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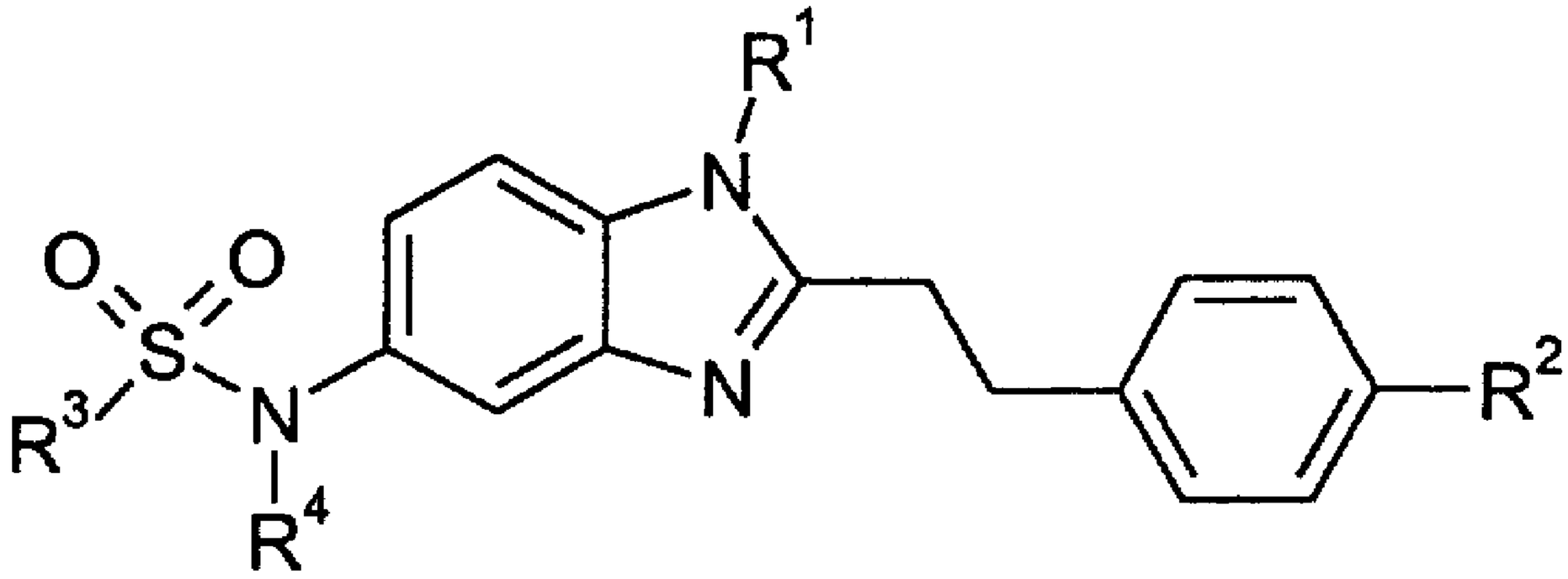
(72) Inventeurs/Inventors:
ANDERSKEWITZ, RALF, DE;
BRAUN, CHRISTINE, CH;
BRIEM, HANS, DE;
DISSE, BERND, DE;
HOENKE, CHRISTOPH, DE;
...

(73) Propriétaire/Owner:

(54) Titre : DERIVES DE BENZIMIDAZOLE D'ARYLSULPHONAMIDE-SUBSTITUE, PROCEDE DE PREPARATION ET LEURS UTILISATIONS COMME COMPOSITIONS PHARMACEUTIQUES

(54) Title: ARYLSULPHONAMIDE-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES, PROCESSES FOR PREPARING THEM AND THEIR USE AS PHARMACEUTICAL COMPOSITIONS



(I)

(57) Abrégé/Abstract:
The invention relates to arylsulphonamide-substituted benzimidazole derivatives of general formula (I) (see formula I), wherein the groups R^1, R^2, R^3 and R^4 may have the meanings given in the claims and specification, processes for preparing them as well as the use of arylsulphonamide-substituted benzimidazole derivatives as pharmaceutical compositions, particularly as pharmaceutical compositions with a tryptase-inhibiting activity.

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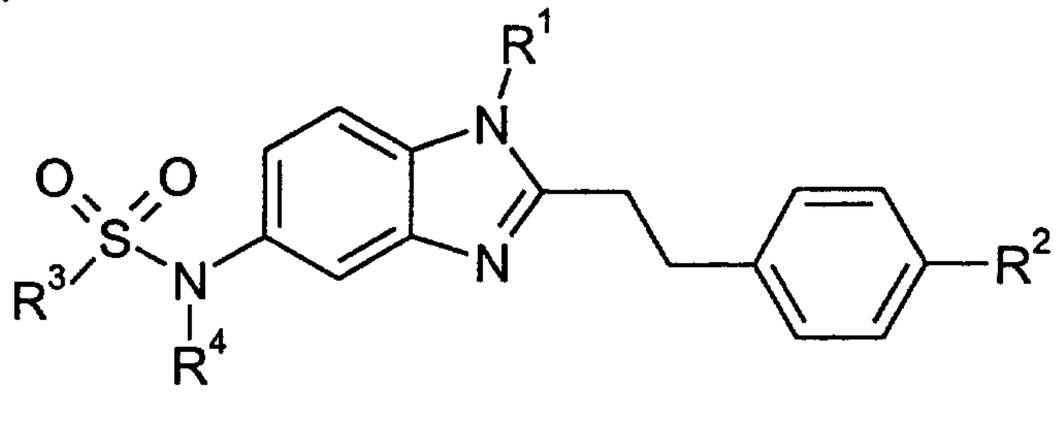
(72) Inventeurs(suite)/Inventors(continued): JENNEWEIN, HANS-MICHAEL, DE; SPECK, GEORG, DE

(73) Propriétaires(suite)/Owners(continued):BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG, DE

(74) Agent: FETHERSTONHAUGH & CO.

Abstract

The invention relates to arylsulphonamide-substituted benzimidazole derivatives of general formula (I)



(I),

wherein the groups R^1, R^2, R^3 and R^4 may have the meanings given in the claims and specification, processes for preparing them as well as the use of arylsulphonamide-substituted benzimidazole derivatives as pharmaceutical compositions, particularly as pharmaceutical compositions with a tryptase-inhibiting activity.

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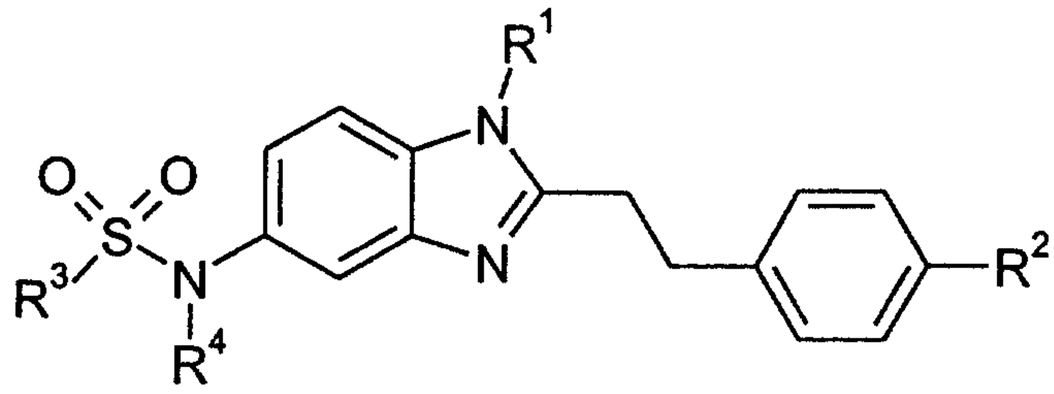
Arylsulphonamide-substituted benzimidazole derivatives, processes for preparing them and their use as pharmaceutical compositions

The invention relates to arylsulphonamide-substituted benzimidazole derivatives of general formula (I)



(I),

wherein the groups R^1, R^2, R^3 and R^4 may have the meanings given in the claims and specification, processes for preparing them as well as the use of arylsulphonamide-substituted benzimidazole derivatives as pharmaceutical compositions, particularly as pharmaceutical compositions with a tryptase-inhibiting activity.

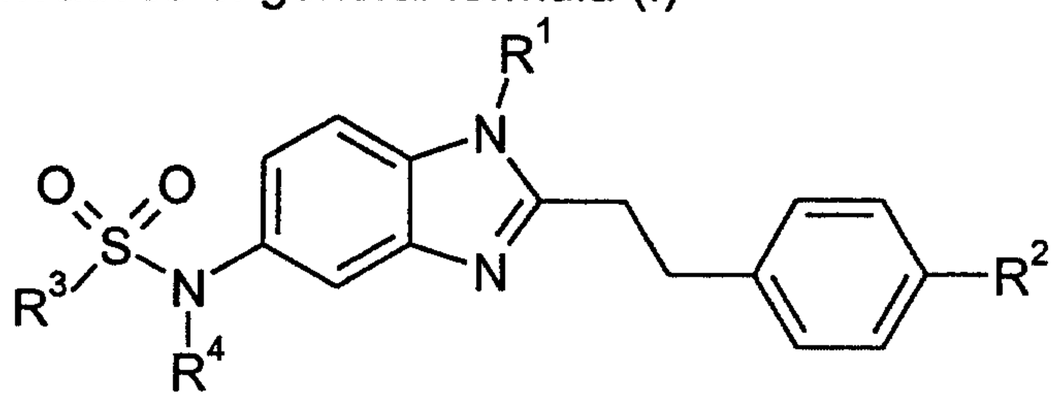
Background of the invention

Benzimidazole derivatives are known from the prior art as active substances having valuable pharmaceutical properties. Thus, International Patent Application WO 98/37075 discloses, in addition to other bicyclic heterocycles, benzimidazoles which can be used to good effect for the prevention and treatment of venous and arterial thrombotic diseases, on the basis of their thrombin-inhibiting activity.

In contrast to the use of benzimidazole derivatives as described above and known from the prior art, the aim of the present invention is to prepare new tryptase-inhibitors which can be used, on the basis of their tryptase-inhibiting properties, for the prevention and treatment of inflammatory and/or allergic diseases.

Detailed description of the invention

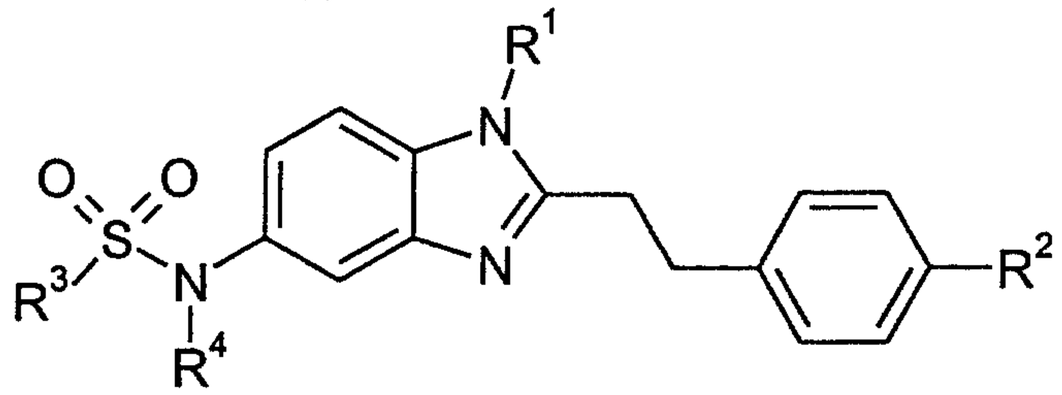
Surprisingly, it has been found that arylsulphonamide-substituted benzimidazole derivatives of general formula (I)



(I),

wherein the groups R^1, R^2, R^3 and R^4 may have the meanings given hereinbefore, have a tryptase-inhibiting effect and may be used according to the invention for the prevention and treatment of diseases in which tryptase inhibitors may develop a therapeutic effect.

The present invention is directed to arylsulphonamide-substituted benzimidazole derivatives of general formula (I)



(I),

wherein

R^1 denotes a group selected from the group C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkinyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1-C_4-alkoxy, CF_3, phenoxy, COOH, halogen, -CO(C_1-C_4-alkoxy), -CONH_2, -CO-NH(C_1-C_4-alkyl), -CO-N(C_1-C_4-alkyl)$_2$, -NH_2, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$ or C_1-C_4-alkoxy-phenoxy, or

a C_3-C_8-cycloalkyl optionally linked via a C_1-C_4-alkylene bridge, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1-C_4-alkoxy, carboxy, halogen, C_1-C_4-alkoxycarbonyl or CF_3, or

phenyl-C_1-C_4-alkyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1-C_4-alkoxy, carboxy, halogen, C_1-C_4-alkoxycarbonyl or CF_3, or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge, which may contain one or two hetero atoms selected from the group oxygen, nitrogen or sulphur and which may optionally be substituted by C_1-C_4-alkyl or benzyl;

R^2 denotes -C(=NH)NH_2 or –CH_2-NH_2;

R^3 denotes phenyl, benzyl, naphthyl, furanyl, benzofuranyl, quinolyl, isoquinolyl, thienyl or benzothienyl;

R^4 denotes hydrogen, a C_1-C_6-alkyl group, which may be mono- or disubstituted by one or two of the groups $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

a 5-, 6- or 7-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge or via a C_1-C_4-alkylene-CO bridge which may optionally contain one, two or three hetero atoms selected from the group oxygen, nitrogen or sulphur and which may optionally be substituted by C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, benzyl or pyridyl;

C_3-C_8-cycloalkyl, which may be mono- or disubstituted by one or two of the groups $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

phenyl, benzyl or phenylethyl, which may be mono- or disubstituted at the phenyl ring by one or two of the groups $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl$)_2$, $-C_1$-C_4-alkyl-NH_2, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$,
optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

According to the invention, the preferred arylsulphonamide-substituted benzimidazole derivatives of general formula (I) are those wherein

R^1 denotes C_1-C_5-alkyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1-C_4-alkoxy, CF_3, phenoxy, COOH, $-CO(C_1$-C_4-alkoxy), $-CONH_2$, $-CO-NH(C_1$-C_4-alkyl), $-CO-N(C_1$-C_4-alkyl$)_2$ or C_1-C_4-alkoxy-phenoxy, or

a C_3-C_8-cycloalkyl optionally linked via a C_1-C_4-alkylene bridge, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1-C_4-alkoxy, carboxy, halogen, C_1-C_4-alkoxycarbonyl or CF_3, or

phenyl-C_1-C_4-alkyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1-C_4-alkoxy, carboxy, C_1-C_4-alkoxycarbonyl or CF_3, or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge, which may contain one or two hetero

atoms selected from the group oxygen, nitrogen or sulphur and which may optionally be substituted by C_1-C_4-alkyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl , quinolyl, benzothienyl or naphthyl;

R^4 denotes a C_1-C_6-alkyl group, which is mono- or disubstituted by one or two of the groups $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

a 5-, 6- or 7-membered, saturated or unsaturated nitrogen-heterocyclic group linked directly or via a C_1-C_4-alkylene bridge or via a C_1-C_4-alkylene-CO bridge, which may optionally contain one or two other hetero atoms selected from the group oxygen, nitrogen or sulphur and which may optionally be substituted by C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, benzyl or pyridyl;

cyclopropyl, cyclopentyl or cyclohexyl, each of which is mono- or disubstituted by one or two of the groups $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

phenyl, benzyl or phenylethyl, which are mono- or disubstituted at the phenyl ring by one or two of the groups $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$,
optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Preferred are arylsulphonamide-substituted benzimidazole derivatives of general formula (I), wherein

R^1 denotes methyl, ethyl, propyl, butyl or pentyl, each of which may be substituted by one of the groups hydroxy, methoxy, ethoxy, propoxy, CF_3, phenoxy, COOH, $CONH_2$, CONHMe or methoxy-phenoxy, or

benzyl, phenylethyl or phenylpropyl, which may be mono- or disubstituted at the phenyl ring by one or two of the groups hydroxy, methoxy, ethoxy, carboxy, methoxycarbonyl, ethoxycarbonyl or CF_3, or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge, which may contain one or two hetero atoms selected from the group oxygen or nitrogen and may optionally be substituted by methyl, ethyl, propyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, quinolyl, benzothienyl or naphthyl;

R^4 denotes a group selected from the group ethyl, propyl, butyl, pentyl and hexyl, each of which is mono- or disubstituted by one or two of the groups $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

a 5-, 6- or 7-membered, saturated or unsaturated nitrogen-heterocyclic group linked directly or via a C_1-C_4-alkylene bridge or via a C_1-C_3-alkylene-CO bridge, which may optionally contain one or two other hetero atoms selected from the group oxygen or nitrogen and may optionally be substituted by methyl, ethyl, propyl, 3-hydroxypropyl or benzyl, or

cyclopentyl or cyclohexyl, each of which is mono- or disubstituted by one or two of the groups $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

benzyl or phenylethyl, which are mono- or disubstituted at the phenyl ring by one or two of the groups $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$,

optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Particularly preferred are arylsulphonamide-substituted benzimidazole derivatives of general formula (I), wherein

R^1 denotes methyl, ethyl optionally substituted by hydroxy, methoxy, ethoxy, phenoxy or methoxy-phenoxy; propyl optionally substituted by hydroxy, methoxy or ethoxy, or butyl or pentyl, or

benzyl which may be mono- or disubstituted at the phenyl ring by one or two of the groups hydroxy, carboxy, methoxycarbonyl, ethoxycarbonyl, methoxy, ethoxy or CF_3, phenylethyl or phenylpropyl, or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a methylene or ethylene bridge which contains oxygen or nitrogen as the heteroatom and may optionally be substituted by methyl, ethyl, propyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$, preferably $-C(=NH)NH_2$;

R^3 denotes phenyl, benzyl , quinolyl, benzothienyl or naphthyl, preferably phenyl , quinol-8-yl, benzo[*b*]thien-3-yl or naphthyl;

R^4 denotes ethyl or propyl, each of which is substituted by one of the groups $-NH_2$, $-N(methyl)_2$, $-N(ethyl)_2$, $-N(n\text{-}propyl)_2$ or $-C(=NH)NH_2$, or

a 5-, 6- or 7-membered, saturated or unsaturated nitrogen-heterocyclic group linked directly or via a methylene or ethylene bridge or a carbonylmethyl bridge, which may contain an oxygen as a further heteroatom and may optionally be substituted by methyl, ethyl, propyl, 3-hydroxypropyl or benzyl, or

cyclopentyl or cyclohexyl, each of which is substituted by one of the groups $-NH_2$, $-N(methyl)_2$, $-N(ethyl)_2$, $-N(n\text{-}propyl)_2$ or $-C(=NH)NH_2$, or

benzyl which is substituted at the phenyl ring by one of the groups $-NH_2$, $-N(methyl)_2$, $-N(ethyl)_2$, $-N(n\text{-}propyl)_2$ or $-C(=NH)NH_2$,

optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Also particularly preferred are arylsulphonamide-substituted benzimidazole derivatives of general formula (I), wherein

R^1 denotes methyl, ethyl, hydroxyethyl, methoxyethyl, methoxy-phenoxy-ethyl, propyl, hydroxypropyl, ethoxypropyl, pentyl, or

benzyl, which is mono- or disubstituted at the phenyl ring by one or two of the groups carboxy, ethoxycarbonyl or CF_3, phenylethyl or phenylpropyl, or a tetrahydrofuranyl linked via a methylene bridge;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$, preferably $-C(=NH)NH_2$;

