Description

Substituted benzimidazoles

The invention relates to novel substituted benzimidazoles, a process for their preparation and use thereof as pharmaceuticals.

The application WO 94/12478 describes, inter alia, benzimidazole derivatives which inhibit blood platelet aggregation.

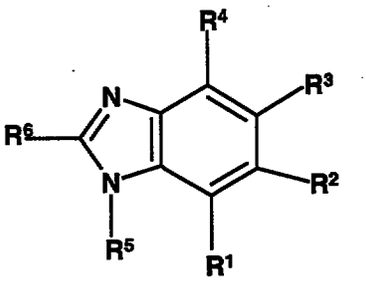
NFκB is a heterodimeric transcription factor which can activate a large number of genes which code, inter alia, for proinflammatory cytokines such as IL-1, IL-2, TNFα or IL-6. NFκB is present in the cytosol of cells, complexed with its naturally occurring inhibitor IκB. The stimulation of cells, for example by cytokines, leads to the phosphorylation and subsequent proteolytic degradation of IκB. This proteolytic degradation leads to the activation of NFκB, which subsequently migrates into the nucleus of the cell and there activates a large number of proinflammatory genes.

In disorders such as rheumatoid arthritis (in the case of inflammation), osteoarthritis, asthma, cardiac infarct, Alzheimer's disease or atherosclerosis, NFκB is activated beyond the normal extent. The inhibition of NFκB is also of benefit in cancer therapy, since it is employed there for the reinforcement of the cytostatic therapy. It was possible to show that pharmaceuticals such as glucocorticoids, salicylates or gold salts, which are employed in rheumatic therapy, intervene in an inhibitory manner at various points in the NFκB-activating signal chain or interfere directly with the transcription of the genes.

The first step in the signal cascade mentioned is the degradation of IκB. This phosphorylation is regulated by the specific IκB kinase. To date, no inhibitors are known which specifically inhibit IκB kinase.

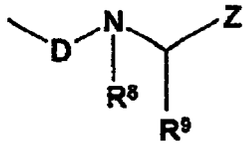
In the attempt to obtain active compounds for the treatment of rheumatoid arthritis (in the case of inflammation), osteoarthritis, asthma, cardiac infarct, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies) or atherosclerosis, it has now been found that the benzimidazoles according to the invention are strong and very specific inhibitors of IκB kinase.

The invention therefore relates to the compounds of the formula I



(I)

and/or a stereoisomeric form of the compounds of the formula I and/or a physiologically tolerable salt of the compounds of the formula I, where one of the substituents R^1, R^2, R^3 and R^4 is a radical of the formula II



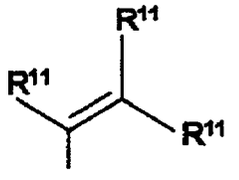
(II)

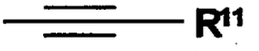
in which D is -C(O)-, -S(O)- or -$S(O)_2$-,

R^8 is hydrogen or (C_1-C_4)-alkyl,

R^9 is

1. a characteristic radical of an amino acid,
2. aryl, in which aryl is unsubstituted or substituted,
3. heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
4. a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
5. (C_1-C_6)-alkyl, in which alkyl is straight-chain or branched and is unsubstituted or mono-, di- or trisubstituted independently of one another by
   - 5.1 aryl, in which aryl is unsubstituted or substituted,
   - 5.2 heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
   - 5.3 a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
   - 5.4 -O-R^{11},

5.5 =O,
5.6 halogen,
5.7 -CN,
5.8 $-CF_3$,
5.9 $-S(O)_x-R^{11}$, in which x is the integer zero, 1 or 2,
5.10 $-C(O)-O-R^{11}$,
5.11 $-C(O)-N(R^{11})_2$,
5.12 $-N(R^{11})_2$,
5.13 (C_3-C_6)-cycloalkyl,
5.14 a radical of the formula 

or
5.15 a radical of the formula 

in which

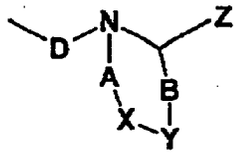
R^{11} is
a) a hydrogen atom,
b) (C_1-C_6)-alkyl, in which alkyl is unsubstituted or mono-, di- or trisubstituted
1. aryl, in which aryl is unsubstituted or substituted,
2. heteroaryl having 5 to 14 ring members,
3. a heterocycle having 5 to 12 ring members,
4. halogen,
5. $-N-(C_1-C_6)_n$-alkyl, in which n is the integer zero, 1 or 2 and alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or by –COOH,
6. $-O-(C_1-C_6)$-alkyl or
7. -COOH,
c) aryl, in which aryl is unsubstituted or substituted,
d) heteroaryl having 5 to 14 ring members or
e) a heterocycle having 5 to 12 ring members and

in the case of $(R^{11})_2$, R^{11} independently of one another has the meaning of a) to e)

Z is
1. aryl, in which aryl is unsubstituted or substituted,
2. heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
3. a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
4. $-(C_1-C_6)$-alkyl, in which alkyl is substituted or unsubstituted or
5. $-C(O)-R^{10}$, in which

R^{10} is
1. $-O-R^{11}$ or
2. $-N(R^{11})_2$, or

R^8 and R^9 form, together with the nitrogen atom and carbon atom to which they are each bonded, a heterocyclic ring of the formula IIa



(IIa)

in which D, Z and R^{10} are as defined in formula II,

A is a nitrogen atom or the radical $-CH_2-$,

B is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

X is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

Y is absent or is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$, or

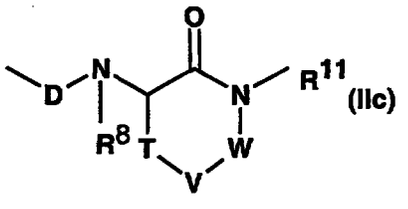
X and Y together form a phenyl, 1,2-diazine, 1,3-diazine or a 1,4-diazine radical,

where the ring system formed by N, A, X, Y, B and the carbon atom contains not more than one oxygen atom, X is not an oxygen atom, sulfur atom or nitrogen atom if A is a nitrogen atom, contains not more than one sulfur atom, contains 1, 2, 3 or 4 nitrogen atoms and where an oxygen atom and sulfur atom do not occur at the same time,

where the ring system formed by N, A, X, Y, B and the carbon atom is unsubstituted or mono-, di- or trisubstituted independently of one another by (C_1-C_8)-alkyl, in which alkyl is unsubstituted or mono- or disubstituted by

1.1. -OH
1.2. (C_1-C_8)-alkoxy,
1.3. halogen,
1.4. $-NO_2$,
1.5. $-NH_2$,
1.6. $-CF_3$,
1.6. -OH,
1.7. methylenedioxy,
1.8. $-C(O)-CH_3$,
1.9. -CH(O),
1.10. -CN,
1.11. -COOH,
1.12. $-C(O)-NH_2$,
1.13. (C_1-C_4)-alkoxycarbonyl,
1.14. phenyl,
1.15. phenoxy,
1.16. benzyl,
1.17. benzyloxy or
1.18. tetrazolyl, or

R^9 and Z together with the carbon atoms to which they each are bonded form a heterocyclic ring of the formula IIc



in which D, R^8 and R^{11} are as defined in formula II,

T is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

W is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

V is absent or is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$, or

T and V or V and W together form a phenyl, 1,2-diazine, 1,3-diazine or a 1,4-diazine radical,

where the ring system formed by N, T, V, W and two carbon atoms contains not more than one oxygen atom, not more than one sulfur atom and 1, 2, 3 or 4 nitrogen atoms, where an oxygen atom and sulfur atom do not occur at the same time, and where the ring system formed by N, T, V, W and two carbon atoms is unsubstituted or mono-, di- or trisubstituted independently of one another by the substituents defined above under 1.1. to 1.18., and

the other substituents R^1, R^2, R^3 and R^4 in each case independently of one another are

1. a hydrogen atom,
2. halogen,
3. (C_1-C_4)-alkyl
4. heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
5. a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
6. (C_1-C_6)-alkyl,
7. -CN,
8. $-O-(C_0-C_4)$-alkyl-aryl,
9. $-O-(C_1-C_4)$-alkyl,
10. $-OR^{11}$,
11. $-N(R^{11})_2$,
12. $-S(O)_x-R^{11}$, in which x is the interger zero, 1 or 2,
13. NO_2 or
14. $-CF_3$,

R^5 is

1. a hydrogen atom,
2. -OH or
3. =O, and

R^6 is

1. aryl, in which aryl is unsubstituted or substituted,
2. phenyl, mono- or disubstituted by
   - 2.1 -CN,
   - 2.2 $-NO_2$,
   - 2.3 $-O-(C_1-C_4)$-alkyl,
   - 2.4 $-N(R^{11})_2$,

2.5 $-NH-C(O)-R^{11}$,

2.6 $-S(O)_x-R^{11}$, in which x is the interger zero, 1 or 2,

2.7 $-C(O)-R^{11}$ or

2.8 $-(C_1-C_4)$-alkyl-NH_2,

4. a heterocycle having 5 to 12 ring members, unsubstituted or mono-, di- or trisubstituted.

A preferred compound of the formula I is one where
one of the substituents R^1, R^2, R^3 and R^4 is a radical of the formula II in which

R^8 is a hydrogen atom,

R^9 is

1. a characteristic radical of an amino acid or
2. (C_1-C_6)-alkyl, in which alkyl is linear or branched and is unsubstituted or mono- or disubstituted by a radical from the group consisting of
pyrrole, pyrrole mono- or disubstituted by $-(C_1-C_4)$-alkyl, pyrazole, phenyl, imidazole, triazole, thiophene, thiazole, oxazole, isoxazole, pyridine, pyrimidine, indole, benzothiophene, benzimidazole, benzoxazole, benzothiazole, azetidine, pyrroline, pyrrolidine, piperidine, isothiazole, diazepine, thiomorpholine, -CN, morpholine, azepine, pyrazine, 1,3,4-oxadiazole, $-N(R^{13})$-phenyl, in which R^{13} is as defined below; (C_3-C_6)-cycloalkyl, $-OR^{11}$, $-NH(R^{11})$, in which R^{11} is in each case as defined above, $-S(O)_x-R^{12}$, in which x is zero, 1 or 2 and R^{12} is naphthyl, pyrimidinyl, morpholinyl or phenyl, which are unsubstituted or mono- or disubstituted by –OH, (C_1-C_4)-alkyl, $-CF_3$, halogen, $-O-(C_1-C_4)$-alkyl, -COOH, $-C(O)-O-(C_1-C_4)$-alkyl, $-NH_2$ or $-NH-C(O)-(C_1-C_4)$-alkyl or $C(O)-R^{12}$, in which R^{12} is as defined above,

Z is $-C(O)-R^{10}$, tetrazole, (C_1-C_6)-alkyl, in which alkyl is linear or branched and is unsubstituted or mono- or disubstituted by phenyl or –OH, or 1,3,4-oxadiazole, in which 1,3,4-oxadiazole is unsubstituted or monosubstituted by
$-NH_2$, $-NH(C_1-C_4)$-alkyl, $-N-[(C_1-C_4)\text{-alkyl}]_2$, $-NH-C(O)-(C_1-C_4)$-alkyl, $-NH-C(O)-NH-(C_1-C_4)$-alkyl, $-NH-C(O)-NH-(C_3-C_7)$-cycloalkyl, -NH-C(O)-NH-aryl, -NH-C(O)-NH-

phenyl, -NH-SO_2-aryl, -NH-SO_2-(C_1-C_4)-alkyl, -OH or -(C_1-C_4)-alkyl, in which

R^{10} is -O-R^{11}, phenyl, pyrimidine, -OH, morpholinyl, -N(R^{11})$_2$ or -NH_2,

R^{11} is
1. -(C_1-C_4)-alkyl,
2. R^{13} or
3. -N(R^{13})$_2$, in which
   R^{13} independently of one another is
   a) a hydrogen atom,
   b) -(C_1-C_6)-alkyl,
   c) -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl,
   d) -(C_1-C_6)-alkyl-N(R^{13})$_2$,
   e) halogen or
   f) -(C_0-C_4)-alkyl, mono- or disubstituted by aryl, imidazolyl, morpholinyl or phenyl, or

R^8 and R^9, together with the nitrogen atom and carbon atom to which they are each bonded, form a ring of the formula IIa from the group consisting of pyrrole, pyrroline, pyrrolidine, pyridine, piperidine, piperylene, pyridazine, pyrimidine, pyrazine, piperazine, pyrazole, imidazole, pyrazoline, imidazoline, pyrazolidine, imidazolidine, oxazole, isoxazole, 2-isoxazolidine, isoxazolidine, morpholine, isothiazole, thiazole, tetrazole, 1,2,3,5-oxathiadiazole-2-oxides, oxadiazolones, isoxazolones, triazolones, oxadiazolidinediones, triazoles which are substituted by F, CN, CF_3 or COO-(C_1-C_4)-alkyl, 3-hydroxypyrro-2,4-diones, 5-oxo-1,2,4-thiadiazoles, 1,3,4-oxadiazole, isothiazolidine, thiomorpholine, indazole, thiadiazole, benzimidazole, quinoline, triazole, phthalazine, quinazoline, quinoxaline, purine, pteridine, indole, tetrahydroquinoline, tetrahydroisoquinoline and isoquinoline, or

R^9 and Z, together with the carbon atoms to which they are each bonded, form a ring of the formula IIc from the group consisting of pyrrole, pyrroline, pyrrolidine, pyridine, piperidine, piperylene, pyridazine, pyrimidine, pyrazine, piperazine, pyrazole, imidazole, pyrazoline, imidazoline, pyrazolidine, imidazolidine, oxazole, isoxazole, 2-isoxazolidine, isoxazolidine, morpholine, isothiazole, thiazole, isothiazolidine, thiomorpholine, indazole, thiadiazole, benzimidazole, quinoline, triazole, phthalazine, quinazoline, quinoxaline, purine, pteridine, indole, tetrahydroquinoline, tetrahydroisoquinoline, isoquinoline, tetrazole, 1,2,3,5-oxathiadiazole-2-oxides, oxadiazolones, isoxazolones, triazolones,

oxadiazolidinediones, triazoles which are substituted by F, CN, CF_3 or COO-(C_1-C_4)-alkyl, 3-hydroxypyrrole-2,4-diones, 1,3,4-oxadiazole and 5-oxo-1,2,4-thiadiazoles and

the other substituents R^1, R^2, R^3 and R^4 in each case independently of one another are

1. a hydrogen atom,
2. halogen,
3. (C_1-C_4)-alkyl,
4. -CN,
5. -NO_2,
6. -O-(C_0-C_4)-alkyl-aryl,
7. -O-(C_1-C_4)-alkyl,
8. -N-(C_0-C_4)-alkyl-aryl,
9. -N-(C_1-C_4)-alkyl or
10. -CF_3,

R^5 is
1. a hydrogen atom,
2. -OH or
3. =O, and

R^6 is
1. phenyl, mono- or disubstituted by
   - 1.1 -CN,
   - 1.2 -NO_2,
   - 1.3 -O-(C_1-C_4)-alkyl,
   - 1.4 -NH_2 or
   - 1.5 -(C_1-C_4)-alkyl-NH_2 or
2. heteroaryl having 5 to 14 ring members, unsubstituted or mono- to trisubstituted by -N-R^{14}, in which R^{14} is -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl or phenyl, halogen, -OH or -(C_1-C_4)-alkyl, or
3. a heterocycle having 5 to 12 ring members, unsubstituted or mono- to trisubstituted by -N-R^{14}, in which R^{14} is -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl or phenyl, halogen, -OH or -(C_1-C_4)-alkyl.

The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine. The term "(C_1-C_6)-alkyl" is understood as meaning hydrocarbon radicals whose carbon chain is linear or branched and contains 1 to 6 carbon atoms. The term "C_0-alkyl" is understood as meaning a covalent

bond. Cyclic alkyl radicals are, for example, 3- to 6-membered monocyclic systems such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The expression "R^8 and R^9, together with the nitrogen atom and carbon atom to which they are each bonded, form a heterocyclic ring of the formula IIa" is understood as meaning radicals which are derived from pyrrole, pyrroline, pyrrolidine, imidazole, pyrazole, oxazole, tetrazole, 1,2,3,5-oxathiadiazole-2-oxides, triazolones, oxadiazolones, isoxazolones, 1,3,4-oxadiazole, oxadiazolidinediones, triazoles which are substituted by F, CN, CF_3 or COO-(C_1-C_4)-alkyl, 3-hydroxypyrro-2,4-diones, 5-oxo-1,2,4-thiadiazoles, isoxazole, indole, isoxazoline, isoxazolidine, morpholine, thiazole, isothiazole, isothiazoline, purine, isothiazolidine, thiomorpholine, pyridine, piperidine, pyrazine, piperazine, pyrimidine, pyridazine, isoindole, indazole, benzimidazole, phthalazine, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, pteridine, imidazolidine, carboline and benzo-fused derivatives of these heterocycles.

The term aryl is understood as meaning aromatic hydrocarbon radicals having 6 to 14 carbon atoms in the ring. (C_6-C_{14})-Aryl radicals are, for example, phenyl, naphthyl, for example 1-naphthyl, 2-naphthyl, biphenylyl, for example 2-biphenylyl, 3-biphenylyl and 4-biphenylyl, anthryl or fluorenyl. Biphenylyl radicals, naphthyl radicals and, in particular, phenyl radicals are preferred aryl radicals. Aryl radicals, in particular phenyl radicals, can be monosubstituted or polysubstituted, preferably monosubstituted, disubstituted or trisubstituted, by identical or different radicals, preferably by radicals from the group consisting of (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkoxy, in particular (C_1-C_4)-alkoxy, halogen, nitro, amino, trifluoromethyl, hydroxyl, hydroxy-(C_1-C_4)-alkyl such as hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkoxycarbonyl, phenyl, phenoxy, benzyl, benzyloxy, tetrazolyl. The same applies, for example, to radicals such as arylalkyl or arylcarbonyl. Arylalkyl radicals are, in particular, benzyl and also 1- and 2-naphthylmethyl, 2-, 3- and 4-biphenylylmethyl and 9-fluorenylmethyl. Substituted arylalkyl radicals are, for example, benzyl radicals and naphthylmethyl radicals substituted in the aryl moiety by one or more (C_1-C_8)-alkyl radicals, in particular (C_1-C_4)-alkyl radicals, for example 2-, 3- and 4-methylbenzyl, 4-isobutylbenzyl, 4-tert-butylbenzyl, 4-octylbenzyl, 3,5-dimethylbenzyl, pentamethylbenzyl, 2-, 3-, 4-, 5-, 6-, 7- and 8-methyl-1-naphthylmethyl, 1-, 3-, 4-, 5-, 6-, 7- and 8-

methyl-2-naphthylmethyl, by one or more (C_1-C_8)-alkoxy radicals, in particular (C_1-C_4)-alkoxy radicals, benzyl radicals and naphthylmethyl radicals substituted in the aryl moiety, for example 4-methoxybenzyl, 4-neopentyloxybenzyl, 3,5-dimethoxybenzyl, 3,4-methylenedioxybenzyl, 2,3,4-trimethoxybenzyl, nitrobenzyl radicals, for example 2-, 3- and 4-nitrobenzyl, halobenzyl radicals, for example 2-, 3- and 4-chloro- and 2-, 3- and 4-fluorobenzyl, 3,4-dichlorobenzyl, pentafluorobenzyl, trifluoromethylbenzyl radicals, for example 3- and 4-trifluoromethylbenzyl or 3,5-bis(trifluoromethyl)benzyl.

In monosubstituted phenyl radicals, the substituent can be located in the 2-position, the 3-position or the 4-position. Disubstituted phenyl can be substituted in the 2,3-position, the 2,4-position, the 2,5-position, the 2,6-position, the 3,4-position or the 3,5-position. In trisubstituted phenyl radicals, the substituents can be located in the 2,3,4-position, the 2,3,5-position, the 2,4,5-position, the 2,4,6-position, the 2,3,6-position or the 3,4,5-position.

The explanations for the aryl radicals apply accordingly to divalent arylene radicals, for example to phenylene radicals which can be present, for example, as 1,4-phenylene or as 1,3-phenylene.

Phenylene-(C_1-C_6)-alkyl is in particular phenylenemethyl (-C_6H_4-CH_2-) and phenyleneethyl, (C_1-C_6)-alkylenephenyl is in particular methylenephenyl (-CH_2-C_6H_4-). Phenylene-(C_2-C_6)-alkenyl is in particular phenyleneethenyl and phenylenepropenyl.

The expression "heteroaryl having 5 to 14 ring members" represents a radical of a monocyclic or polycyclic aromatic system having 5 to 14 ring members, which contains 1, 2, 3, 4 or 5 heteroatoms as ring members. Examples of heteroatoms are N, O and S. If a number of heteroatoms are contained, these can be identical or different. Heteroaryl radicals can likewise be monosubstituted or polysubstituted, preferably monosubstituted, disubstituted or trisubstituted, by identical or different radicals from the group consisting of (C_1-C_8)-alkyl, in particular (C_1-C_4)-alkyl, (C_1-C_8)-alkoxy, in particular (C_1-C_4)-alkoxy, halogen, nitro, -$N(R^{11})_2$, trifluoromethyl, hydroxyl, hydroxy-(C_1-C_4)-alkyl such as hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, formyl, acetyl, cyano, hydroxycarbonyl, aminocarbonyl, (C_1-C_4)-alkoxycarbonyl, phenyl, phenoxy,

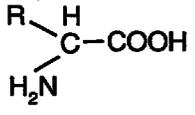
benzyl, benzyloxy, tetrazolyl. Heteroaryl having 5 to 14 ring members preferably represents a monocyclic or bicyclic aromatic radical which contains 1, 2, 3 or 4, in particular 1, 2 or 3, identical or different heteroatoms from the group consisting of N, O and S and which can be substituted by 1, 2, 3 or 4, in particular 1 to 3, identical or different substituents from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, fluorine, chlorine, nitro, -N(R^{11})$_2$, trifluoromethyl, hydroxyl, hydroxy-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, phenyl, phenoxy, benzyloxy and benzyl. Heteroaryl particularly preferably represents a monocyclic or bicyclic aromatic radical having 5 to 10 ring members, in particular a 5-membered or 6-membered monocyclic aromatic radical which contains 1, 2 or 3, in particular 1 or 2, identical or different heteroatoms from the group consisting of N, O and S and can be substituted by 1 or 2 identical or different substituents from the group consisting of (C_1-C_4)-alkyl, halogen, hydroxyl, -N(R^{11})$_2$, (C_1-C_4)-alkoxy, phenyl, phenoxy, benzyloxy and benzyl.

The expression "heterocycle having 5 to 12 ring members" represents a monocyclic or bicyclic 5-membered to 12-membered heterocyclic ring which is partly saturated or completely saturated. Examples of heteroatoms are N, O and S. The heterocycle is unsubstituted or substituted on one or more carbon atoms or on one or more heteroatoms by identical or different substituents. These substituents have been defined above for the radical heteroaryl. In particular, the heterocyclic ring is monosubstituted or polysubstituted, for example monosubstituted, disubstituted, trisubstituted or tetrasubstituted, on carbon atoms by identical or different radicals from the group consisting of (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl, (C_1-C_8)-alkoxy, for example (C_1-C_4)-alkoxy such as methoxy, phenyl-(C_1-C_4)-alkoxy, for example benzyloxy, hydroxyl, oxo, halogen, nitro, amino or trifluoromethyl and/or it is substituted on the ring nitrogen atoms in the heterocyclic ring by (C_1-C_8)-alkyl, for example (C_1-C_4)-alkyl such as methyl or ethyl, by optionally substituted phenyl or phenyl-(C_1-C_4)-alkyl, for example benzyl. Nitrogen heterocycles can also be present as N-oxides or as quaternary salts.

Examples of the expressions heteroaryl having 5 to 14 ring members or heterocycle having 5 to 12 ring members are radicals which are derived from pyrrole, furan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, tetrazole, 1,3,4-oxadiazole, 1,2,3,5-oxathiadiazole-2-

oxides, triazolones, oxadiazolones, isoxazolones, oxadiazolidinediones, triazoles which are substituted by F, CN, CF_3 or COO-(C_1-C_4)-alkyl, 3-hydroxypyrro-2,4-diones, 5-oxo-1,2,4-thiadiazoles, pyridine, pyrazine, pyrimidine, indole, isoindole, indazole, phthalazine, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, carboline and benzo-fused, cyclopenta-, cyclohexa- or cyclohepta-fused derivatives of these heterocycles. Particularly preferred radicals are 2- or 3-pyrrolyl, phenylpyrrolyl such as 4- or 5-phenyl-2-pyrrolyl, 2-furyl, 2-thienyl, 4-imidazolyl, methylimidazolyl, for example 1-methyl-2-, -4- or -5-imidazolyl, 1,3-thiazol-2-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-, 3- or 4-pyridyl-N-oxide, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 5-indolyl, substituted 2-indolyl, for example 1-methyl-, 5-methyl-, 5-methoxy-, 5-benzyloxy-, 5-chloro- or 4,5-dimethyl-2-indolyl, 1-benzyl-2- or -3-indolyl, 4,5,6,7-tetrahydro-2-indolyl, cyclohepta[b]-5-pyrrolyl, 2-, 3- or 4-quinolyl, 1-, 3- or 4-isoquinolyl, 1-oxo-1,2-dihydro-3-isoquinolyl, 2-quinoxalinyl, 2-benzofuranyl, 2-benzothienyl, 2-benzoxazolyl or benzothiazolyl or dihydropyridinyl, pyrrolidinyl, for example 2- or 3-(N-methylpyrrolidinyl), piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrothienyl or benzodioxolanyl.

The structural formula of α-amino acids is as follows:



The α-amino acids differ from one another by the radical R, which in the context of the present application is described as a "characteristic radical" of an amino acid. In the case where R^9 is the characteristic radical of an amino acid, the characteristic radicals employed are preferably those of the following naturally occurring α-amino acids: glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid. Those particularly preferred are histidine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, arginine, glutamic acid and aspartic acid. Preferred characteristic radicals of an amino acid which are furthermore employed as the radical R^9 are also non-naturally occurring amino acids such as 2-aminoadipic acid, 2-aminobutyric acid, 2-aminoisobutyric acid, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 2-aminopimelic acid,

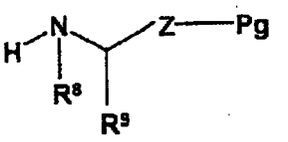
phenylglycine, 3-(2-thienyl)alanine, 3-(3-thienyl)alanine, sarcosine, 2-(2-thienyl)glycine, 2-aminoheptanoic acid, pipecolic acid, hydroxylysine, N-methylisoleucine, 6-N-methyllysine, N-methylvaline, norvaline, norleucine, ornithine, allo-isoleucine, 4-hydroxyproline, allo-hydroxylysine, allo-threonine, 3-hydroxyproline, 3-(2-naphthyl)alanine, 3-(1-naphthyl-alanine), homophenylalanine, homocysteine, 2-amino-3-phenylaminoethylpropionic acid, homocysteic acid, homotryptophan, cysteic acid, 3-(2-pyridyl)alanine, 3-(3-pyridyl)alanine, 3-(4-pyridyl)alanine, phosphinothricin, 4-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, 3-fluorophenylalanine, 3-fluorophenylalanine, 2-fluorophenylalanine, 4-chlorophenylalanine, 4-nitrophenylalanine, 4-aminophenylalanine, cyclohexylalanine, citrulline, 5-fluorotryptophan, 5-methoxytryptophan, 2-amino-3-phenylaminopropionic acid, methionine sulfone, methionine sulfoxide or -NH-NR^{11}-$CON(R^{11})_2$, which are optionally also substituted. In the case of natural but also of non-naturally occurring amino acids which have a functional group such as amino, hydroxyl, carboxyl, mercapto, guanidyl, imidazolyl or indolyl, this group can also be protected.

