoxybenzoic acid. Slightly brown solid.

Example 69

5

69.1

By the method of Example 59.1, 6-bromoveratrum-aldehyde, 4-aminobenzonitrile and benzylisonitrile gave (RS)-N-benzyl-2-(2-bromo-4,5-dimethoxyphenyl)-2-(4-cyano-phenylamino)acetamide in a yield of 47%. Colourless solid.

10

69.2

A solution of 2.4 g of the nitrile obtained in Example 69.1 in 10 ml of dimethylacetamide was admixed with 0.41 ml of acrylic acid, 1.51 ml of triethylamine, 22 mg of palladium acetate and 122 mg of tri-o-tolylphosphine and heated at 120°C for 2 hours. The reaction mixture was diluted with water, adjusted to pH 1 using 1N HCl and then extracted with EtOAc. The organic phase was concentrated under reduced pressure. The residue was dissolved in MeOH and filtered. The filtrate was concentrated under reduced pressure. The residue was stirred in Et₂O. The solid was filtered off and dried under high vacuum. This gave 1.71 g (73%) of (E)-(RS)-3-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenyl]acrylic acid as a beige solid.

20

25

69.3

A solution of 236 mg of the nitrile obtained above in 2 ml of EtOH and 3 ml of THF was admixed with 5 ml of 1N HCl and 106 mg of Pd/C 10% and hydrogenated for 2 hours. The reaction mixture was filtered. The filtrate was extracted with EtOAc. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography. This gave 44 mg (18%) of (RS)-3-[2-[benzylcarbamoyl-(4-cyanophenylamino)methyl]-4,5-dimethoxyphenyl]propionic acid as a slightly yellow solid.

30

35

69.4

By the method of Example 36.3, the nitrile obtained in Example 69.3 gave (E)- and/or (Z)-(RS)-3-[2-[benzylcarbamoyl-[4-(N-hydroxycarbamimidoyl)phenyl-amino]methyl]-4,5-dimethoxyphenyl]propionic acid in a yield of 26%. Beige lyophilizate.

69.5

Reduction by the method of Example 45 of the amidoxime obtained above gave (RS)-3-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenyl]-propionic acid in a yield of 63%. White lyophilizate.

15

Example 70

70.1

By the method of Example 16, 3-nitro-benzaldehyde, 4-aminobenzonitrile and benzylisonitrile gave (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(3-nitrophenyl)acetamide in a yield of 11%. Light-yellow crystalline solid.
ISP-MS: 387.2 [M+H], 409.3 [M+Na].

70.2

A solution of 1.4 g of the nitro compound obtained above in 80 ml of THF was admixed with 140 mg of Pd/C 10% and hydrogenated for 6 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂/MeOH 19:1). This gave 1.15 g (89%) of (RS)-2-(3-aminophenyl)-N-benzyl-2-(4-cyanophenylamino)acetamide as a yellow foam. ISP-MS: 357.2 [M+H], 379.3 [M+Na].

70.3

By the method of Example 50.1, the amine obtained above was reacted with acetyl chloride to give colourless

(RS)-2-(3-acetylamino-phenyl)-N-benzyl-2-(4-cyanophenylamino)-acetamide in a yield of 99%. ISP-MS: 399.4 [M+H], 421.3 [M+Na], 437.3 [M+K].

5 70.4

By the method of Example 36.3 and starting from the above nitrile, (E)- and/or (Z)- (RS)-2-(3-acetylamino-phenyl)-N-benzyl-2-[4-(N-hydroxycarbamimidoyl)phenylamino]acetamide was obtained in quantitative yield. Colourless solid.

10

70.5

By the method of Example 45, the amidoxime obtained according to Example 70.4 was reduced to (RS)-2-(3-acetylamino-phenyl)-N-benzyl-2-(4-carbamimidoyl-phenylamino)acetamide acetate (1:1) in a yield of 65%. Colourless powder.

15

Example 71

20

At 5-10°C, dry HCl gas was introduced into a solution of 386 mg of the nitrile from Example 70.1 in 20 ml of MeOH and 10 ml of CHCl₃ for 2 hours. The reaction solution was subsequently concentrated under reduced pressure. The residue was taken up in 30 ml of NH₃-saturated MeOH. The solution was allowed to stand at RT overnight and then heated at 40°C for 4 hours and finally concentrated under reduced pressure. The residue was purified by silica gel chromatography. This gave 160 mg (35%) of (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(3-nitrophenyl)acetamide acetate (1:1) as a yellow solid. ISP-MS: 404.4 [M+H].