R^3 denotes phenyl, benzyl, quinolyl, benzothienyl or naphthyl, preferably phenyl, quinol-8-yl, benzo[*b*]thien-3-yl or naphthyl;

R^4 denotes diethylaminoethyl, diethylaminopropyl, or
a pyridine, pyrimidine, pyrrolidine, morpholine, azepine or piperidine linked directly or via a methylene or carbonylmethyl bridge, each of which may be substituted by methyl, 3-hydroxypropyl or benzyl, or
cyclohexyl substituted by-$N(n\text{-propyl})_2$, or
benzyl which is substituted at the phenyl ring by $-N(methyl)_2$ or $-C(=NH)NH_2$,
optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Of particular importance according to the invention are arylsulphonamide-substituted benzimidazole derivatives of general formula (I), wherein

R^1 denotes methyl, hydroxyethyl, methoxyethyl, methoxy-phenoxy-ethyl, propyl, hydroxypropyl, ethoxypropyl, phenylethyl, phenylpropyl or a tetrahydrofuranyl linked via a methylene bridge, preferably methyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$, preferably $-C(=NH)NH_2$;

R^3 denotes phenyl, benzyl, quinol-8-yl, benzo[*b*]thien-3-yl or naphthyl;

R^4 denotes diethylaminoethyl, diethylaminopropyl, or
a pyridine linked directly or via a methylene or ethylene bridge, which may be substituted by methyl or benzyl, or
a pyrrolidine linked directly or via a methylene or ethylene bridge, which may be substituted by methyl or benzyl, or
a piperidine linked directly or via a methylene or ethylene bridge which may be substituted by methyl or benzyl, or
a morpholine linked directly or via a methylene or ethylene bridge, or
an azepine linked directly or via a methylene or ethylene bridge,
cyclohexyl substituted by $-N(n\text{-propyl})_2$, or

benzyl substituted at the phenyl ring by -N(methyl)$_2$,
optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

The following compounds are of particular interest according to the invention:

- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzylsulfonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(3-diethylaminopropyl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-{N-[(N'-methyl-pyrrolidin-3-yl)methyl]-benzenesulphonylamino}-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-{N-[(N'-methyl-pyrrolidin-2-yl)methyl]-benzenesulphonylamino}-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-{N-[(N'-benzyl-pyrrolidin-3-yl)]-benzenesulphonylamino}-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(pyrrolidin-3-yl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(piperidin-4-yl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(N'-benzyl-piperidin-4-yl)-benzenesulphonylamino]-benzimidazole;
- 1-(2-Methoxyethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole;
- 1-[2-(2-Methoxyphenoxy)ethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-naphth-1-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-naphth-2-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-azepin-1-ylethyl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-piperidin-1-ylethyl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-pyrrolidin-1-ylethyl)-benzenesulphonylamino]-benzimidazole;

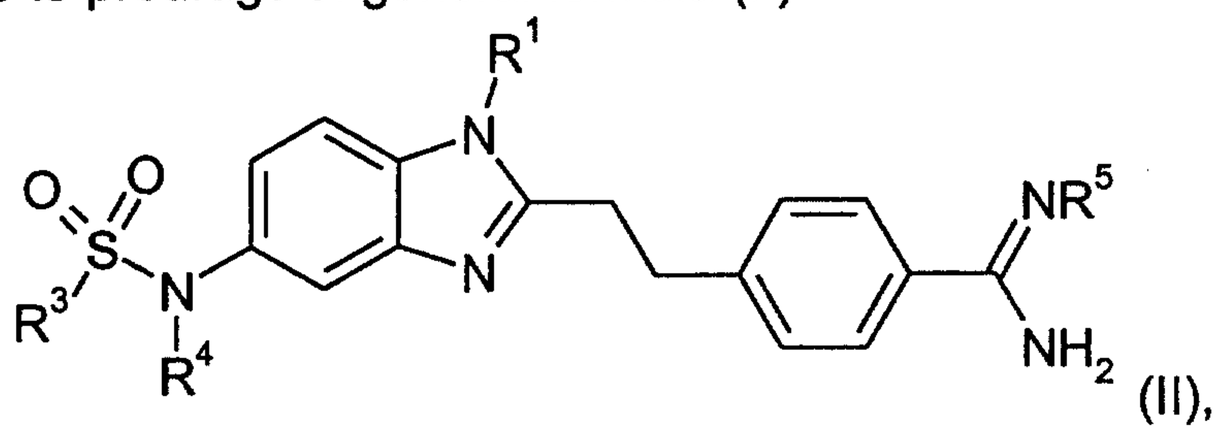
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzo[*b*]thien-3-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(pyrid-2-ylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(pyrid-3-ylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-benzyl-piperid-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-morpholinoethyl)-naphth-2-ylsulphonylamino]-benzimidazole
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-pyrid-4"-yl-piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-benzyl-piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-(3"-hydroxypropyl)-piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazol
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-chinol-8-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-isochinol-5-ylsulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-dimethylaminobutyl)-benzenesulphonylamino]-benzimidazole;
- 1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-methyl-1,4-diazepin-1-yl-carbonylmethyl)-benzenesulphonylamino]-benzimidazole.

A further aspect of the present invention is directed to the use of the compounds of general formula (I) for preparing a pharmaceutical composition for the prevention and/or treatment of diseases in which tryptase inhibitors may be of therapeutic value.

It is preferred according to the invention to use compounds of general formula (I) for the purpose mentioned above, for preparing a pharmaceutical composition for the prevention and/or treatment of inflammatory and/or allergic diseases. It is particularly preferable to use the compounds of general formula (I) as mentioned above for preparing a pharmaceutical composition for the prevention and/or treatment of bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, allergic otitis, allergic gastro-intestinal disorders, Crohn's disease, ulcerative colitis, anaphylactic shock, septic shock, shock lung (ARDS) and arthritis.

It is also advantageous to use the compounds of general formula (I) as mentioned above for preparing a pharmaceutical composition for the prevention and/or treatment of fibroses such as lung fibrosis, fibrosing alveolitis and scarring, collagenoses such as lupus erythematodes and sclerodermia as well as arteriosclerosis, psoriasis and neoplasm.

In addition to the abovementioned compounds of general formula (I) the present invention also relates to compounds which are only converted into the therapeutically effective compounds of general formula (I) by the body after being taken by the patient, on the basis of a functionality which can be cleaved *in vivo* . Such compounds are known as prodrugs. According to another aspect the invention therefore relates to prodrugs of general formula (II)



(II),

wherein

R^1 and R^3 may be as hereinbefore defined and

R^4 may be as hereinbefore defined or may denote C_1-C_4-alkyl which is substituted by a group selected from the group $-C(=NOH)NH_2$, $-C(=NCOO-C_1-C_{12}\text{-alkyl})NH_2$ or $-C(=NCOO-C_1-C_8\text{-alkyl-phenyl})NH_2$;

R^5 may denote hydroxy, $-COO-C_1-C_{12}$-alkyl, -CO-phenyl, -CO-pyridyl or $-COO-C_1-C_8$-alkyl-phenyl, whilst in the abovementioned group the phenyl ring may be substituted in each case by C_1-C_4-alkyl, C_1-C_4-alkoxy, OH, halogen or CF_3,

optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Preferred are prodrugs of general formula (II), wherein

R^1 and R^3 may be as hereinbefore defined and

R^4 may be as hereinbefore defined or may denote C_1-C_4-alkyl which is substituted by a group selected from among

-C(=NOH)NH_2, -C(=NCOO-C_1-C_6-alkyl)NH_2 or
-C(=NCOO-C_1-C_6-alkyl-phenyl)NH_2;

R^5 may denote hydroxy, -COO-C_1-C_6-alkyl, -CO-phenyl, -CO-pyridyl or -COO-C_1-C_6-alkyl-phenyl, whilst in the abovementioned group the phenyl ring may be substituted in each case by C_1-C_4-alkyl, C_1-C_4-alkoxy, OH, halogen or CF_3,

optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Particularly preferred are prodrugs of general formula (II), wherein
R^1, R^3 and R^4 may be as hereinbefore defined and
R^5 may denote hydroxy, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, benzoyl, benzyloxycarbonyl or nicotinoyl,

optionally in the form of their tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

The term alkyl groups (including those which are part of other groups), unless otherwise stated, denotes branched and unbranched alkyl groups with 1 to 12 carbon atoms, preferably 1 – 8 carbon atoms, most preferably 1 to 6 carbon atoms. Examples are: methyl, ethyl, propyl, butyl, pentyl, hexyl, etc. Unless otherwise stated, the above terms propyl, butyl, pentyl or hexyl also include all the possible isomeric forms. For example, the term propyl also includes the two isomeric groups n-propyl and iso-propyl, the term butyl includes n-butyl, iso-butyl, sec. butyl and tert.-butyl, the term pentyl includes iso-pentyl, neopentyl, etc. In some cases common abbreviations are also used to denote the abovementioned alkyl groups, such as Me for methyl, Et for ethyl etc.

The term alkenyl groups (including those which are part of other groups) denotes branched and unbranched alkenyl groups having 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms, provided that they have at least one double bond, for example the alkyl groups mentioned above as well, provided that they have at least one double bond, such as for example vinyl (provided that no unstable enamines or enolethers are formed), propenyl, iso-propenyl, butenyl, pentenyl and hexenyl.

The term alkinyl groups (including those which are part of other groups) denotes alkinyl groups having 2 to 6 carbon atoms, provided that they have at least one triple bond, e.g. ethinyl, propargyl, butinyl, pentinyl and hexinyl.

The term halogen generally denotes fluorine, chlorine, bromine or iodine.

Examples of cycloalkyl groups with 3 - 8 carbon atoms according to the invention are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Examples of 5-, 6- or 7-membered, saturated or unsaturated heterocycles which may contain nitrogen, oxygen or sulphur as heteroatoms, include, unless otherwise stated in the definitions, furan, tetrahydrofuran, tetrahydrofuranon, γ-butyrolactone, α-pyran, γ-pyran, dioxolan, tetrahydropyran, dioxane, thiophene, dihydrothiophene, thiolan, dithiolan, pyrrole, pyrroline, pyrrolidine, pyrazole, pyrazoline, pyrazolidine, imidazole, imidazoline, imidazolidine, triazole, tetrazole, pyridine, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, tetrazine, morpholine, thiomorpholine, diazepan, oxazole, isoxazole, oxazine, thiazole, isothiazole, thiadiazole, oxadiazole and pyrazolidine, wherein the heterocyclic group may be substituted as stated in the definitions.

Unless otherwise specified, the two alkyl groups in the dialkylaminosubstituents $-N(C_1\text{-}C_4\text{-alkyl})_2$ may be identical or different.

"=O" denotes an oxygen atom linked via a double bond.

The substituted benzimidazole derivatives of formula (I) as well as the prodrugs of general formula (II) may be obtained by various methods of synthesis. Possible approaches based on and using conventional methods of chemical synthesis are hereinafter described by way of example. Diagram 1 shows one possible method of synthesising the basic benzimidazole structure of the compounds according to the invention.

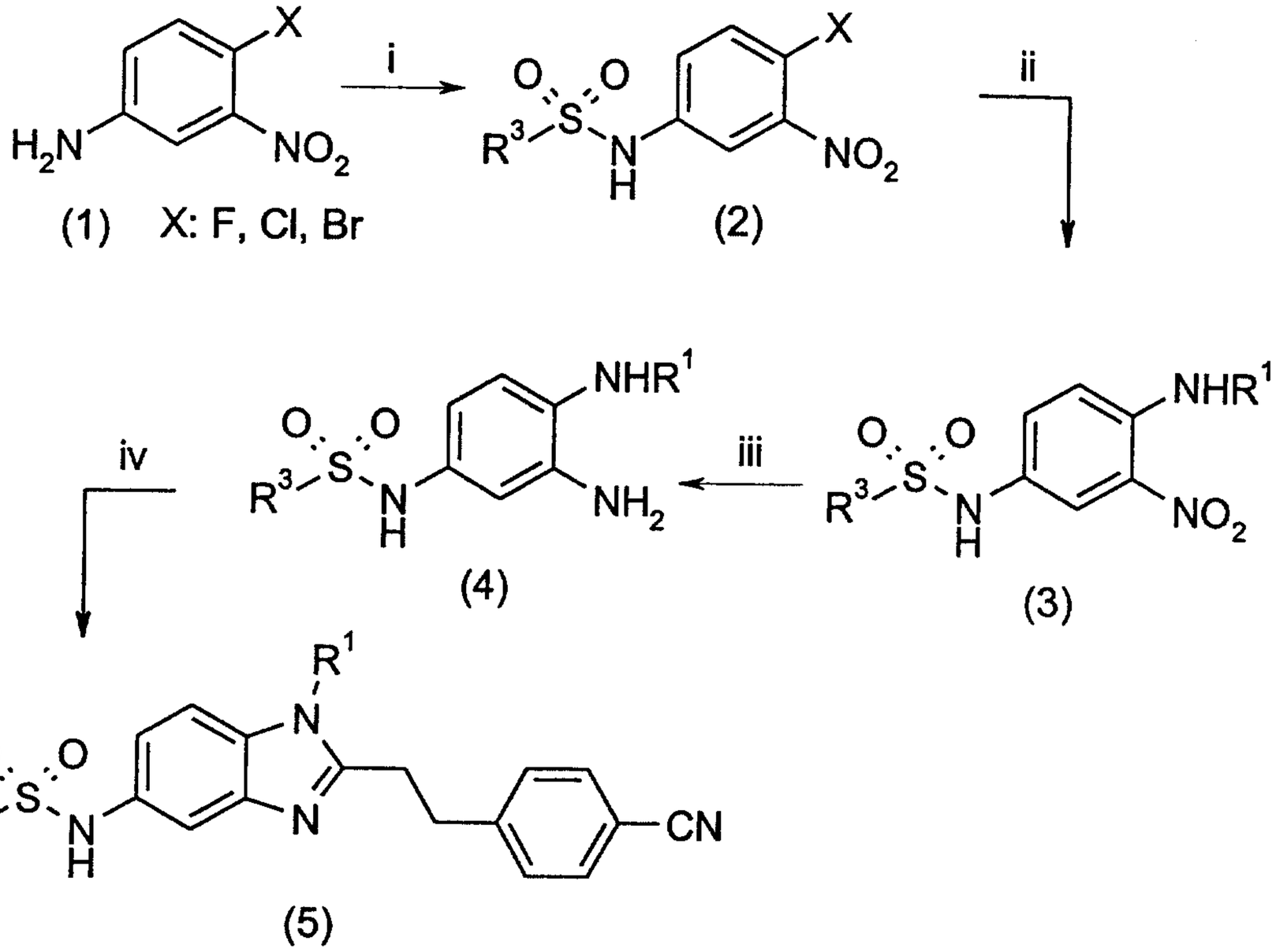


Diagram 1:

In a first step (diagram, step i) the 3-nitro-4-halo-anilines (1) are reacted to form the sulphonamides (2). For this purpose the compounds (1) are taken up in a suitable organic, anhydrous solvent and combined with the desired arylsulphonic acid chloride optionally in the presence of an organic base, while cooling. Suitable organic solvents may be halogenated hydrocarbons such as dichloromethane or chloroform as well as solvents selected from among dioxan, tetrahydrofuran, dimethylformamide, acetonitrile and pyridine. It is preferred according to the invention to use pyridine or pyridine mixed with dichloromethane or chloroform as solvent. If an organic base is added, amines such as triethylamine, diisopropylethylamine, N-methylmorpholine or pyridine are primarily used. The arylsulphonic acid chloride is preferably added at temperatures below ambient temperature, particularly between -40°C and 20°C, most preferably at –20°C to 10°C. After the reaction has ended (about 0.5 – 2h) the mixture is worked up by conventional methods. The compounds (2) may optionally be purified by crystallisation from nonpolar organic solvents such as, for example, diethylether and petroleum ether, optionally mixed with ethyl acetate.

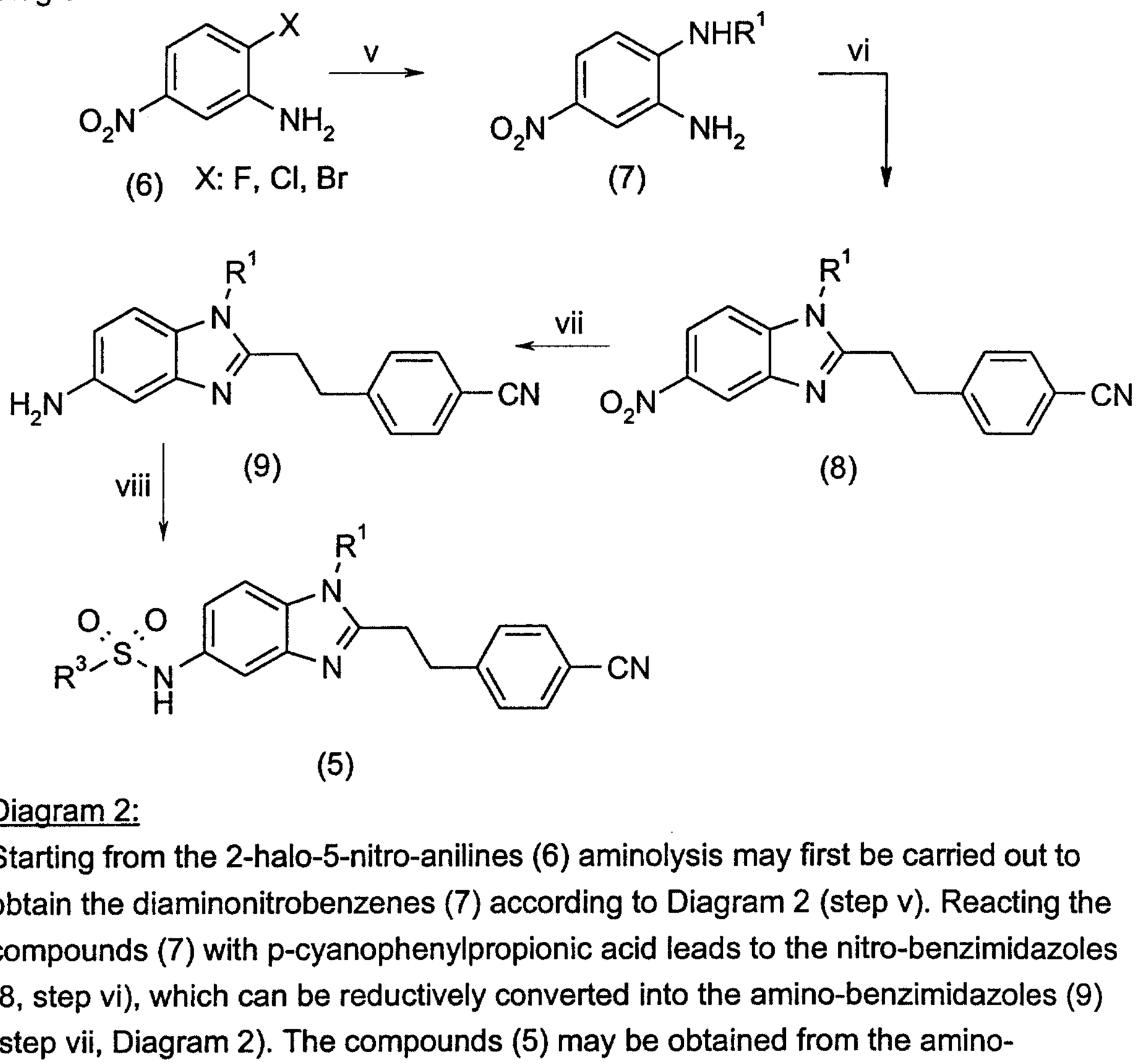
In a second step (Diagram 1, step ii) the sulphonamides (2) are reacted to form the compounds (3). The aminolysis of the compounds (2) with the primary amines R^1-NH_2 is carried out in suitable organic solvents such as for example dimethylsulphoxide, N,N-dimethylformamide, N-methylpyrrolidone, acetone or optionally in water or alcohols at ambient temperature or in a temperature range from 30-80°C, preferably 40-50°C.