Suitable protective groups for this are preferably the N-protective groups customarily used in peptide chemistry, for example protective groups of the urethane type, benzyloxycarbonyl (Z), t-butoxycarbonyl (Boc), 9-fluorenyl-oxycarbonyl (Fmoc), allyloxycarbonyl (Aloc) or of the acid amide type, in particular formyl, acetyl or trifluoroacetyl, and of the alkyl type, for example benzyl. In the case of an imidazole radical in R^9, for example, the sulfonic acid derivative of the formula IV employed for the sulfonamide formation is used as a protective group of the imidazole nitrogen, which can be removed again, in particular in the presence of bases such as sodium hydroxide solution.

The starting substances for the chemical reactions are known or can be easily prepared by methods known from the literature.

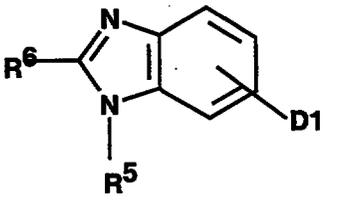
The invention further relates to a process for the preparation of the compounds of the formula I and/or a stereoisomeric form of the compounds of the formula I and/or of a physiologically tolerable salt of the compounds of the formula I, which comprises

a) reacting a compound of the formula IV



(IV)

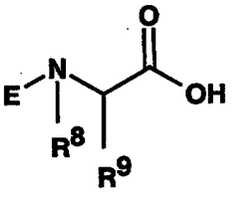
in which Pg is a suitable protective group (e.g. methyl ester), an amide group or a hydroxyl group and Z, R^8 and R^9 are as defined in formula II, with an acid chloride or an activated ester of the compound of the formula III



(III)

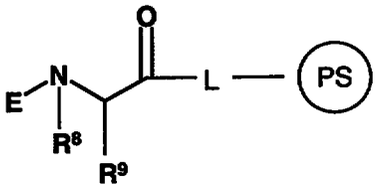
where D1 is -COOH or sulfonylhalogen and R^5 and R^6 are as defined in formula I, in the presence of a base or, if appropriate, of a dehydrating agent in solution and, after removal of the protective group, converting into a compound of the formula I, or

b) reacting a compound of the formula IVa



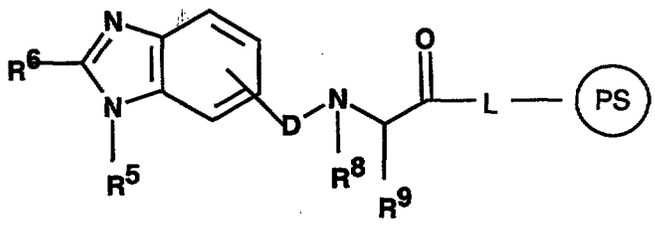
(IVa)

in which R^8 and R^9 are as defined in formula II and E is an N-amino protective group, with its carboxyl group coupled via an intermediate chain L to a polymeric resin of the formula PS, a compound of the formula V



(V)

resulting, which, after selective removal of the protective group E, is reacted with a compound of the formula III, where R^5 and R^6 are as defined in formula I, in the presence of a base or, if appropriate, of a dehydrating agent to give

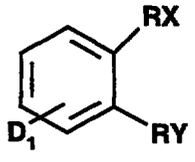


(VI)

a compound of the formula VI

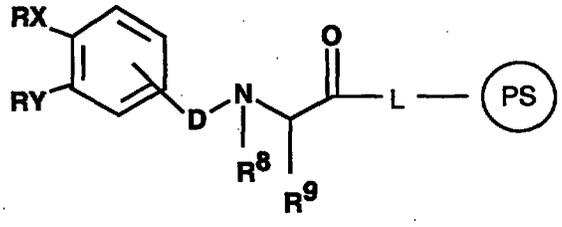
and converting the compound of the formula VI, after removal of the support material, into a compound of the formula I, or

c) reacting a compound of the formula V, after selective removal of the protective group E, with a compound of the formula VII



(VII)

where D_1 is -COOH or sulfonylhalogen and RX is halogen and RY is a radical $-NO_2$ or -NH-E and E is a protective group, to give a compound of the formula VIII

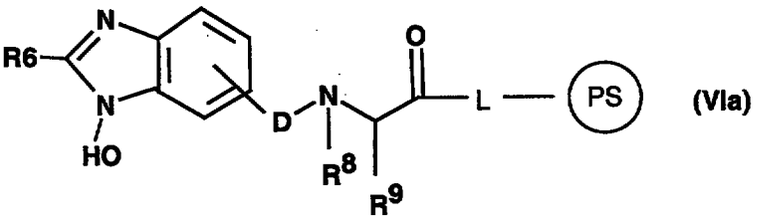


(VIII)

and then reacting the compound of the formula VIII with a compound of the formula IX

$$NH_2\text{-}R^6 \qquad \text{(IX)}$$

in which R^6 is as defined in the compound of the formula I, to give an intermediate compound of the formula VIa



(VIa)

then either converting the intermediate compound of the formula VIa into a compound of the formula I after removal of the support material or reducing it, for example, with tributylphosphine to give a compound of the formula VI and converting into a compound of the formula I after removal of the support material, or

d) converting a compound of the formula I into a physiologically tolerable salt.

In process variant a), the acid functions of the compounds of the formula IVa are provided with a protective group Pg; this selective carboxylic acids derivatization is carried out according to methods such as are described in Houben-Weyl "Methoden der Org. Chemie" [Methods of Organic Chemistry], Volume 15/1. In process variant b), the amino functions of the starting compounds of the formula IVa are provided with a protective group E; this selective amino groups derivatization is carried out according to methods such as are described in Houben-Weyl "Methoden der Org. Chemie" [Methods of Organic Chemistry], Volume 15/1.

A suitable protective group Pg preferably used for this is the carboxyl protective groups customary in peptide chemistry, for example protective groups of the alkyl ester type, such as methyl, ethyl, tert-butyl, isopropyl, benzyl, fluorenylmethyl, allyl, aryl ester type, such as phenyl, amide type, such as amide or benzhydrylamine. Suitable protective groups E used for this are preferably the N-protective groups customary in peptide chemistry, for example protective groups of the urethane type, such as benzyloxycarbonyl (Z), t-butoxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (Fmoc) and allyloxycarbonyl (Aloc) or of the acid amide type, in particular formyl, acetyl or trifluoroacetyl of alkyl type such as benzyl.

The (trimethylsilyl)ethoxycarbonyl (Teoc) group has also proven particularly suitable for this (P. Kociénski, Protecting Groups, Thieme Verlag 1994).

Starting materials used for the preparation of the benzimidazole derivatives of the formula III are preferably 2,3- and 3,4-diaminobenzoic acids and aryl- or heteroarylaldehydes, which are reacted at 145°C in the presence of nitrobenzene as a solvent. The acids mentioned are furthermore reacted with methyl or ethyl imidates, which are prepared from the corresponding arylnitriles or heteroarylnitriles in a Pinner reaction.

For the condensation of the compounds of the formula IV with those of the formula III, the coupling methods which are well-known per se to the person skilled in the art are advantageously used (see, for example, Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Volume 15/1 and 15/2, Georg Thieme Verlag, Stuttgart, 1974). Suitable condensing agents or coupling reagents are compounds such as carbonyldiimidazole, carbodiimides such as dicyclohexylcarbodiimide or diisopropylcarbodiimide (DIC), O-((cyano(ethoxycarbonyl)methylene)-amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) or propanephosphonic anhydride (PPA).

The condensations can be carried out under standard conditions. During the condensation, as a rule it is necessary for the non-reacting amino groups present to be protected by reversible protective groups. The same applies to carboxyl groups not involved in the reaction, which during the condensation are preferably present as (C_1-C_6)-alkyl esters, benzyl esters or tert-butyl esters. Amino group protection is unnecessary if the amino groups are still present in the form of precursors such as nitro groups or cyano groups and are only formed by hydrogenation after the condensation. After the condensation, the protective groups present are removed in a suitable manner. For example, NO_2 groups (guanidino protection in amino acids), benzyloxycarbonyl groups and benzyl groups in benzyl esters can be removed by hydrogenation. The protective groups of the tert-butyl type are removed acidically, while the 9-fluorenylmethoxycarbonyl radical is removed by secondary amines.

The polymeric support designated in the formulae V and VI by PS is a crosslinked polystyrene resin having a linker designated as the intermediate chain L. This linker carries a suitable functional group, for example amine, known, for example, as Rink amide resin, or an OH group, known, for example, as Wang resin or Kaiser's oxime resin). Alternatively,

other polymeric supports such as glass, cotton or cellulose having various intermediate chains L can be employed.

The intermediate chain designated by L is covalently bonded to the polymeric support and allows a reversible, amide-like or ester-like bond with the compound of the formula IVa, which remains stable during the further reaction on the bonded compound of the formula IVa; but under strongly acidic reaction conditions, e.g. mixtures with trifluoroacetic acid, releases the group located on the linker again. The release of the desired compound of the formula I from the linker can be carried out at various positions in the reaction sequence.

A. General procedure for the coupling of protected aminocarboxylic acids of the formula IVa to the solid support according to procedure b):

The synthesis was carried out in reactors each having a reaction volume of 15 ml. Each of the reactors was filled with 0.179 g of Rink amide AM resin (Fmoc-Rink amide AM/Nova-Biochem; loading 0.56 mmol/g; i.e. 0.1 mmol/reactor). For the removal of the Fmoc protective group from the resin, a 30% strength piperidine/DMF solution was metered into each reactor and the mixture was shaken for 45 minutes (min). It was then filtered and the resin was washed 3 times with dimethylformamide (DMF).

For the coupling of the protected amino acid, a 0.5 molar solution of the corresponding Fmoc-amino acid (0.3 mmol in DMF), a solution of HOBt (0.33 mmol in DMF) and a solution of DIC (0.33 mmol in DMF) were each added to the resin thus prepared and the mixture was shaken at 35°C for 16 hours (h). The resin was then washed with DMF a number of times.
To check the coupling, a few resin beads were removed and subjected to a KAISER test; in all cases the test was negative.
The removal of the Fmoc protective group was carried out, as mentioned above, using 30% strength piperidine/DMF solution.

For the coupling of the benzimidazolecarboxylic acids, a 0.1 molar solution of the corresponding 4- or 5-substituted acid (0.4 mmol in DMF); a 0.5 molar solution of the coupling reagent TOTU (0.44 mmol in DMF) and a 0.5 molar solution of DIPEA (0.6 mmol in DMF) were added and the mixture was shaken at 40°C for 16 hours. It was then washed a number of times with DMF.

To check the reaction, a few beads of resin were again removed and subjected to a KAISER test.

For the removal of the desired substances from the solid support, the resin was washed a number of times with dichloromethane. The cleavage solution (50% dichloromethane and 50% of a mixture of 95% TFA, 2% H_2O, 3% triisopropylsilane) was then added and the mixture was shaken at room temperature for 1 h. The mixture was filtered and the filtrate was concentrated to dryness. The residue was precipitated with diethyl ether and filtered.

The solid residues usually contained the desired products in high purity or were fractionated, for example, on a reverse phase (eluent: A: H_2O/0.1% TFA, B: acetonitrile/0.1% TFA) using preparative high-pressure liquid chromatography. Lyophilization of the fractions obtained yielded the desired products.

The preparation of physiologically tolerable salts of compounds of the formula I capable of salt formation, including their stereoisomeric forms, is carried out in a manner known per se. With basic reagents such as hydroxides, carbonates, hydrogencarbonates, alkoxides and also ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine or triethanolamine or alternatively basic amino acids, for example lysine, ornithine or arginine, the carboxylic acids form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts. If the compounds of the formula I contain basic groups, stable acid addition salts can also be prepared using strong acids. For this, both inorganic and organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexyl-amidosulfonic, trifluoromethylsulfonic, acetic, oxalic, tartaric, succinic or trifluoroacetic acid are suitable.

The invention also relates to pharmaceuticals which comprise an efficacious amount of at least one compound of the formula I and/or of a physiologically tolerable salt of the compounds of the formula I and/or an optionally stereoisomeric form of the compounds of the formula I, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

On account of the pharmacological properties, the compounds according to the invention are suitable for the prophylaxis and therapy of all those disorders in whose course an increased activity of IkB kinase is involved. These include, for example, asthma, rheumatoid arthritis (in the case of inflammation), osteoarthritis, Alzheimer's disease, carcinomatous disorders (potentiation of cytotoxic therapies), cardiac infarct, cardiac insufficiency, acute coronary syndrome (unstable angina pectoris), septic shock, acute and chronic kidney failure, stroke or atherosclerosis.

The pharmaceuticals according to the invention are in general administered orally or parenterally. Rectal, inhalative or transdermal administration is also possible.

The invention also relates to a process for the production of a pharmaceutical, which comprises bringing at least one compound of the formula I into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries.

Suitable solid or pharmaceutical preparation forms are, for example, granules, powders, coated tablets, tablets, (micro)capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions, and preparations having protracted release of active compound, in whose preparation customary auxiliaries, such as excipients, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavorings, sweeteners and solubilizers are used. Frequently used auxiliaries which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactoprotein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as cod liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

The pharmaceutical preparations are preferably produced and administered in dose units, each unit containing as active constituent a certain dose of the compound of the formula I according to the invention. In the case of solid dose units such as tablets, capsules, coated tablets or suppositories, this dose can be up to approximately 1000 mg, preferably from approximately 50 mg to 300 mg and in the case of injection solutions

in ampoule form up to approximately 300 mg, preferably from approximately 10 mg to 100 mg.

For the treatment of an adult patient weighing approximately 70 kg, depending on the efficacy of the compound according to formula I, daily doses of approximately 20 mg to 1000 mg of active compound, preferably from approximately 100 mg to 500 mg, are indicated. Under certain circumstances, however, even higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else of a number of smaller dose units and by multiple administration of subdivided doses at specific intervals.

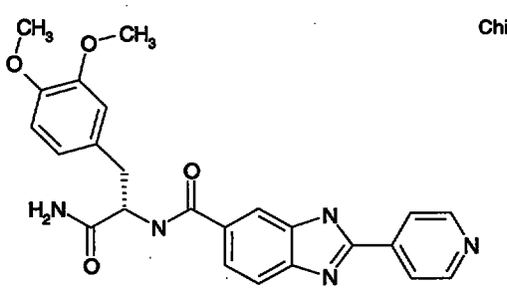
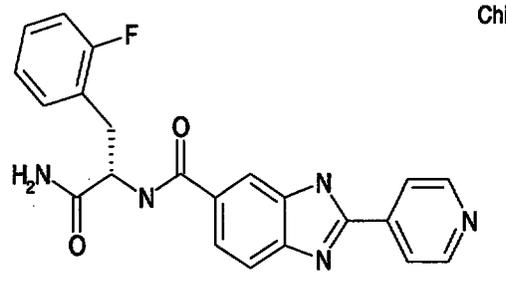
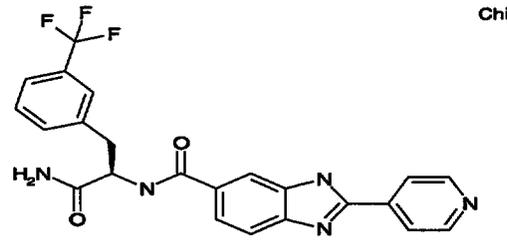
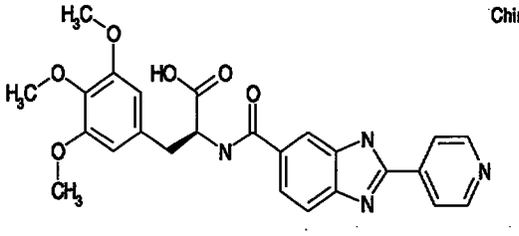
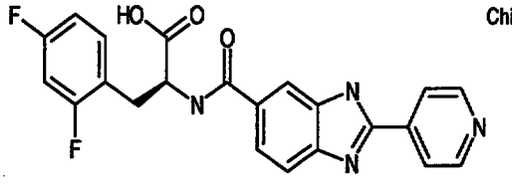
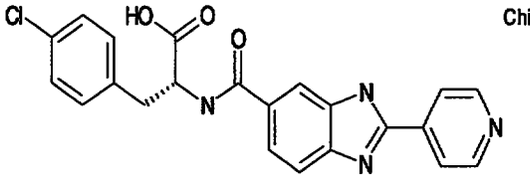
As a rule, final products are determined by mass-spectroscopic methods (FAB-, ESI-MS). Temperatures are given in degrees Celsius, RT means room temperature (22-26°C). Abbreviations used are either explained or correspond to the customary conventions.

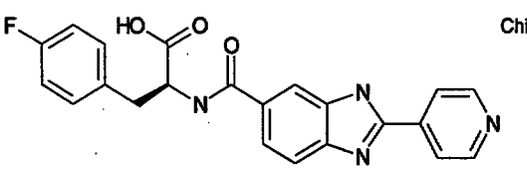
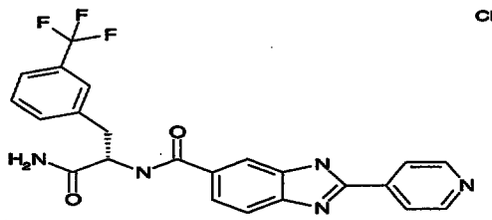
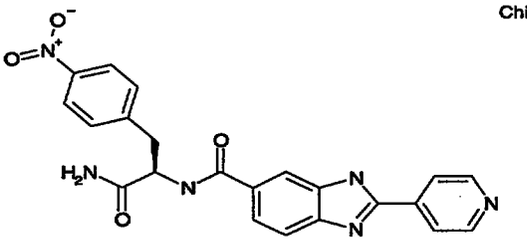
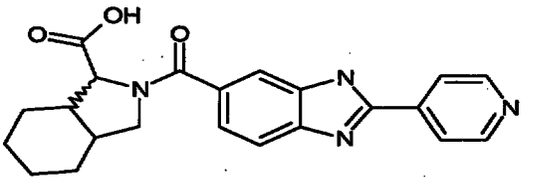
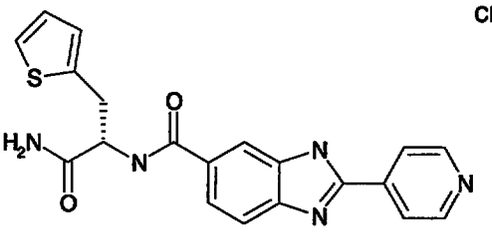
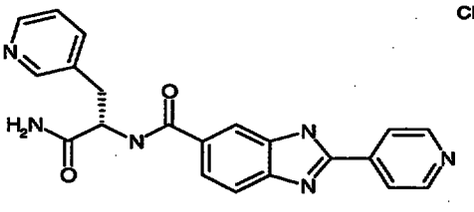
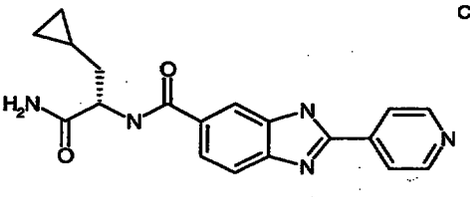
Examples according to process variant b) as in the general working procedure

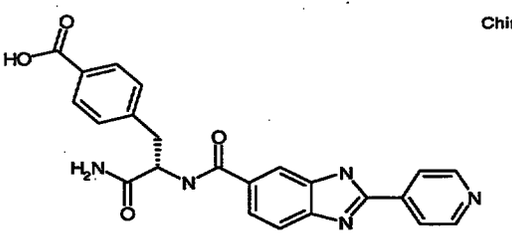
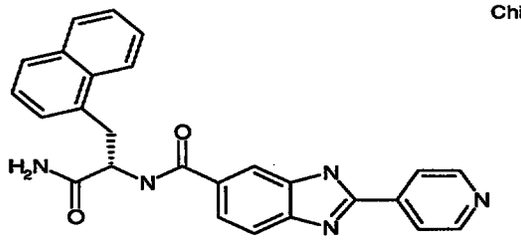
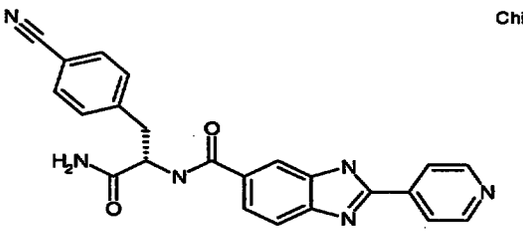
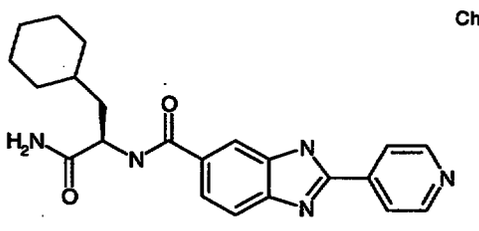
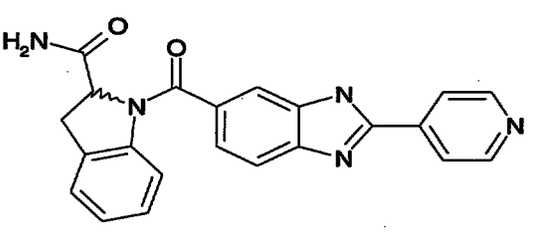
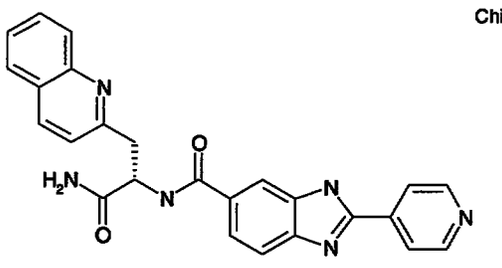
HPLC (RP 18; UV 210 nm): gradient 0-15 min. B = 5-70% (A = 100% H_2/0.1% trifluoroacetic acid; B = 100% acetonitrile/0.1% trifluoroacetic acid)

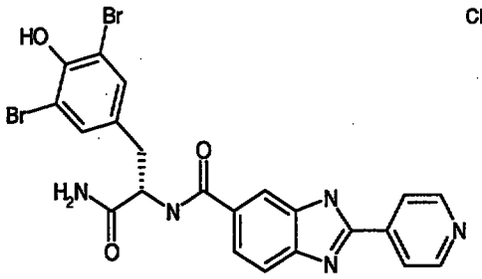
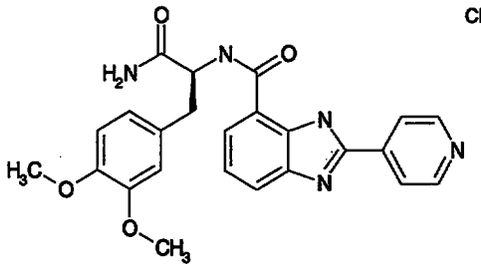
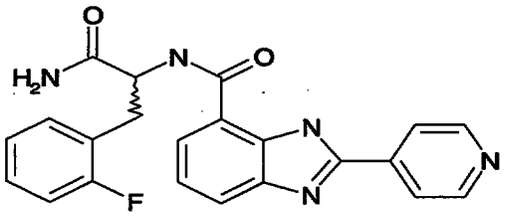
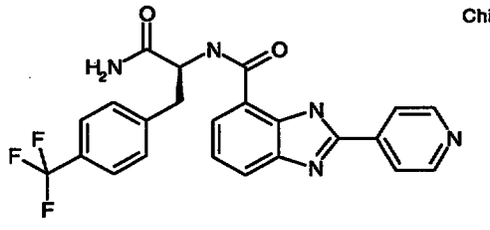
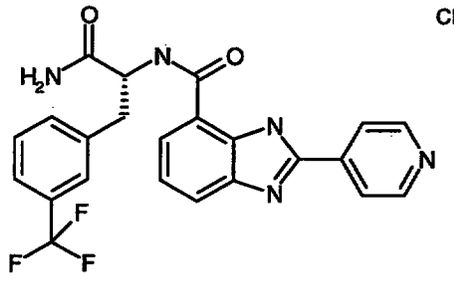
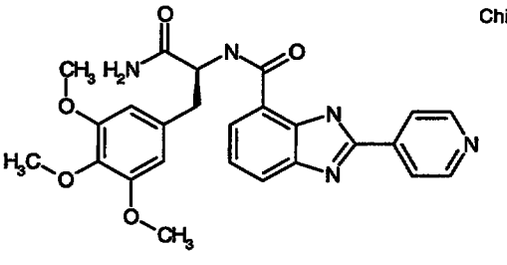
The examples in Table 1 which follows have been prepared analogously to process variant b) as in the general working procedure.

