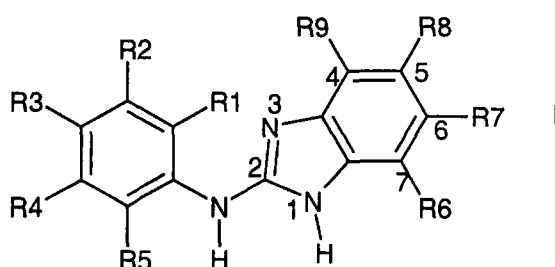


SUBSTITUTED 2-ANILINO-BENZIMIDAZOLES AND THEIR USE AS NHE INHIBITORS

Substituted benzimidazoles, processes for their preparation, their use as
5 medicaments, and medicaments comprising them

The invention relates to substituted benzimidazoles of the formula I



10 in which:

R1 and R5

independently of one another are F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by
15 fluorine,

or

R1 and R5

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or partially or completely substituted by
20 fluorine,

or

R1 and R5

are OH, O-alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by
25 fluorine,

or

R1 and R5

are OCOR₁₀, NR₁₁R₁₂, COR₁₃, COOH, COOR₁₄, CONR₁₁R₁₂, -(O)_n-
SO_mR₁₅,

n is zero or 1;
m is zero, 1 or 2;

or

R1 and R5

5 are O-phenyl,
which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, Br, I, alkyl having 1 to 4 carbon atoms, OH, O-alkyl having 1 to 4 carbon atoms, NR₁₆R₁₇, CN or (C₁-C₄)-alkylsulfonyl,

10 which is unsubstituted or partially or wholly fluorinated,
R₁₆ and R₁₇

are H or alkyl having 1 to 4 carbon atoms,
where the alkyl groups are unsubstituted or partially or wholly fluorinated,

15 R₁₀ is H or alkyl having 1 to 4 carbon atoms,
which is unsubstituted or partially or completely substituted by fluorine,

R₁₁ and R₁₂

20 independently of one another are H, alkyl having 1 to 4 carbon atoms, which may be partially or completely fluorinated and any desired CH₂ group may be replaced by O or NR₁₈

or R₁₁ and R₁₂

together are a 5-, 6- or 7-membered ring;

or R₁₁ and R₁₂

25 are COR₁₉ or SO₂R₂₀;

R₁₈, R₁₉ and R₂₀

independently of one another are H or alkyl having 1 to 4 carbon atoms,

30 which is unsubstituted or partially or completely substituted by fluorine;

R₁₃ and R₁₄

are alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

R15

is alkyl or O-alkyl having 1 to 4 carbon atoms,

5

where the alkyl groups are unsubstituted or partially or wholly fluorinated,

or

R15 is OH or NR₂₁R₂₂;

R₂₁ and R₂₂

10

independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine, in which any desired CH₂ group can be replaced by O or NR₂₃;

15

R₂₃

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

or

20

R₂₁ and R₂₂

together form a 5-, 6- or 7-membered ring;

but R₁ and R₅ must not simultaneously be Cl or CH₃;

R₂, R₃ and R₄

are H or one of the radicals R₂, R₃ or R₄ may be F;

25

R₆, R₇, R₈ and R₉

independently of one another are H, F, Cl, Br, I, CN, alkyl or O-alkyl having 1 to 4 carbon atoms,

which are unsubstituted or wholly or completely substituted by fluorine,

30

or R₆, R₇, R₈ and R₉

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,

or R₆, R₇, R₈ and R₉

are OH, OCOR₂₄ or NR₂₅R₂₆;

R₂₄

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine;

5 R₂₅ and R₂₆

independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,

10 or

R₂₅ and R₂₆

are COR₂₇;

or R₂₅ and R₂₆,

together with the nitrogen atom to which they are bonded,

15 form a 5-, 6- or 7-membered ring, in which any desired CH₂ group can be replaced by O or NR₁₈;

R₂₇

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely

20 substituted by fluorine,

and their pharmaceutically tolerable salts or trifluoroacetates.