The reduction of the nitro groups to form the compounds (4, Diagram 1, step iii) is carried out for example by catalytic hydrogenation in organic solvents such as for example methanol, ethanol, isopropanol, tetrahydrofuran, optionally also in admixture with dimethylformamide, ethyl acetate, dioxan or acetic acid, at elevated hydrogen pressure or at normal pressure at temperatures between 0-50°C, preferably at 20-40°C. Suitable catalysts are conventional hydrogenation catalysts. Palladium and Raney nickel are preferred. According to the invention, palladium is preferred. Palladium on charcoal (5%) is particularly preferred as the catalyst. An alternative method of reducing the nitro compounds (3) envisages the use of reduction agents such as $Na_2S_2O_4$ or $SnCl_2$. This reaction is carried out in protic, water-miscible organic solvents such as short-chained alcohols (methanol, ethanol, isopropanol) or in a mixture of the abovementioned solvents with water, optionally with acetic acid, dimethylformamide or ethyl acetate. The reaction is normally carried out at elevated temperature, preferably by refluxing the solvent or solvent mixture in question. After the reaction of the starting compounds (3) is complete, the mixture is worked up in the usual way. The compounds (4) may be purified for example by crystallisation from nonpolar organic solvents such as diethylether, petroleum ether, optionally mixed with ethyl acetate.

In a fourth step (Diagram 1, step iv) cyclisation to form the benzimidazoles (5) is carried out by reacting the sulphonamide derivatives (4) with p-cyanophenylpropionic acid in the presence of dehydrating reagents. The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan. Suitable dehydrating agents include for example isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilan, phosphorus oxychloride, thionylchloride, trimethylchlorosilan, phosphorus trichloride, phosphorus pentoxide, ethyl 1,2-dihydro-2-ethoxy-quinoline-1-carboxylate (EEDQ), *i*-propyl 1,2-dihydro-2-*i*-propyloxy-quinoline-1-carboxylate (IIDQ), N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-

1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride. It may be appropriate to add a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine. The reaction is usually carried out at temperatures between 0 and 150°C, preferably at temperatures between 20 and 120°C.

An alternative method of obtaining the compounds (5) is shown by way of example in Diagram 2.

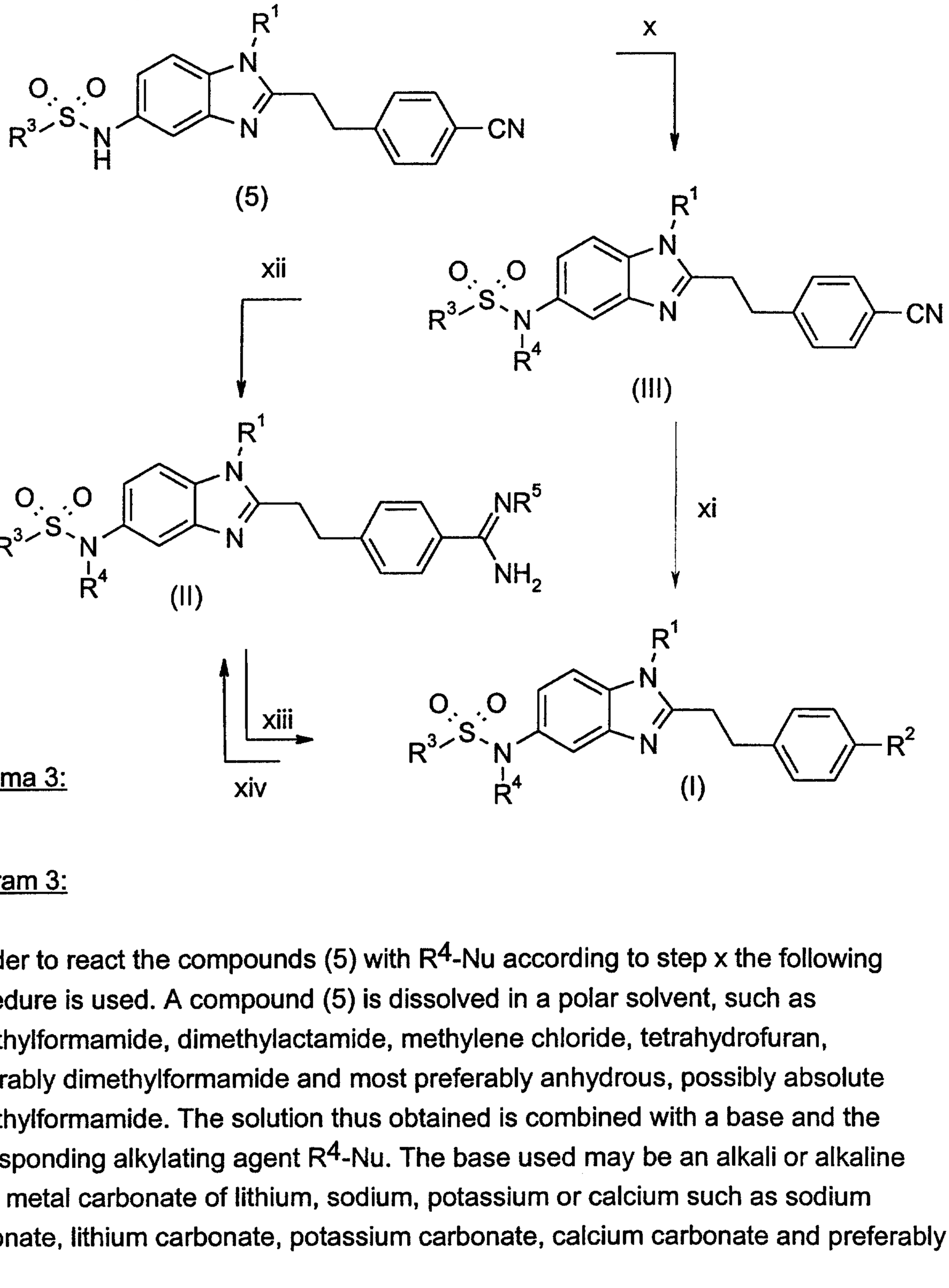


(5)

Diagram 2:

Starting from the 2-halo-5-nitro-anilines (6) aminolysis may first be carried out to obtain the diaminonitrobenzenes (7) according to Diagram 2 (step v). Reacting the compounds (7) with p-cyanophenylpropionic acid leads to the nitro-benzimidazoles (8, step vi), which can be reductively converted into the amino-benzimidazoles (9) (step vii, Diagram 2). The compounds (5) may be obtained from the amino-benzimidazoles (9) by reaction with the corresponding arylsulphonic acid chlorides (Diagram 2, step viii). The synthesis outlined in Diagram 2 may be carried out experimentally analogously to the procedure described for steps i-iv (Diagram 1). Step v is carried out analogously to the method according to step ii, step vi analogously to the method according to step iv, step vii analogously to the method described for step ii and, finally, step viii according to the experimental method in step i.

Starting from the benzimidazoles (5) which may be obtained according to Diagrams 1 and 2, the intermediates of formula (III) (cf. Diagram 3) are obtained by reaction with the compounds R^4-Nu, where Nu denotes a nucleofugic leaving group such as for example chlorine, bromine, iodine, methanesulphonate, methyltriflate, p-toluenesulphonate etc. Alternatively, the intermediates (III) may be obtained from the compounds (5) by reductive amination by reacting with correspondingly substituted ketones or aldehydes under reductive conditions.



Schema 3:

Diagram 3:

In order to react the compounds (5) with R^4-Nu according to step x the following procedure is used. A compound (5) is dissolved in a polar solvent, such as dimethylformamide, dimethylactamide, methylene chloride, tetrahydrofuran, preferably dimethylformamide and most preferably anhydrous, possibly absolute dimethylformamide. The solution thus obtained is combined with a base and the corresponding alkylating agent R^4-Nu. The base used may be an alkali or alkaline earth metal carbonate of lithium, sodium, potassium or calcium such as sodium carbonate, lithium carbonate, potassium carbonate, calcium carbonate and preferably

potassium carbonate. It is also possible to use the alkali or alkaline earth metal hydroxides of lithium, sodium, potassium, magnesium or calcium, but preferably sodium hydroxide, potassium hydroxide, lithium hydroxide and calcium hydroxide in alcohol or water. The reaction mixture is stirred for 0.5-8h, preferably 1-4h at elevated temperature, preferably at 50-120°C, particularly at the reflux temperature of the solvent used. After the reaction is complete the mixture is worked up in the usual way and the crude product obtained is purified by crystallisation or chromatography on silica gel.

If the intermediates (III) are obtained from the compounds (5) by reductive amination, the following procedure is used. The compound (5) is dissolved in a suitable solvent such as for example dichloromethane, dichloroethane, methanol, ethanol, tetrahydrofuran or toluene, and at between 0-60°C, preferably at 20-40°C, the corresponding carbonyl compound is added in the presence of an acid, preferably a carboxylic acid, most preferably a short-chained carboxylic acid, particularly acetic acid. Then a suitable reduction agent is added. Suitable reduction agents which may be used according to the invention are $Na[HB(OAc)_3]$, $Na[BH_3CN]$, $NaBH_4$, $Pd/C-H_2$, preferably $Na[HB(OAc)_3]$. After working up in the usual way the product is purified by crystallisation or chromatography on silica gel.

According to step xi the compounds of general formula (I) according to the invention may be obtained from the intermediates (III). Various methods may be used to prepare the compounds of general formula (I) according to the invention wherein R^2 denotes $-C(=NH)NH_2$.

A compound of general formula (I) is obtained for example by treating a compound of general formula (III) with a corresponding alcohol such as methanol, ethanol, n-propanol, isopropanol or benzylalcohol optionally mixed with another organic solvent such as for example chloroform, nitrobenzene or toluene in the presence of an acid such as hydrochloric acid or by reacting a corresponding amide with a trialkyloxonium salt such as triethyloxonium-tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxan at temperatures between -10 and 50°C, but preferably at 0-20°C and subsequent aminolysis with alcoholic ammonia solution for example. Alternatively the compounds of general formula (I) may be obtained by reacting a compound of general formula (III) with sulphur nucleophiles such as e.g. hydrogen sulphide, ammonium or sodium sulphide, sodium hydrogen sulphide, carbon disulphide, thioacetamide or bistrimethylsilylthioether, optionally in the presence of bases such as triethylamine, ammonia, sodium hydride or sodium alkoxide in solvents such as methanol, ethanol, water, tetrahydrofuran, pyridine, dimethylformamide or 1,3-dimethyl-imidazolidin-2-one at 20-100 °C , and

subsequently treating them with a suitable methylating agent such as e.g. methyl iodide or dimethylsulphate in a solvent such as acetonitrile or acetone at temperatures between -10 and 50°C, but preferably at 0-20°C, and then treating them with ammonia, ammonium carbonate or ammonium chloride in a suitable alcohol, such as for example methanol, ethanol, isopropanol etc. at temperatures between -10 and 50°C, but preferably at 0-20°C.

Moreover, the compounds of general formula (I) according to the invention may be obtained by treating a compound of general formula (III) with lithium hexamethyl disilazide in a suitable organic solvent such as e.g. tetrahydrofuran at temperatures between –20 and 50 °C, but preferably at 0-20 °C and subsequently hydrolysing with dilute hydrochloric acid at 0-5 °C.

Another alternative method of obtaining compounds of general formula (I) is by treating a compound of general formula (III) with ammonium chloride and trimethylaluminium in a suitable organic solvent such as e.g. toluene at temperatures between 20 and 150 °C, but preferably at 110 °C.

Compounds of general formula (I) wherein R^2 denotes $-CH_2-NH_2$ may be obtained from the intermediates (III) for example by catalytic hydrogenation on Raney nickel. These reactions are preferably carried out in protic organic solvents such as short-chained alcohols (methanol, ethynol or isopropanol) at temperatures between 10-40°C, preferably at 20-30°C under normal pressure.

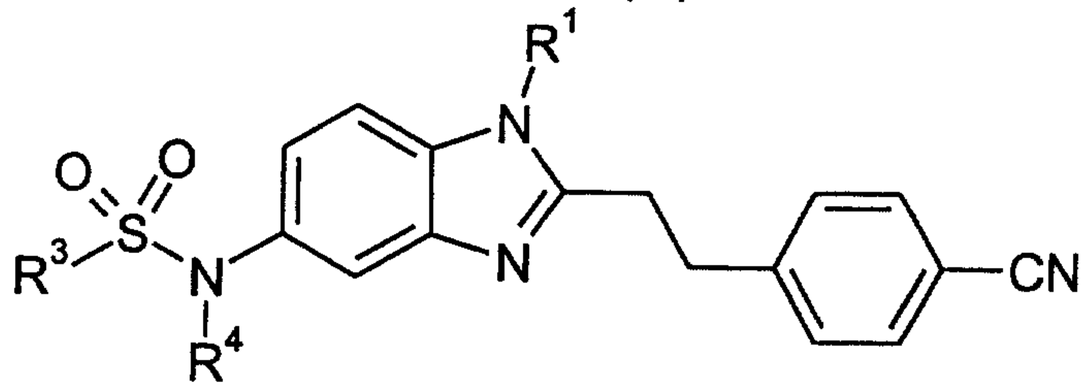
A compound of general formula (II) is obtained for example by treating a compound of general formula (III, Diagram 3, step xii) with hydroxylamine in the presence of carbonates or alkoxides of alkali or alkaline earth metals in solvents such as methanol, ethanol, n-propanol or isopropanol optionally in admixture with dioxan or tetrahydrofuran. The alkoxides may be prepared from the respective alkali metals or metal hydrides and the corresponding alcohol. The reaction is preferably carried out at 20-100°C, most preferably at the boiling temperature of the solvent used.

Compounds of general formula (II) may alternatively be obtained by treating a compound of general formula (III) with a corresponding alcohol such as methanol, ethanol, n-propanol, isopropanol or benzylalcohol in the presence of an acid such as hydrochloric acid or by reacting a corresponding amide with a trialkyloxonium salt such as triethyloxonium tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxan at temperatures between -10 and 50°C, but preferably at 0-20°C and subsequently treating with hydroxylamine in the presence of bases in a suitable alcohol, such as methanol, ethanol, isopropanol etc. at temperatures between -10 and 50°C, but preferably at 0-20°C.

A compound of general formula (I) is obtained for example by treating a compound of general formula (II, Diagram 3, step xiii) with hydrogen in the presence of hydrogenation catalysts such as Raney nickel or rhodium/aluminium oxide in water or methanol optionally with the addition of acids such as hydrochloric acid or methanesulphonic acid or by treating with hydrogen in the presence of palladium/charcoal in acetic acid/acetic anhydride at 20-50 °C and 1-5 bar hydrogen pressure, preferably at ambient temperature and normal pressure.

The acyl- or alkoxycarbonyl prodrugs (II) of the compound of general formula (I) are obtained by reacting the compounds of general formula (I) with the corresponding acid chlorides in the presence of bases such as e.g. triethylamine, N-methyl-morpholine, diethylisopropylamine or DBU in a suitable solvent such as methylene chloride, chloroform, tetrahydrofuran, acetonitrile, dimethylformamide or dimethylsulphoxide.

In accordance with their central role in the synthesis of the compounds of general formula (I) according to the invention as well as the synthesis of the prodrugs of general formula (II), a further aspect of the present invention is directed to the intermediates of general formula (III)



(III)

wherein the groups R^1, R^3 and R^4 may be as hereinbefore defined.
The compounds of general formula (III) are valuable intermediates for preparing the benzimidazole derivatives of general formula (I) according to the invention as well as the prodrugs of general formula (II) according to the invention.

On the basis of their pharmacological properties the compounds according to the invention may be used as pharmaceutical compositions, particularly as pharmaceutical compositions with a tryptase-inhibiting effect. They may be used in any circumstances where tryptase inhibitors are able to develop a therapeutic effect.

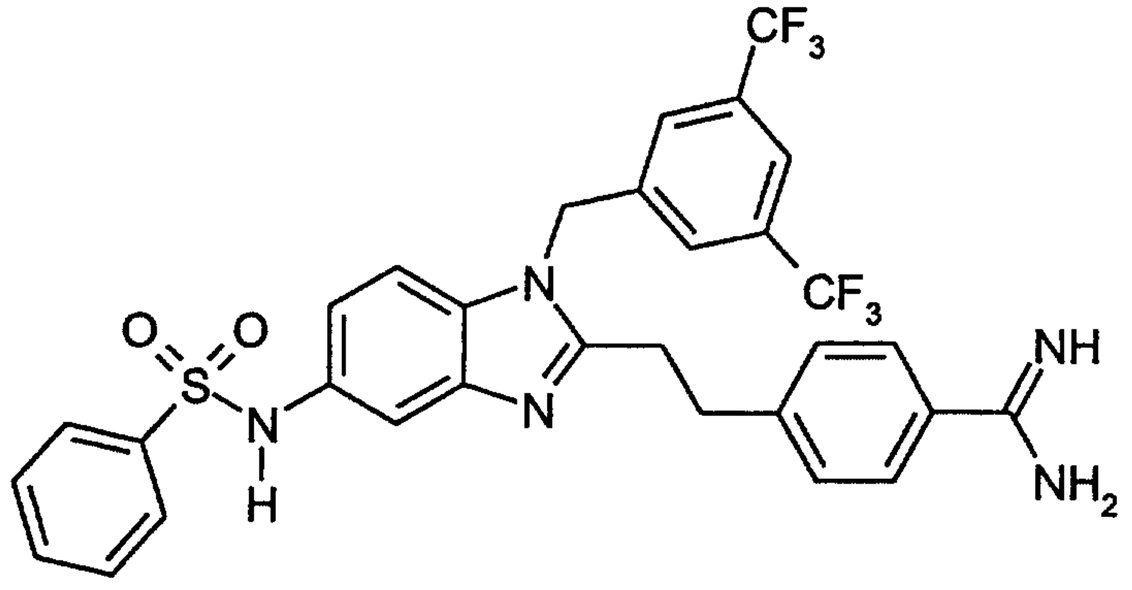
The compounds of general formula (I) according to the invention are preferably used to prepare a pharmaceutical composition for the prevention and/or treatment of inflammatory and/or allergic diseases. It is particularly preferred to use the compounds of general formula (I) for the purpose mentioned at the beginning,

namely for preparing a pharmaceutical composition for the prevention and/or treatment of bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, allergic otitis, allergic gastro-intestinal disorders, Crohn's disease, ulcerative colitis, anaphylactic shock, septic shock, shock lung (ARDS) and arthritis.