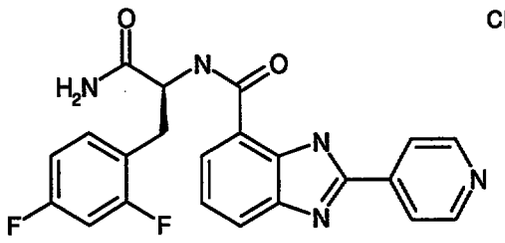
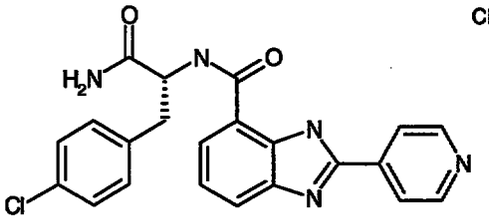
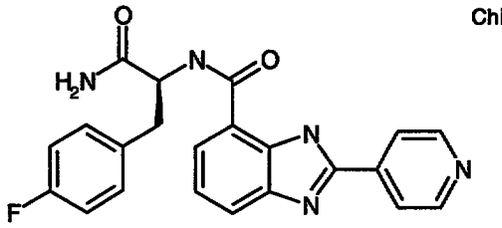
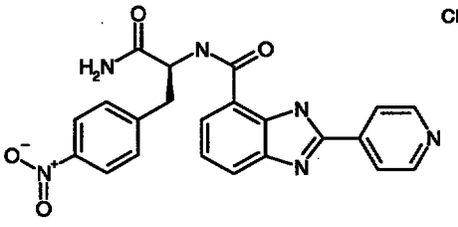
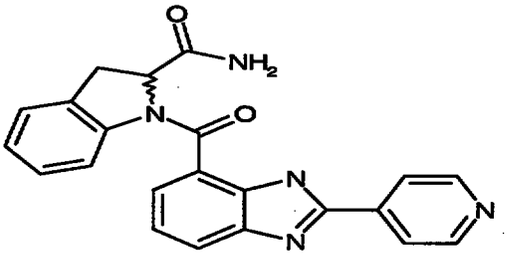
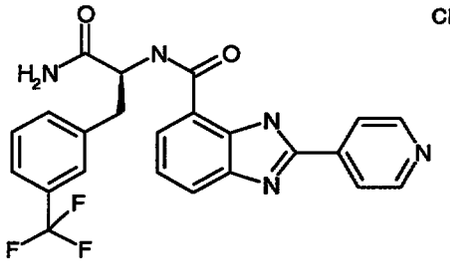
Table 1:

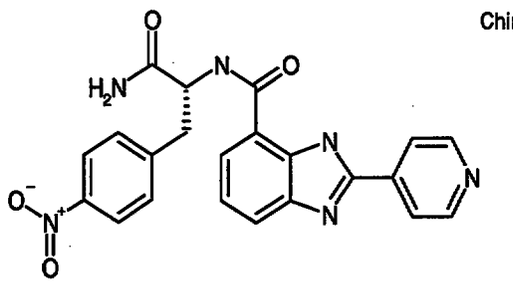
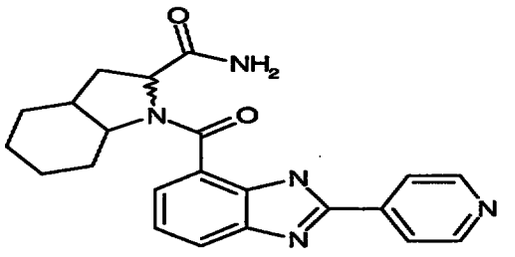
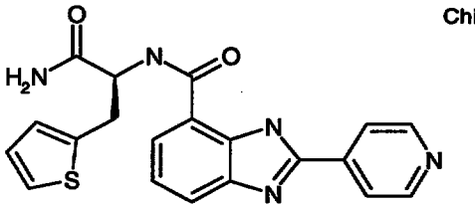
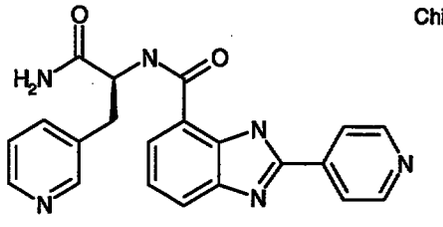
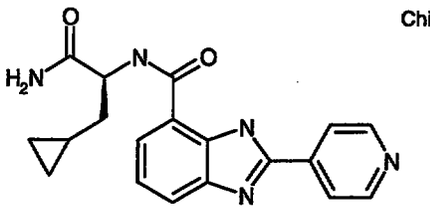
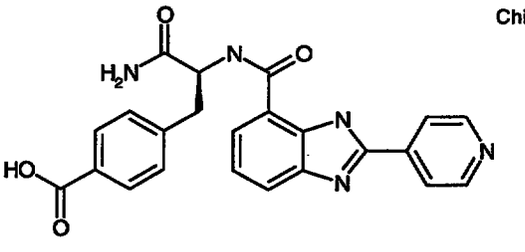
Example	Structure	Empirical formula	MS (M+ H)	Note
1	 Chiral	$C_{24}H_{23}N_5O_4$	446.12	b)
2	 Chiral	$C_{22}H_{18}FN_5O_2$	403.89	b)
3	 Chiral	$C_{23}H_{18}F_3N_5O_2$	453.90	b)
4	 Chiral	$C_{25}H_{24}N_4O_6$	476.1	b)
5	 Chiral	$C_{22}H_{16}F_2N_4O_3$	422.03	b)
6	 Chiral	$C_{22}H_{17}ClN_4O_3$	421.88 419.94	b)

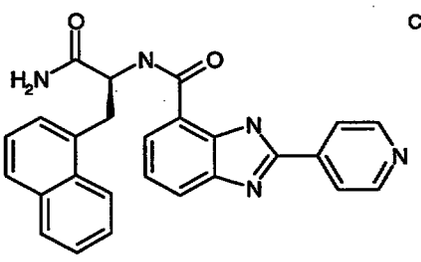
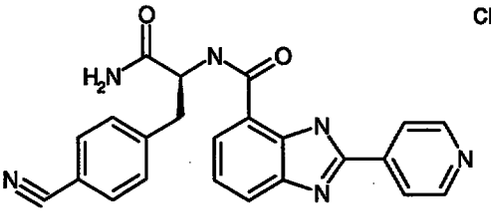
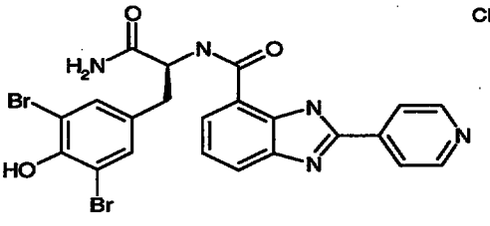
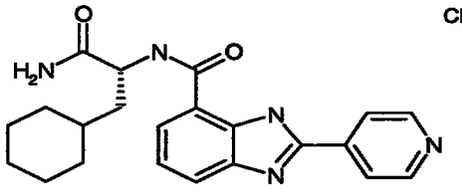
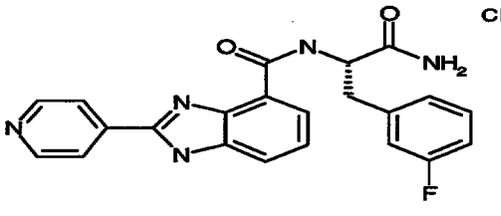
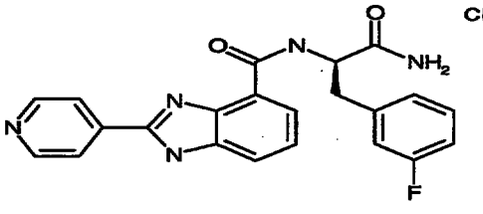
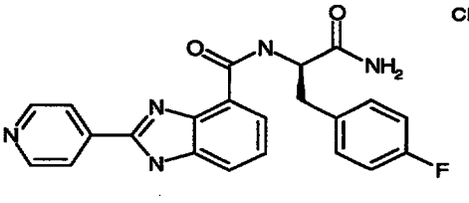
Example	Structure	Empirical formula	MS (M+ H)	Note
7	 Chiral	$C_{22}H_{17}FN_4O_3$	403.87	b)
8	 Chiral	$C_{23}H_{18}F_3N_5O_2$	453.91	b)
9	 Chiral	$C_{22}H_{18}N_6O_4$	430.84	b)
10		$C_{22}H_{22}N_4O_3$	389.87	b)
11	 Chiral	$C_{20}H_{17}N_5O_2S$	391.79	b)
12	 Chiral	$C_{21}H_{18}N_6O_2$	387.22	b)
13	 Chiral	$C_{19}H_{19}N_5O_2$	349.79	b)

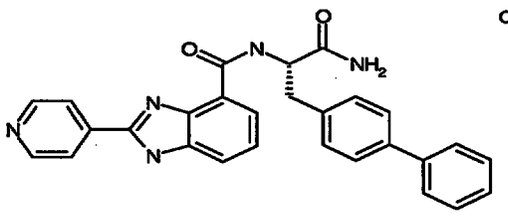
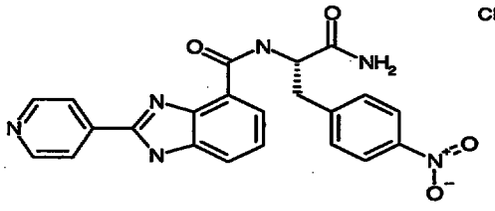
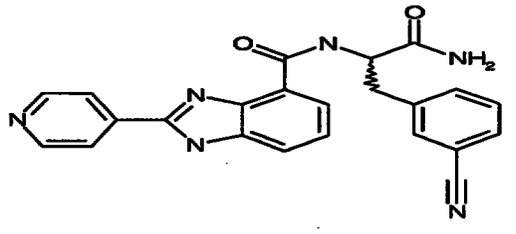
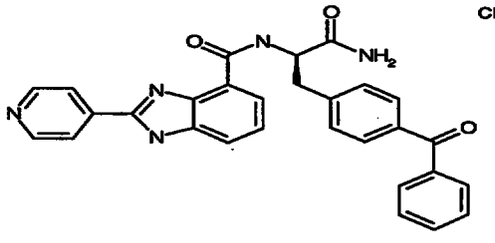
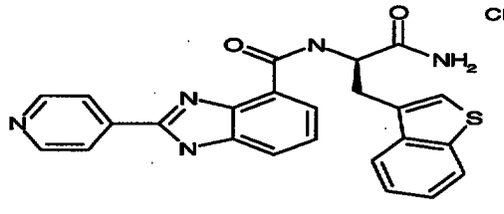
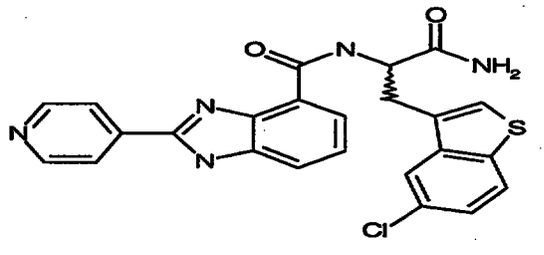
Example	Structure	Empirical formula	MS (M+ H)	Note
14	 Chiral	$C_{23}H_{19}N_5O_4$	430.04	b)
15	 Chiral	$C_{26}H_{21}N_5O_2$	435.89	b)
16	 Chiral	$C_{23}H_{18}N_6O_2$	410.4352	b)
18	 Chiral	$C_{22}H_{25}N_5O_2$	392.18	b)
19		$C_{22}H_{17}N_5O_2$	383.86	b)
20	 Chiral	$C_{25}H_{20}N_6O_2$	437.10	b)

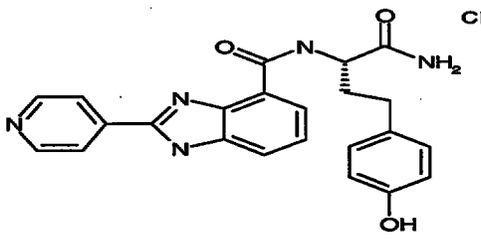
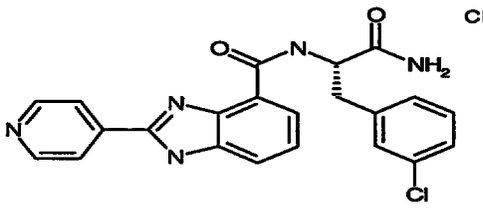
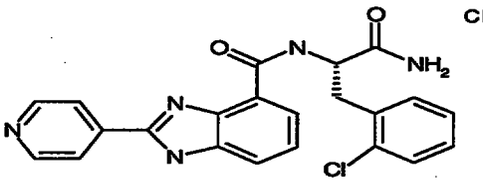
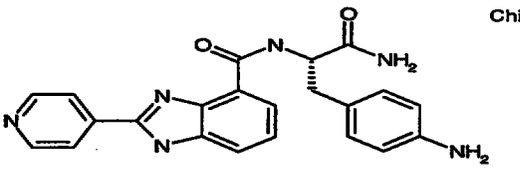
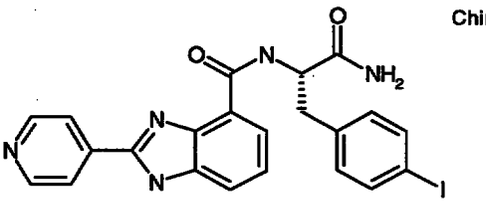
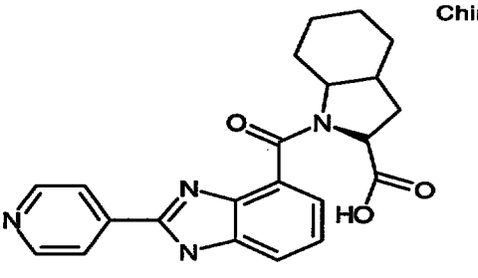
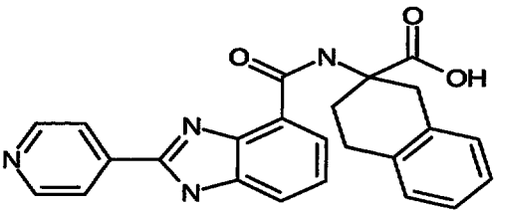
Example	Structure	Empirical formula	MS (M+ H)	Note
21	 Chiral	$C_{22}H_{17}Br_2N_5O_3$	559.94 561.82	b)
22	 Chiral	$C_{24}H_{23}N_5O_4$	446.12	b)
23		$C_{22}H_{18}FN_5O_2$	403.96	b)
24	 Chiral	$C_{23}H_{18}F_3N_5O_2$	454.08	b)
25	 Chiral	$C_{23}H_{18}F_3N_5O_2$	453.99	b)
26	 Chiral	$C_{25}H_{25}N_5O_5$	476.17	b)

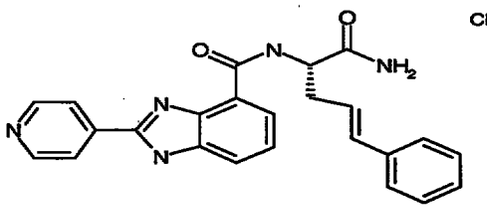
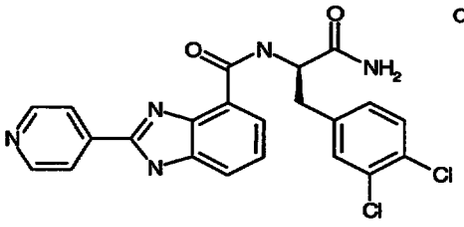
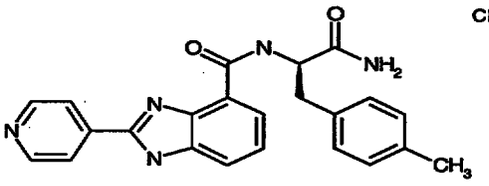
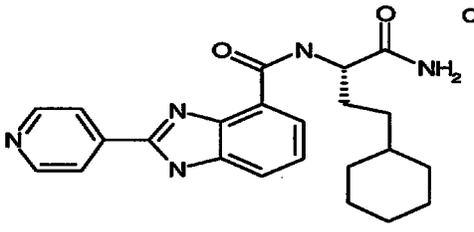
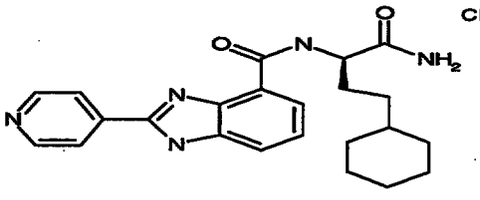
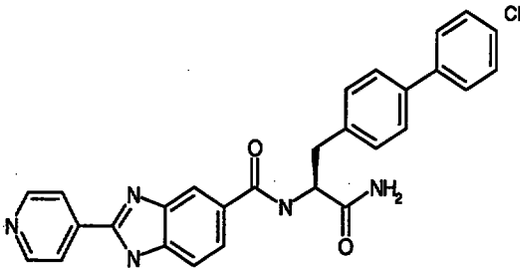
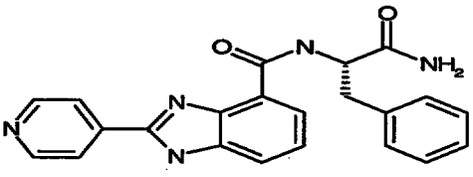
Example	Structure	Empirical formula	MS (M+ H)	Note
27	 Chiral	$C_{22}H_{17}F_2N_5O_2$	421.31	b)
28	 Chiral	$C_{22}H_{18}ClN_5O_2$	419.94	b)
29	 Chiral	$C_{22}H_{18}FN_5O_2$	403.80	b)
30	 Chiral	$C_{22}H_{18}N_6O_4$	431.07	b)
31		$C_{22}H_{17}N_5O_2$	383.74	b)
32	 Chiral	$C_{23}H_{18}F_3N_5O_2$	453.97	b)

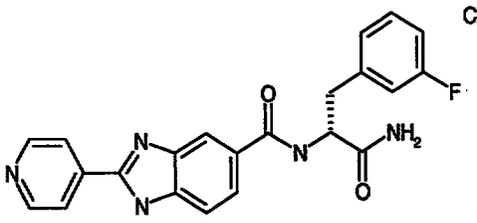
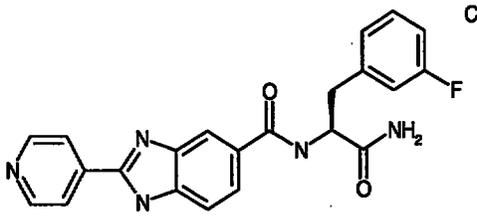
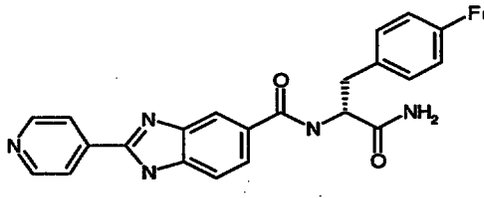
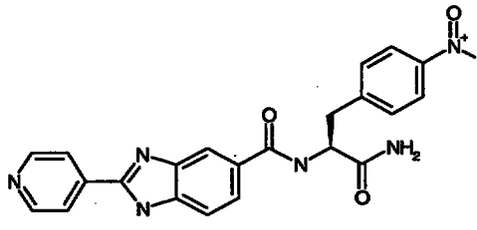
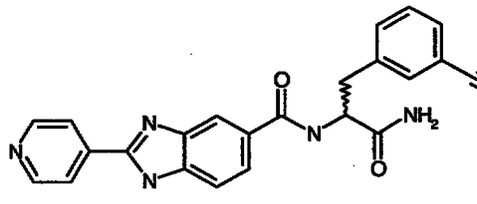
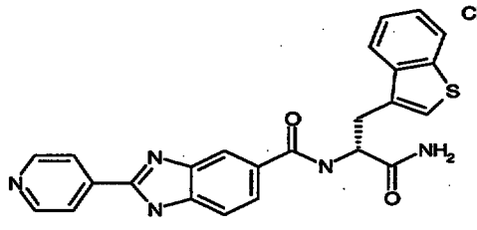
Example	Structure	Empirical formula	MS (M+ H)	Note
33	 Chiral	$C_{22}H_{18}N_6O_4$	430.83	b)
34		$C_{22}H_{23}N_5O_2$	389.95	b)
35	 Chiral	$C_{20}H_{17}N_5O_2S$	392.20	b)
36	 Chiral	$C_{21}H_{18}N_6O_2$	387.04	b)
37	 Chiral	$C_{19}H_{19}N_5O_2$	349.98	b)
38	 Chiral	$C_{23}H_{19}N_5O_4$	429.74	b)

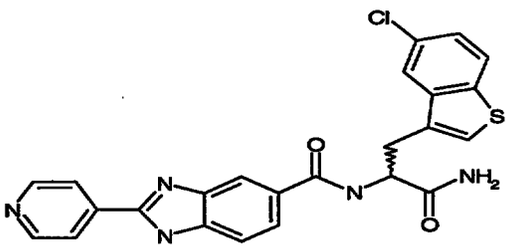
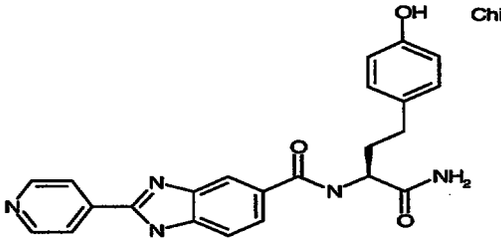
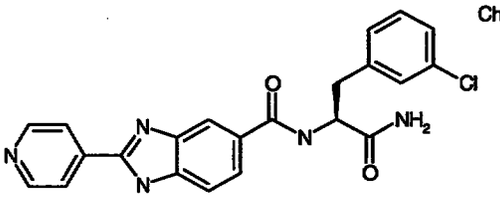
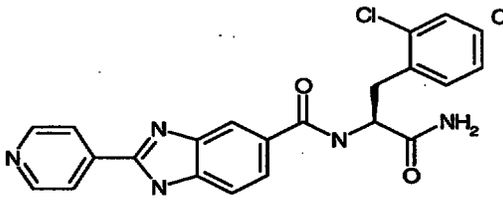
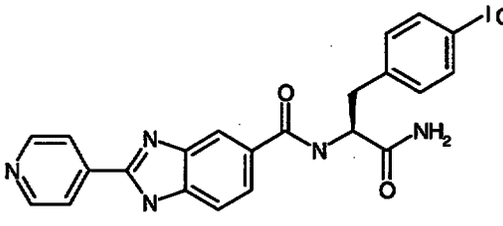
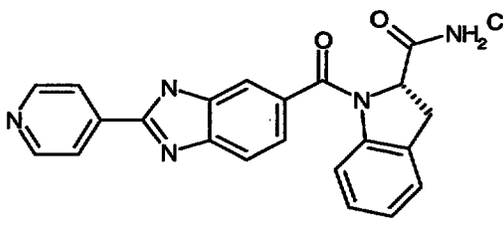
Example	Structure	Empirical formula	MS (M+ H)	Note
39	 Chiral	$C_{26}H_{21}N_5O_2$	435.90	b)
40	 Chiral	$C_{23}H_{18}N_6O_2$	410.44	b)
41	 Chiral	$C_{22}H_{17}Br_2N_5O_3$	559.99 561.85	b)
42	 Chiral	$C_{22}H_{25}N_5O_2$	391.83	b)
43	 Chiral	$C_{22}H_{18}FN_5O_2$	404.17	b)
44	 Chiral	$C_{22}H_{18}FN_5O_2$	404.08	b)
45	 Chiral	$C_{22}H_{18}FN_5O_2$	403.88	b)

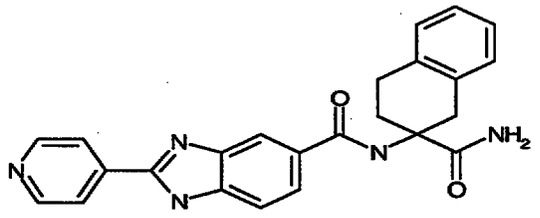
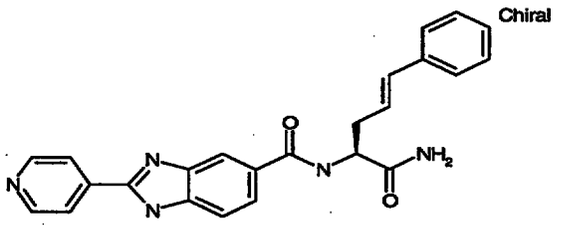
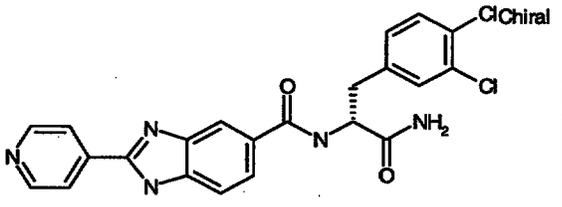
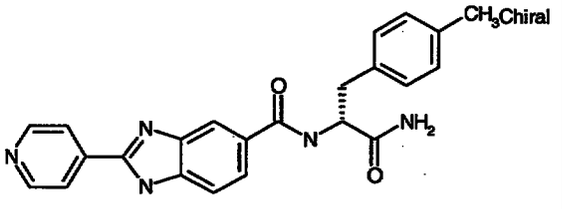
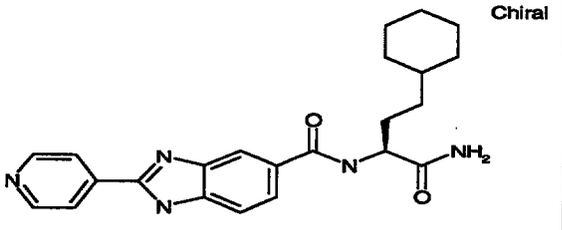
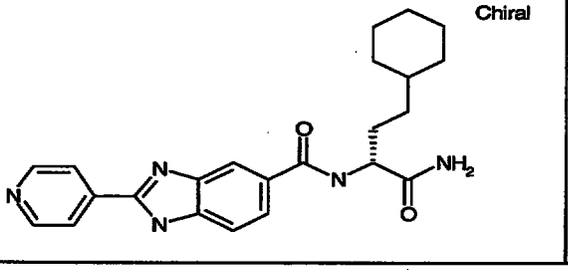
Example	Structure	Empirical formula	MS (M+ H)	Note
46	 Chiral	$C_{28}H_{23}N_5O_2$	462.18	b)
47	 Chiral	$C_{22}H_{18}N_6O_4$	431.03	b)
48		$C_{23}H_{18}N_6O_2$	411.1	b)
49	 Chiral	$C_{29}H_{23}N_5O_3$	489.93	b)
50	 Chiral	$C_{24}H_{19}N_5O_2S$	442.1	b)
51		$C_{24}H_{18}ClN_5O_2S$	475.98	b)

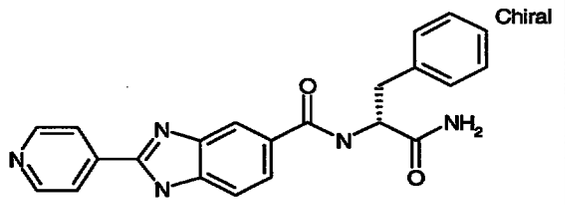
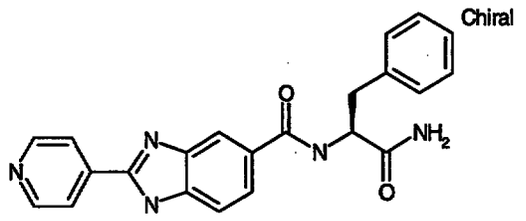
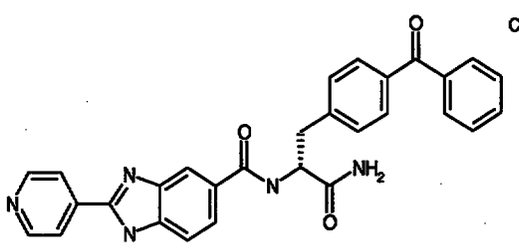
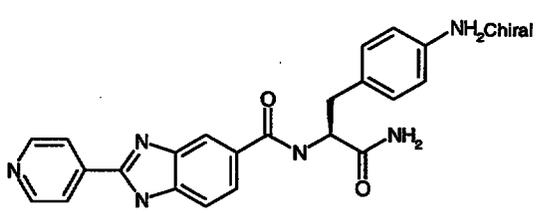
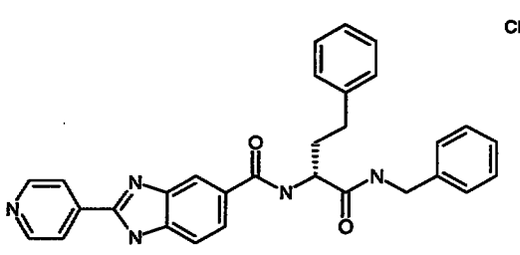
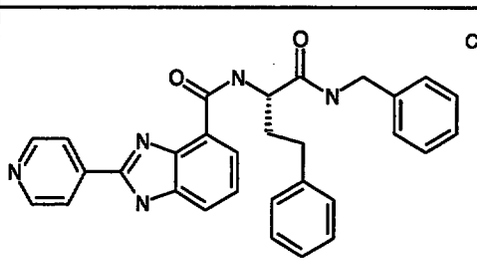
Example	Structure	Empirical formula	MS (M+ H)	Note
52	 Chiral	$C_{23}H_{21}N_5O_3$	416.27	b)
53	 Chiral	$C_{22}H_{18}ClN_5O_2$	421.88 419.84	b)
54	 Chiral	$C_{22}H_{18}ClN_5O_2$	421.91	b)
55	 Chiral	$C_{22}H_{20}N_6O_2$	400.94	b)
56	 Chiral	$C_{22}H_{18}IN_5O_2$	510.72	b)
57	 Chiral	$C_{22}H_{22}N_4O_3$	389.85	b)
58		$C_{24}H_{20}N_4O_3$	411.88 413.14	b)

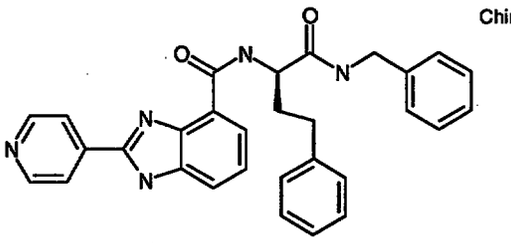
Example	Structure	Empirical formula	MS (M+ H)	Note
59	 Chiral	$C_{24}H_{21}N_5O_2$	412.01	b)
60	 Chiral	$C_{22}H_{17}Cl_2N_5O_2$	456.02 454.13	b)
61	 Chiral	$C_{23}H_{21}N_5O_2$	400.14	b)
62	 Chiral	$C_{23}H_{27}N_5O_2$	406.21	b)
63	 Chiral	$C_{23}H_{27}N_5O_2$	406.12	b)
64	 Chiral	$C_{28}H_{23}N_5O_2$	462.21	b)
65	 Chiral	$C_{22}H_{19}N_5O_2$	385.67	b)

Example	Structure	Empirical formula	MS (M+ H)	Note
66	 Chiral	$C_{22}H_{18}FN_5O_2$	403.92	b)
67	 Chiral	$C_{22}H_{18}FN_5O_2$	404.02	b)
68	 F Chiral	$C_{22}H_{18}FN5O_2$	404	b)
69	 Chiral	$C_{22}H_{18}N6O_4$	430.96	b)
70		$C_{23}H_{18}N_6O_2$	411.04	b)
71	 Chiral	$C_{24}H_{19}N_5O_2S$	441.81	b)

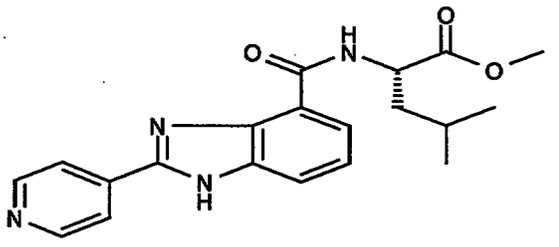
Example	Structure	Empirical formula	MS (M+ H)	Note
72		C_{24} H_{18} Cl N_5 O_2 S	477.96 475.97	b)
73		C_{23} H_{21} N_5 O_3	416.13	b)
74		C_{22} H_{18} Cl N_5 O_2	419.98 421.90	b)
75		C_{22} H_{18} Cl N_5 O_2	420.12	b)
76		C_{22} H18 I N_5 O_2	512.06	b)
77		C_{22} H_{17} N_5 O_2	384.1	b)

Example	Structure	Empirical formula	MS (M+ H)	Note
78		$C_{24}H_{21}N_5O_2$	412.1	b)
79		$C_{24}H_{21}N_5O_2$	412.07	b)
80		$C_{22}H_{17}Cl_2N_5O_2$	456.05 453.89	b)
81		$C_{23}H_{21}N_5O_2$	399.95	b)
82		$C_{23}H_{27}N_5O_2$	406.04	b)
83		$C_{23}H_{27}N_5O_2$	405.87	b)

Example	Structure	Empirical formula	MS (M+ H)	Note
84	 Chiral	$C_{22}H_{19}N_5O_2$	385.78	b)
85	 Chiral	$C_{22}H_{19}N_5O_2$	385.78	b)
86	 Chiral	$C_{29}H_{23}N_5O_3$	490.1	b)
87	 NH_2 Chiral	$C_{22}H_{20}N_6O_2$	400.44	b)
88	 Chiral	$C_{30}H_{27}N_5O_2$	490.3	b)
89	 Chiral	$C_{30}H_{27}N_5O_2$	490.27	b)

Example	Structure	Empirical formula	MS (M+ H)	Note
90	 Chiral	$C_{30}H_{27}N_5O_2$	490.22	b)

Example 91 (2-(Pyridyl-4-yl)-1H-benzimidazole-4-carbonyl)-(L)-leucine methyl ester (1)



Ammonium 3-nitrophthalamidate (1a). 100 g (518 mmol) of 3-nitrophthalic anhydride were introduced at room temperature (RT) and treated rapidly with 170 ml of concentrated ammonium hydroxide solution with stirring. The mixture was stirred at RT for 1 hour (h). The precipitate was filtered off and dried in a desiccator.