25

30

Example 72

35

A solution of 201 mg of 2,6-dimethoxyisonicotinaldehyde (I. Kompis et al., Eur. J. Med. Chem. - Chim. Ther.

(1977), 12, 531) and 575 mg of 4-aminobenzamidine ditoluenesulphonate in 4.8 ml of THF/H₂O 9:1 was admixed with 0.15 ml of benzylisonitrile. The reaction mixture was stirred at RT for 6 hours and subsequently concentrated under reduced pressure. The residue was suspended in diethyl ether. The solid was filtered off and recrystallized from EtOH/water. This gave 2.02 g (28%) of (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(2,6-dimethoxypyridin-4-yl)acetamide as a colourless crystalline solid.

10

Example 73

By the method of Example 72,

15 73.a

4,6-dimethoxypicolinaldehyde (I. Kompis et al., Eur. J. Med. Chem. - Chim. Ther. (1977), 12, 531), 4-amidinobenzamidine ditoluenesulphonate and benzylisonitrile gave (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-(4,6-dimethoxypyridin-2-yl)acetamide in a yield of 41%, colourless crystalline solid,

73.b

4-benzyloxy-3,5-dimethoxybenzaldehyde, 4-amidinobenzamidine ditoluenesulphonate and benzylisonitrile gave (RS)-N-benzyl-2-(4-benzyloxy-3,5-dimethylphenyl)-2-(4-carbamimidoylphenylamino)acetamide in a yield of 23%. Colourless crystalline solid.

30

Example 74

By the method of Example 1,

74.a

35 3-benzyloxy-5-propoxybenzaldehyde, 4-aminobenzamidine dihydrochloride and benzylisonitrile gave (RS)-N-benzyl-2-(3-

benzyloxy-5-propoxyphenyl)-2-(4-carbamimidoylphenylamino)-
acetamide hydrochloride.

74.b

5 3,5-bis(benzyloxy)benzaldehyde, 4-aminobenzamidine dihydrochloride and benzylisonitrile gave (RS)-N-benzyl-2-(3,5-bis-benzyloxyphenyl)-2-(4-carbamimidoylphenylamino)-acetamide hydrochloride.

10 Example 75

75.a

By the method of Example 59.1, 2,6-diethoxypyridine-4-carbaldehyde (I. Kompis et al., Eur. J. Med. Chem. - Chim. Ther. (1977), 12, 531), 4-aminobenzonitrile and benzylisonitrile gave (RS)-N-benzyl-2-(4-cyanophenylamino)-2-(2,6-diethoxypyridin-4-yl)acetamide.

75.b

20 By the method of Example 71, the product from Example
75.a gave (RS)-N-benzyl-2-(4-carbamimidoylphenylamino)-2-
(2,6-diethoxypyridin-4-yl)acetamide hydrochloride.

Example 76

25

76.1

A solution of 5 g of 2-hydroxy-4-nitrobenzonitrile (W. Borsche, Ann. Chem. (1912) 390, 1) in 80.5 ml of isopropanol was admixed with 1 g of Pd/C 10% and hydrogenated for 1.5 hours. The mixture was subsequently filtered off from the catalyst and the filtrate was concentrated. This gave 3.3 g (80%) of 4-amino-2-hydroxybenzonitrile.

76.2

35 By the method of Example 59.1, the nitrile from
Example 76.1, 4-benzyloxy-3-ethoxybenzaldehyde and

benzylisonitrile gave (RS)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-cyano-3-hydroxyphenylamino)-acetamide.

76.3

- 5 By the method of Example 13, the material obtained above gave (RS)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-[3-hydroxy-4-(N-hydroxycarbamimidoyl)phenylamino]acetamide.

76.4

- 10 Reduction of the amidoxime from Example 76.3 by the method of Example 45 gave (RS)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-carbamimidoyl-3-hydroxyphenylamino)acetamide.

15

Example 77

77.1

- A solution of 14.35 g of 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde in 175 ml of MeOH was admixed with 5.9 g of
20 4-aminobenzonitrile and stirred at RT for 1 hour. This gave a suspension which was admixed with 6.1 ml of benzylisonitrile and then cooled to 0°C. 19 ml of boron trifluoride ethyl etherate were subsequently added dropwise over a period of 15 min. The mixture was allowed to warm to RT and stirred for
25 another 1.5 hours, giving a solution. This was concentrated under reduced pressure. The residue was dissolved in 330 ml of MeOH and 3.6 ml of H₂O. The reaction mixture was stirred at RT overnight, and a solid crystallized out. This was filtered off, washed with MeOH/H₂O 8:2 and Et₂O and dried
30 under high vacuum. This gave 16.3 g (61%) of methyl (RS)-(4-benzyloxy-5-methoxy-2-nitrophenyl)-(4-cyanophenylamino)acetate as a slightly yellow crystalline solid.