It is also advantageous to use the compounds of general formula (I) as mentioned above for preparing a pharmaceutical composition for the prevention and/or treatment of fibroses such as lung fibrosis, fibrosing alveolitis and scarring, collagenoses such as lupus erythematodes and sclerodermia as well as arteriosclerosis, psoriasis and neoplasm.

Procedures by way of example for preparing the compounds according to the invention will be described in more detail hereinafter. The Examples which follow serve solely as a detailed illustration without restricting the subject matter of the invention.

Example 1: N-{2-[2-(4-amidinophenyl)-ethyl]-1-(3,5-bis-trifluoromethyl-benzyl)-benzimidazol-5-yl}-benzenesulphonamide-hydrochloride



a) N-{4-fluoro-3-nitro-phenyl}-benzenesulphonamide

4-fluoro-3-nitro-aniline (7.8 g, 50 mmol) is taken up in 50 mL pyridine and cooled to 10°C. The benzenesulphonic acid chloride (7.0 mL, about 55 mmol) is added dropwise with stirring within about 20 min at 10-20 °C. The mixture is stirred for about 0.5 h at ambient temperature and poured onto ice water. After acidifying with conc. hydrochloric acid the mixture is extracted with 150 mL ethyl acetate, washed with water, dried and concentrated by evaporation. The residue is dissolved in diethylether, diluted with petroleum ether and cooled. The crystals formed are filtered off, washed with diethylether/petroleum ether and dried.
Yield: 12.2 g (82.4 %); m.p.: 118 - 120 °C;

b) N-{3-nitro-4-(3,5-bis-trifluoromethyl-benzylamino)-phenyl}-benzenesulphonamide

N-{4-fluoro-3-nitro-phenyl}-benzenesulphonamide (3.0 g, 10 mmol), 3,5-bis-trifluoromethylbenzylamine (3.0 g, 12.5 mmol) and N-methylmorpholine (2.2 mL, 20 mmol) in 25 mL dimethylsulphoxide are kept for 6 h at 60 – 100 °C, diluted with 150 mL ethyl acetate, washed with water, dilute hydrochloric acid and water again, dried and concentrated by evaporation until not quite dry. The residue is combined with 80 mL EtOH and evaporated down to a residual volume of about 50 mL. The crystals precipitated after cooling are filtered off and washed with EtOH and petroleum ether.
Yield: 4.0 g (81.6%)
m.p.: 190 - 193 °C

c) N-{3-amino-4-(3,5-bis-trifluoromethyl-benzylamino)-phenyl}-benzenesulphonamide

N-{3-nitro-4-(3,5-bis-trifluoromethyl-benzylamino)-phenyl}-benzenesulphonamide (8.6 g, 16.6 mmol) in 200 mL methanol are refluxed and within 0.5 h combined with a solution of $Na_2S_2O_4$ (14.2 g, mmol) in 50 mL water. The mixture is refluxed until totally decolorised (this takes about 1 h). After cooling the mixture is diluted with water. About 100 mL of the methanol/water mixture are distilled off, the resulting solution is cooled, the crystals precipitated are filtered off and washed with water. The crystals are dissolved in ethyl acetate, dried and evaporated down until not quite dry. After cooling the crystals precipitated are filtered off and washed with diethylether.

Yield: 5.8 g (71.6%)

m.p.: 170 - 172 °C

d) N-{2-[2-(4-Cyanophenyl)-ethyl]-1-(3,5-bis-trifluoromethyl-benzyl)-benzimidazol-5-yl}-benzenesulphonamide

N-{3-amino-4-(3,5-bis-trifluoromethyl-benzylamino)-phenyl}-benzenesulphonamide (5.5 g, 11.2 mmol) and *p*-cyano-phenylpropionic acid (2.35 g, 13.4 mmol) are taken up in 50 mL $POCl_3$, and stirred for 2 h at 100-120 ° C. A precipitate settles out from the initially clear solution in the course of the reaction. After cooling it is diluted with 100 mL ethyl acetate/diethylether = 1/1. The crystals are filtered off and washed with diethylether.

Yield: 5.35g (71.5%)

m.p.: 140-144 °C

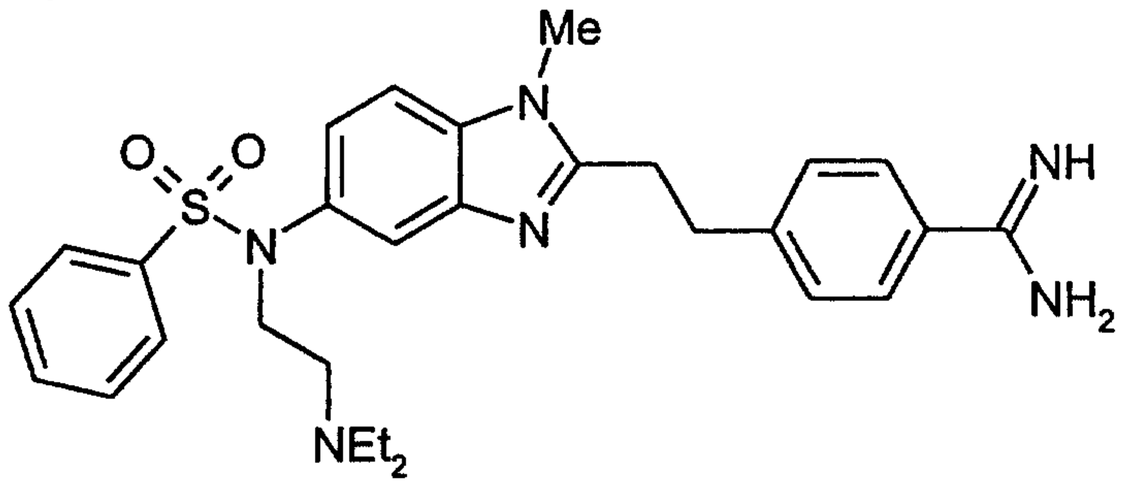
e) N-{2-[2-(4-amidinophenyl)-ethyl]-1-(3,5-bis-trifluoromethyl-benzyl)-benzimidazol-5-yl}-benzenesulphonamide-hydrochloride

N-{2-[2-(4-Cyanophenyl)-ethyl]-1-(3,5-bis-trifluoromethyl-benzyl)-benzimidazol-5-yl}-benzenesulphonamide hydrochloride (1.5 g, 2.3 mmol) is taken up in 50 mL of a saturated ethanolic hydrochloric acid solution cooled to 0 °C. It is stirred to dissolve the educt completely and then kept overnight at 0-5 °C. The ethanol is distilled off at a maximum of 40 °C and the residue is taken up in 40 mL of a saturated ethanolic ammonia solution at 0 °C. It is stirred for 2 h at ambient temperature, 3 h at 50-60 °, combined with another 10 mL of saturated NH_3 solution and refluxed for 2 h. It is combined with 20 mL water and 25 mL ethyl acetate and stirred for 0.5 h at ambient temperature. The crystals precipitated are filtered off and washed with ethyl acetate and diethylether.

Yield: 0.9 g (70.3%)

m.p.: > 220 °C

Example 2: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)-dihydrochloride



a) N^1-methyl-1,2-diamino-4-nitrobenzene

2-fluoro-5-nitro-aniline (15.0 g, 160 mmol) is taken up in 480 mL of 40% aqueous methylamine solution and stirred for 2.5 days at ambient temperature and for 2 h at 40-50 °C. It is diluted with water, the solid is filtered off, washed with water and dried.
Yield: 26 g (97%)
m.p.: 171-173 °C

b) 2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-5-nitro-benzimidazole

N^1-methyl-1,2-diamino-4-nitrobenzene (8.3 g, 49.6 mmol) and *p*-cyano-phenylpropionic acid (9.6 g, 55 mmol) are taken up in 90 mL $POCl_3$, and refluxed for 1.5 h. After cooling the excess $POCl_3$ is decomposed with ice water. It is made alkaline with NH_3 with stirring / cooling and stirred for 1 h at ambient temperature. The solid is filtered off, washed with water and recrystallised from DMF.
Yield: 11.7 g (76,4%)
m.p.: 202-204 °C

c) 5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole

2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-5-nitro-benzimidazole (5.5 g, 18 mmol) in 150 mL THF/75 mL methanol is hydrogenated in the presence of 1.0 g of 5% Pd/C at ambient temperature and normal pressure. The catalyst is filtered off, the filtrate is evaporated down until not completely dry, diluted with 100 mL acetonitrile and evaporated down to to a residual volume of 30 mL. The crystal slurry is cooled and filtered. The crystals are washed with cold acetonitrile and ether.
Yield: 4.7 g (94%)
m.p.: 187-192 °C

d) N-{2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-(benzenesulphonamide)

5 mmol of 5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole are reacted to form the title compound in the manner described according to Example 1 (step a).

Yield: 91.3%

m.p.: 222-225 °C

e) N-{2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)

N-{2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-(benzenesulphonamide) (5.9 mmol), diethylaminoethyl chloride (7.0 mmol), 4.0 g of K_2CO_3 and catalytic quantities of KI are refluxed in 50 mL dimethylformamide for 1.5 h. After cooling the mixture is poured onto ice water, extracted with 100 mL ethyl acetate, dried and concentrated by evaporation. The residue is filtered with 95/5 CH_2Cl_2/methanol through a dry packed silica gel column. After evaporation the residue is crystallised from ethyl acetate and diethylether.

Yield: 78.5%

m.p.: 120-122 °C

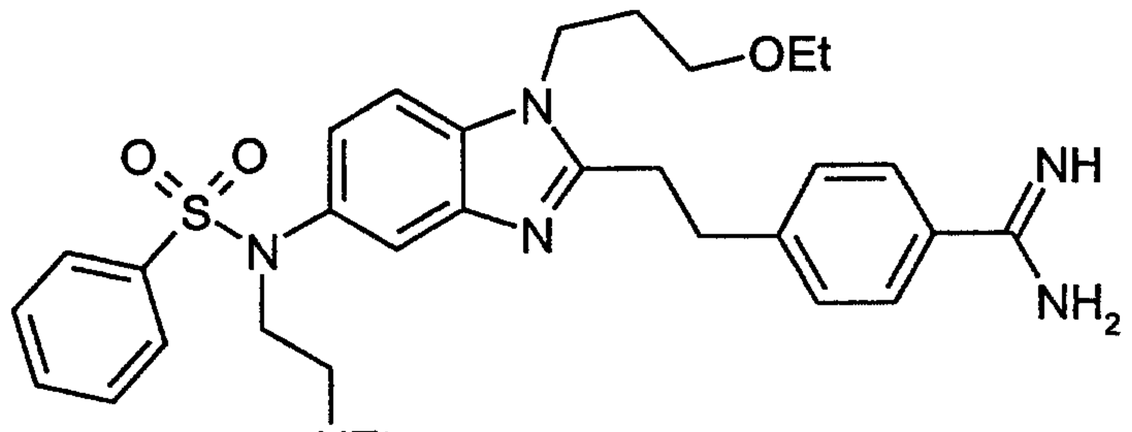
f) N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)-dihydrochloride

The title compound is prepared starting from 2.7 mmol of N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide) analogously to the method described in Example 1 (step e).

Yield: 70.1% (amorphous solid)

Mass: calc.: [532], found: $[M+H]^+$ 533, $[M+2H]^{2+}$ 267.

Example 3: N-{2-[2-(4-amidinophenyl)-ethyl]-1-(3-ethoxy-propyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)-dihydrochloride



a) N^1-(3-ethoxy-propyl)-1,2-diamino-4-nitro-benzene

2-fluoro-5-nitro-aniline (5.0 g, 32 mmol) and 3-ethoxypropylamine (11.5 mL, 96 mmol) in 15 mL dimethylsulphoxide are stirred for 10 h at 100-110 °C. The mixture is diluted with 100 mL ethyl acetate, washed 2x with water, dried and concentrated by evaporation. The product is crystallised from ethyl acetate/diethylether.

Yield: 6.1 g (79.7%)

m.p.: 69-70 °C

b) 2-[2-(4-Cyanophenyl)-ethyl]-1-(3-ethoxy-propyl)-5-nitro-benzimidazole

25.3 mmol of N^1-(3-ethoxy-propyl)-1,2-diamino-4-nitro-benzene are reacted to form the title compound in the manner described according to Example 2 (step b). For working up the mixture is poured onto ice water, covered with ethyl acetate, made alkaline with aqueous ammonia solution and extracted. Crystals from ethyl acetate.

Yield: 76.0%

m.p.: 112-114 °C

c) 5-amino-2-[4-cyanomethyl-phenyl]-1-(3-ethoxy-propyl)- benzimidazole

20 mmol of 2-[4-cyanomethyl-phenyl]-1-(3-ethoxy-propyl)-5-nitro-benzimidazole are reacted to form the title compound in the manner described according to Example 2 (step c). The substance is crystallised from ethyl acetate/diethylether.

d) N-{2-[4-Cyanomethyl-phenyl]-1-(3-ethoxy-propyl)-benzimidazol-5-yl}-(benzenesulphonamide)

6 mmol of 5-amino-2-[4-cyanomethyl-phenyl]-1-(3-ethoxy-propyl)-benzimidazole are reacted to form the title compound in the manner described according to Example 1 (step a).

Yield: 85.3%

e) N-{2-[2-(4-Cyanophenyl)-ethyl]-1-(3-ethoxy-propyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)

6 mmol of N-{2-[2-(4-cyanophenyl)-ethyl]-1-(3-ethoxy-propyl)-benzimidazol-5-yl}-(benzenesulphonamide) are reacted to form the title compound in the manner described according to Example 2 (step e).

Yield: 71%

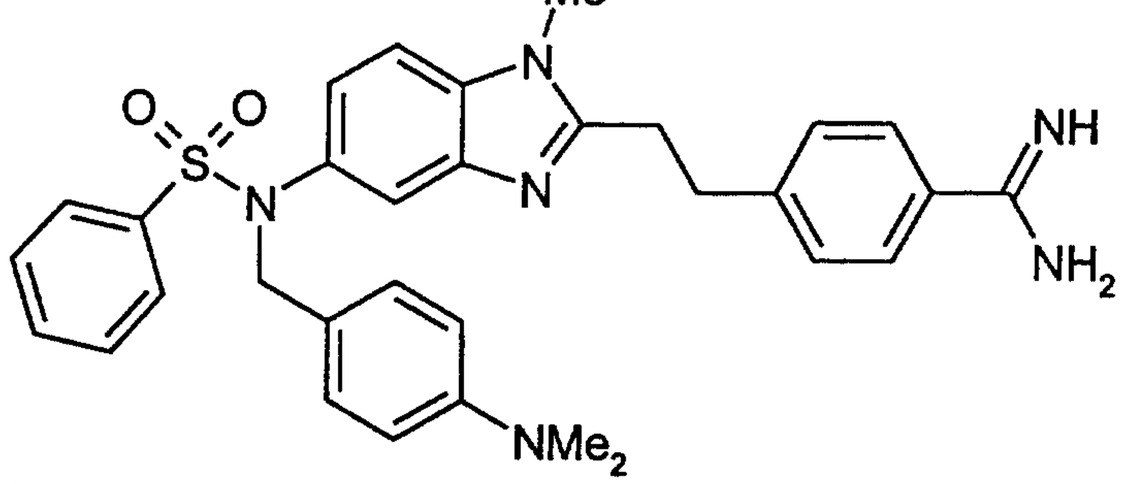
f) N-{2-[2-(4-amidinophenyl)-ethyl]-1-(3-ethoxy-propyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)-dihydrochloride

6 mmol of N-{2-[2-(4-cyanophenyl)-ethyl]-1-(3-ethoxy-propyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide) are reacted to form the title compound in the manner described according to Example 2 (step f).

Yield: 40.5%

Mass: calc.: [604], found: $[M+H]^+$ 605, $[M+2H]^{2+}$ 303

Example 4: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(4-dimethylaminobenzyl)-(benzenesulphonamide)-dihydrochloride



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a) 2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-5-(4-dimethylaminobenzylamino)-benzimidazole

5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole (1.0 g, 3.6 mmol) which is obtainable according to Example 2 (step c) and 4-dimethylamino-benzaldehyde (0.59 g, 3.0 mmol) in 25 mL of CH_2Cl_2 with 0.22 mL of AcOH are combined with $Na[HB(OAc)_3]$ (2.2 g, 10.3 mmol) at ambient temperature with stirring. The mixture is stirred for 1 h at ambient temperature, covered with water, carefully acidified with conc hydrochloric $acid_{aq}$ and then made alkaline with 4N NaOH solution. The organic phase is separated off, dried and concentrated by evaporation. The product is chromatographed over silica gel (CH_2Cl_2/methanol = 5/1) and crystallised from ethyl acetate.

Yield: 1.2 g (81%)

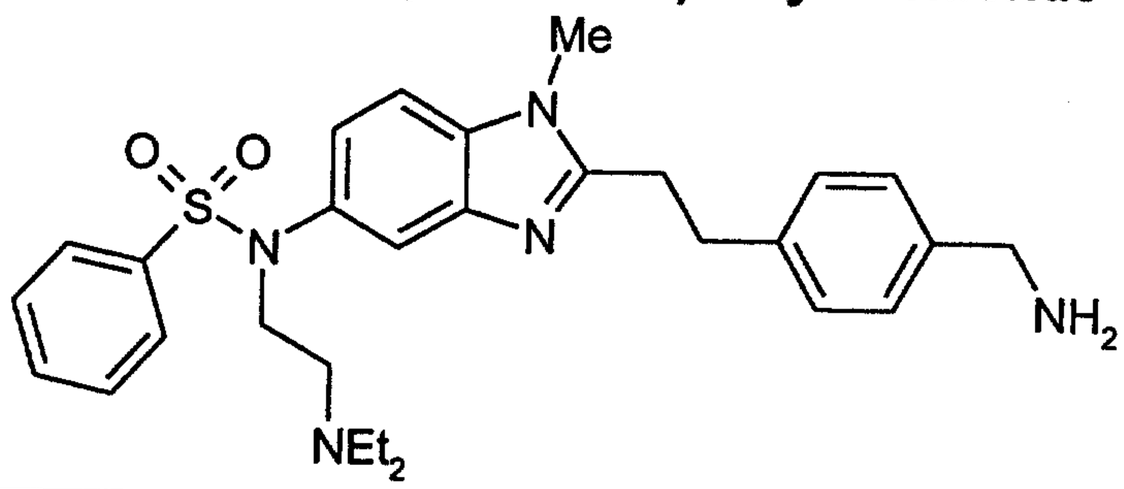
b) N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(4-dimethylaminobenzyl)-(benzenesulphonamide)-dihydrochloride

2.8 mmol of 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-(4-dimethylaminobenzylamino)-benzimidazole are reacted to form the title compound according to the instructions given in Example 1 (step a) and Example 1 (step e).

Yield: 39% (solid foam)

Mass: calc.: [566], found: $[M+H]^+$ 567, $[M+2H]^{2+}$ 284.