Yield: 95.6 g (88%).

2-Amino-3-nitrobenzoic acid (1b). 22 g (105.2 mmol) of ammonium 3-nitrophthalamidate (1a) were treated with stirring with 165 ml of sodium hypochlorite solution. After 5 minutes, a solution of 8.8 g of sodium hydroxide in 22 ml of water was added and the mixture was then stirred at 70°C for 1 h. The suspension was poured into 500 ml of water with stirring. The resulting clear solution was acidified with concentrated HCl. The precipitate was filtered off and dried in a desiccator.

Yield: 9.68 g (51%).

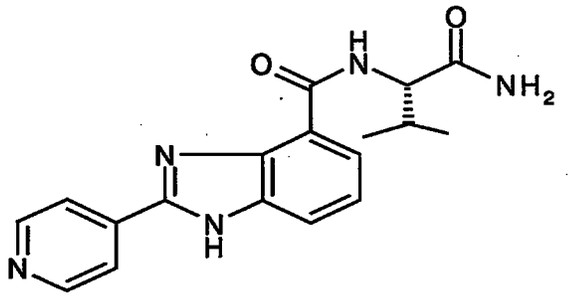
2,3-Diaminobenzoic acid (1c). 14 g (76.9 mmol) of 2-amino-3-nitrobenzoic acid (1b) were dissolved in 500 ml of methanol, treated with Pd/C and hydrogenated with hydrogen. After 4 h, the catalyst was filtered off with suction and concentrated. A dark-brown solid was obtained. Yield: 11.67 g (99%).

2-(Pyrid-4-yl)-1H-benzimidazole-4-carboxylic acid (1d). 700 mg (4.6 mmol) of 2,3-diaminobenzoic acid (1c) and 0.47 ml (4.95 mmol) of 4-pyridylaldehyde were dissolved in 40 ml of nitrobenzene and heated at 145°C for 2 h with stirring. The mixture was then cooled and the precipitate was filtered off with suction. The precipitate was washed with ethyl acetate and dried in a desiccator. Yield: 800 mg (73%).

(2-(Pyrid-4-yl)-1H-benzimidazole-4-carbonyl)-(L)-leucine methyl ester (1). 120 mg (0.5 mmol) of 2-(pyrid-4-yl)-1H-benzimidazole-4-carboxylic acid (1d) and 84 mg (0.5 mmol) of H-(L)-leucine methyl ester were dissolved in 5 ml of DMF. 164 mg (0.5 mmol) of TOTU (O-[(cyano-(ethoxycarbonyl)methylidene)amino-1,1,3,3-tetramethyl]uronium tetra-

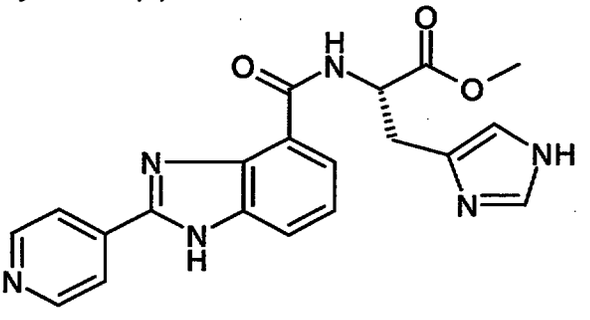
fluoroborate) and 0.086 ml of diisopropylethylamine were added and the mixture was stirred at RT for 3 h. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate, the solution was washed with water, and the organic phase was dried using anhydrous sodium sulfate and concentrated. Yield: 180 mg (98%). $(M+H)^+ = 367.1$ (Cl^+)

Example 92 (2-(Pyrid-4-yl)-1H-benzimidazole-4-carbonyl)-(L)-valinamide (2)



120 mg (0.5 mmol) of 2-(pyrid-4-yl)-1H-benzimidazole-4-carboxylic acid (1d) and 76.4 mg (0.5 mmol) of H-(L)-valinamide were dissolved in 5 ml of DMF. 164 mg (0.5 mmol) of TOTU (O-[(cyano(ethoxycarbonyl)methyl-idene)amino-1,1,3,3-tetramethyl]uronium tetrafluoroborate) and 0.086 ml of diisopropylethylamine were added and the mixture was stirred at RT for 3 h. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate, the solution was washed with saturated sodium chloride solution, and the organic phase was dried using anhydride sodium sulfate and concentrated.
Yield: 168 mg (99%). $(M+H)^+ = 338.2$ (Cl^+)

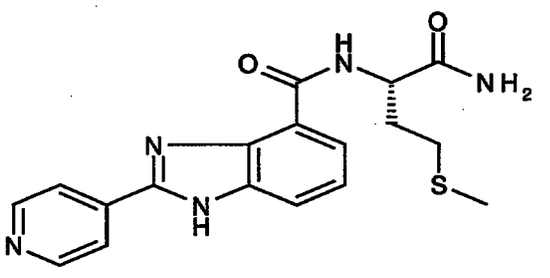
Example 93 (2-(Pyrid-4-yl)-1H-benzimidazole-4-carbonyl)-(S)-histidine methyl ester (3)



(2-(Pyrid-4-yl)-1H-benzimidazole-4-carbonyl)-(L)-histidine(Trt) methyl ester (3a).

120 mg (0.5 mmol) of 2-(pyrid-4-yl)-1H-benzimidazole-4-carboxylic acid (1d) and 242 mg (0.5 mmol) of H-(L)-histidine(Trt) methyl ester were dissolved in 5 ml of DMF. 164 mg (0.5 mmol) of TOTU and 0.172 ml of diisopropylethylamine were added and the mixture was stirred at RT for 3 h. The clear solution was concentrated. The residue was dissolved in ethyl acetate, the solution was washed with water, and the organic phase was dried using anhydrous sodium sulfate and concentrated. Yield: 380 mg of crude product. $(M+H)^+ = 633.3$ (ES^+).

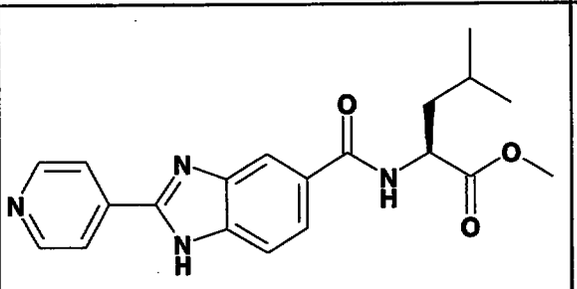
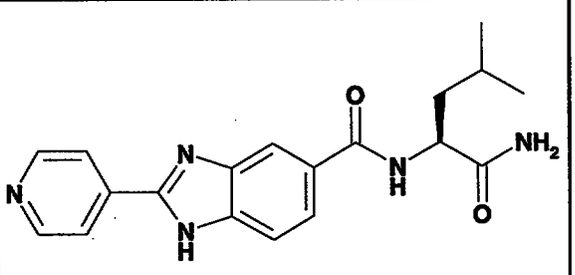
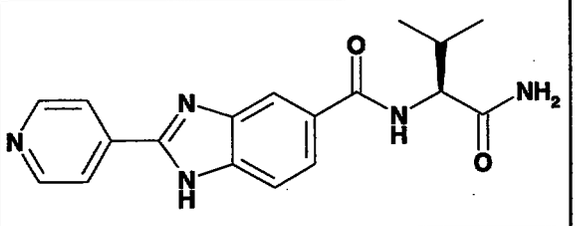
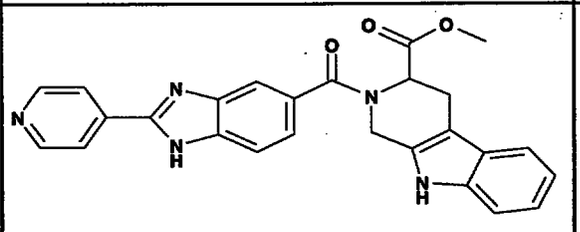
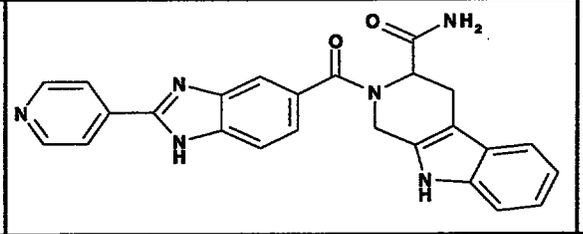
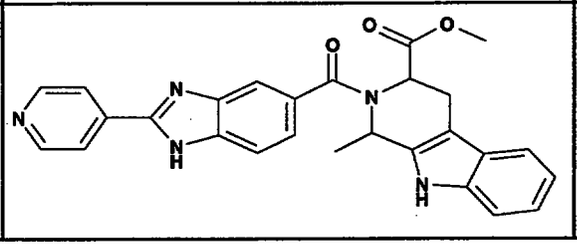
Example 94 2-(Pyrid-4-yl)-1H-benzimidazole-4-carbonyl)-(L)-methioninamide (4)

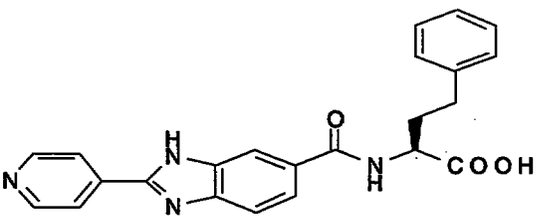
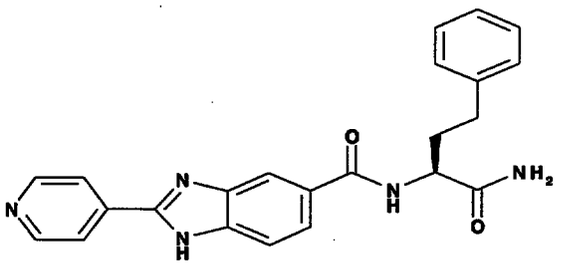
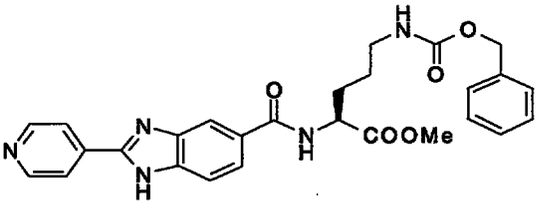
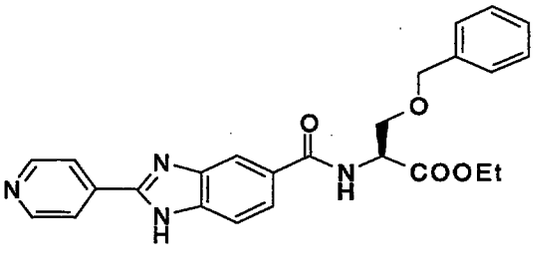
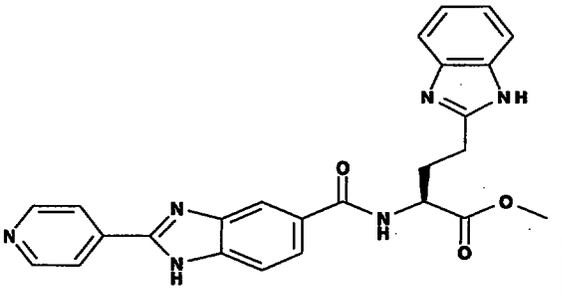
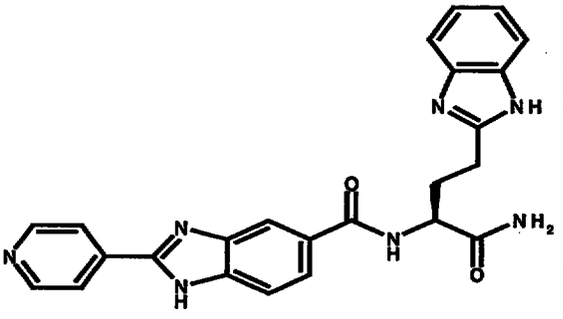


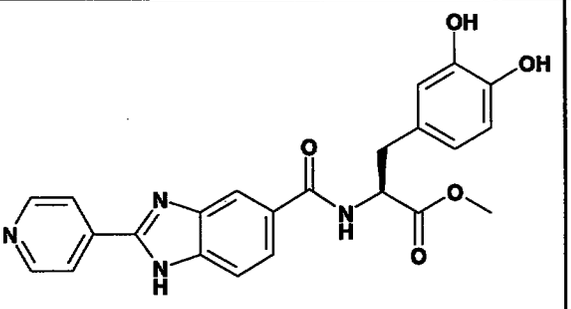
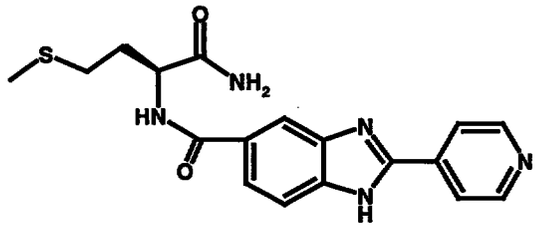
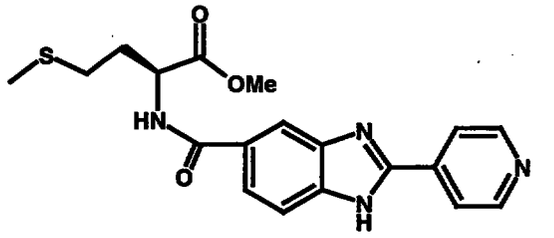
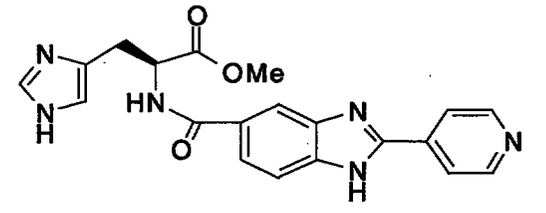
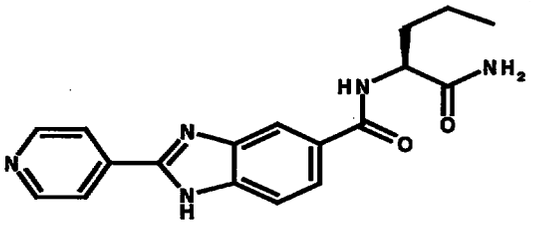
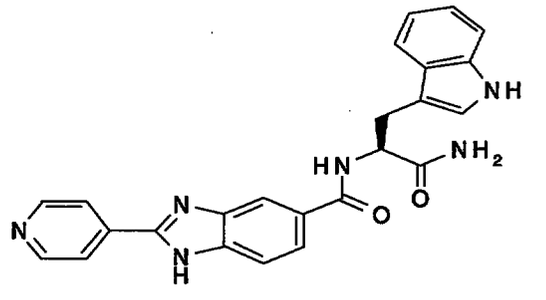
120 mg (0.5 mmol) of 2-(pyrid-4-yl)-1H-benzimidazole-4-carboxylic acid (1d) and 74.2 mg (0.5 mmol) of H-(L)-methioninamide were dissolved in 5 ml of DMF. 164 mg (0.5 mmol) of TOTU and 0.086 ml of diisopropylethylamine were added and the mixture was stirred at RT for 3 hours. The clear solution was concentrated. The residue was dissolved in ethyl acetate, the solution was washed with saturated sodium chloride solution, and the organic phase was dried using anhydrous sodium sulfate and concentrated. Yield: 149 mg (81%) $(M+H)^+ = 370.2$ (ES^+).

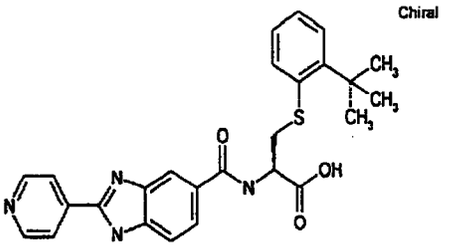
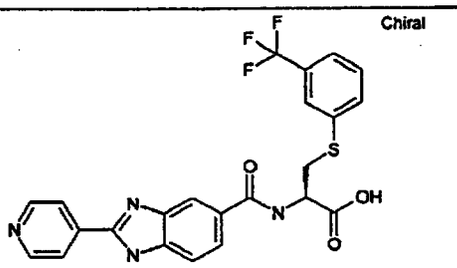
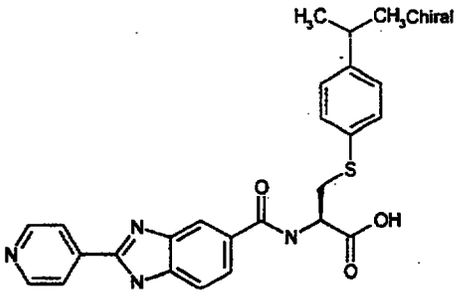
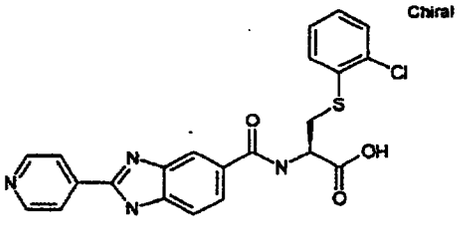
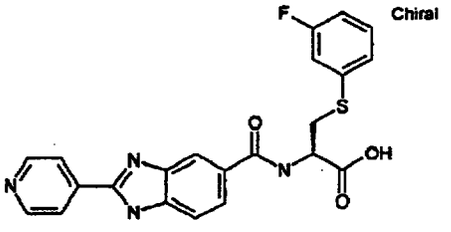
The examples mentioned in Table 2 which follows have been prepared analogously to Examples 91 to 94.

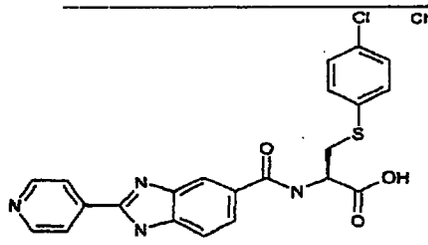
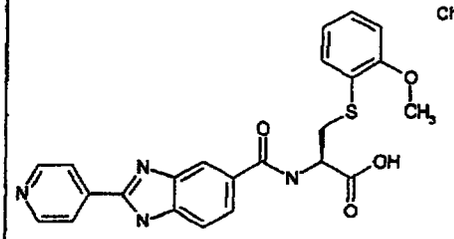
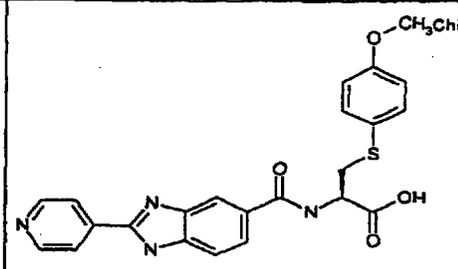
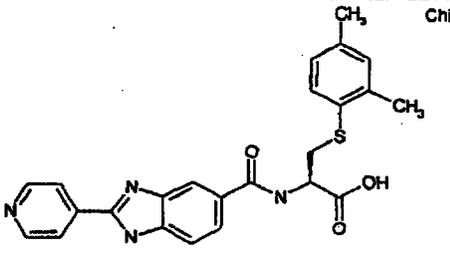
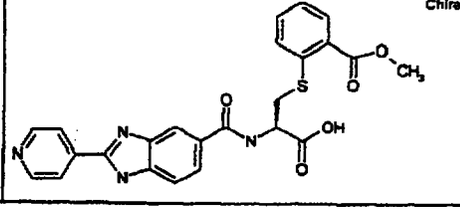
Table 2:

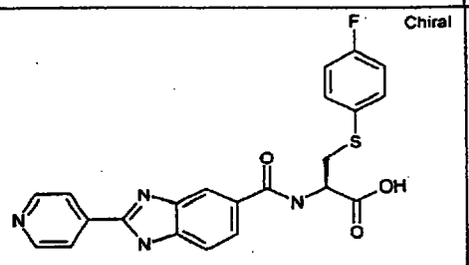
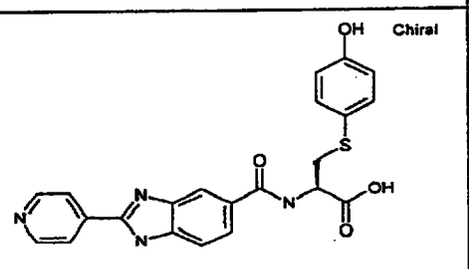
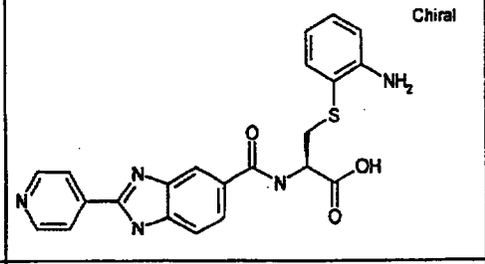
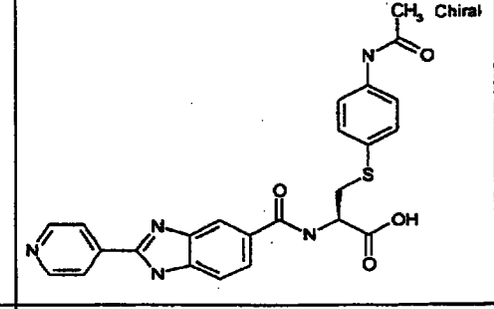
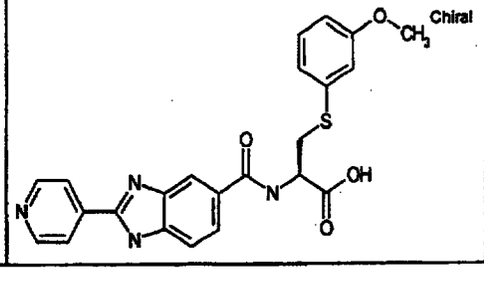
Example	Structure	Empirical formula	MS (M+ H)	Note
95		M.W. = 366.42 $C_{20}H_{22}N_4O_3$	367.1	Process variant a)
96		M.W. = 351.41 $C_{19}H_{21}N_5O_2$	352.2	a)
97		M.W. = 337.38 $C_{18}H_{19}N_5O_2$	338.2	a)
98		M.W. = 451.49 $C_{26}H_{21}N_5O_3$	452.2	a)
99		M.W. = 436.48 $C_{25}H_{20}N_6O_2$	437.2	a)
100		M.W. = 465.52 $C_{27}H_{23}N_5O_3$	466.2	a)

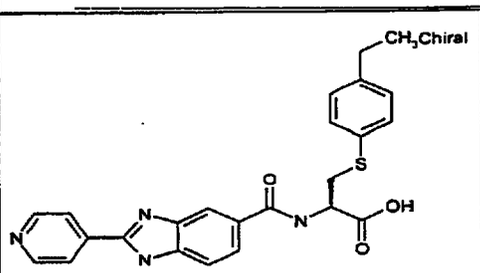
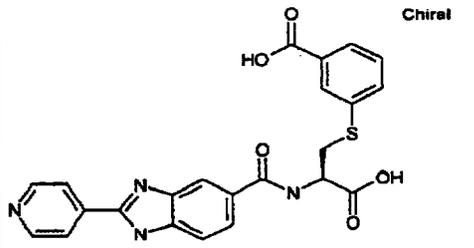
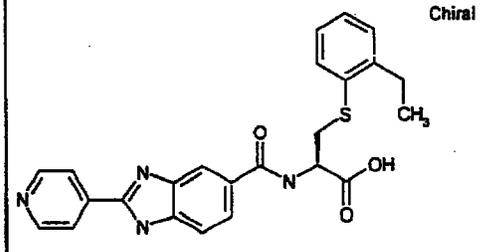
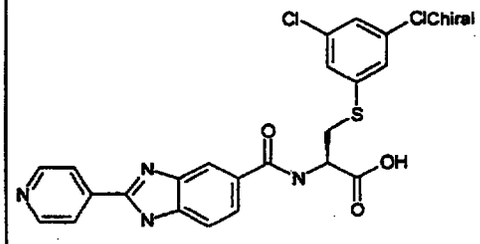
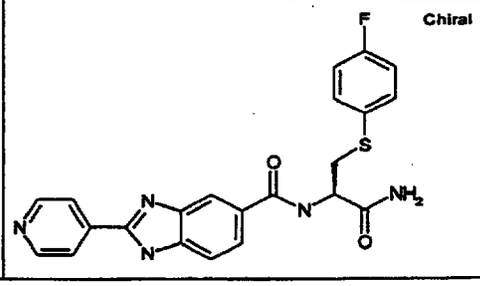
Example	Structure	Empirical formula	MS (M+ H)	Note
101		M.W. = 400.44 $C_{23}H_{20}N_4O_3$	401.2	a)
102		M.W. = 399.46 $C_{23}H_{21}N_5O_2$	400.2	a)
103		M.W. = 501.55 $C_{27}H_{27}N_5O_5$	502.3	a)
104		M.W. = 444.49 $C_{25}H_{24}N_4O_4$	445.3	a)
105		M.W. = 454.49 $C_{25}H_{22}N_6O_3$	455.1	a)
106		M.W. = 439.48 $C_{24}H_{21}N_7O_2$	440.2	a)