Preferred compounds of the formula I are those in which:

R₁ and R₅

25 independently of one another are F, Cl, Br, CN, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, cycloalkyl having 3 to 7 carbon atoms, O-alkyl having 1 to 4 carbon atoms, OH, OCF₃, OCH₂CF₃, OCF₂CF₃, OCOR₁₀, NR₁₁R₁₂, COR₁₃, COOH, COOR₁₄, CONR₁₁R₁₂, -O_m-SO₂R₁₅ or O-phenyl;

30 m is zero or 1;

R₁₀

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃,

R11 and R12

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, where any desired CH₂ group may be replaced by O or NR₁₈ and where R₁₁ and R₁₂, together with the nitrogen to which they are bonded, may form a 5-, 6- or 7-membered ring,

or R₁₁ and R₁₂

are COR₁₉ or SO₂R₂₀;

R₁₈, R₁₉ and R₂₀

independently of one another are H or alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃,

R₁₃ and R₁₄

are alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

R₁₅

is alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, OH, O-alkyl, having 1 to 4 carbon atoms, OCF₃, OCH₂CF₃, OCF₂CF₃ or NR₂₁R₂₂;

R₂₁ and R₂₂

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

or

R₂₁ and R₂₂, together with the nitrogen atom to which they are bonded, are -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂- or -(CH₂)₂-NR₃₀-(CH₂)₂;

R₃₀

is H, CH₃ or CF₃;

but R₁ and R₅ must not simultaneously be Cl or CH₃,

R₂, R₃ and R₄

are H or one of the radicals R₂, R₃ or R₄ may be F;

R₆, R₇, R₈ and R₉

independently of one another are H, F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, cycloalkyl having 3 to 7 carbon

atoms, OH, O-alkyl having 1 to 4 carbon atoms, OCF₃, OCH₂CF₃,
OCF₂CF₃, OCOR₂₄ or NR₂₅R₂₆;

R₂₄

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

5 R₂₅ and R₂₆

independently of one another are H, alkyl having 1 to 4 carbon
atoms, CF₃, CH₂CF₃, CF₂CF₃, COR₂₇;

or

R₂₅ and R₂₆,

10 together with the nitrogen to which they are bonded, are a 5-, 6- or 7-
membered ring;

R₂₇

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or
CF₂CF₃

15 and their pharmaceutically tolerable salts or trifluoroacetates.

Particularly preferred compounds of the formula I are those in which:

R₁ and R₅

20 independently of one another are F, Cl, Br, CN, methyl, ethyl, isopropyl,
CF₃, cyclopropyl, OH, O-methyl, O-ethyl, O-isopropyl, OCF₃, O-acetyl, NH₂,
NMe₂, NEt₂, N-pyrrolidino, N-piperidino, N-morpholino, N-(N'-methyl)-
piperazino, NHSO₂Me, acetyl, COOH, COOR₁₄, CONR₁₁R₁₂, SO₂R₁₅ or
O-phenyl,

25 R₁₁ and R₁₂ independently of one another are H, methyl or ethyl;

R₁₄ is methyl or ethyl,

R₁₅ is CH₃, CF₃, OH, OCH₃, OCF₃ or NR₂₁R₂₂;

R₂₁ and R₂₂

independently of one another are H or methyl;

30 but R₁ and R₅ are not simultaneously Cl or CH₃,

R₂, R₃ and R₄

are H;

R6, R7, R8 and R9

independently of one another are H, F, Cl, CN, CH₃, C₂H₅, isopropyl, CF₃, cyclopropyl, OH, OCH₃, OCF₃, O-acetyl or NR₂₅R₂₆;

R₂₅ and R₂₆

5 independently of one another are H, methyl or acetyl;

and their pharmaceutically tolerable salts or trifluoroacetates.

Very particularly preferred compounds of the formula I are those in which:

R₁ and R₅

10 independently of one another are F, Cl, Br, CN, methyl, ethyl, isopropyl, CF₃, cyclopropyl, OH, O-methyl, O-ethyl, O-isopropyl, OCF₃, O-acetyl, NH₂, NMe₂, NEt₂, N-pyrrolidino, N-piperidino, N-morpholino, N-(N'-methyl)-piperazino, NHSO₂Me, acetyl, COOH, COOR₁₄, CONR₁₁R₁₂, SO₂R₁₅ or O-phenyl,

15

R₁₁ and R₁₂ independently of one another are H, methyl or ethyl;

R₁₄ is methyl or ethyl,

R₁₅ is CH₃, CF₃, OH, OCH₃, OCF₃ or NR₂₁R₂₂;

R₂₁ and R₂₂

20 independently of one another are H or methyl;

but R₁ and R₅ are not simultaneously Cl or CH₃,

R₂, R₃ and R₄

are H;

R₆ and R₉

25 independently of one another are H, F, Cl, CN, CH₃, CF₃, cyclopropyl, OH, OCH₃, OCF₃, O-acetyl or NR₂₅R₂₆;

R₂₅ and R₂₆

independently of one another are H, methyl or acetyl;

R₇ and R₈

30 independently of one another are H, F or OH;

and their pharmaceutically tolerable salts or trifluoroacetates.