Example 5: N-{2-[2-(4-aminomethyl-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)-dihydrochloride

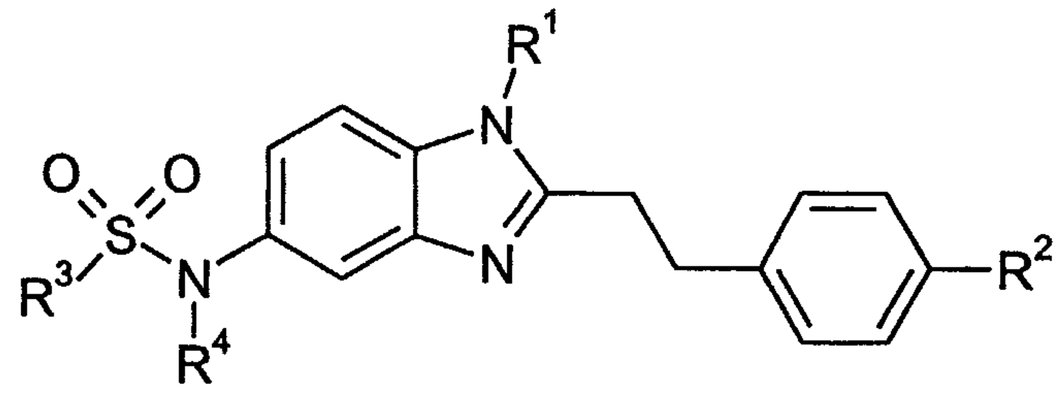


N-{2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide) (obtainable according to Example 2, step e) (1.6 g, 3.1 mmol) in 50 mL methanol is hydrogenated at ambient temperature and normal pressure in the presence of Raney nickel. The catalyst is filtered off and the filtrate is neutralised by the addition of ethereal hydrochloric acid solution. It is concentrated by evaporation and chromatographed over silica gel (CH_2Cl_2/methanol = 7/3).

Yield: 1.0 g (54.5%)

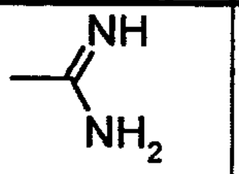
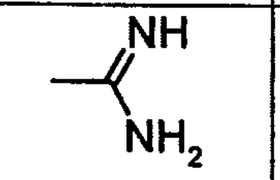
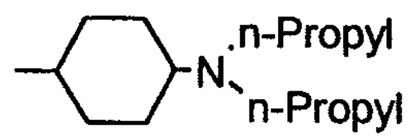
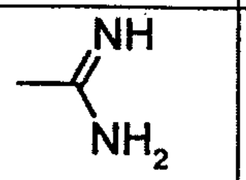
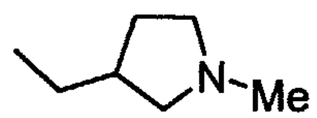
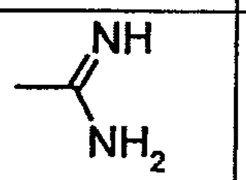
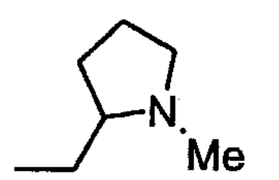
Mass: calc.: [519], found: $[M+H]^+$ 520

The Table which follows contains other compounds of general formula (I) synthesised according to the invention analogously to the Examples described hereinbefore.



(I),

Table 1:

No	-R^1	-R^2	-R^3	-R^4	Chemical name
6	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(3-diethylaminopropyl)-benzenesulphonylamino]-benzimidazole
7	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-dipropylamino-cyclohexanyl)-benzenesulphonylamino]-benzimidazole
8	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(1-methylpyrrolidin-3-yl-methyl)-benzenesulphonylamino]-benzimidazole
9	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(1-methylpyrrolidin-2-yl-methyl)-benzenesulphonylamino]-benzimidazole

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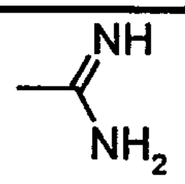
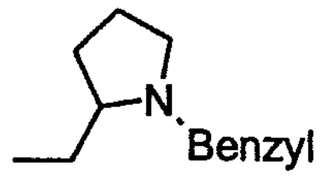
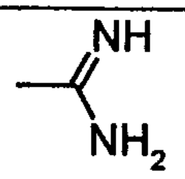
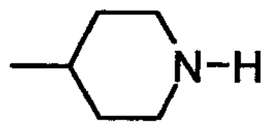
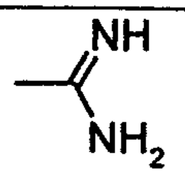
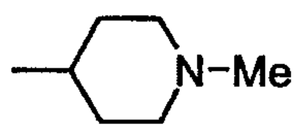
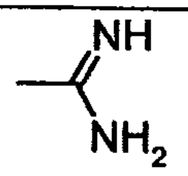
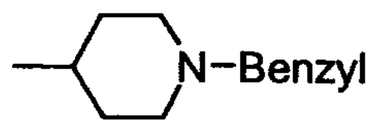
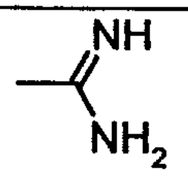
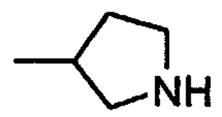
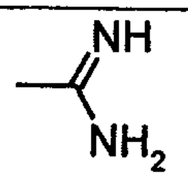
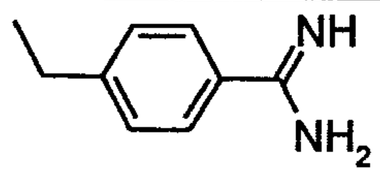
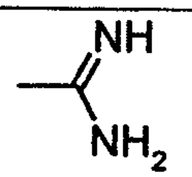
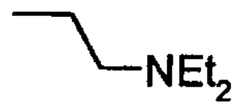
No	-R^1	-R^2	-R^3	-R^4	Chemical name
10	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(1-benzylpyrrolidin-3-yl-methyl)-benzenesulphonylamino]-benzimidazole
11	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-piperidinyl)-benzenesulphonylamino]-benzimidazole
12	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(1-methyl-piperidin-4-yl)-benzenesulphonylamino]-benzimidazole
13	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(1-benzyl-piperidin-4-yl)-benzenesulphonylamino]-benzimidazole
14	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(3-pyrrolidinyl)-benzenesulphonyl-amino]-benzimidazole
15	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-amidinobenzyl)-benzenesulphonyl-amino]-benzimidazole
16			phenyl		1-(2-hydroxyethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole

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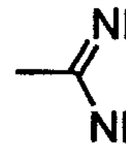
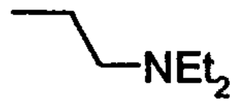
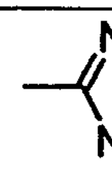
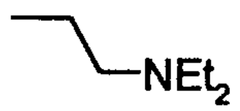
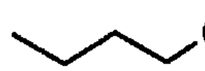
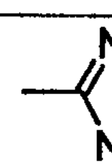
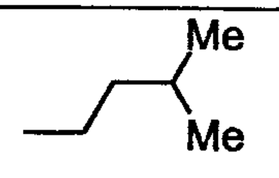
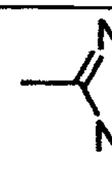
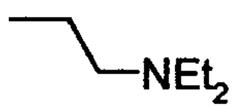
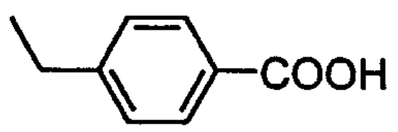
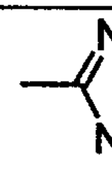
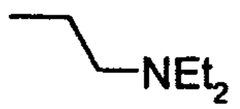
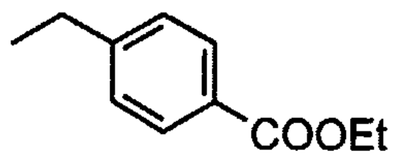
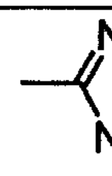
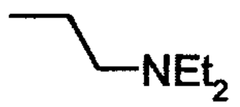
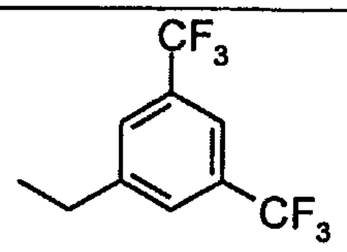
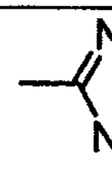
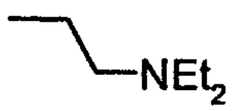
No	-R1	-R2	-R3	-R4	Chemical name
17			phenyl		1-(2-methoxyethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
18	-n-propyl		phenyl		1-n-propyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
19			phenyl		1-(3-hydroxypropyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
20			phenyl		1-isoamyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
21			phenyl		1-(4-carboxybenzyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
22			phenyl		1-(4-ethoxycarbonylbenzyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
23			phenyl		1-(3,5-Ditrifluoromethylbenzyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole

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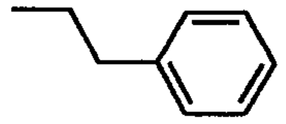
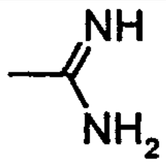
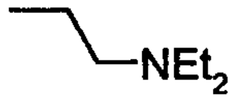
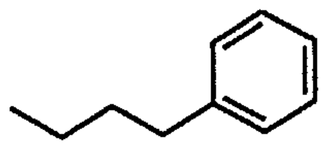
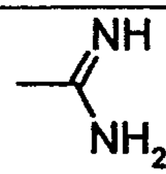
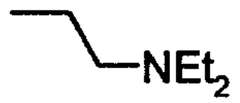
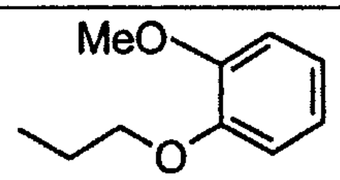
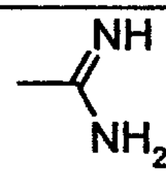
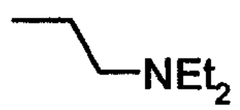
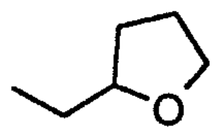
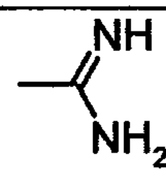
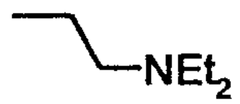
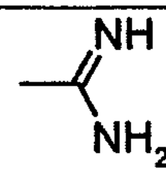
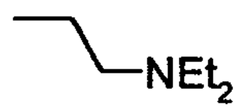
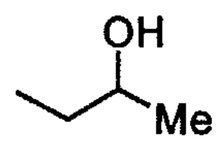
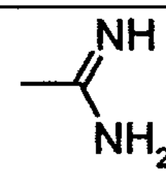
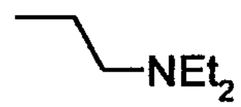
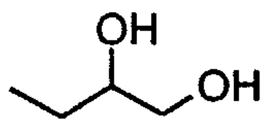
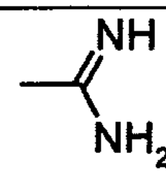
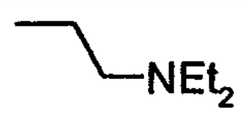
No	-R1	-R2	-R3	-R4	Chemical name
24			phenyl		1-(2-phenylethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
25			phenyl		1-(3-phenylpropyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
26			phenyl		1-[2-(2-methoxyphenoxy)ethyl]-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
27			phenyl		1-(2-tetrahydrofurylmlethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
28	-methyl		1-naphthyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-naphth-1-ylsulphonylamino]-benzimidazole
29			phenyl		1-(2-hydroxypropyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
30			phenyl		1-(2,3-dihydroxypropyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole

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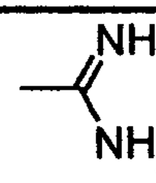
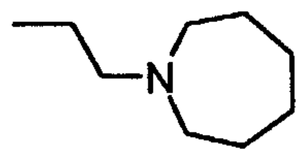
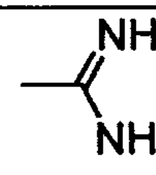
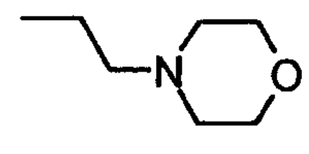
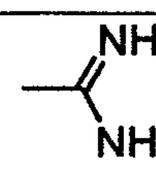
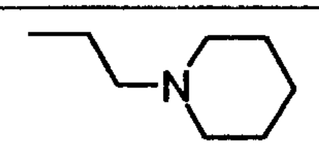
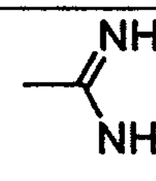
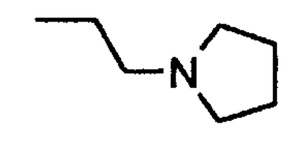
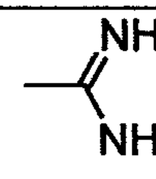
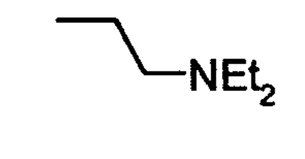
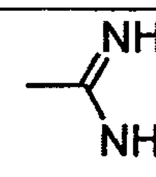
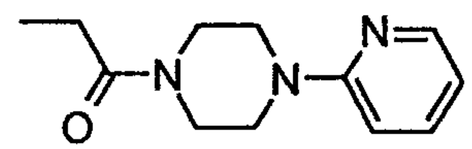
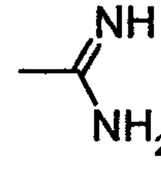
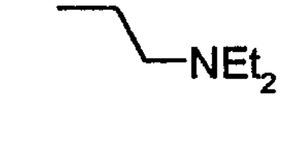
No	-R^1	-R^2	-R^3	-R^4	Chemical name
31	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-azepin-1-ylethyl)-benzenesulphonylamino]-benzimidazole
32	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-morpholin-4-ylethyl)-benzenesulphonylamino]-benzimidazole
33	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-piperidin-1-ylethyl)-benzenesulphonylamino]-benzimidazole
34	-methyl		phenyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-pyrrolidin-1-ylethyl)-benzenesulphonylamino]-benzimidazole
35	-methyl		2-naphthyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-naphth-2-ylsulphonylamino]-benzimidazole
36	-methyl		phenyl		N-{2-[(2-(4-amidino-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-[4'-(pyrid-2-yl)-piperazyl-carbonylmethyl)-(benzenesulphonamide)
37	-methyl		Benzyl		1-methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzylsulphonylamino]-benzimidazole

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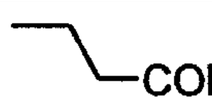
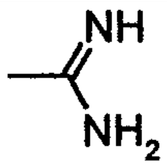
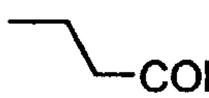
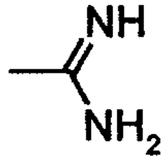
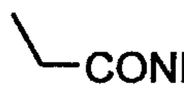
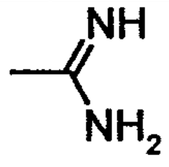
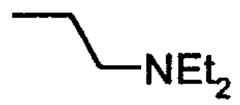
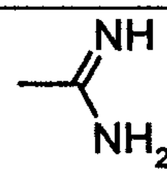
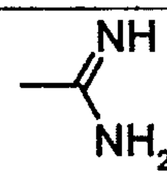
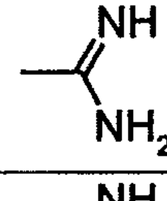
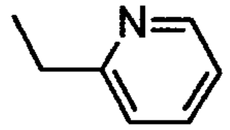
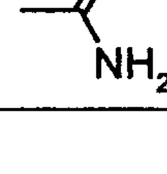
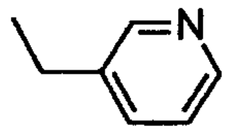
No	-R1	-R2	-R3	-R4	Chemical name
38			Phenyl		1-(2-Methylaminocarbonyl-ethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
39			Phenyl		1-(2-Aminocarbonyl-ethyl)-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
40			Phenyl		1-Aminocarbonylmethyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzenesulphonylamino]-benzimidazole
42	Methyl		Phenyl	Methyl	1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-N-methyl-benzenesulphonylamino]-benzimidazole
43	Methyl		Benzo[b]-thien-3-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-benzo[b]thien-3-ylsulphonylamino]-benzimidazole
44	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(pyrid-2-ylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole;
45	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(pyrid-3-ylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole;

5

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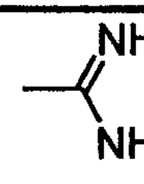
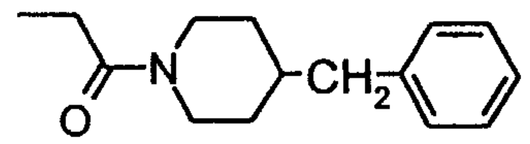
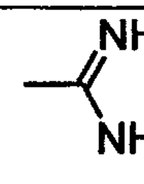
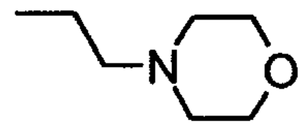
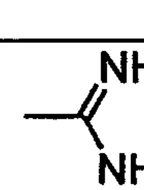
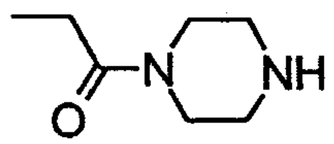
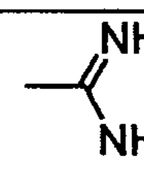
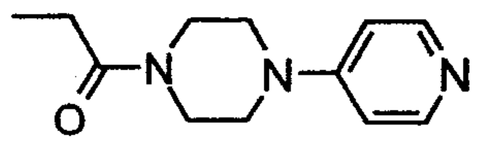
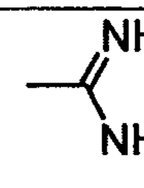
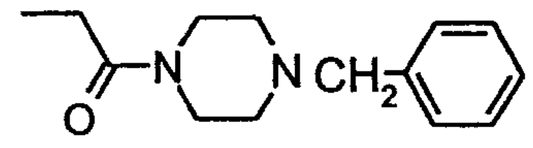
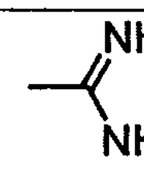
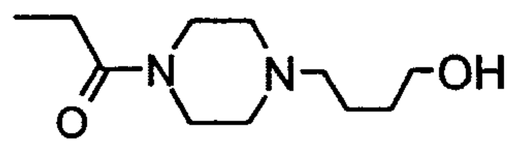
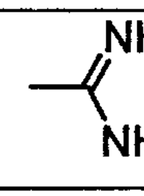
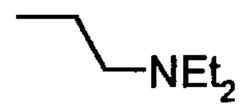
No	-R1	-R2	-R3	-R4	Chemical name
46	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-benzyl-piperid-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
47	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-morpholinoethyl)-naphth-2-ylsulphonylamino]-benzimidazole
48	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
49	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-pyrid-4"-yl-piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
50	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-benzyl-piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
51	Methyl		Naphth-2-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4'-(3"-hydroxypropyl)-piperazin-1-yl-carbonylmethyl)-naphth-2-ylsulphonylamino]-benzimidazole
52	Methyl		Quinol-8-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-quinol-8-ylsulphonylamino]-benzimidazole;