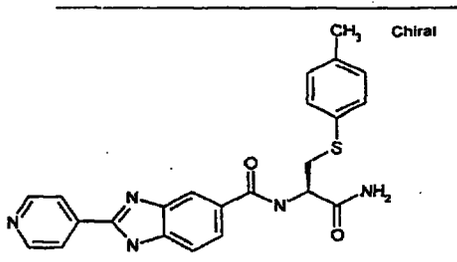
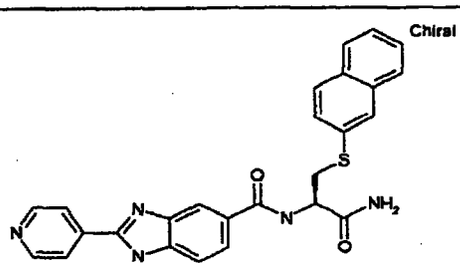
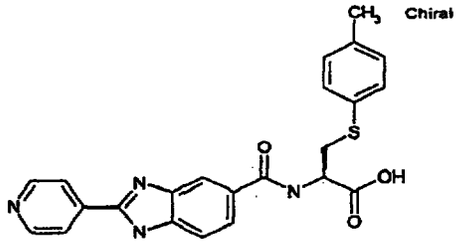
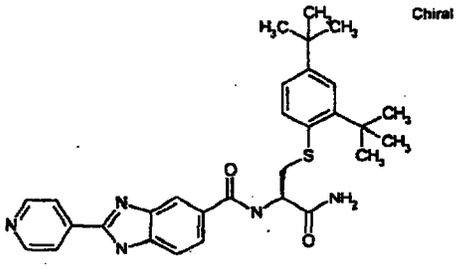
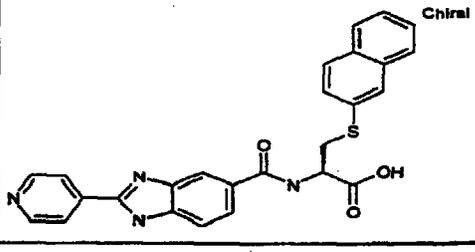
Example	Structure	Empirical formula	MS (M+ H)	Note
107		M.W. = 432.44 $C_{23}H_{20}N_4O_5$	433.2	a)
108		M.W. = 369.45 $C_{18}H_{19}N_5O_2S$	370.1	a)
109		M.W. = 384.46 $C_{19}H_{20}N_4O_3S$	385.1	a)
110		M.W. = 390.40 $C_{20}H_{18}N_6O_3$	391.1	a)
111		M.W. = 337.38 $C_{18}H_{19}N_5O_2$	338.2	a)
112		M.W. = 424.47 $C_{24}H_{20}N_6O_2$	425.2	a)

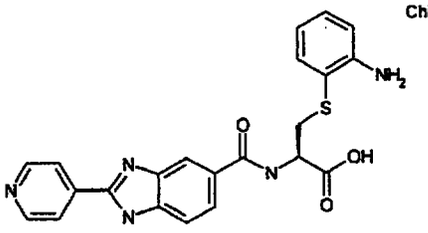
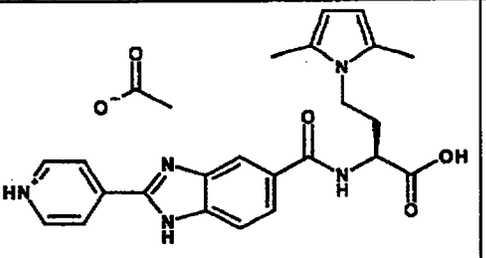
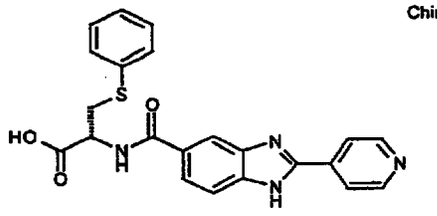
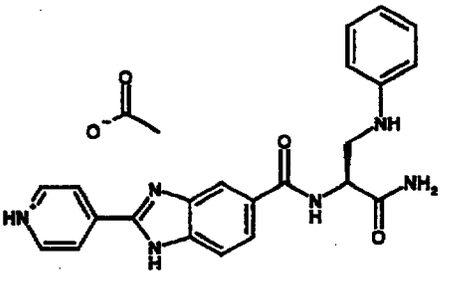
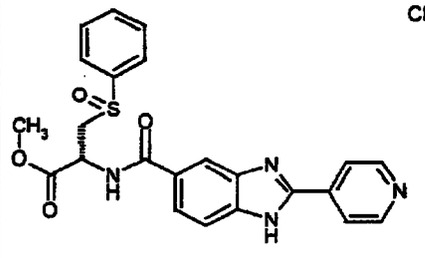
Example	Structure	Empirical formula	MS (M+ H)	Note
113	 Chiral	M.W. = 474.59 $C_{26}H_{26}N_4O_3S$	476	a)
114	 Chiral	M.W. = 486.48 $C_{23}H_{17}F_3N_4O_3S$	487	a)
115	 Chiral	M.W. = 460.56 $C_{25}H_{24}N_4O_3S$	462	a)
116	 Chiral	M.W. = 452.92 $C_{22}H_{17}ClN_4O_3S$	454	a)
117	 Chiral	M.W. = 436.47 $C_{22}H_{17}FN_4O_3S$	437	a)

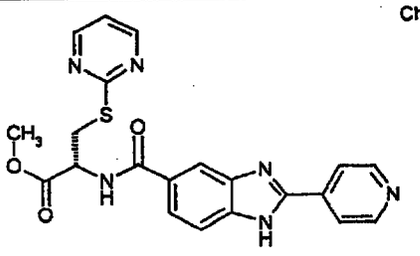
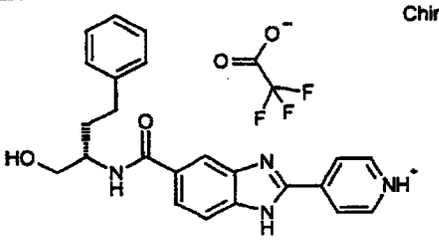
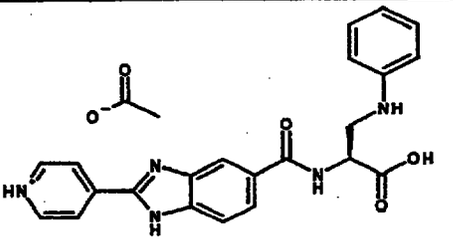
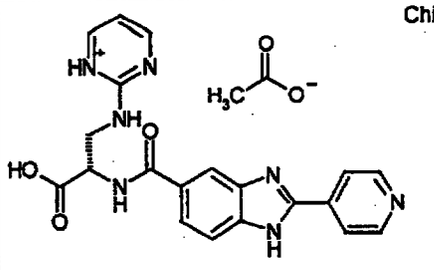
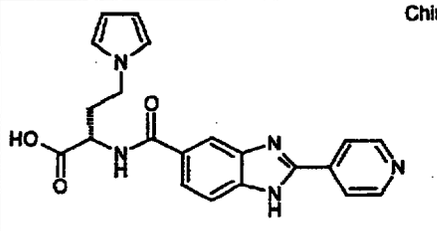
Example	Structure	Empirical formula	MS (M+ H)	Note
118	 Chiral	M.W. = 452.92 $C_{22}H_{17}ClN_4O_3S$	454	a)
119	 Chiral	M.W. = 448.50 $C_{23}H_{20}N_4O_4S$	449	a)
120	 CH_3Chiral	M.W. = 448.50 $C_{23}H_{20}N_4O_4S$	449	a)
121	 Chiral	M.W. = 446.53 $C_{24}H_{22}N_4O_3S$	447	a)
122	 Chiral	M.W. = 476.51 $C_{24}H_{20}N_4O_5S$	477	a)

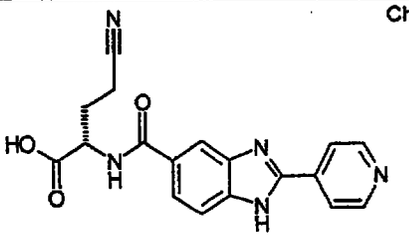
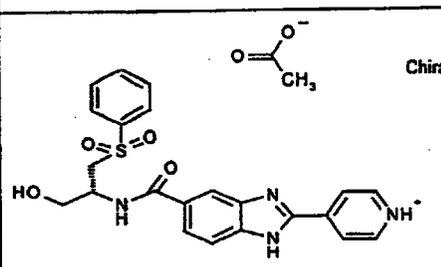
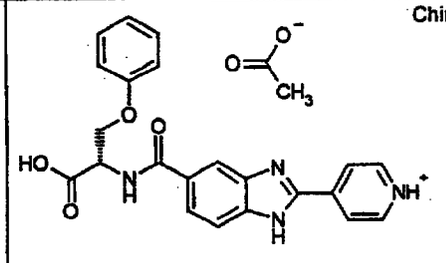
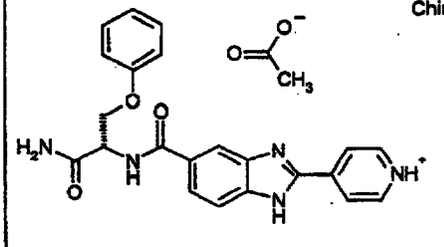
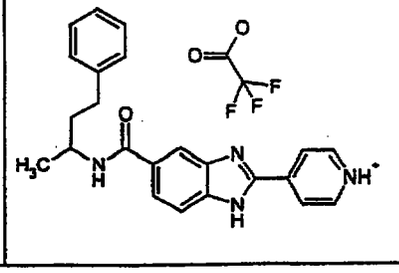
Example	Structure	Empirical formula	MS (M+ H)	Note
123		M.W. = 436.47 $C_{22}H_{17}FN_4O_3S$	437	a)
124		M.W. = 434.48 $C_{22}H_{18}N_4O_4S$	435	a)
125		M.W. = 433.49 $C_{22}H_{19}N_5O_3S$	434	a)
126		M.W. = 475.53 $C_{24}H_{21}N_5O_4S$	476	a)
127		M.W. = 448.50 $C_{23}H_{20}N_4O_4S$	449	a)

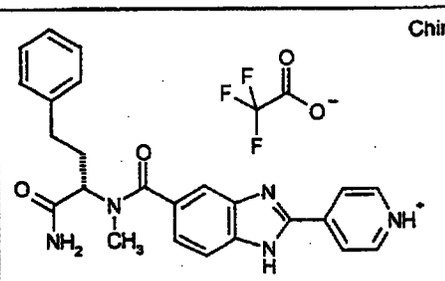
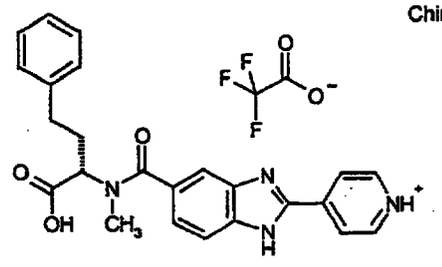
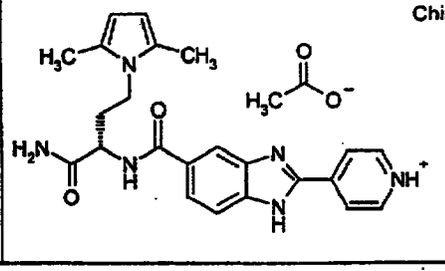
Example	Structure	Empirical formula	MS (M+ H)	Note
128		M.W. = 446.53 $C_{24}H_{22}N_4O_3S$	447	a)
129		M.W. = 462.49 $C_{23}H_{18}N_4O_5S$	463	a)
130		M.W. = 446.53 $C_{24}H_{22}N_4O_3S$	447	a)
131		M.W. = 487.37 $C_{22}H_{18}Cl_2N_4O_3S$	488	a)
132		M.W. = 435.48 $C_{22}H_{18}FN_5O_2S$	436	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
133	 Chiral	M.W. = 431.52 $C_{23}H_{21}N_5O_2S$	432	a)
134	 Chiral	M.W. = 467.55 $C_{26}H_{21}N_5O_2S$	468	a)
135	 Chiral	M.W. = 432.50 $C_{23}H_{20}N_4O_3S$	433	a)
136	 Chiral	M.W. = 529.71 $C_{30}H_{35}N_5O_2S$	531	a)
137	 Chiral	M.W. = 468.54 $C_{26}H_{20}N_4O_3S$	469	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
138	Chiral 	M.W. = 433.49 $C_{22}H_{19}N_5O_3S$	434	a)
139		M.W. = 417.47 $C_{23}H_{23}N_5O_3$	418.3	a)
140	Chiral 	M.W. = 418.48 $C_{22}H_{18}N_4O_3S$	419.2	a)
141		M.W. = 400.44 $C_{22}H_{20}N_6O_2$	401.2	a)
142	Chiral 	M.W. = 448.50 $C_{23}H_{20}N_4O_4S$	449.3	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
143	Chiral 	M.W. = 434.48 $C_{21}H_{18}N_6O_3S$	435.5	a)
144	Chiral 	M.W. = 386.46 $C_{23}H_{22}N_4O_2$	387.2	a)
145		M.W. = 401.43 $C_{22}H_{19}N_5O_3$	402.2	a)
146	Chiral 	M.W. = 403.40 $C_{20}H_{17}N_7O_3$	404.2	a)
147	Chiral 	M.W. = 389.42 $C_{21}H_{19}N_5O_3$	390.2	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
148	 Chiral	M.W. = 349.35 $C_{18}H_{15}N_5O_3$	350.3	a)
149	 Chiral	M.W. = 436.49 $C_{22}H_{20}N_4O_4S$	437.0	a)
150	 Chiral	M.W. = 402.41 $C_{22}H_{18}N_4O_4$	403.0	a)
151	 Chiral	M.W. = 401.43 $C_{22}H_{19}N_5O_3$	402.0	a)
152		M.W. = 370.46 $C_{23}H_{22}N_4O$	371.2	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
153	 Chiral	M.W. = 413.48 $C_{24}H_{23}N_5O_2$	414	a)
154	 Chiral	M.W. = 414.47 $C_{24}H_{22}N_4O_3$	415.2	a)
155	 Chiral	M.W. = 416.49 $C_{23}H_{24}N_6O_2$	417.3	a)

M.W. means molecular weight

Example 156

The following compounds were prepared according to process variant a):

a) Preparation of 2-fluoroisonicotinic acid:

5.00 g (45 mmol) of 2-fluoro-4-methylpyridine and 1.00 g (17 mmol) of KOH were treated with 50 ml of pyridine and heated under reflux. 20.00 g (127 mmol) of potassium permanganate were added in portions in the course of 30 minutes at this temperature and the mixture was heated under reflux for a further 1.5 hours. It was then cooled in an ice bath, treated with 100 ml of water and brought to a pH of 1 using concentrated hydrochloric acid. After the addition of 100 ml of ethyl acetate, the insoluble residue was filtered off and the aqueous phase was extracted a further two times with 100 ml of ethyl acetate each time. The combined ethyl acetate phases were dried over magnesium sulfate and concentrated under reduced pressure. 2.70 g of 2-fluoroisonicotinic acid were obtained.

Yield: 42%

b) Preparation of (2-fluoropyridin-4-yl)methanol:

12.60 g (89 mmol) of 2-fluoroisonicotinic acid were introduced into 300 ml of toluene with 13.3 ml (95 mmol) of triethylamine and treated with 9.08 ml (95 mmol) of ethyl chloroformate and stirred at room temperature (20°-23°C) for 1 hour (h). The triethylammonium chloride was then filtered off and the toluene phase was concentrated under reduced pressure. The residue was taken up in 200 ml of absolute THF and cooled to –78°C. A suspension of lithium aluminum hydride (3.55 g, 95 mmol) in THF was added dropwise at this temperature and the mixture was stirred for a further 30 minutes. The reaction mixture was then allowed to come to room temperature and poured onto 1 l of ice water. This was followed by extraction 4 times with 300 ml of ethyl acetate, drying of the combined ethyl acetate phase over magnesium sulfate and evaporation of the solvent yielded the crude product, which after purification by means of medium-pressure chromatography (CH_2Cl_2:MeOH such as 9:1) yielded 5.10 g (40 mmol) of the desired product. Yield 45%

c) Preparation of 2-fluoropyridine-4-carbaldehyde

A solution of 5 g (39 mmol) of (2-fluoropyridin-4-yl)methanol in dichloromethane was added dropwise to a solution of 4.6 ml (54 mmol) of oxalyl chloride and 7.6 ml (106 mmol) of dimethyl sulfoxide (DMSO) in 450 ml of dichloromethane at –78°C and the mixture was stirred for 15 minutes. 24 ml (180 mmol) of triethylamine were then added and the reaction solution was slowly warmed to room temperature. It was poured onto 500 ml of water and washed once each with 10% strength citric acid (200 ml) and 10% strength sodium carbonate solution. The dichloromethane phase was dried over magnesium sulfate and concentrated under reduced pressure. Yield 4.60 g (37 mmol), 94%.

d) Preparation of 2-(2-fluoropyridin-4-yl)-1H-benzoimidazole-5-carboxylic acid:

2.00 g (15 mmol) of 2-fluoropyridine-4-carbaldehyde were suspended in 100 ml of nitrobenzene with 2.40 g (15 mmol) of 3,4-diaminobenzoic acid and stirred at 145°C for 3 h. The reaction solution was then cooled to 0°C and the crystals slowly forming in the course of this were filtered off. 2.53 g (9.8 mmol) of the desired benzimidazole were obtained. Yield 62%

e) Preparation of 2-(2-methylaminopyridin-4-yl)-1H-benzoimidazole-5-carboxylic acid:

100 mg (0.38 mmol) of 2-(2-fluoropyridin-4-yl)-1H-benzoimidazole-5-carboxylic acid were dissolved in 5 ml of methanol. The methanol solution was then saturated with gaseous methylamine and the reaction

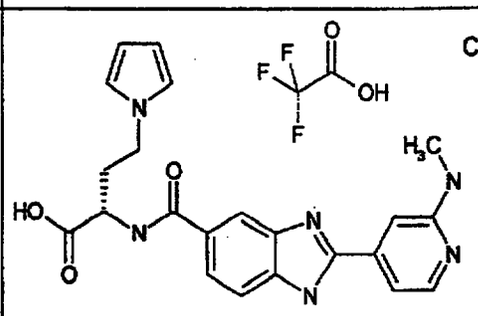
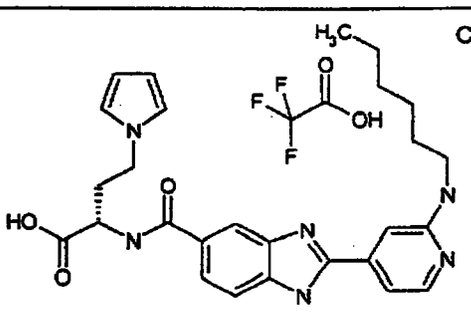
mixture was stirred at 120°C in an autoclave for 10 h under autogenous pressure. Medium-pressure chromatography (CH_2Cl_2:MeOH = 2:1) yielded 56 mg (0.21 mmol) of the substitution product. Yield 55%

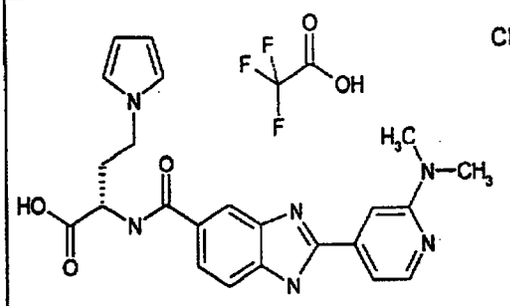
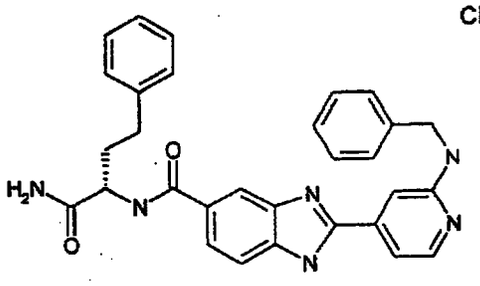
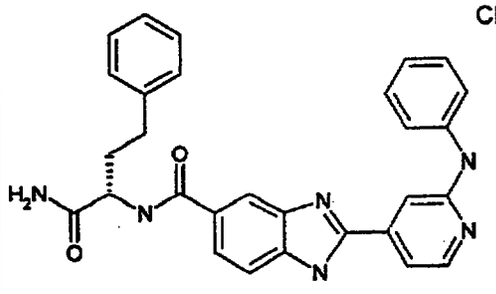
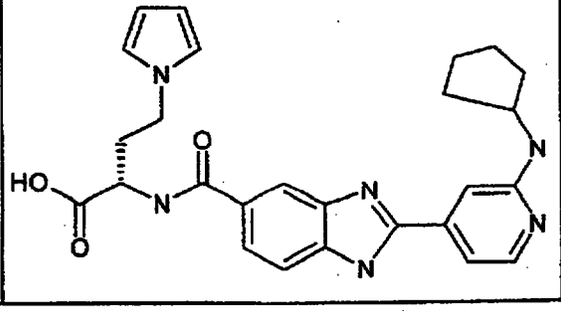
f) Preparation of 2-(S)-{[2-(2-methylaminopyridin-4-yl)-1H-benzoimidazole-5-carbonyl]amino]-4-pyrrol-1-yl butyric acid trifluoroacetate:

50 mg (0.186 mmol) of 2-(2-fluoropyridin-4-yl)-1H-benzoimidazole-5-carboxylic acid were dissolved in 3 ml of DMF and cooled to 0°C. 100 µl (0.58 mmol) of diisopropylethylamine and 64 mg (0.195 mmol) of TOTU were added to this mixture. 33 mg (0.196 mmol) of 2-(S)-amino-4-pyrrol-1-ylbutyric acid were then added and the reaction solution was allowed to come to room temperature. It was stirred for 18 h, then poured onto 20 ml of 10% strength sodium hydrogencarbonate solution and extracted 3 times with n-butanol (50 ml). After the evaporation of the butanol, the residue was purified by means of preparative HPLC (acetonitrile, 0.1% strength trifluoroacetic acid). 40 mg (0.075 mmol) of the coupled product were thus obtained. Yield 42%

The examples mentioned in Table 3 which follows were prepared analogously:

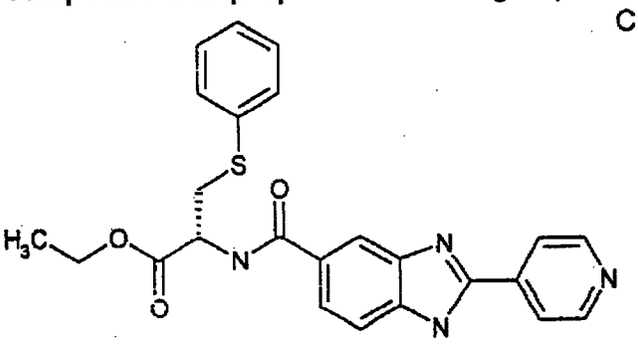
Table 3

Example	Structure	Empirical formula	MS (M+ H)	Note
157	 Chiral	$C_{24}H_{23}F_3N_6O_5$	419.2	a)
158	 Chiral	$C_{29}H_{33}F_3N_6O_5$	489.3	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
159	Chiral 	$C_{25}H_{25}F_3N_6O_5$	433.0	a)
160	Chiral 	$C_{30}H_{28}N_6O_2$	505.2	a)
161	Chiral 	$C_{29}H_{26}N_6O_2$	491.2	a)
162		$C_{26}H_{28}N_6O_3$	473.3	a)

Example 163

The following compound was prepared according to process variant a):



a) Preparation of ethyl 2-(S)-amino-3-phenylsulfanyl propionate

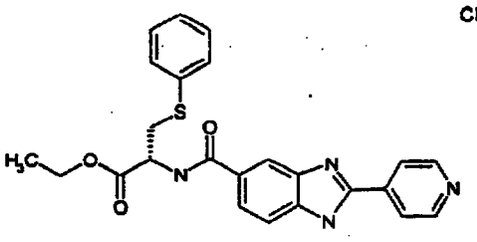
1.7 ml (23 mmol) of thionyl chloride were added dropwise at −10°C to 1.00 g (5 mmol) of 2-(S)-amino-3-phenylsulfanylpropionic acid dissolved in 10 ml of methanol. The reaction solution was then allowed to come to room temperature and 5 ml of DMF were added. It was then heated at 70°C for 23 h and, after cooling to −10°C, 1 ml (13.5 mmol) of thionyl chloride was added again. It was then stirred at 70°C for a further 14 h. After the evaporation of the liquid phase, the residue was taken up in water and rendered basic with concentrated aqueous ammonia solution and extracted 3 times with ethyl acetate (75 ml each time). After drying over magnesium sulfate and evaporation, the product was obtained as an oil which was used without further purification for the coupling with the carboxylic acid component. Yield 830 mg (3.7 mmol), 74%

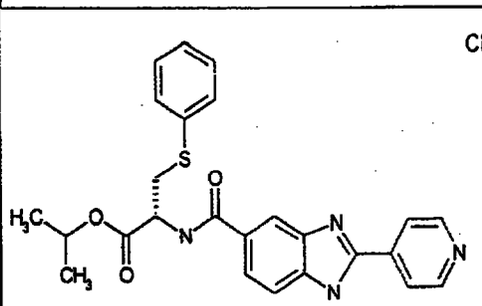
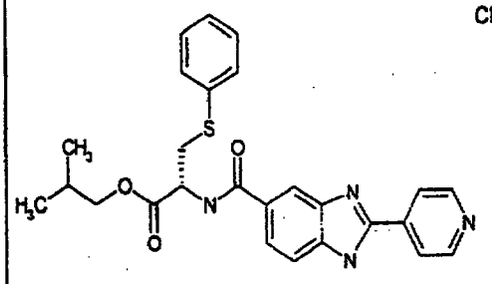
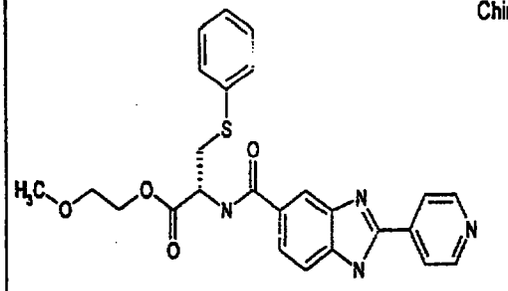
b) Preparation of ethyl 3-phenylsulfanyl-2-(S)-[(2-pyridin-4-yl-1H-benzoimidazole-5-carbonyl)amino]propionate

In this case, the standard TOTU coupling with 188 mg (0.83 mmol) of ethyl 2-(S)-amino-3-phenylsulfanylpropionate and 200 mg (0.83 mmol) of 2-pyridin-4-yl-1H-benzoimidazole-5-carboxylic acid yielded the desired product. Yield 43% (160 mg, 0.36 mmol)

The examples mentioned in Table 4 which follows were prepared analogously:

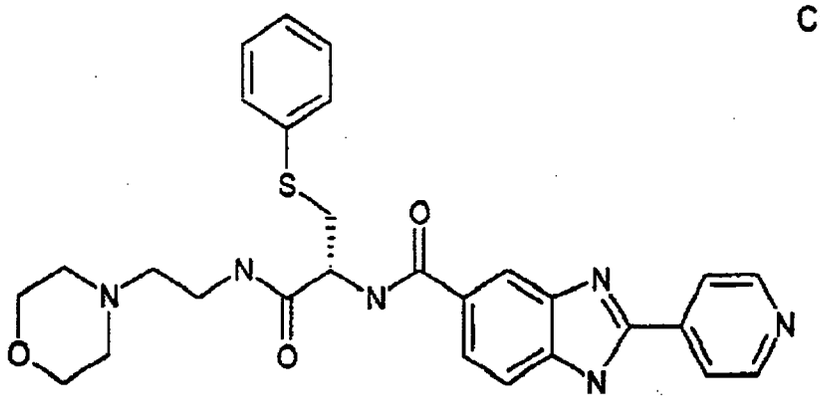
Table 4

Example	Structure	Empirical formula	MS (M+ H)	Note
164	 Chiral	$C_{24}H_{22}N_4O_3S$	447.1	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
165	 Chiral	$C_{25}H_{24}N_4O_3S$	461.3	a)
166	 Chiral	$C_{26}H_{26}N_4O_3S$	475.2	a)
167	 Chiral	$C_{25}H_{24}N_4O_4S$	477.3	a)