35 77.2

A solution of 4.47 g of the nitrile obtained above in

100 ml of THF was admixed with 1.79 g of Pt/C 5% and hydrogenated for 1 day. The mixture was subsequently filtered off from the catalyst and concentrated under reduced pressure. The residue was purified by silica gel chromatography (toluene/EtOAc 2:1). This gave 2.24 g (50%) of methyl (RS)-(2-amino-4-benzyloxy-5-methoxyphenyl)-(4-cyanophenylamino)acetate as a slightly orange solid. ISP-MS: 440.3 [M+Na].

10 77.3

A solution of 1.79 g of the material obtained in Example 77.2 in 60 ml of CH₂Cl₂ was admixed with 4 ml of DMF and 2.21 ml of diisopropylethylamine and cooled to 0°C. 1.21 ml of phenylsulphonyl chloride in 10 ml of CH₂Cl₂ were then added dropwise over a period of 20 min. The mixture was then allowed to warm to RT over a period of 3 hours. The reaction solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography (toluene/EtOAc 4:1). This gave 635 mg (21%) of methyl (RS)-[4-benzyloxy-2-(bisphenylsulphonylamino)-5-methoxyphenyl]-(4-cyanophenylamino)acetate as a slightly brown solid. ISP-MS: 698.2 [M+H], 720.2 [M+Na].

77.4

25 By the method of Example 25, 795 mg of the nitrile obtained in Example 77.3 gave (RS)-[4-benzyloxy-2-(bisphenylsulphonylamino)-5-methoxyphenyl]-(4-cyanophenylamino)acetic acid. This was reacted by the method of Example 36.1, but using methyl (S)-phenylglycinate instead of methyl L-alaninate hydrochloride, to give a 1:1 mixture of methyl (S)-[(R)- and -(S)-2-[4-benzyloxy-2-(bisphenylsulphonylamino)-5-methoxyphenyl]-2-(4-cyanophenylamino)acetylaminophenyl] acetate. The latter in turn was dissolved in 20 ml of THF and admixed with 11 ml of 1N LiOH solution. The reaction mixture was heated at 60°C for 6 hours and at 40°C overnight. The THF was subsequently

distilled off under reduced pressure. The aqueous solution that remained was diluted with 2% strength citric acid and extracted with EtOAc. The organic phase was washed with saturated NaCl solution, dried over MgSO₄, filtered off and concentrated under reduced pressure. The residue was dissolved in 25 ml of EtOH and mixed with 3.07 ml of triethylamine and 794 mg of hydroxylamine hydrochloride. The reaction solution was heated under reflux overnight and then concentrated under reduced pressure. The residue was purified by two-fold silica gel chromatography (EtOAc/acetone/H₂O/HOAc 6:2:1:1). This gave 256 mg (29%) of a 1:1 mixture of (S)-[(R)- and -[(S)-2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-[4-[(E)- and/or -[(Z)-N-hydroxycarbamimidoyl]phenylamino]acetylaminophenylacetic acid as a slightly brown lyophilizate. ISP-MS: 710:1 [M+H], 732.2 [M+Na].

77.5

A solution of 190 mg of the amidoxime obtained above in 8 ml of EtOH and 1 ml of HOAc was admixed with a spatula tip of Raney nickel and hydrogenated overnight. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography. This gave the two epimers

a) (S)-[(R)-2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid acetate (1:1) and

b) (S)-[(S)-2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid acetate (1:1), both as colourless lyophilisates. ISP-MS: 694.2 [M+H].

Example 78

78.1

5.9 g of 4-aminobenzonitrile were added to a solution

of 14.3 g of 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde in 350 ml of allyl alcohol. The yellow suspension was stirred at RT for 1.5 hours. 6.1 ml of benzyllisonitrile were then added and the reaction mixture was cooled to 0°C. 19 ml of boron trifluoride etherate were added dropwise. The suspension was allowed to warm to RT. The solid was subsequently filtered off, washed with diethyl ether and suspended in 200 ml of allyl alcohol and 18 ml of water. The reaction mixture was stirred at RT overnight and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (toluene/acetone 9:1). The product was recrystallized from THF/hexane. This gave 7.35 g (45%) of allyl (RS)-(4-benzyloxy-5-methoxy-3-nitrophenyl)-(4-cyanophenylamino)acetate as light-yellow crystals. ISN-MS: 472.1 [M-H].