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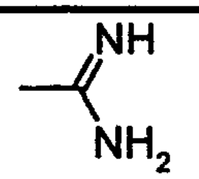
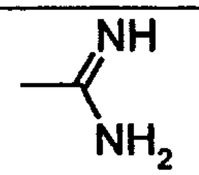
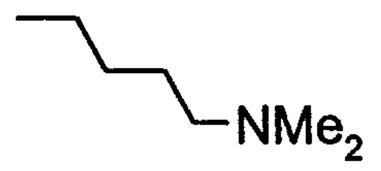
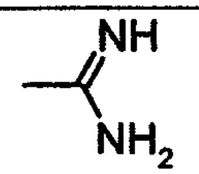
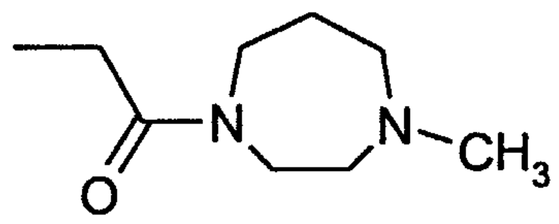
No	-R^1	-R^2	-R^3	-R^4	Chemical name
53	Methyl		Isoquinol-5-yl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(2-diethylaminoethyl)-isoquinol-5-ylsulphonylamino]-benzimidazole;
54	Methyl		Phenyl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-dimethylaminobutyl)-benzenesulphonylamino]-benzimidazole
55	Methyl		Phenyl		1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-5-[N-(4-methyl-1,4-diazepin-1-yl-carbonylmethyl)-benzenesulphonylamino]-benzimidazole

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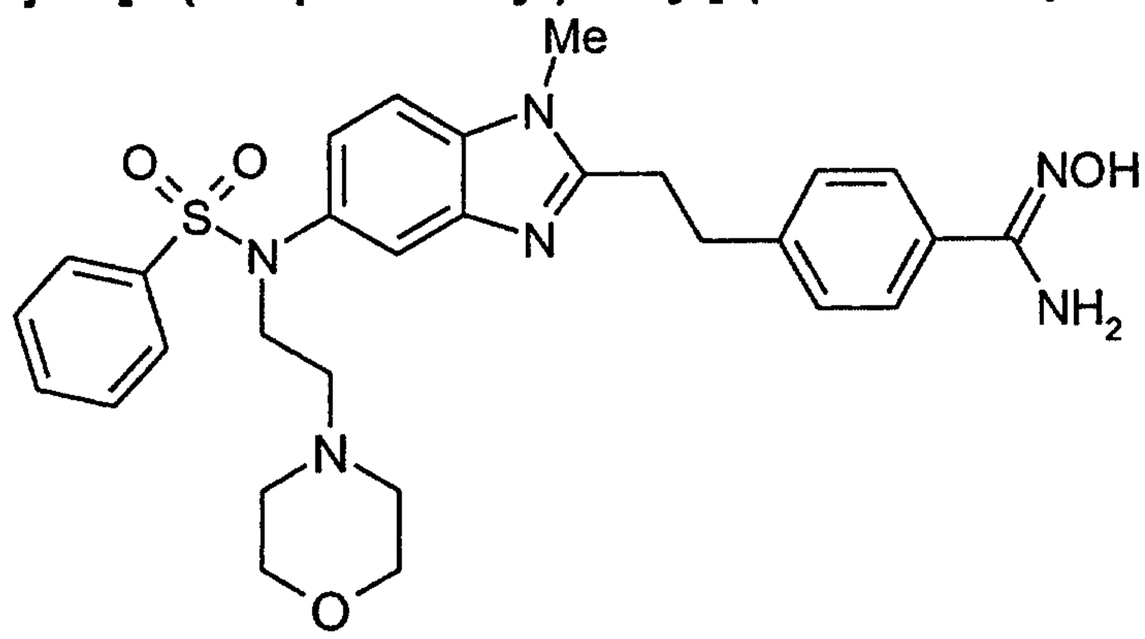
Example 56: N-{2-[2-(4-(amino-hydroximinomethyl)-phenyl)-ethyl]-1methyl-benzimidazol-5-yl}-N-[2-(morpholin-4-yl)-ethyl]-(benzenesulphonamide)



a) N-{2-[2-(4-(amino-hydroximinomethyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-(benzenesulphonamide)

3 mmol of N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-(benzenesulphonamide), which may be obtained according to Example 2 (step d), $NH_2OH*HCl$ (1.3 g) and Na_2CO_3 (2.2 g) in 50 mL methanol/tetrahydrofuran are refluxed for 2 h. The solvent is distilled off, the residue is taken up in water, extracted with ethyl acetate and combined with water. The crystals precipitated are suction filtered and washed with ethyl acetate, acetonitrile and diethylether. Yield: 84 %

b) N-{2-[2-(4-(amino-hydroximinomethyl)-phenyl)-ethyl]-1methyl-benzimidazol-5-yl}-N-(morpholin-1-yl-ethyl-(benzenesulphonamide)

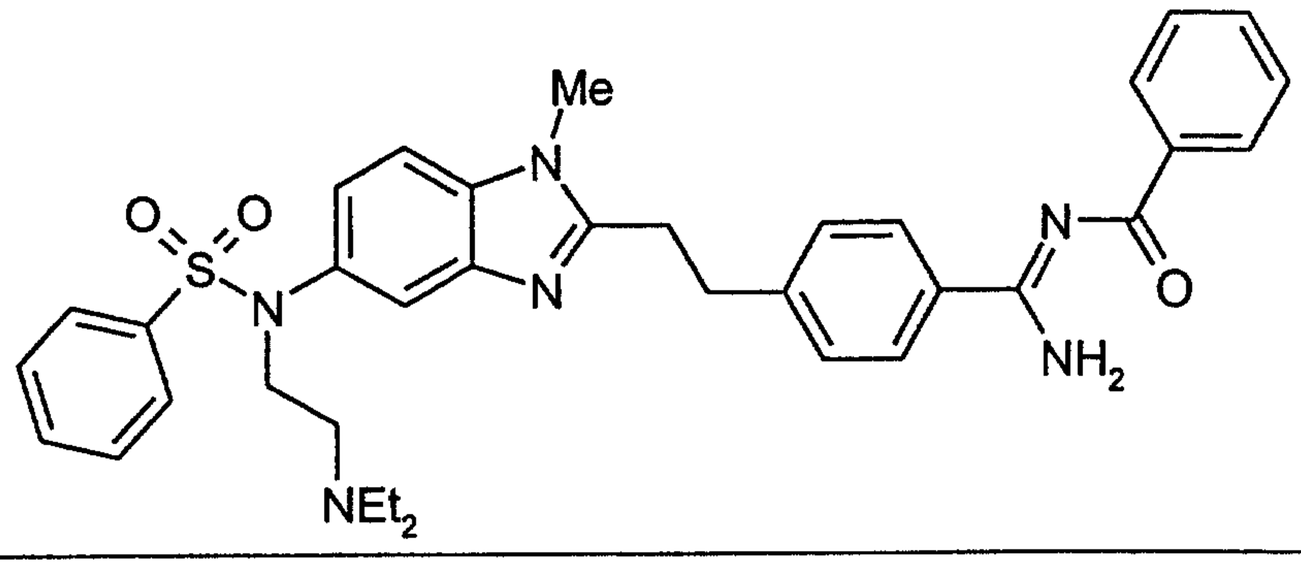
Starting from 5 mmol of N-{2-[2-(4-(amino-hydroximinomethyl)-phenyl)-ethyl]-1methyl-benzimidazol-5-yl}-(benzenesulphonamide) the title compound is synthesised by reacting with N-(2-chloroethyl)-morpholine analogously to Example 2 (step e).

Yield: 64%

m.p.: 183-186 °C

Mass: calc.: [562], found: $[M+H]^+$ 563, $[M+2H]^{2+}$ 282.

Example 57: N-{2-[2-(4-(amino-benzoylimino-methyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)

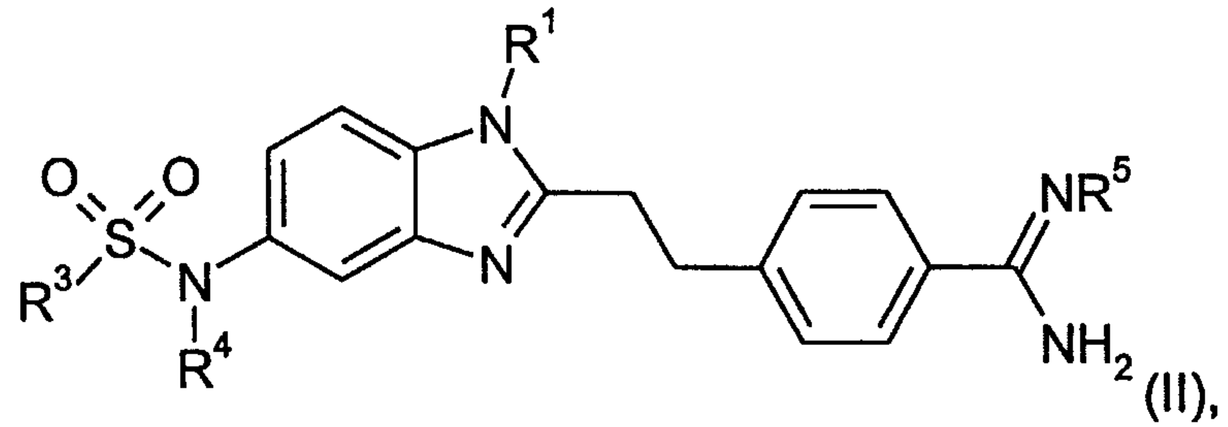


N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide) (Example 2, 2.0 g, 3.0 mmol) and TEA (0.6 mL, 6.0 mmol) in 100 mL ethyl acetate/CH_2Cl_2 1/1 are combined with benzoyl chloride (0.5 mL, 3.3 mmol) at ambient temperature with stirring. The mixture is stirred for 2 h at ambient temperature, diluted with 50 mL CH_2Cl_2, washed with water, dried and concentrated by evaporation. The product is purified by chromatography over silica gel (CH_2Cl_2/methanol = 10/1).

Yield. 1.0 g (47.6%)

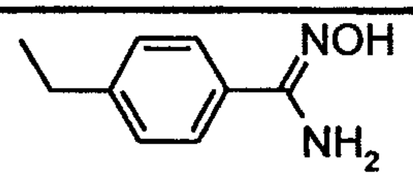
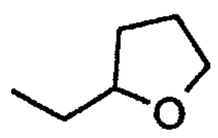
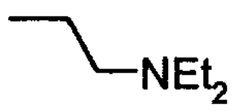
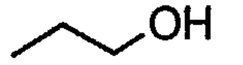
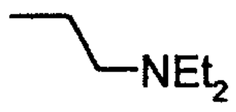
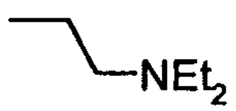
Mass: calc.: [636], found: $[M+H]^+$ 637.

The Table which follows contains other prodrugs of general formula (II) synthesised according to the invention analogously to the Examples described hereinbefore.



(II),

Table 2

No	-R^1	-R^3	-R^4	-R^5	Chemical name
58	-Methyl	Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(4-(amino-hydroximinomethyl)-benzyl)-(benzenesulphonamide)
59		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(tetrahydrofuran-2-yl-methyl)-benzimidazol-5-yl}-N-diethylamino-ethyl-(benzenesulphonamide)
60		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(2-hydroxyethyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
61		Phenyl		-OH	N-{2-[4-(Amino-hydroximinomethyl)-phenyl]-1-(2-methoxy-ethyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)

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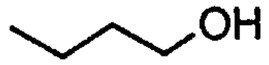
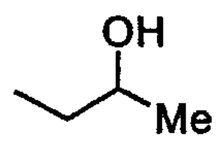
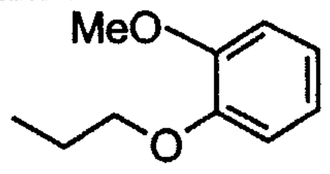
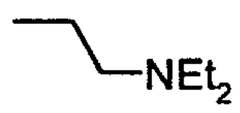
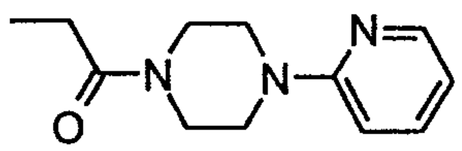
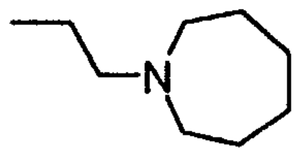
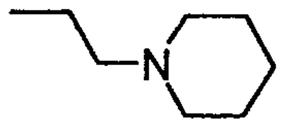
No	-R1	-R3	-R4	-R5	Chemical name
62		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(3-hydroxypropyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
63		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(2-hydroxypropyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
64	-Methyl	2-Naphthyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(2-naphthyl-sulphonamide)
65		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-[2-(2-methoxyphenyloxy)-ethyl]-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
66	-Methyl	Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-[4'-(pyrid-2-yl)-piperazyl-carbonylmethyl)-(benzenesulphonamide)
67	-Methyl	Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1methyl-benzimidazol-5-yl}-N-(azepan-1-yl-ethy)l-(benzenesulphonamide)
68	-Methyl	Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1methyl-benzimidazol-5-yl}-N-(piperidin-1-yl-ethy)l-(benzenesulphonamide)

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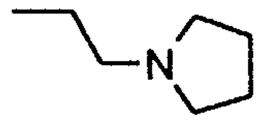
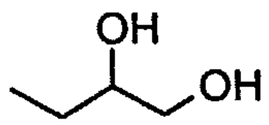
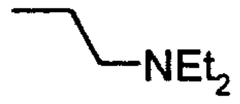
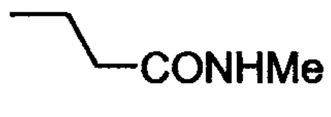
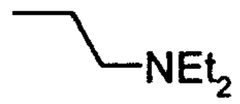
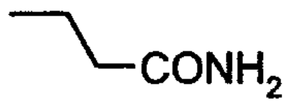
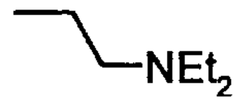
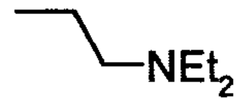
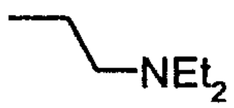
No	-R^1	-R^3	-R^4	-R^5	Chemical name
69	-Methyl	Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1methyl-benzimidazol-5-yl}-N-(pyrrolidin-1-yl-ethy)l-(benzenesulphonamide)
70		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(2,3-dihydroxypropyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
71		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(2-methylaminocarbonyl-ethyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
72		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(2-aminocarbonylethyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
73		Phenyl		-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-(aminocarbonylmethyl)-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
74	-Methyl	Phenyl	-Methyl	-OH	N-{2-[2-(4-(Amino-hydroximinomethyl)-phenyl)-ethyl]-1-methyl}-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
75	-Methyl	Phenyl		-COOMe	N-{2-[2-(4-(Amino-methoxycarbonylimino-methyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)

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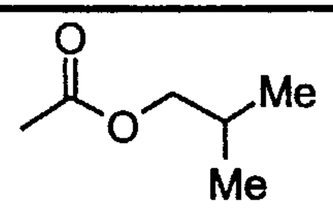
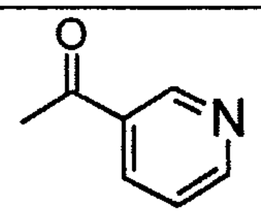
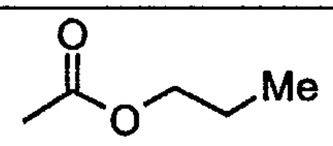
No	-R^1	-R^3	-R^4	-R^5	Chemical name
76	-Methyl	Phenyl			N-{2-[2-(4-(Amino-isobutoxycarbonylimino-methyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
77	-Methyl	Phenyl			N-{2-[2-(4-(Amino-nicotinoylimino-methyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)
78	-Methyl	Phenyl			N-{2-[2-(4-(Amino-*n*-propoxycarbonylimino-methyl)-phenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-diethylaminoethyl-(benzenesulphonamide)

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The structure of the compounds of general formula (I) according to the invention as well as that of the prodrugs of general formula (II) was confirmed by ^{1}-H-NMR spectroscopy.

Example 1:
^{1}H-NMR (250 MHz, DMSO-d6): δ=10.08 (1H, s, NH); 9.31; 9.13 (4H, 2s, -C(=NH_2^+)NH_2); 8.09-6.83 (15H, m, aryl-H); 5.66 (2H, s, N-CH_2-Phenyl); 3.18 (4H, m, -CH_2CH_2-).

Example 2:
^{1}H-NMR (250 MHz,DMSO-d6):δ=10.71; 9.41; 9.21 (5H,3s,H^+; -C(=NH_2^+)NH_2); 7.89-6.88 (12H,m,aryl-H); 4,09; 3.16 (4H,2m,N-CH_2CH_2-N); 3.76 (3H,s,N-CH_3); 3.26 (4H,m,-CH_2CH_2); 3.15 (4H,m,N-($\underline{CH_2}CH_3$)$_2$; 1.16 (6H,m,N-($CH_2\underline{CH_3}$)$_2$).

Example 3:
^{1}H-NMR (250 MHz, DMSO-d6): δ=11.03; 9.59; 9.42 (5H, 3s, H^+; -C(=NH_2^+)NH_2); 8.05-6.95 (12H, m, aryl-H); 4.31; 3.06 (4H, 2m, N-CH_2CH_2-N).

Example 4:
^{1}H-NMR (250 MHz, CD_3OD): δ=7.70-6.49 (16H, m, aryl-H); 3.60 (3H, s, N-CH_3); 3.33 (2H, s, N-CH_2-); 3.21 (4H, s, -CH_2-CH_2-); 2.79 (6H, s, N-(CH_3)$_2$).

Example 5:
^{1}H-NMR (250 MHz, DMSO-d6): δ=10.93; 8.57 (4H, 2s, NH_3; H^+); 7.88-6.90 (12H, m, aryl-H); 4.13; 3.15 (4H, 2m, N-CH_2CH_2N); 3.77 (3H, s, N-CH_3); 4.00 (2H, m, N-CH_2); 3.17 (4H, m, N-(CH_2-CH_3)$_2$); 1.16 (6H, m, N-(CH_2CH_3)$_2$).

Example 6:
^{1}H-NMR (250 MHz, DMSO-d6): δ=10.33; 9.33; 9.13 (5H, 3s, H^+; -C(=NH_2^+)NH_2); 4.13; 3.00 (4H, 2m, N-CH_2-CH_2CH_2N); 3.70 (3H, s, N-CH_3); 3.22 (4H, s, -CH_2-CH_2-); 2.97 (4H, m, N-(CH_2CH_3)$_2$; 1.72 (2H, m, N-CH_2-CH_2-CH_2); 1.14 (6H, m, N-(CH_2CH_3)$_2$).

Example 7:
^{1}H-NMR (250 MHz, DMSO-d6): δ=10.25 (1H, s, H^+); 9.46; 9.29 (4H, 2s, -C(=NH_2^+)NH_2); 7.95-6.77 (12H, m, aryl-H); 4.24 (2H, m, CH-N-cyclohexyl); 3.78 (3H, s, N-CH_3); 3.27 (4H, s, -CH_2-CH_2-); 2.94-0.99 (16H, m, CH_2-cyclohex.; N-($CH_2CH_2CH_3$)$_2$); 0.84 (6H, m, N-($CH_2CH_2CH_3$)$_2$).

Example 8:

^{1}H-NMR (250 MHz, DMSO-d6): δ=11.12; 9.40; 9.20 (5H, 3s, H^+; -C(=NH_2^+)NH_2); 7.99-6.91 (12H, m, aryl-H); 3.85 (3H, s, N-CH_3); 2.48 (3H, s, N-CH_3-pyrrol.); 3.25 (4H, s, -CH_2CH_2-); 3.78-1.51 (9H, m, CH-/CH_2-pyrrol.).