Example 168

The following compound was prepared according to process variant a):


Chiral

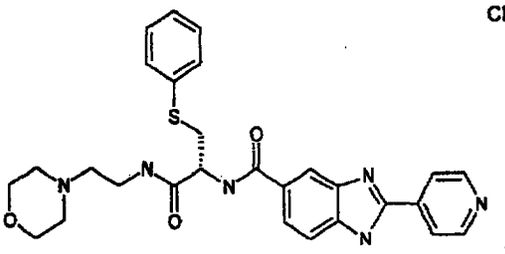
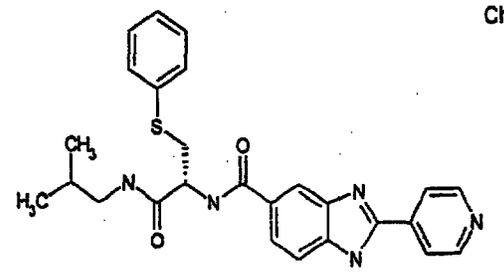
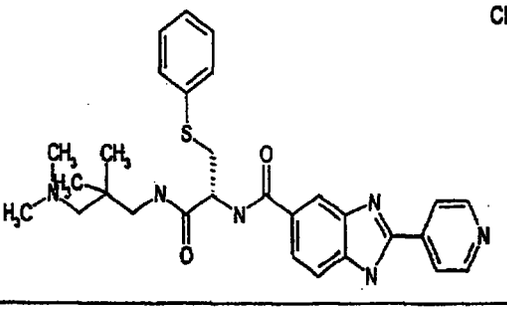
a) Preparation of 2-pyridin-4-yl-1H-benzoimidazole-5-carboxylic acid [1-(2-morpholin-4-ylethylcarbamoyl)-2-phenylsulfanylethyl]amide

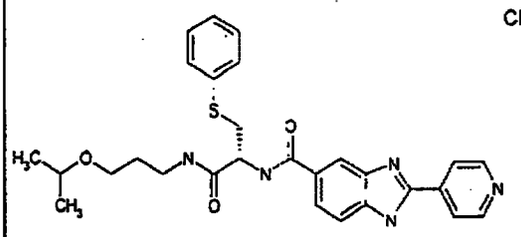
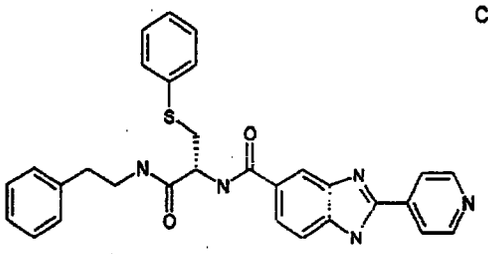
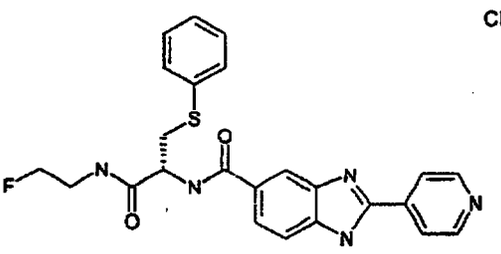
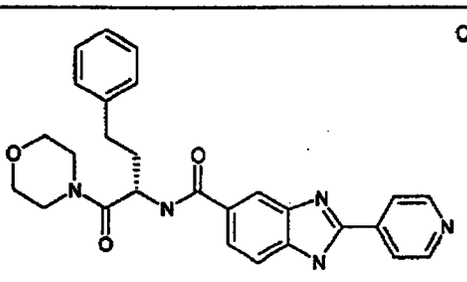
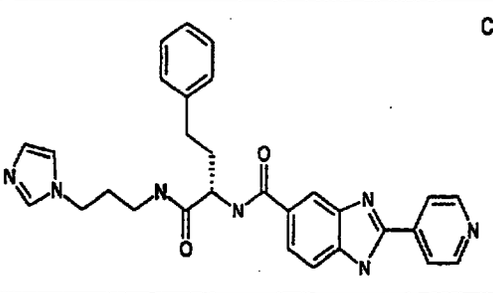
100 mg (0.24 mmol) of 3-phenylsulfanyl-2-[(2-pyridin-4-yl-1H-benzoimidazole-5-carbonyl)amino]propionic acid were dissolved in 10 ml of DMF. 68 µl (0.39 mmol) of disopropylethylamine and 248 mg (0.48 mmol) of benzotriazol-1-yloxytripyrrolidinephosphonium hexafluorophosphates

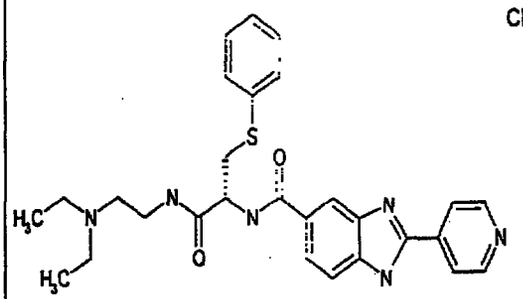
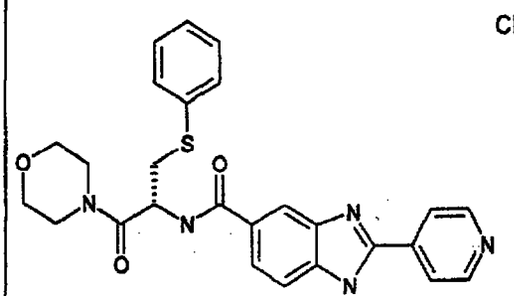
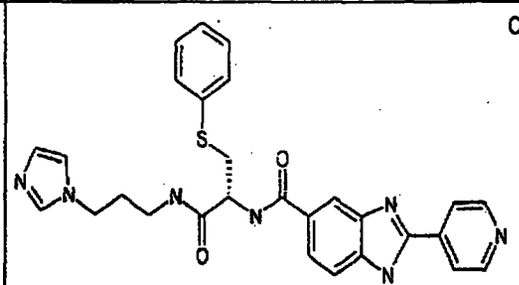
were added to this mixture at 0°C. It was then allowed to come to room temperature and stirred for 24 h. The solvent was removed in a high vacuum at room temperature and the residue was purified by means of medium-pressure chromatography (CH_2Cl_2:MeOH = 8:2). Yield 73 mg (0.1376 mmol), 57%.

The examples mentioned in Table 5 which follows were prepared analogously:

Table 5

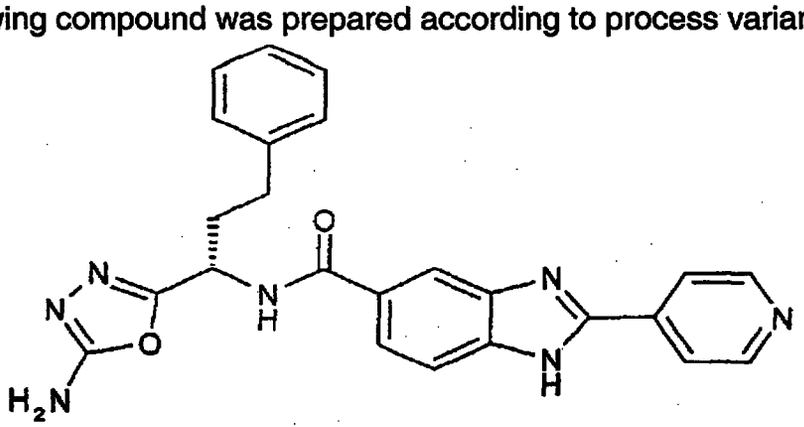
Example	Structure	Empirical formula	MS (M+ H)	Note
169	Chiral 	$C_{28}H_{30}N_6O_3S$	531.2	a)
170	Chiral 	$C_{26}H_{27}N_5O_2S$	474.2	a)
171	Chiral 	$C_{29}H_{34}N_6O_2S$	531.2	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
172	Chiral 	$C_{28}H_{31}N_5O_3S$	518.2	a)
173	Chiral 	$C_{30}H_{27}N_5O_2S$	522.7	a)
174	Chiral 	$C_{24}H_{22}FN_5O_2S$	464.1	a)
175	Chiral 	$C_{27}H_{27}N_5O_3$	470.2	a)
176	Chiral 	$C_{29}H_{29}N_7O_2$	508.2	a)

Example	Structure	Empirical formula	MS (M+ H)	Note
177	 Chiral	$C_{28}H_{32}N_6O_2S$	517.3	a)
178	 Chiral	C26H25N_5O_3S	488.2	a)
179	 Chiral	$C_{28}H_{27}N_7O_2S$	526.2	a)

Example 180:

The following compound was prepared according to process variant a):



a) Preparation of Z-homophenylalanine hydrazide:

5 g (16 mmol) of Z-homophenylalanine were dissolved in 100 ml of methyl tert-butyl ether at room temperature, treated with 3.3 g (16 mmol) of N,N'-dicyclohexylcarbodiimide and 50 mg of dimethylaminopyridine and the

mixture was stirred at room temperature for 2 h. The reaction mixture was then filtered through a folded filter, and the filtrate was washed with 1M potassium hydrogensulfate solution, saturated sodium hydrogencarbonate solution and water. The organic phase was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in 20 ml of dry ethanol, treated with 0.78 ml (16 mmol) of hydrazine hydrate and stirred at room temperature for 2 h. The course of the reaction was monitored by means of thin-layer chromatography (TLC), and after completion of the reaction the mixture was concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/n-heptane 1:1 and Z-homophenylalanine hydrazide was obtained, which was reacted further in this manner.

b) Preparation of benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl] carbamate

0.66 g of Z-homophenylalanine hydrazide was suspended in 10 ml of water at room temperature, treated with 200 mg of potassium hydrogencarbonate and 0.4 ml of a cyanogen bromide solution (5 M in acetonitrile) was then added. The mixture was stirred at room temperature for 3 h and then extracted a number of times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was stirred with methyl tert-butyl ether, filtered off with suction and dried under reduced pressure. The benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]carbamate was employed in the next stage without further purification.

c) Preparation of 5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-ylamine:

0.33 g of benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]-carbamate were dissolved in 50 ml of dry methanol at room temperature, treated under argon with hydrogenation catalyst (10% palladium on carbon) and hydrogenated at room temperature for 3 h. The reaction mixture was filtered off through Celite, the filtrate was concentrated under reduced pressure and the residue was dried in a high vacuum. 5-(1-Amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-ylamine was obtained, which was employed in the next stage without further purification.

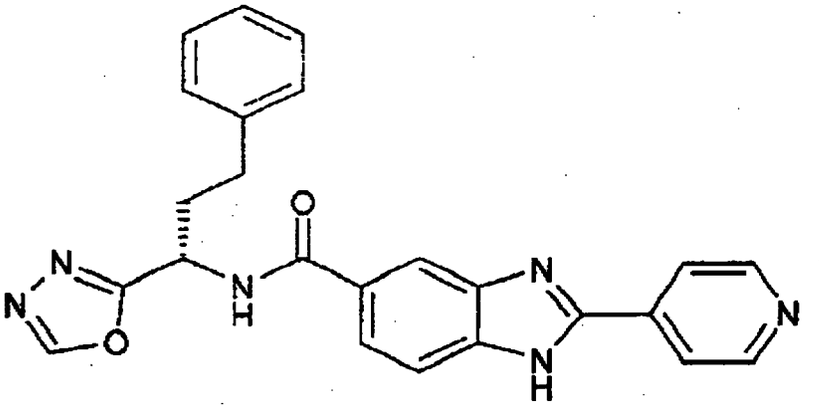
d) Preparation of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]amide:

0.18 g of 5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-ylamine was dissolved in 10 ml of dry dimethylformamide at room temperature, treated with 200 mg of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid, 270 mg

of TOTU and 0.12 ml of diisopropylamine and stirred at room temperature for 4 h. The reaction mixture was concentrated, and the residue was taken up in ethyl acetate and washed successively with water, saturated sodium hydrogencarbonate solution, water and saturated sodium chloride solution. The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was stirred with methyl tert-butyl ether, filtered off and dried in a high vacuum. 2-Pyridin-4-yl-1H-benzimidazole-5-carboxylic acid [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]amide, which melts at 160°C with decomposition, is obtained.

Example 181:

The following compound was prepared according to process variant a):



a) Z-Homophenylalanine hydrazide was prepared as described in Example 180.

b) Preparation of benzyl (1-[1,3,4]oxadiazol-2-yl-3-phenylpropyl]-carbamate:

1 g of Z-homophenylalanine hydrazide was suspended in 8 ml of ethyl orthoformate at room temperature and the mixture was heated under reflux for 4 h. The cooled reaction mixture was treated with methyl tert-butyl ether, the precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate/n-heptane 1/1 and yielded benzyl (1-[1,3,4]oxadiazol-2-yl-3-phenylpropyl)carbamate, which was employed in the next stage.

c) The preparation of 1-[1,3,4]oxadiazol-2-yl-3-phenylpropylamine is carried out analogously to the preparation of 5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-ylamine as described in Example 180.

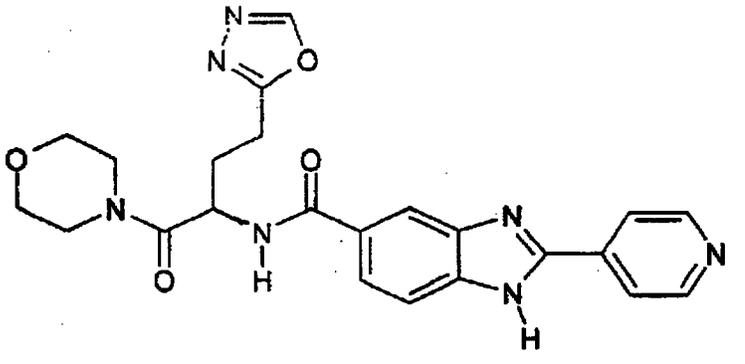
d) Preparation of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid (1-[1,3,4]oxadiazol-2-yl-3-phenylpropyl)amide:

220 mg of 1-[1,3,4]oxadiazole-2-yl-3-phenylpropylamine were dissolved in 10 ml of dry dimethylformamide at room temperature, treated with 260 mg

of 2-pyridin-4-yl-1H-benzimidazol-5-carboxylic acid, 350 mg of TOTU and 0.15 ml of diisopropylamine and stirred at room temperature for 4 h. The reaction mixture was concentrated, the residue was taken up in ethyl acetate and the mixture was washed successively with water, saturated sodium hydrogencarbonate solution, water and saturated sodium chloride solution. The organic phase was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel using dichloromethane/methanol 8/1 and yielded 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid (1-[1,3,4]oxadiazol-2-yl-3-phenylpropyl)amide which melts at 103°C with decomposition.

Example 182

The following compound was prepared according to process variant a):



a) Preparation of L-N-benzoyloxycarbonyl-4-([1,3,4]oxadiazol-2-yl)-2-aminobutanoic acid

1 g of Z-glutamic acid γ-hydrazide was suspended in 20 ml of trimethyl orthoformate with 30 mg of para-toluenesulfonic acid and the mixture was stirred at room temperature. The suspension clarified within 30 minutes, and the solution resulting in this way was filtered and diluted with 100 ml of water. After addition of 20 ml of 2N hydrochloric acid, it was extracted 5 times with ethyl acetate and the combined organic phases were then dried over sodium sulfate. After filtration, the solution was concentrated under reduced pressure and a viscous opaque mass was obtained.

b) Preparation of L-*N*-benzyloxycarbonyl-4-([1,3,4]oxadiazol-2-yl)-2-aminobutanoic acid morpholide

300 mg of L-*N*-benzyloxycarbonyl-4-(1,3,4]oxadiazol-2-yl)-2-aminobutanoic acid and 200 mg of EDC hydrochloride were dissolved in 20 ml of dichloromethane and then treated with 2 ml of morpholine. After stirring at room temperature for 2 days, the solution was extracted 3 times by shaking with saturated sodium hydrogencarbonate solution, 3 times by shaking with aqueous citric acid solution and once by shaking with saturated sodium

hydrogencarbonate solution. The organic phase was dried over sodium sulfate and concentrated after filtration under reduced pressure. A yellowish opaque residue was obtained.

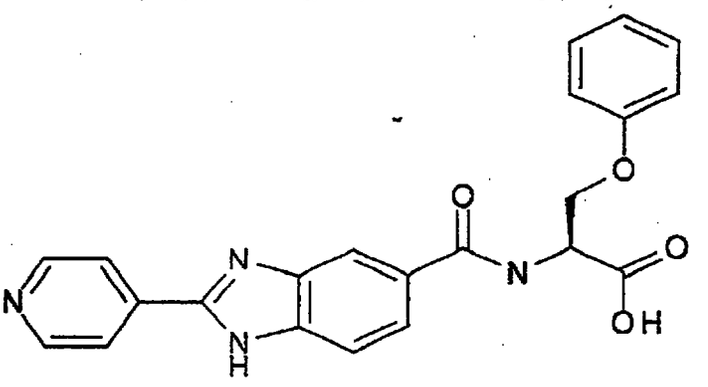
c) Preparation of L-4-([1,3,4]oxadiazol-2-yl)-2-aminobutanoic acid morpholide

70 mg of L-*N*-benzoyloxycarbonyl-4-([1,3,4]oxadiazol-2-yl)-2 aminobutanoic acid morpholide were dissolved in 20 ml of methanol and treated with 1 spatula tipful of palladium on active carbon (5%) and the suspension was stirred under a hydrogen atmosphere. After three hours, the catalyst was filtered off through Celite and the filtrate was concentrated under reduced pressure after filtration through a 0.45 μm filter.

d) Preparation of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid [1-(morpholine-4-carbonyl)-3-[1,3,4]oxadiazol-2-ylpropyl]amide

43 mg of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid, 75 mg of HATU and 51 mg of diisopropylethylamine were dissolved in 1 ml of *N,N*-dimethylformamide and treated with 40 mg of L-4-([1,3,4]oxadiazol-2-yl)-2-aminobutanoic acid morpholide in 0.4 ml of *N,N*-dimethylformamide after stirring for 10 min. After stirring at room temperature for 7 h, 200 mg of aminomethylpolystyrene (1.37 mmol/g) and 20 ml of *N,N*-dimethylformamide were added. After 1 h, the mixture was filtered and the *N,N*-dimethylformamide was distilled off under reduced pressure. The residue was digested with cold acetonitrile. The insoluble residue was discarded and the acetonitrile solution was subjected to gradient filtration on RP18 silica gel using water/acetonitrile mixtures. A glassy yellowish solid was isolated.

Example 183 3-Phenoxy-2-[(2-pyridin-4-yl-1H-benzoimidazole-2-carbonyl)amino]propionic acid hydrogenacetate



a) 2-Pyridin-4-yl-1H-benzoimidazole-5-carboxylic acid (in the following called compound I) [lacuna] 15.2 g (0.1 mol) of 3,4-diaminobenzoic acid

were suspended in 1 l of nitrobenzene and treated with 11.2 g (0.104 mol) of pyridine-4-aldehyde. The mixture was then heated with vigorous stirring for 8 h at 145°C to 155°C. After cooling of the solution, the precipitated product was filtered off with suction and washed thoroughly with ethyl acetate and dichloromethane. For purification, the crude product was heated to boiling in a mixture of 300 ml of methanol, 100 ml of dichloromethane and 10 ml of DMF. After cooling, the undissolved product was filtered off and washed with dichloromethane. The material obtained was taken up in approximately 200 ml of DMSO, then the mixture was heated until a homogeneous solution resulted – cooled to approximately 50°C and treated with 200 ml of methanol – the product crystallized after approximately 30 min at RT. The precipitate was filtered off and washed thoroughly with methanol. Yield: 19.4 g.

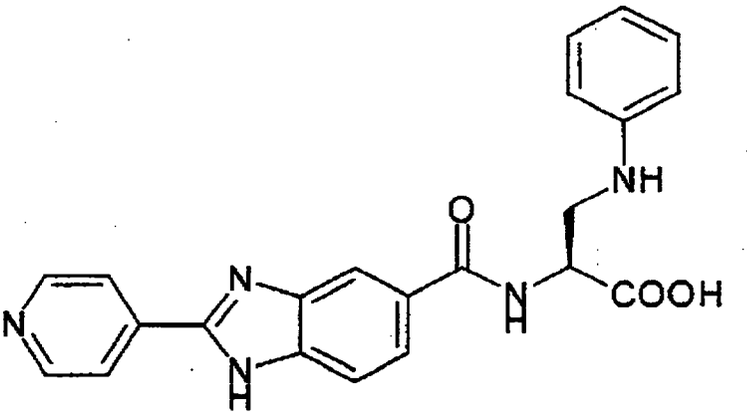
b) (S)-2-Amino-3-phenoxypropionic acid hydrochloride (m.w. 217.6)

2.8 g of trt-Ser-OMe (Bachem), 0.75 of phenol and 2.25 g of triphenylphosphine were dissolved together in 60 ml of THF, absolute, and treated dropwise with 1.49 g of diethyl azodicarboxylate at 0°C in the course of 30 min. The reaction mixture was stirred at 0°C for 30 min and warmed to RT (about 1 h). For working-up, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (heptane:EA = 1.5:1). The methyl (S)-2-tritylamino-3-phenoxypropionate thus obtained crystallized slowly in long needles, and was heated under reflux for 1 h in 5 M HCl to remove the protective groups. The reaction solution was evaporated to dryness under reduced pressure by coevaporating a number of times with toluene and the residue was recrystallized from a little tert-butanol.

Process step c)

239 mg of 2-pyridin-4-yl-1H-benzoimidazole-5-carboxylic acid from a) were suspended in 10 ml of DMF and treated successively with 328 mg of TOTU and 0.17 ml of ethyldiisopropylamine. The mixture was stirred at RT for 45 min and 217.6 mg of (S)-2-amino-3-phenoxypropionic acid hydrochloride prepared as under b) were added to the resulting clear solution, and 0.34 ml of ethyldiisopropylamine was added. After stirring for 4 h, the mixture was concentrated under reduced pressure and the title compound was isolated by flash chromatography on silica gel (DCM:MeOH:AcOH:water = 70:10:1:1). The title compound obtained had an m.w. of 402.41, molecular mass of 402 and the empirical formula $C_{22}H_{18}N_4O_4$.

Example 184 3-Phenylamino-2-[(2-pyridin-4-yl-1H-benzoimidazole-5-carbonyl)amino]propionic acid hydrogenacetate



a) L-2-Amino-3-phenylaminopropionic acid

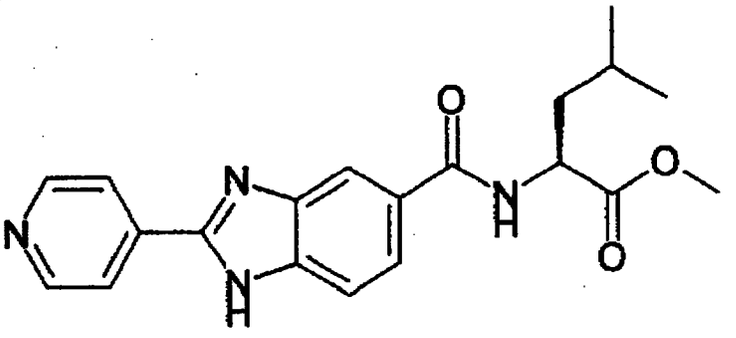
2.74 g of triphenylphosphine were dissolved in 30 ml of acetonitrile with warming and cooled to –35°C to –45°C with exclusion of moisture (the phosphine precipitated in finely divided form in the course of this) and 1.82 ml of diethyl azodicarboxylate were then added dropwise at this temperature in the course of 40 min. The mixture was stirred at –35°C for 15 min. A solution of 2.5 g of N-benzyloxycarbonyl-L-serine in 5 ml in acetonitrile and 2 ml of THF was added dropwise to this mixture, and in the course of this the temperature was not allowed to rise above –35°C. The mixture was then allowed to react at –35°C for 1 h and warmed to RT. The reaction solution was freed from the solvent under reduced pressure and the crude product was immediately purified using medium-pressure chromatography on silica gel. (DCM/AcCN: 20/1). After removing the solvent, 1.4 g of clean N-benzoyloxycarbonyl-L-serine-β-lactone were obtained (see also Org. Synth. 1991 (70) 1ff) in fine needles. 1.2 g of the lactone were dissolved in 10 ml of acetonitrile and heated under reflux for 2 h with 0.51 g of aniline. After removal of the solvent, the product was isolated by chromatography on silica gel (DCM/MeOH/AcOH = 10/5/1). 1.1 g (68%) of L-2-benzyloxycarbonylamino-3-phenylaminopropionic acid were thus obtained.

To remove the protective group, the Z-protected derivative was dissolved in methanol, 80 mg of catalyst (10% Pd-C) were added under inert gas, and hydrogen was passed in until the Z-protective group was completely removed. After filtering off the catalyst and evaporating the filtrate, 0.58 g of L-2-amino-3-phenylaminopropionic acid (92%) was obtained as yellowish soft needles.

Process step b)

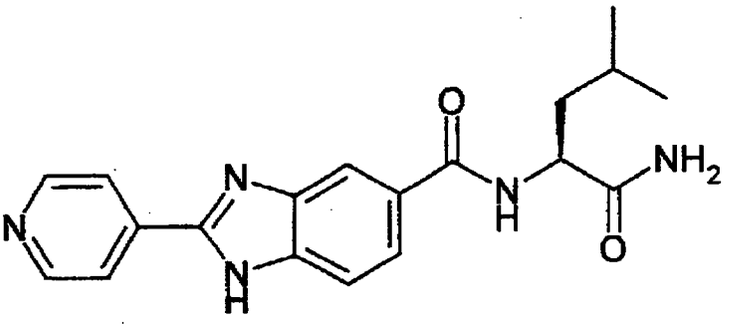
239 mg of 2-pyridin-4-yl-1H-benzoimidazole-5-carboxylic acid prepared as in Example 183 were suspended in 10 ml of DMF and treated successively with 328 mg of TOTU and 0.17 ml of ethyldiisopropylamine. The mixture was stirred at RT for 45 min and 180.2 mg of (S)-2-amino-3-phenyl-aminopropionic acid prepared according to a) and 0.34 ml of ethyldiisopropylamine were added to the resulting clear solution. After stirring for 4 h, the mixture was concentrated under reduced pressure and the title compound was isolated by flash chromatography on silica gel (DCM;MeOH:AcOH:water = 70:10:1:1). The title compound obtained had an m.w. of 401.43 and the empirical formula $C_{22}H_{19}N_5O_3$.

Example 185



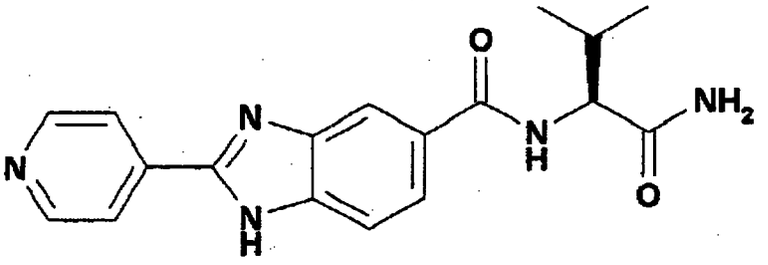
239.2 mg (1 mmol) of the compound I prepared as in Example 183 were treated successively with 182.7 mg (1 mmol) of H-Leu-OMe HCl, 328 mg (1 mmol) of TOTU and 0.34 ml (2 mmol) of ethyldiisopropylamine in approximately 8 ml of DMF. After 6 h at RT, the solvent was distilled off under reduced pressure, the residue was taken up in EA and the mixture was washed 3 times each with water and saturated NaCl solution. The organic phase was dried and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (DCM/MeOH: 15/1). Yield: approximately 200 mg.