78.2

2 g of dimedone(5,5-dimethyl-1,3-cyclo-hexanedione) and 1.8 g of tetrakis(triphenyl-phosphine)palladium were added to a solution of 7.1 g of the nitrile obtained according to Example 78.1 in 75 ml of THF. The reaction mixture was stirred at RT for 30 min and subsequently admixed with activated carbon, stirred at RT for another 30 min and then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by two-fold silica gel chromatography (first CH₂Cl₂/MeOH 19:1, then EtOAc). This gave 2.25 g (35%) of (RS)-(4-benzyloxy-5-methoxy-2-nitrophenyl)-(4-cyanophenylamino)acetic acid as yellow solid. ISP-MS: 434.3 [M+H].

78.3

By the method of Example 36.1, using 1.67 g of the nitrile obtained according to Example 78.2 and methyl (S)-phenylglycinate instead of methyl L-alaninate hydrochloride, 1.03 g (46%) of a 1:1 mixture of methyl (S)-[(R)- and -(S)-2-(4-benzyloxy-5-methoxy-2-nitrophenyl)-2-(4-cyanophenylamino)acetylaminophenyl acetate were obtained as

a red-brown solid foam. ISP-MS: 581.1 [M+H], 603.0 [M+Na].

78.4

By the method of Example 27, 636 mg of the
5 nitrocompound from Example 78.3 gave 235 mg (40%) of a 1:1
mixture of methyl (S)-[(R)- and -[(S)-2-(2-amino-4-benzyloxy-
5-methoxyphenyl)-2-(4-cyanophenylamino)-acetylaminophenyl-
acetate as a colourless crystalline solid. ISN-MS: 549.1
[M+H].

10

78.5

By the method of Example 50.1, 100 mg of the above
aminonitrile and phenylacetyl chloride gave 118 mg (98%) of a
1:1 mixture of methyl (S)-[(R)- and -[(S)-2-(4-benzyloxy-
15 5-methoxy-2-phenylacetylaminophenyl)-2-(4-cyanophenyl-
amino)acetylaminophenylacetate as a colourless solid foam.
ISN-MS: 667.2 [M-H].

78.6

20 By the method of Example 36.2, 108 mg of the nitrile
obtained in Example 78.5 gave 104 mg (98%) of a 1:1 mixture
of (S)-[(R)- and -[(S)-2-(4-benzyloxy-5-methoxy-
2-phenylacetylaminophenyl)-2-(4-cyanophenylamino)acetyl-
amino]phenylacetic acid as a solid, slightly yellow foam.
25 ISP-MS: 655.1 [M+H].

78.7

By the method of Example 36.3, 180 mg of the above
30 nitrile gave 133 mg (70%) of a 1:1 mixture of (S)-[(R)- and -
[(S)-2-(4-benzyloxy-5-methoxy-2-phenylacetylaminophenyl)-
2-[4-[(E)- and/or -[(Z)-N-hydroxycarbamimidoyl]phenyl-
amino]acetylaminophenylacetic acid as a colourless powder.
ISP-MS: 688.2 [M+H], 710.1 [M+Na].

35

78.8

The epimer mixture from Example 78.7 gave, by the method of Example 33 and after chromatographic separation of the product over silica gel, the two epimers

- 5 a) (S)-[(R)-2-(2-benzenesulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl-amino]phenylacetic acid acetate (1:1) and
b) (S)-[(S)-2-(2-benzenesulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl-
10 amino]phenylacetic acid acetate (1:1), both as colourless powder. ISP-MS: 672.3 [M+H].

Example 79

- 15 By the methods of Examples 78.5-78.8, but using acetic anhydride instead of phenylacetyl chloride, the product from Example 78.4 gave, after chromatographic separation, the two epimers (S)-[(R)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-cyanophenylamino)-
20 acetylamino]phenylacetic acid and (S)-[(S)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-cyanophenylamino)acetyl-amino]phenylacetic acid. Via the respective amidoximes, these were reacted to give the two epimers
a) (S)-[(R)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-2-
25 (4-carbamimidoylphenylamino)acetylamino]-phenylacetic acid acetate and
b) (S)-[(S)-2-(2-acetylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetylamino]-phenylacetic acid acetate. ISP-MS: 596.2 [M+H].