Example 9:

^{1}H-NMR (250 MHz, DMSO-d6): δ=9.52; 9.35 (4H, 2s, -C(=NH_2^+)NH_2); 8.02-6.90 (12H, m, aryl-H); 3.91 (N-CH-pyrrol.); 3.79 (3H, s, N-CH_3); 3.23 (3H, s, N-CH_3-pyrrol.); 3.28-1.53 (8H, -CH_2-pyrrol.); 3.40 (4H, s, -CH_2-CH_2-).

Example 10:

^{1}H-NMR (250MHz,CD_3OD):δ=7.76-6.83 (17H,m,aryl-H); 3.71 (3H,s,N-CH_3); 3.47; 3.35 (2H,m,N-CH_2-); 3.28 (5H,m,-CH_2CH_2-,CH-pyroll.); 2,91-1.64 (6H,m,CH_2-pyroll.).

Example 11:

^{1}H-NMR (250MHz,DMSO-d6):δ=9.29; 9.09; 8.97; 8.31 (6H,m,H^+;-C(=NH_2^+)NH_2); 7.86-6.68 (12H,m,aryl-H); 4.51 (1H,m,CH-pip.); 3.72 (3H,s,N-CH_3); 3.14 (4H,s,-CH_2-CH_2); 3.32-2.87 (4H,m,N-CH_2-pip.); 2.00-1.34 (4H,m,CH_2-pip.).

Example 12:

^{1}H-NMR (250MHz,CD_3OD):δ=7.95-6.87 (12H,m,aryl-H); 4.67 (1H,m,pip.CH); 3.75 (3H,s,N-CH_3); 3.33 (4H,s,-CH_2-CH_2-); 3.58-3.14 (4H,m,N-CH_2-pip.); 2.79 (3H,s,N-CH_3-pip.); 2.24-1.61 (4H,m,CH_2-pip.).

Example 13:

^{1}H-NMR (250 MHz, DMSO-d6): δ=10.40; 9.52; 9.29 (5H, 3s, H^+, -C(=NH_2^+)NH_2); 4.57 (1H, m, N-CH Pip.); 4.22 (2H, s, N-CH_2-Phenyl); 3.81 (3H, s, N-CH_3); 3.30 (4H, s, -CH_2-CH_2-); 3.19-1.67 (8H, m, pip.-CH_2-).

Example 14:

^{1}H-NMR (250MHz,DMSO-d6):δ=7.95-7.51 (12H,m,aryl-H); 4.82 (1H,m,pyrrol.-H), 3.73 (3H,s,N-CH_3); 3.25 (4H,s,-CH_2-CH_2-); 3.47-1.37 (6H,m,CH_2-pyrrol.);

Example 16:

^{1}H-NMR (250 MHz, DMSO-d6): δ=11.03; 9.62; 9.42 (5H, 3s, H^+; -C(=NH_2^+)NH_2); 8.14-7.23 (12H, m, aryl-H); 4.63; 3.68 (4H, 2m, N-CH_2CH_2-O); 4.20; 3.72 (4H, 2m, N-CH_2CH_2-N); 3.81 (1H, t, J=5.5 Hz, OH); 3.64; 3.44 (4H, 2m, -CH_2CH_2-); 3.20 (4H, qu, J=7.0 Hz, N-(CH_2CH_3)$_2$; 1.20 (6H, t, J=7.0 Hz, N-(CH_2-CH_3)$_2$).

Example 17:

^{1}H-NMR (250 MHz, DMSO-d6): δ=10.08 (4H, broad, -C(=NH_2^+)NH_2); 7.79-6.82 (12H, m, aryl-H); 4.36 (2H, m, N-CH_2-CH_2-O); 3.64 (2H, m, N-CH_2CH_2O-); 3.60; 2.42 (4H, 2m, N-CH_2CH_2-N); 3.22 (4H, s, -CH_2-); 3.17 (3H, s, OCH_3); 2.38 (4H, qu, J=7.0 Hz, N-(CH_2-CH_3)$_2$); 0.83 (6H, t, J=7.0 Hz, N-(CH_2-CH_3)$_2$).

Example 18:

^{1}H-NMR (250 MHz, DMSO-d6):δ=10.64; 9.49; 9.26 (5H,3s,H^+; -C(=NH_2^+)NH_2); 7.95-6.91 (12H,m,aryl-H); 4.20 (2H,m,N-CH_2-); 3.29 (4H,m,-CH_2CH_2-); 3.14 (4H,m,N-($\underline{CH_2}CH_3$)$_2$; 1.70 (2H,m,N-$CH_2\underline{CH_2}$-CH_3); 1.16 (6H,m,N-($CH_2\underline{CH_3}$).

Example 19:

^{1}H-NMR (250 MHz, DMSO-d6): δ= 10.94; 9.58; 9.36 (5H, 3s, H^+; -C(=NH_2^+)NH_2); 8.14-7.20 (12H, m aryl-H); 4.54 (2H, m, N-CH_2); 4.18; 3.62 (4H, 2m, N-CH_2CH_2-N); 3.60 (2H, m, OCH_2; 3.42 (4H, m, -CH_2CH_2-); 3.20 (4H, m, N(-CH_2CH_3)$_2$; 1.94 (2H, m, N-$CH_2CH_2CH_2$-O); 1.21 (6H, m, N-(CH_2CH_3)$_2$). OH in the solvent blind peak.

Example 24:

^{1}H-NMR (250 MHz, DMSO-d6): δ=9.73; 9.54 (4H, 2s, -C(=NH_2^+)NH_2); 8.14-7.04 (17H, m, aryl-H); 4.62; 3.15 (4H, 2m, N-CH_2CH_2-Phenyl); 4.10; 3.02 (4H, 2m, N-CH_2CH_2-N); 3.28; 3.06 (4H, 2m, -CH_2CH_2-); 2.99 (4H, m, N-(CH_2CH_3)$_2$; 1.15 (6H, m, N-(CH_2CH_3)$_2$).

Example 25:

^{1}H-NMR (250MHz,DMSO-d6); δ=10.81; 9.47; 9.30 (5H,3s,H^+;-C(=NH_2^+)NH_2); 7.97-6.89 (7H,m,aryl-H); 4,23 (2H,m,N-$\underline{CH_2}CH_2CH_2$-); 4.10; 3.16 (4H,2m,N-CH_2CH_2-N); 3.19 (4H,m,N-($\underline{CH_2}CH_3$)$_2$);3.18 (4H,m,-CH_2-CH_2-); 2.67 (2H,m,xx-CH_2-); 1,99 (2H,m,xx-CH_2-$\underline{CH_2}$-); 1.14 (6H,m,N-($CH_2\underline{CH_3}$)$_2$.

Example 26:

^{1}H-NMR (250 MHz, DMSO-d6): δ=10.26 (4H, broad, -C(=NH_2^+)NH_2); 7.92-6.80 (16H, m, aryl-H); 4.68 (2H, m, N-CH_2-CH_2O-); 4.28; 2.11 (4H, 2m, N-CH_2CH_2-N); 3.69 (2H, m, N-CH_2CH_2O); 3.58 (3H, s, OCH_3); 3.38 (4H, m, -CH_2-CH_2-); 2.05 (4H, qu, J=7.0 Hz, N-(CH_2CH_3)$_2$); 0.83 (6H, t, J=7.0 Hz, N-(CH_2-CH_3)$_2$).

Example 27:

^{1}H-NMR(250MHz, DMSO-d6): δ=10.30(4H,s, -C(=NH_2^+)NH_2);7.92-6.89(12H,m,aryl-H); 4.46-3.53(13H,m,N-CH_2CH_2-N; N.CH_2-CH-O-CH_2-; -CH_2-CH_2-); 2.45(4H, qu, J=7.0 Hz, N-(CH_2CH_3)$_2$); 1.84-1.44(4H,m, CH_2-THF); 0.86 (6H,t,J=7.Hz, N-(CH_2CH_3)$_2$).

Example 28:

^{1}H-NMR (250 MHz, DMSO-d6): δ=10.87; 9.45; 9.27 (5H, 3s, H^+; -C(=NH_2^+)NH_2); 8.41-6.89 (14H, m, aryl-H); 4.19; 3.12 (4H, 2m, N-CH_2CH_2-N); 3.73 (3H, S, N-CH_3); 3.24 (4H, S, -CH_2-CH_2-); 3.11 (4H, m, N-(CH_2CH_3)$_2$); 1.10 (6H, m, N-(CH_2CH_3)$_2$).

Example 31:

^{1}H-NMR (250 MHz, DMSO-d6): δ=7.80-6.79 (12H, m, aryl-H); 3.74 (3H, s, N-CH_3); 3.67; 2.46 (4H, 2m, N-CH_2CH_2-N); 3.21 (4H, s, -CH_2CH_2-); 2.48 (4H, m, N(-CH_2-CH_2-)$_2$ cyclohept.); 1.82 (4H, m, N-(CH_2CH_2)$_2$ cyclohept.); 1.30 (4H, N-($CH_2CH_2CH_2$) cyclohept).

Example 33:

^{1}H-NMR (250 MHz, DMSO-d6): δ=7.92-6.88 (12H, m, aryl-H); 3.76 (3H, s, M-CH_3); 3.74; 2.27 (4H, m, N-CH_2CH_2-M); 3.24 (4H, s, -CH_2CH_2-); 2.24; 1.53-1.17 (10H, 2m, piper.H);

Example 34:

^{1}H-NMR (250 MHz, DMSO-d6): δ= 7.77-6.76 (12H, m, aryl-H); 3.71 (3H, s, N-CH_3); 3.68; 2.38 (4H, 2m, N-CH_2CH_2-M); 3.79 (4H, s, -CH_2-CH_2-); 2.35; 1.61 (8H, 2m, CH-pyrrol.);

Example 56:

^{1}H-NMR (250 MHz, CH_3OD): δ=7.91-7.26 (12H, m, aryl-H); 4.23; 3.38 (4H, 2m, N-CH_2-CH_2-N); 3.96 (3H, s, N-CH_3); 3.58; 3.38 (4H, 2m, -CH_2CH_2-); 4.00; 3.36 (8H, 2m, CH_3-morpholine).

Example 59:

^{1}H-NMR (250MHz, CD_3OD):δ=7.83-7.05(12H,m,aryl-H); 4.23-3.79 (5H,m,N-CH_2-CH-OXX)3.89;2.75(4H,2m, N-CH_2CH_2-N); 3.34(4H,m,-CH_2CH_2-); 2.68(4H, qu,J=7.0Hz; N($\underline{CH_2}CH_3$,); 2.25-1.63 (4H,m, CH_2-THF); 1.10 (6H,t,J=7.0 Hz, N-$(CH_2CH_3)_2$).

Example 60:

^{1}H-NMR (250 MHz, DMSO-d6): δ=9.57 (1H, s, =N-OH); 7.77-6.86 (12H, m, aryl-H); 5.78 (2H, s, NH_2); 4.98 (1H, t, J=5.5 Hz, OH); 4.23; 3.67 (4H, 2m, N-CH_2CH_2-O); 3.67; 2.42 (4H, 2m, N-CH_2CH_2N); 3.15 (4H, m, -CH_2-CH_2-); 2.40 (4H, qu, J=7.0 Hz, N-$(CH_2CH_3)_2$); 0.84 (6H, t, J=7.0 Hz, N-$(CH_2CH_3)_2$).

Example 61:

^{1}H-NMR(250MHz, DMSO-d6): δ= 9.70 (H, s, OH); 7.90-6.93 (12H, m, aryl-H); 5.85 (2H,s,NH_2); 4.42 (2H,m,N-CH_2-CH_2-O); 3.70 (2H, m, N-CH_2-CH_3-O); 3.63; 2.46 (4H, m,N-CH_2CH_2-N); 3.36 (3H, s, OCH_3); 3.20 (4H,s, -CH_2CH_2-); 2.43 (4H, qu, J=7.0Hz; N-$(CH_2CH_3)_2$; 0.85(6H, t, J=7.0 Hz, N-$(CH_2CH_3)_2$).

Example 62:

^{1}H-NMR (250 MHz, DMSO-d6): δ=9.72 (1H, s, c=N-OH); 7.91-6.96 (12H, m, aryl-H); 5.86 (2H, s, NH_2); 4.79 (1H, t, J=5.5Hz, OH); 4.28 (2H, m, N-$CH_2CH_2CH_2$); 3.71; 2.47 (4H, 2m, N-CH_2CH_2-N); 3.40 (2H, m, OCH_2); 3.21 (4H, s, -CH_2-CH_2-); 2.43 (4H, qu, J=7.0 Hz, N-$(CH_2CH_3)_2$); 1.83 (2H, m, N-$CH_2CH_2CH_2$); 0.85 (6H, t, J=7.0 Hz, N-$(CH_2CH_3)_2$).

Example 63:

^{1}H-NMR (250 MHz, DMSO-d6): δ=9.70 (1H, s, OH); 7.84-6.84 (16H, m, aryl-H); 5.86 (2H, s, NH_2); 4.68 (2H, m, N-CH_2-CH_2-O); 4.28; 2.48 (4H, 2m, N-CH_2CH_2-N); 3.72 (2H, m, N-CH_2-CH_2-O); 3.60 (3H, s, OCH_3); 3.38; 3.24 (4H, 2m, -CH_2-CH_2-); 2.48 (4H, m, N(-$CH_2CH_3)_2$; 0.85 (6H, m, N-$(CH_2CH_3)_2$).

The compounds according to the invention are characterised by their tryptase-inhibiting activity. This ability to inhibit tryptase was investigated using the test described below.

The measurement is carried out in Tris HCl buffer (100 mM), which additionally contains calcium (5 mM) and heparin (100 mg/ml), at pH 7.4. The standard used is rh beta tryptase which may be obtained commercially from Promega, for example. The substrate used is N-p-tosyl-Gly-Pro-Lys-para-nitroaniline in a concentration of 0.6 mM. The substrate is digested with tryptase to form p-nitroaniline which can be

measured at 405 nm. Usually, an incubation period of 5 minutes and an incubation temperature of 37°C are chosen. The enzyme activity used is 0.91 U/ml. The measurements are carried out in an Autoanalyser (Cobas Bio) made by Hofmann LaRoche. The potential inhibitory substances are used in concentrations of 10 µM in the screening, the inhibition of the tryptase being given in percent. The IC_{50} is determined at over 70 % inhibition (concentration at which 50% of the enzyme activity is inhibited). After 5 minutes' pre-incubation of the potential inhibitory substances, the substrate is added to start the reaction, the formation of p-nitroaniline being taken as a measurement of the enzyme activity after 5 minutes, after testing the linearity.

The data obtained after the above test has been carried out (IC50 values) can be found in Table 3.

Table 3:

Example	IC_{50} [µM]
2	0.025
3	0.132
4	0.123
5	0.1
6	0.047
7	0.109
8	0.089
9	0.062
10	0.068
11	0.09
12	0.179
13	0.076
14	0.082
16	0.121
17	0.062
18	0.292
19	0.239
24	0.19
25	0.412
26	0.074
27	0.273

	48
28	0.027
31	0.031
33	0.044
34	0.043
35	0.0066
43	0.025
44	0.022
45	0.022
46	0.03
47	0.0703
48	0.1438
49	0.186
50	0.215
51	0.035
52	0.029
53	0.038
54	0.027
55	0.028

The tryptase inhibitors according to the invention may be administered orally, transdermally, by inhalation or parenterally. The compounds according to the invention occur as active ingredients in conventional preparations, for example in compositions which consist essentially of an inert pharmaceutical carrier and an effective dose of the active substance, such as for example tablets, coated tablets, capsules, powders, solutions, suspensions, emulsions, syrups, suppositories, transdermal systems etc.. An effective dose of the compounds according to the invention is between 1 and 100, preferably between 1 and 50, most preferably between 5-30 mg/dose for oral administration, and between 0.001 and 50, preferably between 0.1 and 10 mg/dose for intravenous or intramuscular administration. For inhalation, according to the invention, solutions containing 0.01 to 1.0, preferably 0.1 to 0.5 % active substance are suitable. For administration by inhalation the use of powders is preferred. It is also possible to use the compounds according to the invention as a solution for infusion, preferably in a physiological saline or nutrient saline solution.

The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. Suitable preparations include for example tablets, capsules, suppositories, solutions, elixirs, emulsions or dispersible powders.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanilline or orange

extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

A therapeutically effective daily dose is between 1 and 800 mg, preferably 10 - 300 mg per adult.

The Examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A)	Tablets	per tablet
	active substance	100 mg
	lactose	140 mg
	corn starch	240 mg
	polyvinylpyrrolidone	15 mg
	magnesium stearate	5 mg
		500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	Tablets	per tablet
	active substance	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
	magnesium stearate	2 mg
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C)	Coated tablets	per coated tablet
	Active substance	5 mg
	Corn starch	41.5 mg
	Lactose	30 mg
	Polyvinylpyrrolidone	3 mg
	Magnesium stearate	0.5 mg
		80 mg

The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine . The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax..

D) Capsules

	per capsule
Active substance	50 mg
Corn starch	268.5 mg
Magnesium stearate	1.5 mg
	320 mg

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E) Ampoule solution

active substance	50 mg
sodium chloride	50 mg
water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

F) Suppositories

Active substance	50 mg
Solid fat	1650 mg
	1700 mg

The solid fat is melted. The ground active substance is homogeneously dispersed at 40°C . It is cooled to 38°C and poured into slightly chilled suppository moulds.

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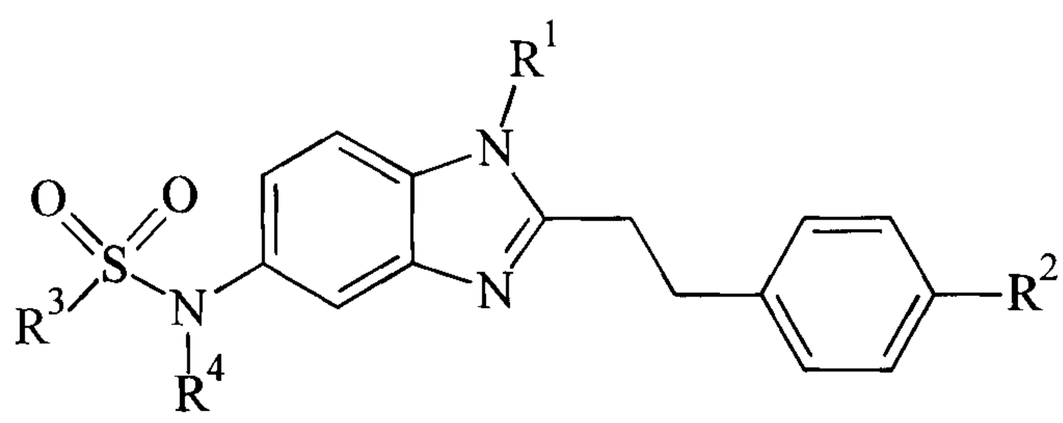
CLAIMS:

1. A benzimidazole derivative selected from a compound of general formula (I)



(I),

wherein

R^1 denotes a group selected from the group C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl, optionally mono-, di- or trisubstituted by one or more groups selected from hydroxy, C_1-C_4-alkoxy, CF_3, phenoxy, COOH, halogen, -CO(C_1-C_4-alkoxy), $-CONH_2$, -CO-NH(C_1-C_4-alkyl), -CO-N(C_1-C_4-alkyl)$_2$, $-NH_2$, -NH(C_1-C_4-alkyl), -N(C_1-C_4-alkyl)$_2$ and C_1-C_4-alkoxy-phenoxy;

a C_3-C_8-cycloalkyl optionally linked via a C_1-C_4-alkylene bridge, optionally mono-, di- or trisubstituted by one or more groups selected from hydroxy, C_1-C_4-alkoxy, carboxy, halogen, C_1-C_4-alkoxycarbonyl and CF_3;

phenyl-C_1-C_4-alkyl, optionally mono-, di- or trisubstituted by one or more groups selected from hydroxy, C_1-C_4-alkoxy, carboxy, halogen, C_1-C_4-alkoxycarbonyl and CF_3; or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge, comprising one or two hetero atoms selected from oxygen, nitrogen and sulphur and which is optionally substituted by C_1-C_4-alkyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, naphthyl, furanyl, benzofuranyl, quinolyl, isoquinolyl, thienyl or benzothienyl;

R^4 denotes hydrogen, a C_1-C_6-alkyl group, optionally mono- or disubstituted by one or two groups selected from $-NH_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$;

a 5-, 6- or 7-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge or via a C_1-C_4-alkylene-CO bridge comprising one, two or three hetero atoms selected from oxygen, nitrogen and sulphur and which is optionally substituted by C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, benzyl or pyridyl;

C_3-C_8-cycloalkyl, optionally mono- or disubstituted by one or two groups selected from $-NH_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$; or

phenyl, benzyl or phenylethyl, optionally mono- or disubstituted at the phenyl ring by one or two groups selected from $-NH_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, $-C_1-C_4\text{-alkyl}-NH_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$;

a tautomer thereof, a racemate thereof, an enantiomer thereof, a diastereomer thereof and a pharmacologically acceptable acid addition salt thereof; wherein the benzimidazole derivative is for prevention or treatment of one or both of an inflammatory disease and an allergic disease.