Example 186



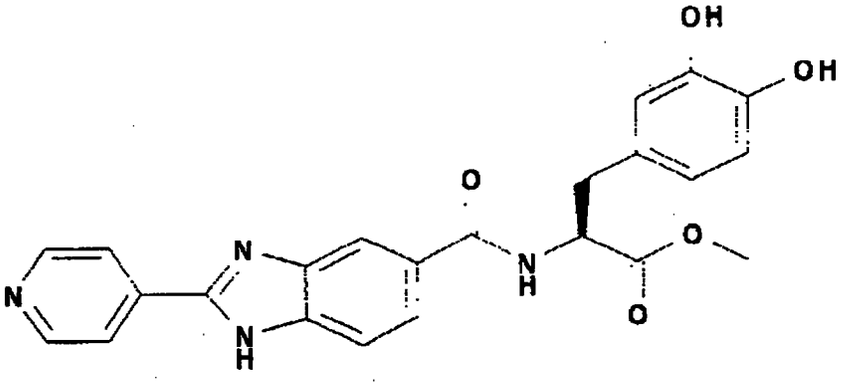
239.2 mg (1 mmol) of the compound I prepared as in Example 183 were treated successively with 166.6 mg (1 mmol) of H-Leu-NH_2 HCl, 328 mg (1 mmol) of TOTU and 0.34 ml (2 mmol) of ethyldiisopropylamine in approximately 8 ml of DMF. After 6 h at RT, the solvent was distilled off under reduced pressure, the residue was taken up in EA and the mixture was washed once with water. The aqueous phase was then saturated with NaCl and extracted twice with EA/THF=1/1. The combined organic phases were washed once with saturated NaCl solution, dried and evaporated to dryness under reduced pressure. The residue was precipitated with dichloromethane and filtered off. For purification, the crude product was boiled with DCM/EA=1/1, filtered off and washed thoroughly with DCM/ether. Yield: approximately 200 mg.

Example 187



239.2 mg (1 mmol) of the compound I prepared as in Example 183 were treated successively with 152.6 mg (1 mmol) of H-Val-NH_2·HCl, 328 mg (1 mmol) of TOTU and 0.34 ml (2 mmol) of ethyldiisopropylamine in approximately 8 ml of DMF. After 6 h at RT, the solvent was distilled off under reduced pressure, the residue was taken up in EA and the mixture was washed once with water. The aqueous phase was then saturated with NaCl and extracted twice with EA/THF=1/1. The combined organic phases were washed once with saturated NaCl solution, dried and evaporated to dryness under reduced pressure. The residue was precipitated with dichloromethane and filtered off. For purification, the crude product was boiled with DCM/EA=1/1, filtered off and washed thoroughly with DCM/ether. Yield: approximately 200 mg.

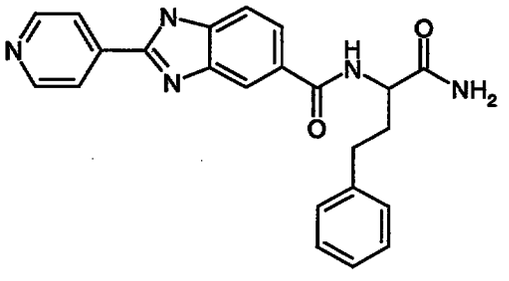
Example 188



239.2 mg (1 mmol) of the compound I prepared in Example 183 were treated successively with 247.7 mg (1 mmol) of H-Dopa-OMe·HCl, 328 mg (1 mmol) of TOTU and 0.34 ml (2 mmol) of ethyldiisopropylamine in approximately 8 ml of DMF. After 6 h at RT, the solvent was distilled off under reduced pressure, the residue was taken up in EA and the mixture was washed 3 times each with water and saturated NaCl solution. The organic phase was dried and evaporated to dryness under reduced pressure. The residue was precipitated with dichloromethane and filtered off. For purification, the crude product was boiled with DCM/EA=1/1, filtered off and thoroughly washed with DCM/ether. Yield: approximately 200 mg.

Example 189

The following compound was prepared according to process variant c):



2.0 g of polystyrene-AM RAM, 160-200 microns (0.64 mmol/g); Rapp Polymer) was added to a plastic syringe, allowed to swell in DMF for 20 min and then treated with a solution of DMF/piperidine (1:1) for 20 min. After washing with DMF, DCM and again with DMF, the resin was used as such in the next synthesis step.

Process step a)

DIC (0.59 ml, 3.84 mmol) was added to a solution of Fmoc-homoPheOH (0.71 g, 3.84 mmol) and HOBt hydrate (0.59 g, 3.84 mmol) in DMF. The

resulting solution was drawn into the abovementioned syringe and the mixture was shaken at RT for 16 hours (h). The resin was washed with DMF (10×15 ml), DCM (4×15 ml) and DMF (2×15 ml), and then stored at 4°C. To check the reaction, a KAISER test was carried out on a few resin beads.

Process step b)

The resin was deprotected and washed as described above. DIC (0.59 ml, 3.84 mmol) was added to a solution of 4-fluoro-3-nitrobenzoic acid (0.71 g, 3.84 mmol) and HOBt hydrate (0.59 g, 3.84 mmol) in DMF (approximately 15 ml). This solution was drawn into the syringe containing the prepared resin and the mixture was shaken at RT for 16 h. The resin was washed with DMF (10×15 ml), and stored at 4°C. To check the reaction, a KAISER test was carried out on a few resin beads.

Process step c)

A solution of 4-(aminomethyl)pyridine (1.4 ml, 12.8 mmol) in DMF (10 ml) was added to the prepared resin and the mixture was shaken at RT for 2 days. The resin was washed with DMF (8×15 ml), DCM (4×15 ml) and DMF (2×15 ml). Note: it was later found that simple heating of the resin mixture in DMA (dimethylacetamide instead of DMF) for 16 h afforded the desired hydroxybenzimidazole; it was thus possible to accelerate the synthesis.

Process step d)

A solution of the resin in DMA was packed into a sealable glass reactor and the reaction mixture was heated at 125°C for 16 h with gentle agitation. It was possible to confirm that cyclization had taken place by means of GC/MS (after removal of an aliquot of the substance from the resin). After washing with DMA (5×15 ml), the resin was used as such in synthesis step e).

Process step e)

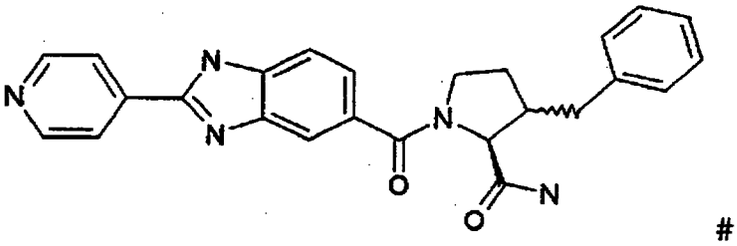
Tributylphosphine (0.6 ml) was added to a solution of the resin (0.5 g) from process step d) in DMA (5.0 ml) and the mixture was gently stirred at 150°C for 6 h. The resin was then washed with DMF (20×10 ml), MeOH (10×10 ml) and DCM (10×10 ml).

Process step f) Cleavage and purification

The resin obtained in process step e) was treated at RT for 3 h with TFA/H_2O (95/5). TFA/H_2O was removed under reduced pressure and a brown glassy solid was obtained as a crude product. The crude product was chromatographed on silica gel (flash chromatography; eluent: 95/5 DCM/2.0 M NH_3 in MeOH, then 92/9 DCM/2.0 M NH_3 in MeOH. The desired fractions were collected and the solvents were removed under reduced pressure. The product was obtained as a white solid. MS (ES; $M+H^+$ = 400) 1H-NMR corresponded to the abovementioned structural formula.

Example 190

The following compound was prepared according to process variant c):



#

A) Synthesis of 3(R/S)-vinyl-2-(S)-azido-3-phenylpropionic acid

a) Lithiumhydroxide (monohydrate, 21 g; 645 mmol) was added to a solution of ethyl 3-vinyl-4-phenylbutyrate (0.129 mol) in aqueous THF (120 ml/20 ml of H_2O). The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was partitioned between AcOEt and aqueous HCl (1M), the phases were separated, and the aqueous phase was washed 2 times with AcOEt. The combined organic phases were washed with saturated sodium chloride solution, dried over $MgSO_4$, filtered and evaporated under reduced pressure. 15.6 g (yield 62%) of acid were obtained, which was employed thus in the following reaction.

b) Triethylamine (1.27 ml) and, 15 minutes later, pivaloyl chloride (1.18 ml) were added to a cooled (-78°C) solution of the abovementioned acid (1.74 g, 9.16 mmol) in anhydrous THF (10 ml). The mixture was stirred at 0°C for 1 h and cooled to –78°C. In a separate flask, n-butyllithium (5.7 ml, 1.6 M in hexane) was slowly added to a cooled (-78°C) solution of S-phenyloxazolidinone (1.64 g) in THF (36 ml). The solution was stirred at –78°C for 1 h, warmed to 0°C and added dropwise to the above solution via a cannula. After addition was complete, the solution was stirred at room temperature overnight. Saturated NH_4Cl solution

(20 ml) was added and the solution was reduced to 1/3 of the volume under reduced pressure. The aqueous solution was extracted 3 times with dichloromethane, and the combined organic phases were washed with aqueous sodium hydroxide solution, dried over $MgSO_4$, filtered and evaporated. The residue was purified by means of flash chromatography (silica gel, 5-20% AcOEt/hexane). 2.06 g (67% yield) of imide were obtained as a mixture of the two diastereomers.

c) 1,1,1,3,3,3-Hexamethyldisilazane potassium salt (14.6 ml, 0.5 molar solution in toluene) was added dropwise to a cooled (-78°C) solution of the imide (1.88 g, 5.61 mmol) in anhydrous THF (15 ml). After 40 min, a cooled (-78°C) solution of trimethylsilyl azide (2.51 g) in THF was added. After a further 35 min, acetic acid (1.47 ml) was added and the solution was stirred overnight at room temperature. The reaction mixture was partitioned between dichloromethane and saturated sodium chloride solution, and the organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was flash-chromatographed on silica gel (eluents: a) DCM/MeOH/aq. ammonia = 95/5/1; b) DCM; starting ratio a:b = 1:10, up to pure DCM). 2.5 g (95% yield) of azido product were obtained.

d) 3 ml of hydrogen peroxide (30%) were added to a cooled solution (0°C) of the above azido compound (2.5 g) in THF (20 ml), H_2O (4 ml) and lithium hydroxide mononohydrate (558 mg). The mixture was stirred at room temperature for 2 h and 19 ml of a 10% strength solution of sodium sulfate were then added. The solution was reduced to 1/10 of the original volume under reduced pressure, the residue obtained was extracted 3 times with ethyl acetate, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The residue was purified on silica gel (flash chromatography, eluents: 1-5% MeOH in 1% strength aqueous ammonia solution/99% DCM). 912 mg of the desired acid (74% yield) were obtained.

B) Synthesis of 2-pyridin-4-yl-1H-benzimoidazole-5-carbonyl-3-R,S-benzyl-S-prolinamide

0.4 g of polystyrene Knorr resin (0.61 mmol/g) resin was added in a plastic syringe, allowed to swell in DMF for 20 min and then treated for 20 min with a solution of DMF/piperidine (1:1). After washing with DMF, DCM and again DMF, the resin was used thus in the next synthesis step.

Process step a)

A solution of 3(R/S)-vinyl-2(S)-azido-3-phenylpropionic acid (see also steps a) – d); 0.28 mmol), PyBOP (0.28 mmol) and DIPEA (0.32 mmol) was added to the above resin. The resulting mixture was shaken at RT for 16 h. The resin was washed with MeOH (3 times 15 ml) and DCM (4 times 15 ml) and dried under reduced pressure. For checking the reaction, a KAISER test was carried out on some resin beads.

Process step b)

Cyclohexene (23 mmol) was added to a 2 M solution of dicyclohexylborane/dimethyl sulfide complex (11.6 mmol) in anhydrous diethyl ether under an inert gas atmosphere. After one hour, a white solid was formed. The solvent was removed under reduced pressure and the above resin and 10 ml of DCM were added. The heterogeneous mixture was gently stirred for 2.5 h until the evolution of gas was complete. The resin was washed with MeOH and dried under reduced pressure. It was then stirred for 1 h with a 50/50 (vol/vol) mixture of ethanolamine and DMF and then washed with MeOH and DCM (3 times each), then dried.

Process step c)

DIC (0.69 mmol) was added to a solution of 4-fluoro-3-nitrobenzoic acid (0.69 mmol) and HOAt (0.69 mmol) in DMF (approximately 5 ml). This solution was drawn into the syringe with the previously prepared resin and the mixture was shaken at room temperature (RT) for 16 h. The resin was washed with DMF (10x15 ml) and dried under vacuum. For monitoring the reaction, a KAISER test was carried out on some resin beads.

Process step d)

A solution of 4-(aminomethyl)pyridine (4.6 mmol) in DMF (4 ml) was added to the previously prepared resin and the mixture was shaken at RT for 32 days. The resin was washed with MeOH and DCM (3x15 ml each) and dried.

Process step e)

A solution of the resin in DMA was filled into a sealable glass reactor and the reaction mixture was heated at 125°C with gentle agitation for 16 h. It was possible to confirm the cyclization which had taken place by CG/MS (after removal of an aliquot of the substance from the resin). The resin was washed with MeOH and DCM (3x15 ml each) and dried.

Process step f)

Tributylphosphine (0.5 ml) was added to a solution of the resin (0.021 mmol) from process step e) in DMA (3.0 ml) and the mixture was gently stirred at 125°C for 5 h. The resin was then washed with DMF

(2 times 10 ml), MeOH (2 times 10 ml) and DCM (3 times 10 ml) and dried under reduced pressure.

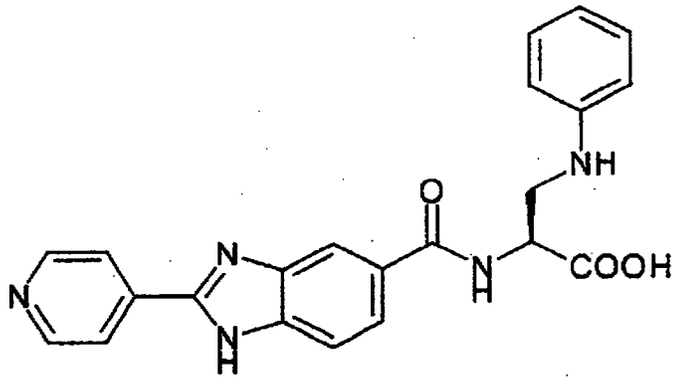
Process step g) Removal and purification

The resin obtained in process step f) was treated with TFA/H_2O (97/3) for 1 h at RT. TFA/H_2O was removed under reduced pressure and a brown glassy solid was obtained as a crude product. The crude product was chromatographed on silica gel (flash chromatography; eluent: 95/5 DCM/2.0M NH_3 in MeOH, then 92/8 DCM/2.0M NH_3 in MeOH. The desired fractions were collected and the solvents were removed under reduced pressure. The product was obtained as a white solid.

MS (ES; $M+H^+$ = 426) 1H-NMR corresponded to the abovementioned structural formula

Example 191

The following compound was prepared according to process variant c):



1.5 g of polystyrene Knorr resin (0.64 mmol/g) was added to a plastic syringe, swollen in 20 ml of DMF and then treated for 20 min with a solution of DMF/piperidine (1:1). After washing with DMF, DCM and again DMF, the resin was used thus in the next synthesis step.

Process step a)

A solution of Fmoc-3R,S-phenyl-S-proline (1.5 mmol), PyBOP (1.5 mmol) and DIPEA (2.1 mmol) in DCM was added to the resin. The resulting mixture was shaken at RT for 16 hours (h). The resin was washed with DCM (4 times 15 ml), MeOH (2 times 15 ml) and DCM and dried under reduced pressure. For monitoring the reaction, a KAISER test was carried out on some resin beads.

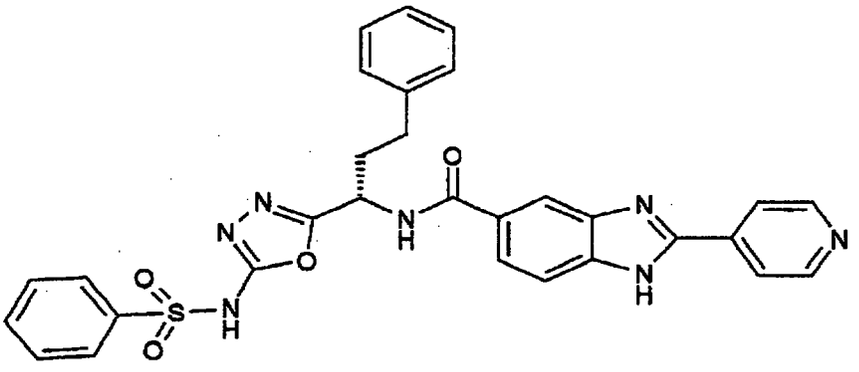
Process step b)

The resin was reacted further to give the desired compound as described in Example 190 under process B.

MS (ES; $M+H^+$ = 412) 1H-NMR corresponded to the abovementioned structural formula.

Example 192:

The following compound was prepared according to process variant a):



a) Preparation of Z-homophenylalanine hydrazide:

Z-Homophenylalanine hydrazide was prepared as described in Example 180a.

b) Preparation of benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]carbamate:

Benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]carbamate was prepared as described in Example 180b.

c) Preparation of benzyl [1-(5-benzenesulfonylamino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]carbamate:

0.35 g of the compound according to Example 192b was dissolved in 5 ml of pyridine at room temperature, treated with 0.13 ml of benzenesulfonyl chloride and stirred at 80°C for 4 h. A further 0.13 ml of benzenesulfonyl chloride were added and the mixture was stirred at 80°C for a further 2 h. The reaction mixture was concentrated in vacuo, and the residue was taken up in ethyl acetate, washed twice with water and once with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacuo. Benzyl [1-(5-benzenesulfonylamino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]carbamate was obtained, which was reacted further without further purification.

d) Preparation of N-[5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide:

0.18 g of the compound 192c was dissolved in 30 ml of dry methanol at room temperature, treated with Pd/C catalyst under argon and hydrogenated at room temperature for 4 h. After filtration, washing of the

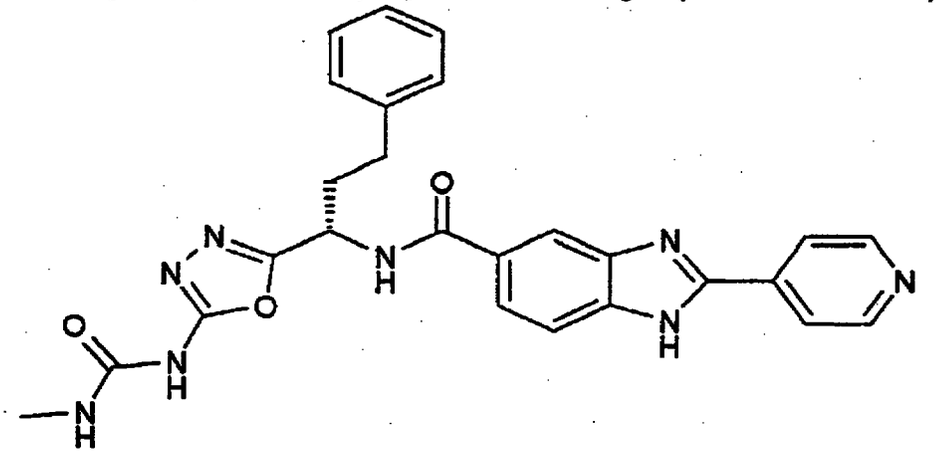
residue with methanol and concentration of the filtrate, N-[5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]benzenesulfonamide was obtained, which was employed in the next stage.

e) Preparation of 2-pyridin-4-yl-1H-benzimidazole-4-carboxylic acid [1-(5-benzenesulfonylamino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]-amide:

70 mg of the compound according to Example 192d were dissolved in 5 ml of dry DMF at room temperature, and treated with 30 µl of diisopropylamine, 48 mg of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid and 66 mg of TOTU. After stirring at room temperature for 4 h, the reaction was complete and the reaction mixture was concentrated. The residue was treated with ethyl acetate and water. The solvents were decanted; the oily residue was treated with warm acetone, the mixture was cooled and the crystalline product was collected on a filter, washed with acetone and dried. 2-Pyridin-4-yl-1H-benzimidazole-4-carboxylic acid [1-(5-benzenesulfonylamino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]amide, which melted from 220°C with decomposition, is obtained.

Example 193:

The following compound was prepared according to process variant a):



a) Preparation of Z-homophenylalanine hydrazide:

Z-Homophenylalanine hydrazide was prepared as described in Example 180a.

b) Preparation of benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl] carbamate:

Benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl] carbamate was prepared as described in Example 180b.

c) Preparation of benzyl {1-[5-(3-methylureido)-1,3,4]oxadiazol-2-yl)-3-phenylpropyl}carbamate:

350 mg of benzyl [1-(5-amino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl] carbamate were dissolved in 5 ml of dry dimethyl sulfoxide, treated with 140 mg of potassium carbonate and 140 mg of methyl isocyanate and stirred at 80°C for 16 h. The reaction mixture was cooled, treated with ethyl acetate, washed twice with water and once with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacuo. Benzyl {1-[5-(3-methylureido)-[1,3,4]oxadiazol-2-yl]-3-phenylpropyl}-carbamate was obtained, which was employed in the next stage (hydrogenolysis) without further purification.

d) Preparation of 1-[5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]-3-methylurea

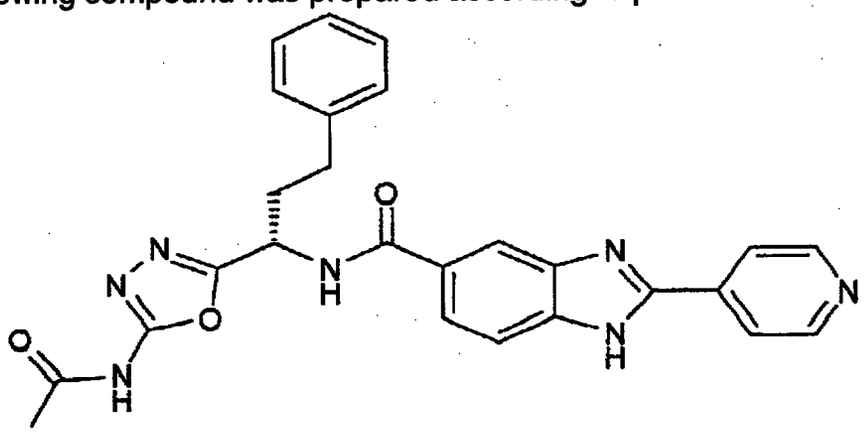
120 mg of the previous compound were dissolved in 20 ml of dry methanol at RT, treated with Pd/C catalyst under argon and hydrogenated at room temperature for 4 h. The reaction mixture was filtered, the residue was washed with methanol and the filtrate was concentrated in vacuo. The 1-[5-(1-amino-3-phenylpropyl)-[1,3,4]oxadiazol-2-yl]-3-methylurea was employed in the next stage without further purification.

e) Preparation of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid {1-[5-(3-methylureido)-[1,3,4]oxadiazol-2-yl]-3-phenylpropyl}amide:

40 mg of the previous compound was dissolved in 3 ml of dry DMF at RT and treated successively with 33 mg of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid, 20 µl of diisopropylamine and 40 mg of TOTU and stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo; the residue was taken up in ethyl acetate/tetrahydrofuran 1/1, washed with water, saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacuo. 2-Pyridin-4-yl-1H-benzimidazole-5-carboxylic acid {1-[5-(3-methylureido)-1[1,3,4]oxadiazol-2-yl]-3-phenylpropyl}amide was obtained, which has m/e = 497.3 (=MH^+) in the mass spectrum.

Example 194:

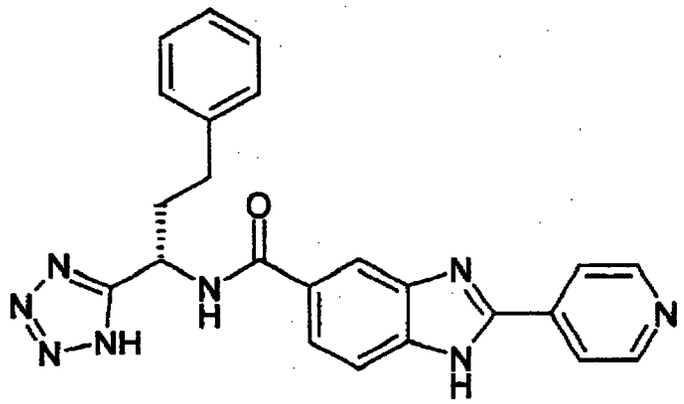
The following compound was prepared according to process variant a):



2-Pyridin-4-yl-1H-benzimidazole-5-carboxylic acid [1-(5-acetylamino-[1,3,4]oxadiazol-2-yl)-3-phenylpropyl]amide was prepared in a principally analogous manner, but with the difference that it was reacted with acetyl chloride instead of with methyl isocyanate. The compound has a melting point of 183-186°C with decomposition.

Example 195:

The following compound was prepared according to process variant a):



a) Preparation of benzyl (1-cyano-3-phenylpropyl)carbamate:

2.78 g of benzyl (1-carbamoyl-3-phenylpropyl)carbamate, prepared from L-homophenylalanine amide hydrochloride and N-Cbz-succinimide, were dissolved in 30 ml of dry pyridine and treated with 6 ml of acetic anhydride. The reaction mixture was stirred at 75°C for 24 h. The cooled solution was concentrated in vacuo, treated with 100 ml of ethyl acetate and then extracted three times by shaking with 50 ml each of 5% strength citric acid solution and saturated sodium chloride solution. The organic extract was dried over magnesium sulfate, filtered, concentrated in vacuo and chromatographed on silica gel using n-heptane/ethyl acetate 1/1. Benzyl

(1-cyano-3-phenylpropyl)carbamate was obtained, which was employed in the next stage without further purification.

b) Preparation of benzyl [3-phenyl-1-(1H-tetrazol-5-yl)propyl]carbamate:

0.15 g of the compound of Example 195a was suspended in 5 ml of dry toluene with 0.115 g of trimethyltin azide and stirred under reflux for 6 h. The cooled reaction mixture was acidified with ethereal hydrochloric acid and allowed to stand overnight in a refrigerator. On the next day, the mixture was concentrated in vacuo and chromatographed on silica gel using dichloromethane/methanol 9/1. The benzyl [3-phenyl-1-(1H-tetrazol-5-yl)propyl]carbamate thus obtained was employed in the next stage without further purification.