Those very particularly especially preferred are

- (1H-benzimidazol-2-yl)-(2,6-dichlorophenyl)amine;
 - 2-(2,6-dichlorophenylamino)-1H-benzimidazol-4-ol;
 - (1H-benzimidazol-2-yl)-(2,6-dimethylphenyl)amine;
 - 5 (1H-benzimidazol-2-yl)-(2-chloro-6-methylphenyl)amine;
 - (2,6-dichlorophenyl)-(5,6-difluoro-1H-benzimidazol-2-yl)amine;
 - (2,6-dichlorophenyl)-(4-methyl-1H-benzimidazol-2-yl)amine;
 - (1H-benzimidazol-2-yl)-(2-chloro-6-fluorophenyl)amine;
 - (1H-benzimidazol-2-yl)-(2,6-dibromophenyl)amine;
 - 10 2-(2,6-dichlorophenylamino)-5-fluorobenzimidazole;
 - 2-(2,6-dichlorophenylamino)-4-fluorobenzimidazole;
 - 2-(2-trifluoromethyl-6-chlorophenylamino)benzimidazole;
 - 2-(2,6-dichlorophenylamino)-4,5-difluorobenzimidazole;
 - 2-(2,6-dichlorophenylamino)-5-hydroxybenzimidazole;
 - 15 2-(2,6-dichlorophenylamino)-4,5,6,7-tetrafluorobenzimidazole;
 - 2-(2,6-dichlorophenylamino)-4,6-difluorobenzimidazole;
 - (1H-benzimidazol-2-yl)-(2-chlorophenyl)amine;
 - (1H-benzimidazol-2-yl)-(2-trifluoromethylphenyl)amine;
 - (1H-benzimidazol-2-yl)-(2-bromophenyl)amine; and
 - 20 (1H-benzimidazol-2-yl)-o-tolylamine;
- and their pharmaceutically tolerable salts or trifluoroacetates.

In addition, the invention comprises the use of substituted benzimidazoles of the formula I for the production of a medicament for the treatment of diseases which are

- 25 influenced by the NHE3 exchange inhibitor, in which

R1 and R5

independently of one another are H, F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms,

- 30 which is unsubstituted or partially or completely substituted by fluorine,

or

R1 and R5

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine,

or

R1 and R5

5 are OH, O-alkyl having 1 to 4 carbon atoms,
which is unsubstituted or partially or completely substituted by fluorine,

or

R1 and R5

10 are OCOR₁₀, NR₁₁R₁₂, COR₁₃, COOH, COOR₁₄, CONR₁₁R₁₂, -(O)_nSO_mR₁₅,

n is zero or 1;

m is zero, 1 or 2;

or

15 R1 and R5

are O-phenyl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, Br, I, alkyl having 1 to 4 carbon atoms, OH, O-alkyl having 1 to 4 carbon atoms, NR₁₆R₁₇, CN or (C₁-C₄)-alkylsulfonyl,

20

which is unsubstituted or partially or wholly fluorinated,

R₁₆ and R₁₇

are H or alkyl having 1 to 4 carbon atoms,

where the alkyl groups are unsubstituted or partially

25

or wholly fluorinated,

R₁₀ is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine,

R₁₁ and R₁₂

30

independently of one another are H, alkyl having 1 to 4 carbon atoms, which may be partially or completely fluorinated and any desired CH₂ group may be replaced by O or NR₁₈

or R₁₁ and R₁₂

together are a 5-, 6- or 7-membered ring;
or R11 and R12

are COR19 or SO₂R20;

R18, R19 and R20

5 independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

R13 and R14

10 are alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

R15

is alkyl or O-alkyl having 1 to 4 carbon atoms,

15 where the alkyl groups are unsubstituted or partially or wholly fluorinated,

or

R15 is OH or NR21R22;

R21 and R22

20 independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine, in which any desired CH₂ group can be replaced by O- or NR23;

25 R23

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

or

30 R21 and R22

together form a 5-, 6- or 7-membered ring;

R2, R3 and R4

are H or F;

R6, R7, R8 and R9

independently of one another are H, F, Cl, Br, I, CN, alkyl or O-alkyl having 1 to 4 carbon atoms,

which are unsubstituted or wholly or completely substituted by

5 fluorine,

or R6, R7, R8 and R9

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,

or R6, R7, R8 and R9

10 are OH, OCOR₂₄ or NR₂₅R₂₆;

R₂₄

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine;

R₂₅ and R₂₆

15 independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,

or

20 R₂₅ and R₂₆

are COR₂₇;

or R₂₅ and R₂₆,

together with the nitrogen atom to which they are bonded,

form a 5-, 6- or 7-membered ring, in which any desired CH₂

25 group can be replaced by O or NR₁₈;

R₂₇

Is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely

substituted by fluorine,

30 and of their pharmaceutically tolerable salts.