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2. A benzimidazole derivative according to claim 1, wherein

R^1 denotes C_1-C_5-alkyl, optionally mono-, di- or trisubstituted by one or more groups selected from hydroxy, C_1-C_4-alkoxy, CF_3, phenoxy, COOH, -CO(C_1-C_4-alkoxy), $-CONH_2$, -CO-NH(C_1-C_4-alkyl), -CO-N(C_1-C_4-alkyl)$_2$ and C_1-C_4-alkoxy-phenoxy;

a C_3-C_8-cycloalkyl optionally linked via a C_1-C_4-alkylene bridge, optionally mono-, di- or trisubstituted by one or more groups selected from hydroxy, C_1-C_4-alkoxy, carboxy, halogen, C_1-C_4-alkoxycarbonyl and CF_3;

phenyl-C_1-C_4-alkyl, optionally mono-, di- or trisubstituted by one or more groups selected from hydroxy, C_1-C_4-alkoxy, carboxy, C_1-C_4-alkoxycarbonyl and CF_3; or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge, comprising one or two hetero atoms selected from oxygen, nitrogen and sulphur and which is optionally substituted by C_1-C_4-alkyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, quinolyl, benzothienyl or naphthyl;

R^4 denotes a C_1-C_6-alkyl group, which is mono- or disubstituted by one or two groups selected from $-NH_2$, -NHmethyl, -N(methyl)$_2$, -NHethyl, -N(ethyl)$_2$, -NH(n-propyl), -N(n-propyl)$_2$, -NH(iso-propyl), -N(iso-propyl)$_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$;

a 5-, 6- or 7-membered, saturated or unsaturated nitrogen-heterocyclic group linked directly or via a C_1-C_4-alkylene bridge or via a C_1-C_4-alkylene-CO bridge, comprising one or two other hetero atoms selected from oxygen, nitrogen and sulphur and which is optionally substituted by C_1-C_4-alkyl, C_1-C_4-hydroxyalkyl, benzyl or pyridyl;

cyclopropyl, cyclopentyl or cyclohexyl, each of which is mono- or disubstituted by one or two groups selected from $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$; or

phenyl, benzyl or phenylethyl, which are mono- or disubstituted at the phenyl ring by one or two groups selected from $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, -NH(n-propyl), $-N(n\text{-propyl})_2$, -NH(iso-propyl), $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$.

3. A benzimidazole derivative according to claim 1, wherein

R^1 denotes methyl, ethyl, propyl, butyl or pentyl, each of which is optionally substituted by a group selected from hydroxy, methoxy, ethoxy, propoxy, CF_3, phenoxy, COOH, $CONH_2$, CONHMe and methoxy-phenoxy;

benzyl, phenylethyl or phenylpropyl, mono- or disubstituted at the phenyl ring by one or two groups selected from hydroxy, methoxy, ethoxy, carboxy, methoxycarbonyl, ethoxycarbonyl and CF_3; or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a C_1-C_4-alkylene bridge, comprising one or two

hetero atoms selected from oxygen and nitrogen and is optionally substituted by methyl, ethyl, propyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, quinolyl, benzothienyl or naphthyl;

R^4 denotes a group selected from ethyl, propyl, butyl, pentyl and hexyl, each of which is mono- or disubstituted by one or two groups selected from $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, $-NH(n\text{-propyl})$, $-N(n\text{-propyl})_2$, $-NH(iso\text{-propyl})$, $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$;

a 5-, 6- or 7-membered, saturated or unsaturated nitrogen-heterocyclic group linked directly or via a C_1-C_4-alkylene bridge or via a C_1-C_3-alkylene-CO bridge, optionally comprising one or two other hetero atoms selected from oxygen and nitrogen and is optionally substituted by methyl, ethyl, propyl, 3-hydroxypropyl or benzyl;

cyclopentyl or cyclohexyl, each of which is mono- or disubstituted by one or two groups selected from $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, $-NH(n\text{-propyl})$, $-N(n\text{-propyl})_2$, $-NH(iso\text{-propyl})$, $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$; or

benzyl or phenylethyl, which are mono- or disubstituted at the phenyl ring by one or two groups selected from $-NH_2$, -NHmethyl, $-N(methyl)_2$, -NHethyl, $-N(ethyl)_2$, $-NH(n\text{-propyl})$, $-N(n\text{-propyl})_2$, $-NH(iso\text{-propyl})$, $-N(iso\text{-propyl})_2$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$.

4. A benzimidazole derivative according to claim 1, wherein

R^1 denotes methyl; ethyl optionally substituted by hydroxy, methoxy, ethoxy, phenoxy or methoxy-phenoxy; propyl optionally substituted by hydroxy, methoxy or ethoxy; butyl or pentyl;

benzyl optionally mono- or disubstituted at the phenyl ring by one or two groups selected from hydroxy, carboxy, methoxycarbonyl, ethoxycarbonyl, methoxy, ethoxy and CF_3; phenylethyl or phenylpropyl; or

a 5- or 6-membered, saturated or unsaturated heterocyclic group linked directly or via a methylene or ethylene bridge which contains oxygen or nitrogen as the hetero atom and is optionally substituted by methyl, ethyl, propyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, quinolyl, isoquinolyl, benzothienyl or naphthyl;

R^4 denotes ethyl or propyl, each of which is substituted by a group selected from $-NH_2$, $-N(methyl)_2$, $-N(ethyl)_2$, $-N(n\text{-}propyl)_2$ and $-C(=NH)NH_2$;

a 5-, 6- or 7-membered, saturated or unsaturated nitrogen-heterocyclic group linked directly or via a methylene or ethylene bridge, optionally comprising an oxygen as a further hetero atom and is optionally substituted by methyl, ethyl, propyl, 3-hydroxypropyl or benzyl;

cyclopentyl or cyclohexyl, each of which is substituted by a group selected from $-NH_2$, $-N(methyl)_2$, $-N(ethyl)_2$, $-N(n\text{-}propyl)_2$ and $-C(=NH)NH_2$; or

benzyl which is substituted at the phenyl ring by a group selected from $-NH_2$, $-N(methyl)_2$, $-N(ethyl)_2$, $-N(n\text{-}propyl)_2$ and $-C(=NH)NH_2$.

5. A benzimidazole derivative according to claim 1, wherein

R^1 denotes methyl, ethyl, hydroxyethyl, methoxyethyl, methoxy-phenoxy-ethyl, propyl, hydroxypropyl, ethoxypropyl, pentyl, or
benzyl, which is mono- or disubstituted at the phenyl ring by one or two group selected from carboxy, ethoxycarbonyl and CF_3, phenylethyl, phenylpropyl, or a tetrahydrofuranyl linked via a methylene bridge;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, quinolyl, benzothienyl or naphthyl;

R^4 denotes diethylaminoethyl, diethylaminopropyl, or a pyridine, pyrimidine, pyrrolidine, morpholine, azepine or piperidine linked directly or via a methylene or methylcarbonyl bridge, each of which is optionally substituted by methyl, 3-hydroxypropyl or benzyl, or
cyclohexyl substituted by $-N(n\text{-}propyl)_2$, or
benzyl which is substituted at the phenyl ring by $-N(methyl)_2$ or $-C(=NH)NH_2$.

6. A benzimidazole derivative according to claim 1, wherein

R^1 denotes methyl, hydroxyethyl, methoxyethyl, methoxy-phenoxy-ethyl, propyl, hydroxypropyl, ethoxypropyl, phenylethyl, phenylpropyl or a tetrahydrofuranyl linked via a methylene bridge;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R^3 denotes phenyl, benzyl, quinol-8-yl, benzo[*b*]thien-3-yl or naphthyl;

R^4 denotes diethylaminoethyl; diethylaminopropyl;
a pyridine linked directly or via a methylene or ethylene bridge, which is optionally substituted by methyl or benzyl;
a pyrrolidine linked directly or via a methylene or ethylene bridge, which is optionally substituted by methyl or benzyl;
a piperidine linked directly or via a methylene or ethylene bridge which is optionally substituted by methyl or benzyl;
a morpholine linked directly or via a methylene or ethylene bridge;
an azepine linked directly or via a methylene or ethylene bridge;
cyclohexyl substituted by $-N(n\text{-propyl})_2$; or
benzyl substituted at the phenyl ring by $-N(methyl)_2$.

7. A benzimidazole derivative according to any one of claims 4, 5 and 6, wherein R^2 is $-C(=NH)NH_2$.

8. A benzimidazole derivative according to any one of claims 4, 5 and 7, wherein R^3 is phenyl, benzo[*b*]thien-3-yl or naphthyl.

9. A benzimidazole derivative according to claim 6 or 7, wherein R^1 is methyl.

10. A use of a benzimidazole derivative as defined in any one of claims 1 to 9 for preventing or treating one or both of an allergic disease and an inflammatory disease.

11. A use according to claim 10, wherein the benzimidazole derivative is a tryptase inhibitor.

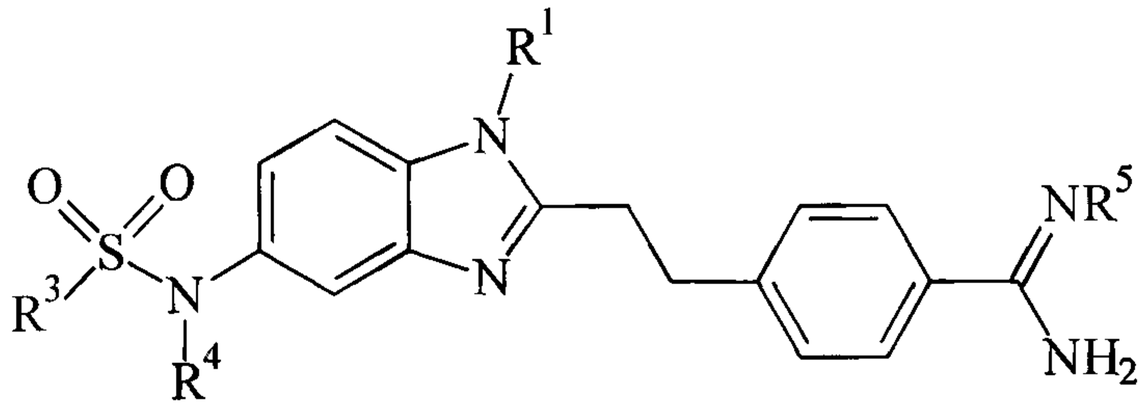
12. A use of a benzimidazole derivative as defined in any one of claims 1 to 9 in manufacture of a medicament for preventing or treating one or both of an inflammatory disease and an allergic disease.

13. A use according to claim 12, wherein the benzimidazole derivative is a tryptase inhibitor.

14. A pharmaceutical composition comprising a benzimidazole derivative as defined in any one of claims 1 to 9 and a pharmaceutically acceptable carrier or diluent for preventing or treating one or both of an allergic disease and an inflammatory disease.

15. A pharmaceutical composition according to claim 14, wherein the benzimidazole derivative is a tryptase inhibitor.

16. A use of a prodrug selected from compounds of general formula (II)



(II),

wherein

R^1 and R^4 are as defined in any one of claims 1 to 6;

R^3 is as defined in any one of claims 1 to 6 or denotes C_1-C_4-alkyl which is substituted by a group selected from among -C(=NOH)NH_2, -C(=NCOO-C_1-C_{12}-alkyl)NH_2 and -C(=NCOO-C_1-C_8-alkyl-phenyl)NH_2;

R^5 denotes hydroxy, -COO-C_1-C_{12}-alkyl, -CO-phenyl, -CO-pyridyl or -COO-C_1-C_8-alkyl-phenyl, wherein, in the -CO-phenyl and the -COO-C_1-C_8-alkyl-phenyl, the phenyl portion thereof is unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, OH, halogen or CF_3;

a tautomer thereof, a racemate thereof, an enantiomer thereof, a diastereomer thereof and a pharmacologically acceptable acid addition salt thereof; wherein the use is in manufacture of a medicament for prevention or treatment of one or both of an allergic and an inflammatory disease.

17. A use according to claim 16, wherein

R^3 is as defined in any one of claims 1 to 6 or denotes C_1-C_4-alkyl which is substituted by a group selected from among -C(=NOH)NH_2, -C(=NCOO-C_1-C_6-alkyl)NH_2 and -C(=NCOO-C_1-C_6-alkyl-phenyl)NH_2; and

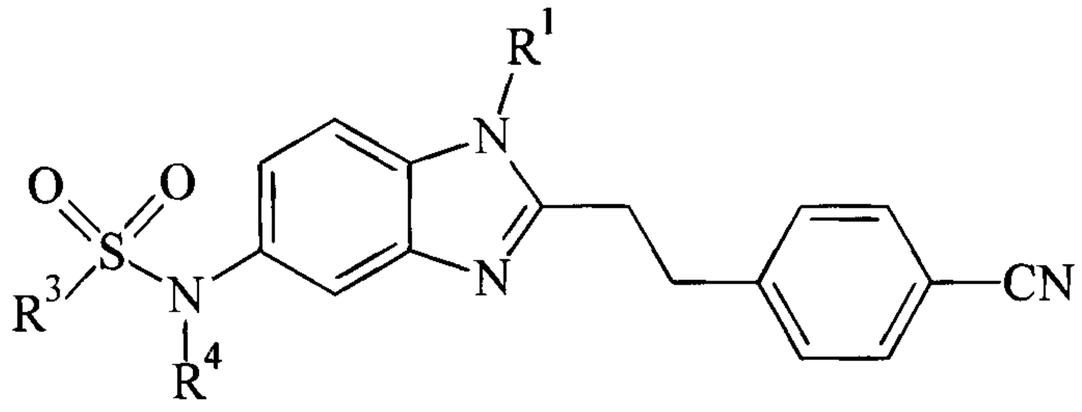
R^5 denotes hydroxy, -COO-C_1-C_6-alkyl, -CO-phenyl, -CO-pyridyl or -COO-C_1-C_6-alkyl-phenyl, wherein, in the -CO-phenyl or the -COO-C_1-C_6-alkyl-phenyl, the phenyl portion thereof is unsubstituted or substituted in each case by C_1-C_4-alkyl, C_1-C_4-alkoxy, OH, halogen or CF_3.

18. A use according to claim 16 or 17, wherein

R^5 denotes hydroxy, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, benzoyl, benzyloxycarbonyl or nicotinoyl.

19. A use according to claim 18, wherein the compound of Formula (II) is a tryptase inhibitor.

20. A use of a compound selected from compounds of general formula (III)

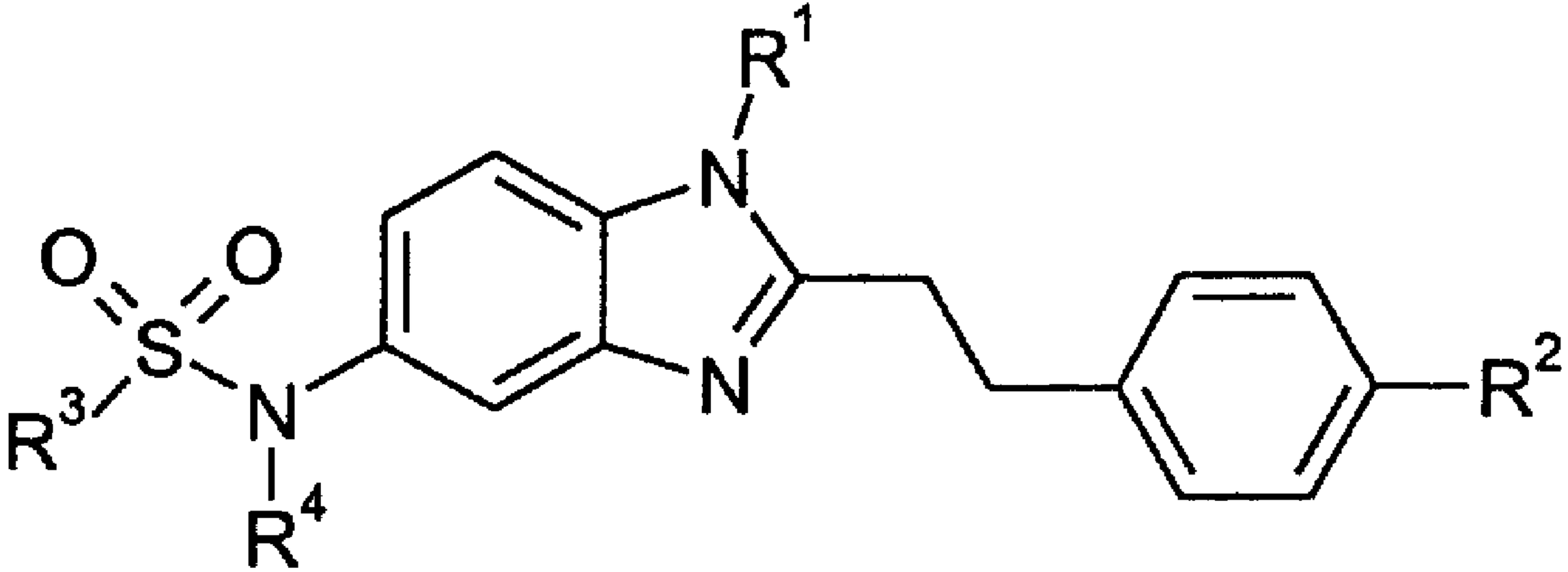


(III),

wherein R^1, R^3 and R^4 are as defined in any one of claims 1 to 8, a tautomer thereof, a racemate thereof, an enantiomer thereof, a diastereomer thereof and a pharmacologically acceptable acid addition salt thereof in manufacture of a medicament for prevention or treatment of one or both of an allergic disease and an inflammatory disease.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS



(I)