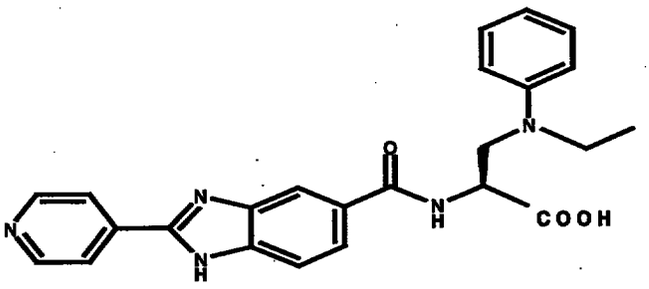
c) Preparation of 3-phenyl-1-(1H-tetrazol-5-yl)propylamine:

337 mg of the compound of Example 195b were dissolved in 2 ml of acetonitrile, treated with 0.477 ml of triethylsilane, one drop of triethylamine and a spatula tipful of palladium(II) chloride and stirred under reflux for 3 h. The cooled solution was filtered, concentrated in vacuo and the residue was dried in a high vacuum. The 3-phenyl-1-(1H-tetrazol-5-yl)propylamine thus obtained was reacted further.

d) Preparation of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid [3-phenyl-1-(1H-tetrazol-5-yl)propyl]amide:

0.9 mmol of the compound of Example 195c was dissolved in 5 ml of dry DMF and treated with 0.9 mmol of 2-pyridin-4-yl-1H-benzimidazole-5-carboxylic acid, 0.365 ml of diisopropylamine and 415 mg of TOTU, and stirred at room temperature for 20 h and at 50°C for a further 4 h. The reaction mixture was concentrated in vacuo; the residue was taken in ethyl acetate, washed with water, saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product thus obtained was chromatographed on silica gel using dichloromethane/methanol/water/-glacial acetic acid 60/10/1/1. 2-Pyridin-4-yl-1H-benzimidazole-5-carboxylic acid [3-phenyl-1-(1H-tetrazol-5-yl)propyl]amide, was obtained, which decomposed from 87°C and had a molecular peak at m/e=425.2 (MH^+), is obtained.

Example 196 3-Phenylaminoethyl-2-[(2-pyridin-4-yl-1H-benzoimidazole-5-carbonyl)amino]propionic acid trifluoroacetate



a) L-2-Amino-3-phenylaminoethylpropionic acid

54.8 g (0.209 mol) of triphenylphosphine were suspended in 600 ml of acetonitrile and cooled to -35°C to -45°C with exclusion of moisture. 36.4 g (0.209 mol) of diethyl azodicarboxylate was then added dropwise at this temperature in the course of 50 min. The mixture was subsequently stirred at -35°C for 15 min. A solution of 50 g (0.209 mol) of N-benzyloxycarbonyl-L-serine in 500 ml of acetonitrile was added dropwise to this mixture, and in the course of this the temperature was not allowed to rise above -35°C. The mixture was then allowed to afterreact at 5°C for 12 h and was warmed to RT. The reaction solution was freed from the solvent under reduced pressure and the crude product was purified by medium-pressure chromatography on silica gel. (DCM/AcCN:25/1) After removal of the solvent, 20.8 g (yield 45%) of clean N-benzyloxycarbonyl-L-serine β-lactone (see also Org. Synth. 1991 (70) 1ff.) were obtained in fine needles. Empirical formula: $C_{11}H_{11}NO_4$; M.W. = 221.2; MS (M+H) 222.1

15.5 ml (63.51 mmol) of N,O-bis(trimethylsilyl)acetamide were added under an argon protective atmosphere to 7.3 ml (57.36 mmol) of N-ethylaniline in 250 ml of acetonitrile and the mixture was stirred at 50°C for 3 h. A solution of the above lactone (10.7 g, 48.37 mmol) dissolved in 250 ml of acetonitrile was then added at 20°C and the mixture was heated under reflux for 17 h. After removal of the solvent, the residue was treated with saturated sodium carbonate solution, the pH of the solution not exceeding 9. The aqueous suspension was washed with a little diethyl ether and then adjusted to a pH of 6 to 7 using concentrated hydrochloric acid and adjusted to a pH of 5 using $NaHPO_4$- buffer. The aqueous solution was extracted with ethyl acetate a number of times. After evaporation of the

solvent, the desired product was obtained in a yield of 45% (7.4 g). Empirical formula: $C_{19}H_{22}N_2O_4$; M.W. = 342.4; MS (M+H) 343.2

6.5 ml (89.1 mmol) of thionyl chloride were added dropwise at -10°C to 75 ml of methanol and the mixture was stirred for 30 min. L-2-aminoethyl-3-phenylaminopropionic acid 8.6 g (25.12 mmol) dissolved in 75 ml of methanol was then added, and the mixture was stirred at -10°C for 30 minutes and at RT for a further 3 h. After evaporation of the solvent, the residue was taken up in ethyl acetate and washed with sodium carbonate solution. After evaporation of the solvent and purification by means of flash chromatography (n-heptane/ethyl acetate 7:3), 4.43 g (50% yield) of methyl L-2-aminoethyl-3-phenylaminopropionate was obtained. Empirical formula: $C_{20}H_{24}N_2O_4$; M.W. = 356.4; MS (M+H) 357.3

For the removal of the protective group, 4.4 g (12.35 mmol) of the Z-protected derivative were dissolved in 500 ml of methanol, 100 mg of catalyst (10% $Pd(OH)_2$-C) were added under inert gas, and hydrogen was passed in until the Z-protected group had been completely removed. After filtering off the catalyst and evaporating the filtrate, 2.8 g of L-2-aminoethyl-3-phenylaminopropionic acid (quant.) were obtained. Empirical formula: $C_{12}H_{18}N_2O_2$; M.W. = 222.3; MS (M+H) 223.1

Process step b)

2.4 g (10.03 mmol) of 2-pyridin-4-yl-1H-benzoimidazole-5-carboxylic acid prepared as in example 183 were suspended in 350 ml of DMF and treated successively with 4.2 g (12.80 mmol) of TOTU and 2.3 ml (13.52 mmol) of ethyldiisopropylamine. The mixture was stirred at RT for 10 min and 2.8 g (12.60 mmol) of methyl (S) 2-amino-3-phenylaminoethylopropionate prepared according to a) were added to the resulting clear solution. After stirring for 2 h, the mixture was concentrated under reduced pressure and the methyl ester of the title compound was isolated by flash chromatography on silica gel (DCM:MeOH = 9:1).

Yield: 4.36 g (98%), empirical formula: $C_{25}H_{25}N_5O_3$; M.W. = 443.5; MS (M+H) 444.3

4.3 g (9.7 mmol) of the methyl ester thus obtained was hydrolyzed in 400 ml of methanol by the addition of 200 ml of 1M sodium hydroxide solution at RT for 2 h. After evaporation of the methanol, the suspension obtained was adjusted to pH = 5 using NaH_2PO_4- solution. The product

precipitates from the solution in the course of this. Purification by means of flash chromatography on silica gel (DCM:MeOH = 4:1) and preparative HPLC (acetonitrile/0.1% TFA) yielded 2.92 g (yield 70%) of 3-phenylaminoethyl-2-[(2-pyridin-4-yl-1H-benzoimidazole-5-carbonyl)amino]propionic acid trifluoroacetate.

Empirical formula: $C_{24}H_{23}N_5O_3$; M.W. = 429.5; MS (M+H) 430.3; melting point: approximately 258°C (with decomposition).

Pharmacological examples

IkB kinase filter test:

The activity of the IkB kinase was determined using the "SigmaTECT™ Protein Kinase Assay System" (Promega catalog 1998, p. 330; analogous to the SigmaTECT™ DNA-dependent protein kinase procedure). The kinase was purified from HeLa cell extracts according to Z.J. Chen (Cell 1996, Vol. 84, pp. 853-862) and incubated with the substrate peptide (biotin-$(CH_2)_8$-DRHDSGLDSMKD-$CONH_2$) (20 µM). The reaction buffer contained 50 mM HEPES, pH 7.5, 10 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 10 mM β-glycerophosphate, 10 mM 4-nitrophenyl phosphate, 1 µM microcystine-LR and 50 µM ATP (comprising 1 µCi of γ-^{33}P-ATP).

Method PKA, PKC, CK II

cAMP-dependent protein kinase (PKA), protein kinase C (PKC) and casein kinase II (CK II) were determined using the appropriate test kits of Upstate Biotechnology according to the procedure of the manufacturer at an ATP concentration of 50 µM. Differently, no phosphocellulose filter, but MultiScreen plates (Millipore; phosphocellulose MS-PH, cat. MAPHNOB10) with the corresponding aspiration system were used. The plates or membranes (IkB kinase) were then measured in a Wallac MicroBeta scintillation counter. 100 µM of the test substance were employed in each case.

Each substance was tested in a duplicate determination. The mean value of the blank (without enzyme) is subtracted from the mean values (enzyme with and without substances) and the % inhibition is calculated. IC_{50} calculations were carried out using the software package GraFit 3.0. Table 6 which follows shows the results.

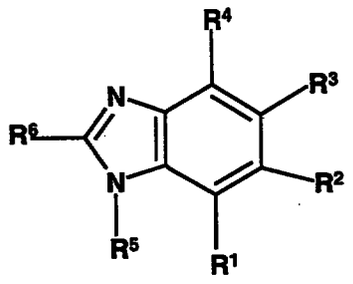
Table 6: Kinase inhibition at a substance concentration of 100 µM or IC_{50} in µM

Example number	IkB kinase IC_{50}	PKA % inhibition	PKC % inhibition	CK II % inhibition
5	25	0	16	19
6	72	0	46	14
7	22	0	15	10
8	4	0	9	7
11	7	0	16	0
12	42	0	16	0
14	7	0	0	0
16	9	0	11	4
20	1	36	63	70
21	34	26	31	60
35	16	n.d.	n.d.	n.d.
37	36	n.d.	n.d.	n.d.
108	1	0	13	92
113	25	24%	7%	17%
180	0.43	n.d.	n.d.	n.d.
181	0.62	n.d.	n.d.	n.d.
192	0.12	n.d.	n.d.	n.d.
193	0.36	n.d.	n.d.	n.d.

n.d. means not determined

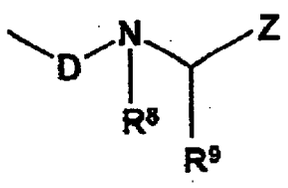
Patent Claims

1. A compound of the formula I



(I)

and/or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I, where one of the substituents R^1, R^2, R^3 and R^4 is a radical of the formula II



(II)

in which D is -C(O)-, -S(O)- or -$S(O)_2$-,

R^8 is hydrogen or (C_1-C_4)-alkyl,

R^9 is

1. a characteristic radical of an amino acid,
2. aryl, in which aryl is unsubstituted or substituted,
3. heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
4. a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
5. (C_1-C_6)-alkyl, in which alkyl is straight-chain or branched and is unsubstituted or mono-, di- or trisubstituted independently of one another by
   - 5.1 aryl, in which aryl is unsubstituted or substituted,
   - 5.2 heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,

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5.3 a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,

5.4 $-O-R^{11}$,

5.5 =O,

5.6 halogen,

5.7 -CN,

5.8 $-CF_3$,

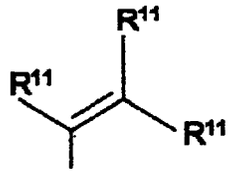
5.9 $-S(O)_x-R^{11}$, in which x is the integer zero, 1 or 2,

5.10 $-C(O)-O-R^{11}$,

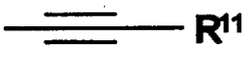
5.11 $-C(O)-N(R^{11})_2$,

5.12 $-N(R^{11})_2$,

5.13 (C_3-C_6)-cycloalkyl,

5.14 a radical of the formula 

or

5.15 a radical of the formula 

in which R^{11} is

a) a hydrogen atom,

b) (C_1-C_6)-alkyl, in which alkyl is unsubstituted or mono-, di- or trisubstituted

1. aryl, in which aryl is unsubstituted or substituted,
2. heteroaryl having 5 to 14 ring members,
3. a heterocycle having 5 to 12 ring members,
4. halogen,
5. $-N-(C_1-C_6)_n$-alkyl, in which n is the integer zero, 1 or 2 and alkyl is unsubstituted or mono-, di- or trisubstituted independently of one another by halogen or by –COOH,
6. $-O-(C_1-C_6)$-alkyl or
7. -COOH,

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c) aryl, in which aryl is unsubstituted or substituted,

d) heteroaryl having 5 to 14 ring members or

e) a heterocycle having 5 to 12 ring members and

in the case of $(R^{11})_2$, R^{11} independently of one another has the meaning of a) to e)

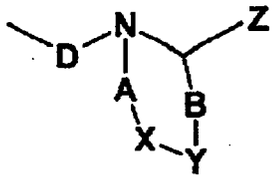
Z is

1. aryl, in which aryl is unsubstituted or substituted,
2. heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
3. a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
4. $-(C_1-C_6)$-alkyl, in which alkyl is substituted or unsubstituted or
5. $-C(O)-R^{10}$, in which

R^{10} is

1. $-O-R^{11}$ or
2. $-N(R^{11})_2$, or

R^8 and R^9 form, together with the nitrogen atom and carbon atom to which they are each bonded, a heterocyclic ring of the formula IIa



(IIa)

in which D, Z and R^{10} are as defined in formula II,

A is a nitrogen atom or the radical $-CH_2-$,

B is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

X is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

Y is absent or is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$, or

X and Y together form a phenyl, 1,2-diazine, 1,3-diazine or a 1,4-diazine radical,

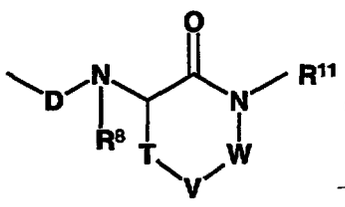
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where the ring system formed by N, A, X, Y, B and the carbon atom contains not more than one oxygen atom, X is not an oxygen atom, sulfur atom or nitrogen atom if A is a nitrogen atom, contains not more than one sulfur atom, contains 1, 2, 3 or 4 nitrogen atoms and where an oxygen and sulfur atom do not occur at the same time,

where the ring system formed by N, A, X, Y, B and the carbon atom is unsubstituted or mono-, di- or trisubstituted independently of one another by (C_1-C_8)-alkyl, in which alkyl is unsubstituted or mono- or disubstituted by

1.1. -OH
1.2. (C_1-C_8)-alkoxy,
1.3. halogen,
1.4. -NO_2,
1.5. -NH_2,
1.6. -CF_3,
1.6. -OH,
1.7. methylenedioxy,
1.8. -C(O)-CH_3,
1.9. -CH(O),
1.10. -CN,
1.11. -COOH,
1.12. -C(O)-NH_2,
1.13. (C_1-C_4)-alkoxycarbonyl,
1.14. phenyl,
1.15. phenoxy,
1.16. benzyl,
1.17. benzyloxy or
1.18. tetrazolyl, or

R^9 and Z together with the carbon atoms to which they each are bonded form a heterocyclic ring of the formula IIc



(IIc)

in which

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D, R^8 and R^{11} are as defined in formula II,

T is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

W is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$,

V is absent or is an oxygen atom, sulfur atom, nitrogen atom or the radical $-CH_2-$, or

T and V or V and W together form a phenyl, 1,2-diazine, 1,3-diazine or a 1,4-diazine radical,

where the ring system formed by N, T, V, W and two carbon atoms contains not more than one oxygen atom, not more than one sulfur atom and 1, 2, 3 or 4 nitrogen atoms, where an oxygen atom and sulfur atom do not occur at the same time, and where the ring system formed by N, T, V, W and two carbon atoms is unsubstituted or mono-, di- or trisubstituted independently of one another by the substituents defined above under 1.1. to 1.18., and

the other substituents R^1, R^2, R^3 and R^4 in each case independently of one another are

1. a hydrogen atom,
2. halogen,
3. (C_1-C_4)-alkyl
4. heteroaryl having 5 to 14 ring members, in which heteroaryl is unsubstituted or substituted,
5. a heterocycle having 5 to 12 ring members, in which the heterocycle is unsubstituted or substituted,
6. (C_1-C_6)-alkyl,
7. -CN,
8. $-O-(C_0-C_4)$-alkyl-aryl,
9. $-O-(C_1-C_4)$-alkyl,
10. $-OR^{11}$,
11. $-N(R^{11})_2$,
12. $-S(O)_xR^{11}$, in which x is the interger zero, 1 or 2,
13. NO_2,
14. $-CF_3$,

R^5 is
1. a hydrogen atom,
2. -OH or
3. =O, and

R^6 is
1. aryl, in which aryl is unsubstituted or substituted,

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2. phenyl, mono- or disubstituted by
   2.1 -CN,
   2.2 $-NO_2$,
   2.3 $-O-(C_1-C_4)$-alkyl,
   2.4 $-N(R^{11})_2$,
   2.5 $-NH-C(O)-R^{11}$,
   2.6 $-S(O)_xR^{11}$, in which x is the interger zero, 1 or 2,
   2.7 $-C(O)-R^{11}$ or
   2.8 $-(C_1-C_4)$-alkyl-NH_2,
3. heteroaryl having 5 to 14 ring members, unsubstituted or mono-, di- or trisubstituted, or
4. a heterocycle having 5 to 12 ring members, unsubstituted or mono-, di- or trisubstituted.

2. A compound of the formula I as claimed in claim 1, wherein one of the substituents R_1, R_2, R_3 and R_4 is a radical of the formula II, in which

R^8 is a hydrogen atom,

R^9 is
1. a characteristic radical of an amino acid,
2. (C_1-C_6)-alkyl, in which alkyl is linear or branched and is unsubstituted or pyrrole mono- or pyrrole mono- or disubstituted by a radical from the group consisting of
pyrrole, pyrrole mono- or disubstituted by-(C_1-C_4)-alkyl, pyrazole, phenyl, imidazole, triazole, thiophene, thiazole, oxazole, isoxazole, pyridine, pyrimidine, indole, benzothiophene, benzimidazole, benzoxazole, benzothiazole, azetidine, pyrroline, pyrrolidine, piperidine, isothiazole, diazepine, thiomorpholine, -CN, morpholine, azepine, 1,3,4-oxodiazole, pyrazine, $-N(R^{13})$-phenyl, (C_3-C_6)-cycloalkyl, $-OR^{11}$, $-NH(R^{11})$, in which R^1 is in each case as defined in claim 1, $-S(O)_x-R^{12}$, in which x is zero, 1 or 2 and R^{12} is naphthyl, pyrimidinyl, morpholinyl or phenyl, which are unsubstituted or mono- or disubstituted by –OH, (C_1-C_4)-alkyl, $-CF_3$, halogen, $-O-(C_1-C_4)$-alkyl, -COOH, $-C(O)-O-(C_1-$

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C_4)-alkyl, $-NH_2$ or –NH-C(O)- (C_1-C_4)-alkyl or C(O)-R^{12}, in which R^{12} is as defined above,

Z is -C(O)-R^{10}, tetrazole, (C_1-C_6)-alkyl, in which alkyl is linear or branched and is unsubstituted or mono- or disubstituted by phenyl or –OH, or 1,3,4-oxadiazole, in which 1,3,4-oxadiazole is unsubstituted or monosubstituted by $-NH_2$, -NH(C_1-C_4)-alkyl, -N-[(C_1-C_4)-alkyl]$_2$, -NH-C(O)-(C_1-C_4)-alkyl, -NH-C(O)-NH-(C_1-C_4)-alkyl, -NH-C(O)-NH-(C_3-C_7)-cycloalkyl, -NH-C(O)-NH-aryl, -NH-C(O)-NH-phenyl, -NH-SO_2-aryl, -NH-SO_2-(C_1-C_4)-alkyl, -OH or -(C_1-C_4)-alkyl, in which

R^{10} is -O-R^{11}, phenyl, pyrimidine, -OH, morpholinyl, -N(R^{11})$_2$ or $-NH_2$,

R^{11} is 1. -(C_1-C_4)-alkyl,
2. R^{13} or
3. -N(R^{13})$_2$, in which
R^{13} independently of one another is
a) a hydrogen atom,
b) -(C_1-C_6)-alkyl,
c) -(C_1-C_4)-alkyl-O-(C_1-C_4)-alkyl,
d) -(C_1-C_6)-alkyl-N(R^{13})$_2$,
e) halogen or
f) -(C_0-C_4)-alkyl, mono- or disubstituted by aryl, imidazolyl, morpholinyl or phenyl, or

R^8 and R^9, together with the nitrogen atom and carbon atom to which they are each bonded, form a ring of the formula IIa from the group consisting of pyrrole, pyrroline, pyrrolidine, pyridine, piperidine, piperylene, pyridazine, pyrimidine, pyrazine, piperazine, pyrazole, imidazole, pyrazoline, imidazoline, pyrazolidine, imidazolidine, oxazole, isoxazole, 2-isoxazolidine, isoxazolidine, morpholine, isothiazole, thiazole, tetrazole, 1,2,3,5-oxathiadiazole-2-oxides, oxadiazolones, isoxazolones, triazolones, oxadiazolidinediones, triazoles which are substituted by F, CN, CF_3 or COO-(C_1-C_4)-alkyl, 3-hydroxypyrro-2,4-diones, 5-oxo-1,2,4-thiadiazoles, 1,3,4-oxadiazole, isothiazolidine, thiomorpholine, indazole, thiadiazole, benzimidazole, quinoline, triazole, phthalazine, quinazoline,

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quinoxaline, purine, pteridine, indole, tetrahydroquinoline, tetrahydroisoquinoline and isoquinoline, or

R^9 and Z, together with the carbon atoms to which they are each bonded, form a ring of the formula IIc from the group consisting of pyrrole, pyrroline, pyrrolidine, pyridine, piperidine, piperylene, pyridazine, pyrimidine, pyrazine, piperazine, pyrazole, imidazole, pyrazoline, imidazoline, pyrazolidine, imidazolidine, oxazole, isoxazole, 2-isoxazolidine, isoxazolidine, morpholine, isothiazole, thiazole, isothiazolidine, thiomorpholine, indazole, thiadiazole, benzimidazole, quinoline, triazole, phthalazine, quinazoline, quinoxaline, purine, pteridine, indole, tetrahydroquinoline, tetrahydroisoquinoline, isoquinoline, tetrazole, 1,2,3,5-oxathiadiazole-2-oxides, oxadiazolones, isoxazolones, triazolones, oxadiazolidinediones, triazoles which are substituted by F, CN, CF_3 or COO-(C_1-C_4)-alkyl, 3-hydroxypyrro-2,4-diones, 1,3,4-oxadiazole and 5-oxo-1,2,4-thiadiazoles and

the other substituents R^1, R^2, R^3 and R^4 in each case independently of one another are

1. a hydrogen atom,
2. halogen,
3. (C_1-C_4)-alkyl,
4. -CN,
5. -NO_2,
6. -O-(C_0-C_4)-alkyl-aryl,
7. -O-(C_1-C_4)-alkyl,
8. -N-(C_0-C_4)-alkyl-aryl,
9. -N-(C_1-C_4)-alkyl or
10. -CF_3,

R^5 is
1. a hydrogen atom,
2. -OH or
3. =O, and

R^6 is
1. phenyl, mono- or disubstituted by
   - 1.1 -CN,
   - 1.2 -NO_2,
   - 1.3 -O-(C_1-C_4)-alkyl,
   - 1.4 -NH_2 or
   - 1.5 -(C_1-C_4)-alkyl-NH_2

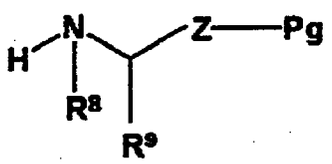
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2. heteroaryl having 5 to 14 ring members, unsubstituted or mono- to trisubstituted by -N-R^{14}, in which R^{14} is -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl or phenyl, halogen, -OH or -(C_1-C_4)-alkyl, or

3. a heterocycle having 5 to 12 ring members, unsubstituted or mono- to trisubstituted by -N-R^{14}, in which R^{14} is -(C_1-C_6)-alkyl, -(C_3-C_6)-cycloalkyl or phenyl, halogen, -OH or -(C_1-C_4)-alkyl.

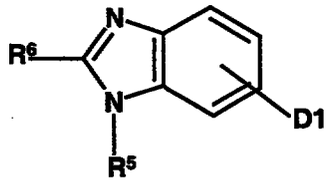
3. A process for the preparation of the compounds of the formula I as claimed in one or more of claims 1 and 2, which comprises

a) reacting a compound of the formula IV



(IV)

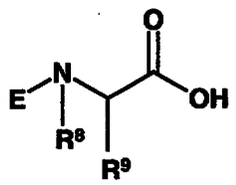
in which Pg is a suitable protective group (e.g. methyl ester), an amide group or a hydroxyl group and Z, R^8 and R^9 are as defined in formula II, with an acid chloride or an activated ester of the compound of the formula III



(III)

where D1 is -COOH or sulfonylhalogen and R^5 and R^6 are as defined in formula I, in the presence of a base or, if appropriate, of a dehydrating agent in solution and, after removal of the protective group, converting into a compound of the formula I, or

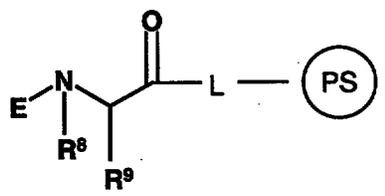
b) reacting a compound of the formula IVa



(IVa)

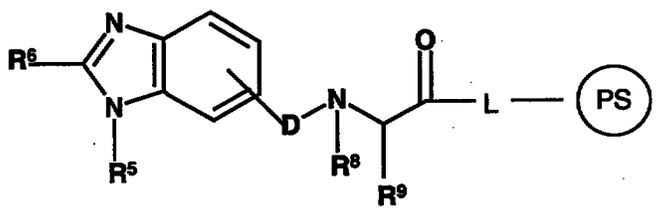
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in which R^8 and R^9 are as defined in formula II and E is an N-amino protective group, with its carboxyl group coupled via an intermediate chain L to a polymeric resin of the formula PS, a compound of the formula V



(V)

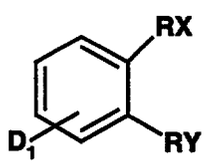
resulting, which, after selective removal of the protective group E, is reacted with a compound of the formula III, where R^5 and R^6 are as defined in formula I, in the presence of a base or, if appropriate, of a dehydrating agent to give a compound of the formula VI



(VI)

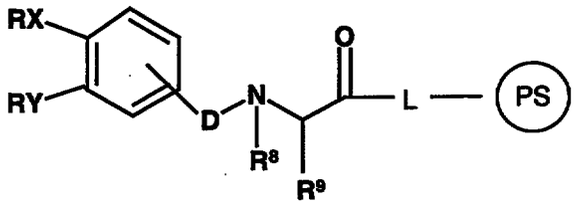
and converting the compound of the formula VI, after removal of the support material, into a compound of the formula I, or

c) reacting a compound of the formula V, after selective removal of the protective group E, with a compound of the formula VII



(VII)

where D_1 is -COOH or sulfonylhalogen and RX is halogen and RY is a radical $-NO_2$ or -NH-E and E is a protective group, to give a compound of the formula VIII



(VIII)

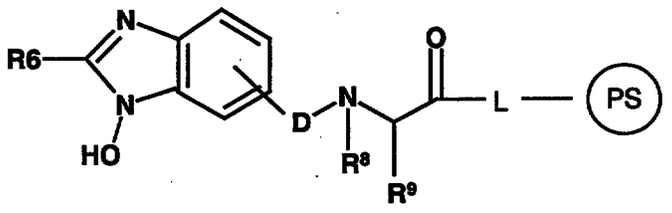
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and then reacting the compound of the formula VIII with a compound of the formula IX

$$NH_2\text{-}R^6 \qquad (IX)$$

in which R^6 is as defined in the compound of the formula I, to give an intermediate compound of the formula VIa

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(VIa)

then either converting the intermediate compound of the formula VIa into a compound of the formula I after removal of the support material or reducing it, for example, with tributylphosphine to give a compound of the formula VI and converting into a compound of the formula I after removal of the support material, or

d) converting a compound of the formula I into a physiologically tolerable salt.

4. A pharmaceutical comprising an efficacious amount of at least one compound of the formula I as claimed in one or more of claims 1 and 2 together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

5. The use of at least one compound of the formula I as claimed in one or more of claims 1 and 2, for the production of pharmaceuticals for the prophylaxis and therapy of disorders in whose course an increased activity of NFκB is involved.

6. The use as claimed in claim 5, for the treatment of rheumatoid arthritis, osteoarthritis, asthma, cardiac infarct, Alzheimer's disease, carcinomatous disorders or atherosclerosis.

7. A process for the production of a pharmaceutical, which comprises bringing at least one compound of the formula I as claimed in one or

more of claims 1 and 2 into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries.

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