30

Example 80

- A solution of 0.024 ml of 4-fluorobenzoyl chloride in 1.0 ml of THF and 0.5 ml of DMF was admixed with 0.038 ml of
35 N,N-diisopropylethylamine and stirred at RT for 5 minutes. 100 mg of the product from Example 5.g were then added. The

reaction mixture was stirred at RT overnight. Another 0.024 ml of 4-fluorobenzoyl chloride and 0.1 ml of N,N-diisopropylethylamine were added, and the mixture was stirred at RT for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was taken up in saturated NaHCO₃ solution and extracted with EtOAc. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc 2:1). The product was crystallized from Et₂O. This gave 20 mg (17%) of (RS)-N-[amino-(4-{[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino}phenyl)methylene]-4-fluorobenzamide as a crystalline solid. ISP-MS: 631.2 [M+H].

15 Example 81

By the method of Example 80, the product from Example 5.g and 2-benzyloxymethylbenzoyl chloride gave (RS)-2-{[amino-(4-{[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino}phenyl)methylene]carbamoyl}-benzyl benzoate in a yield of 21%. Yellow crystalline solid. ISP-MS: 747.4 [M+H].

25 Example 82

By the method of Example 80, the product from Example 5.g and p-nitrophenyl 2,2,2-trichloroethyl-carbonate gave 2,2,2-trichloroethyl (RS)-[amino-(4-{[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)-methyl]amino}phenyl)methylene]-carbamate in a yield of 60%. Crystalline solid. ISP-MS: 683.1 [M+H].

Example 83

35 By the method of Example 80, the product from Example 5.g and methyl 4-nitrophenylcarbonate gave methyl

(RS)-[amino-(4-{[benzylcarbamoyl-(4-benzyloxy-3-ethoxyphenyl)methyl]amino}phenyl)methylene]carbamate in a yield of 91% as a solid. ISP-MS: 567.3 [M+H].

- 5 A compound of the formula I, a hydrate, a solvate or a salt thereof can be used as active ingredient for preparing pharmaceutical preparations like those below.

Example A

10

	per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Maize starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

Example B

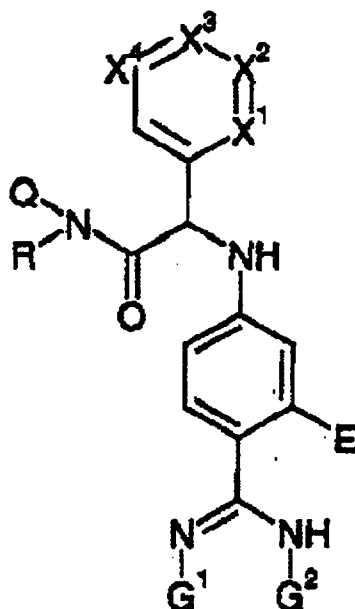
	per capsule
Active ingredient	100.0 mg
Maize starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg



Patent Claims

1. N-(Carbamidophenyl)glycinamide derivatives of the formula

5



in which

- E is hydrogen or OH,
- 10 Q is hydrogen or alkyl,
- R is aryl, cycloalkyl or alkyl which is substituted by R¹, R² and R³,
- R¹ is hydrogen, COOH, COO-alkyl or aryl,
- R² is hydrogen, aryl, cycloalkyl or heteroaryl,
- 15 R³ is hydrogen, aryl or (in a position different from the α-position to the nitrogen atom to which the alkyl group R is attached) OH, alkoxy or optionally protected amino,
- N(Q,R) is COOH- or COO-alkyl-substituted pyrrolidino, piperidino or 1,2,3,4-tetrahydroisoquinolin-3-yl,
- 20 three of the radicals X¹ to X⁴ independently of one another are a group C(R^a), C(R^b) or C(R^c) and the fourth radical is a group C(R^d) or N,
- R^a to R^d independently of one another are H, OH, NO₂, dialkylamino, halogen, alkyl, alkoxy, aryloxy,



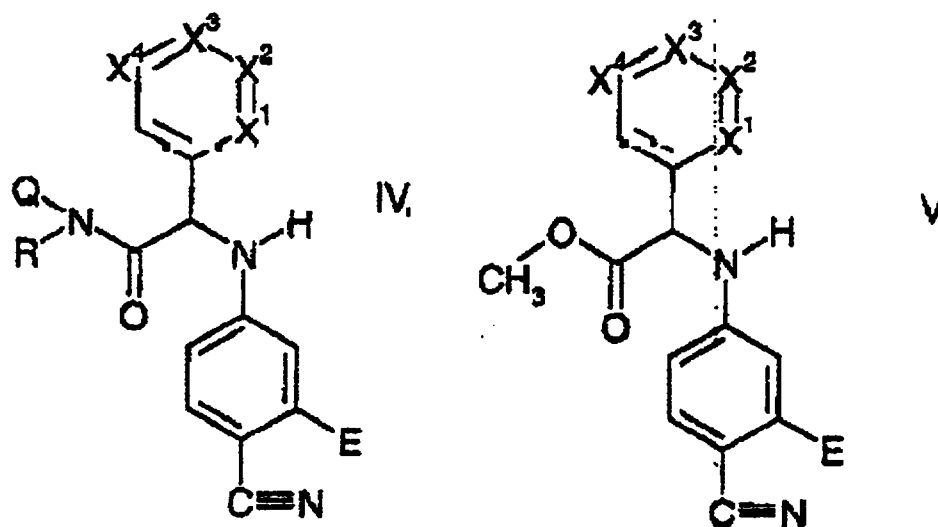
- aralkyloxy, heteroarylalkyloxy, heterocyclylalkyloxy,
COOH, COO-alkyl, NH-SO₂-alkyl, NHSO₂-aryl, NHCO-alkyl,
NHCO-aryl, NHCOO-alkyl, NHCO-alkyl-NH₂, NHCO-alkyl-NH-G,
aralkyl-CONH, alkyl-O-alkyl-CONH, aryl-O-alkyl-CONH,
5 alkyl-COOH, alkyl-COO-alkyl,
O-alkyl-COOH or O-alkyl-COO-alkyl, or
two adjacent groups R^a to R^d together are alkylenedioxy,
where not more than three of the radicals R^a to R^d shall have
the same meaning and X¹ shall not be CCOOH or CCOO-alkyl,
10 G is an amino protective group and
one of the radicals G¹ and G² is hydrogen and the other
radical is hydrogen, alkyl, OH, alkoxy, aroyl, alkanoyl-
OCH₂, aroyl-OCH₂ or a group COO-R^g or OCO-R^g, R^g is
optionally halogen-, OH-, alkoxy-, COOH- or COO-alkyl-
15 substituted alkyl,
and hydrates or solvates and physiologically acceptable salts
thereof.
2. Compounds according to Claim 1, in which E, G² and Q
are hydrogen,
20 R is alkyl, aryl, aralkyl, benzhydryl, cycloalkylalkyl or
heteroarylalkyl,
G¹ is hydrogen, OH or COO-alkyl,
X¹ to X⁴ are a group C(R^a) to C(R^d) and
R^a to R^d independently of one another are H, OH, NO₂,
25 dialkylamino, halogen, alkyl, alkoxy, aryloxy, aralkyloxy,
heteroarylalkyloxy, heterocyclylalkyloxy, COO-alkyl, NHSO₂-
alkyl or NHSO₂-aryl,
where not more than three of the radicals R^a to R^d shall have
the same meaning and X¹ shall not be COO-alkyl.
30 3. Compounds according to Claim 1 or 2, in which E, G¹,
G² and Q are hydrogen.
4. Compounds according to Claim 1 or 3, in which R is
alkyl, in particular methyl or ethyl, which is substituted by
R¹, R² and R³, in particular in which R¹ is aryl, specifically
35 phenyl, or COOH, R² is hydrogen or aryl, specifically phenyl,
and R³ is hydrogen.



5. Compounds according to Claim 1, 3 or 4, in which X^1 to X^4 are a group $C(R^a)$ to $C(R^d)$, in particular a group in which R^a is H, aralkyloxy, specifically carboxybenzyloxy; $NHSO_2$ -aryl, specifically phenylsulphonylamino; aralkyl-CONH, specifically phenylacetyl amino, or O-alkyl-COOH, specifically carboxymethoxy, R^b is H or alkoxy, specifically methoxy or ethoxy, R^c is H, alkoxy, specifically methoxy; or aralkyloxy, specifically benzyloxy, and R^d is H or alkoxy, specifically methoxy.
- 10 6. Compounds according to any of Claims 1 to 5, i.e.:
(R,S)-N-benzyl-2-(4-benzyloxy-3-ethoxyphenyl)-2-(4-carbamimidoylphenylammetamide,
2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-N-benzyl-2-(4-carbamimidoylphenylamino)acetamide.
- 15 7. Compounds according to any of Claims 1 and 3-5, i.e.:
(RS)-[2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl amino]diphenylacetic acid,
(RS)- and (SR)-3-[(RS)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl amino]-3-phenylpropionic acid,
20 (S)-[(R)-2-(4-benzyloxy-3-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl amino]phenylacetic acid,
(S)-[(S)-2-(4-carbamimidoylphenylamino)-2-(3,5-dimethoxyphenyl)acetyl amino]phenylacetic acid,
(RS)-3-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]benzoic acid,
25 (RS)-[2-[benzylcarbamoyl-(4-carbamimidoylphenylamino)methyl]-4,5-dimethoxyphenoxy]acetic acid,
(S)-[(R)-2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl amino]-
30 phenylacetic acid,
(S)-[(S)-2-(2-phenylsulphonylamino-4-benzyloxy-5-methoxyphenyl)-2-(4-carbamimidoylphenylamino)acetyl amino]-phenylacetic acid,
(S)-[(R)-2-(4-benzyloxy-5-methoxy-2-phenylacetyl aminophenyl)-2-(4-carbamimidoylphenylamino)acetyl amino]phenylacetic acid,
35 (S)-[(S)-2-(4-benzyloxy-5-methoxy-2-phenylacetyl aminophenyl)-

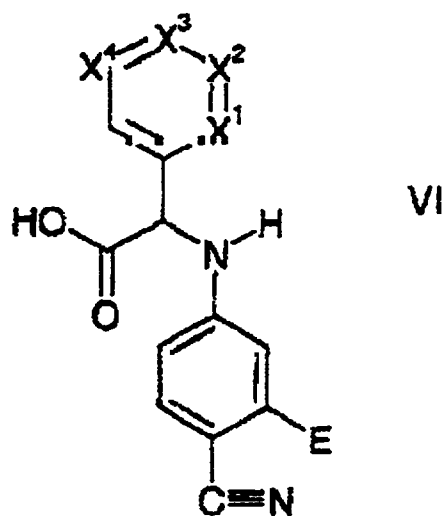
2-(4-carbamimidoylphenylamino)acetylaminophenylacetic acid.

8. Compounds of the formula



5

or

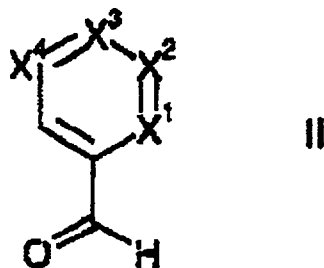


10 in which E, Q, R and X¹ to X⁴ are each as defined in Claim 1.

9. Pharmaceutical preparations comprising a compound according to any of Claims 1-7 as active ingredient.

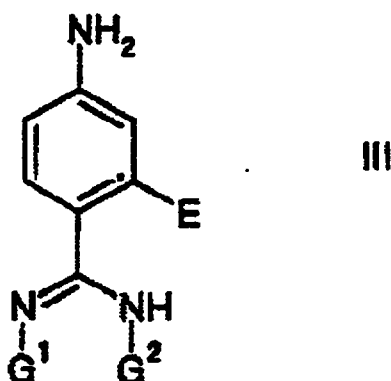
10. Process for preparing the compounds of the formula I according to Claim 1, characterized in that

15 a) an aldehyde of the formula



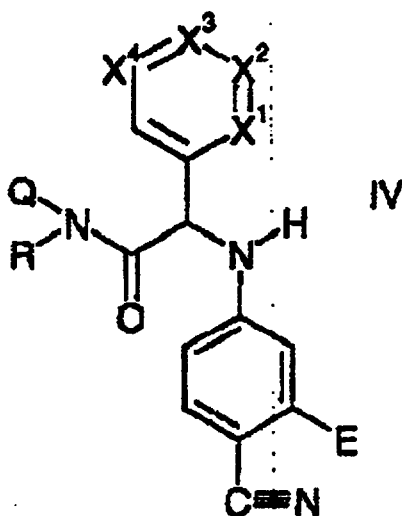
is reacted with an isonitrile of the formula R^1NC and a 4-aminobenzamidine of the formula

5



or

b) the cyano group CN which is contained in an appropriate
10 nitrile of the formula



is converted into an amidino group $C(N-G^1)NH-G^2$,



c) a reactive group contained in a compound I is, if desired, functionally derivatized, and

d) a compound of the formula I is, if desired, converted into a physiologically acceptable salt, or a salt of a

5 compound I is converted into the free acid or base.

11. Compounds according to any of Claims 1-7 for use as medicaments, in particular as inhibitors of the formation of the coagulation factors Xa, IXa and thrombin induced by the factor VIIa and by the tissue factor, specifically as

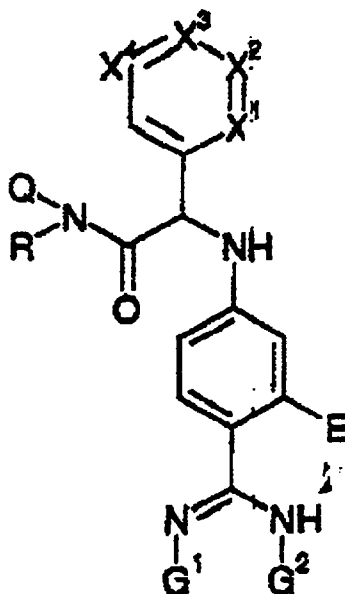
10 medicaments for the treatment and/or prevention of thromboses, apoplexy, cardiac infarction, inflammation and arteriosclerosis, or as antitumour agents.

12. Use of a compound according to any of Claims 1-5 for preparing medicaments for the treatment and/or prevention of
15 thromboses, apoplexy, cardiac infarction, inflammation and arteriosclerosis or for preparing anti-tumour agents.

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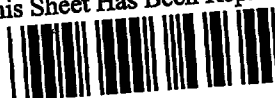
Abstract

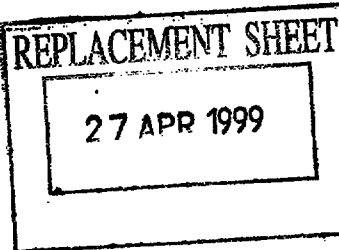
5 The novel N-(4-carbamimidophenylamino)phenyl-
glycineamide derivatives of the formula



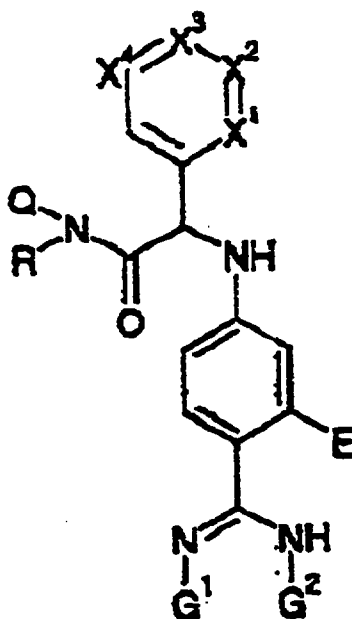
10 in which E, G¹, G², Q, R and X¹ to X⁴ are each as defined in
the description, and hydrates or solvates and physiologically
acceptable salts thereof can be used as inhibitors of the
formation of the coagulation factors Xa, IXa and thrombin
induced by the factor VIIa and by the tissue factor,
15 specifically as medicaments for the treatment and/or
prevention of thromboses, apoplexy, cardiac infarction,
inflammation and arteriosclerosis or as antitumour agents.

This Sheet Has Been Replaced



1N-(4-Carbamimido-Phenyl)-Phenylglycinamid Derivatives

The invention relates to novel N-(4-carb-
5 amimidophenyl)glycineamide derivatives, in particular to
those of the formula



10 in which

E is hydrogen or OH,

Q is hydrogen or alkyl,

R is aryl, cycloalkyl or alkyl which is substituted by R¹,
R² and R³,

15 R¹ is hydrogen, COOH, COO-alkyl or aryl,

R² is hydrogen, aryl, cycloalkyl or heteroaryl,

R³ is hydrogen, aryl or (in a position different from the
α-position to the nitrogen atom to which the alkyl group
R is attached) OH, alkoxy or optionally protected amino,

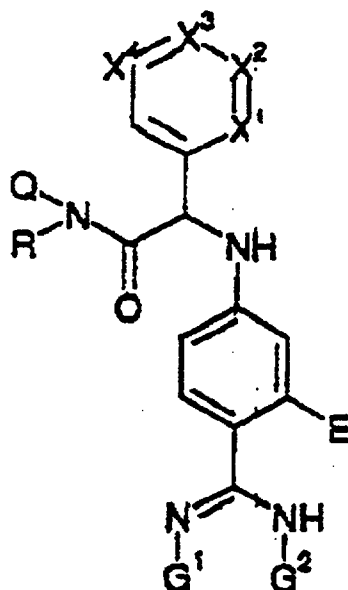
20 N(Q,R) is COOH- or COO-alkyl-substituted pyrrolidino,
piperidino or 1,2,3,4-tetrahydroisoquinolin-3-yl,

three of the radicals X¹ to X⁴ independently of one another

N-(4-Carbamimido-Phenyl)-Phenylglycinamid Derivatives

Abstract

5 The novel N-(4-carbamimidophenylamino)phenyl-glycineamide derivatives of the formula



10 in which E, G¹, G², Q, R and X¹ to X⁴ are each as defined in
the description, and hydrates or solvates and physiologically
acceptable salts thereof can be used as inhibitors of the
formation of the coagulation factors Xa, IXa and thrombin
induced by the factor VIIa and by the tissue factor;
15 specifically as medicaments for the treatment and/or
prevention of thromboses, apoplexy, cardiac infarction,
inflammation and arteriosclerosis or as antitumour agents.