Preferred is the use of compounds of the formula I in which

R1 and R5

independently of one another are H, F, Cl, Br, CN, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, cycloalkyl having 3 to 7 carbon atoms, O-alkyl having 1 to 4 carbon atoms, OH, OCF₃, OCH₂CF₃, OCF₂CF₃, OCOR₁₀, NR₁₁R₁₂, COR₁₃, COOH, COOR₁₄, CONR₁₁R₁₂, -O_m-SO₂R₁₅ or O-phenyl;

m is zero or 1;

R₁₀

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃,

R₁₁ and R₁₂

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, where any desired CH₂ group may be replaced by O or NR₁₈ and where R₁₁ and R₁₂, together with the nitrogen to which they are bonded, may form a 5-, 6- or 7-membered ring,

or R₁₁ and R₁₂

are COR₁₉ or SO₂R₂₀;

R₁₈, R₁₉ and R₂₀

independently of one another are H or alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃,

R₁₃ and R₁₄

are alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

R₁₅

is alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, OH, O-alkyl, having 1 to 4 carbon atoms, OCF₃, OCH₂CF₃, OCF₂CF₃ or NR₂₁R₂₂;

R₂₁ and R₂₂

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

or

R21 and R22, together with the nitrogen atom to which they are bonded, are $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$ or $-(CH_2)_2-NR_{30}-(CH_2)_2$;

R30

5 is H, CH_3 or CF_3 ;

but R1 and R5 must not simultaneously be Cl or CH_3 , and where at most one of the substituents R1 and R5 may be hydrogen;

R2, R3 and R4

are H or F;

10 R6, R7, R8 and R9

independently of one another are H, F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms, CF_3 , CH_2CF_3 , CF_2CF_3 , cycloalkyl having 3 to 7 carbon atoms, OH, O-alkyl having 1 to 4 carbon atoms, OCF_3 , OCH_2CF_3 , OCF_2CF_3 , $OCOR_{24}$ or $NR_{25}R_{26}$;

15 R24

is H, alkyl having 1 to 4 carbon atoms, CF_3 , CH_2CF_3 or CF_2CF_3 ;

R25 and R26,

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF_3 , CH_2CF_3 , CF_2CF_3 , COR_{27} ;

20 or

R25 and R26,

together with the nitrogen to which they are bonded, are a 5-, 6- or 7-membered ring;

R27

25 is H, alkyl having 1 to 4 carbon atoms, CF_3 , CH_2CF_3 or CF_2CF_3

and of their pharmaceutically tolerable salts.

Particularly preferred is the use of compounds of the formula I in which:

30 R1 and R5

independently of one another are H, F, Cl, Br, CN, methyl, ethyl, isopropyl, CF_3 , cyclopropyl, OH, O-methyl, O-ethyl, O-isopropyl, OCF_3 , O-acetyl, NH_2 ,

NMe₂, NEt₂, N-pyrrolidino, N-piperidino, N-morpholino, N-(N'-methyl)-piperazino, NHSO₂Me, acetyl, COOH, COOR₁₄, CONR₁₁R₁₂, SO₂R₁₅ or O-phenyl,

5 R₁₁ and R₁₂ independently of one another are H, methyl or ethyl;

R₁₄ is methyl or ethyl;

R₁₅ is CH₃, CF₃, OH, OCH₃, OCF₃ or NR₂₁R₂₂;

R₂₁ and R₂₂

independently of one another are H or methyl;

10 but R₁ and R₅ are not simultaneously Cl or CH₃, and in which at most one of the substituents R₁ and R₅ is hydrogen;

R₂, R₃ and R₄

are H;

R₆, R₇, R₈ and R₉

15 independently of one another are H, F, Cl, CN, CH₃, C₂H₅, isopropyl, CF₃, cyclopropyl, OH, OCH₃, OCF₃, O-acetyl or NR₂₅R₂₆;

R₂₅ and R₂₆

independently of one another are H, methyl or acetyl;

and of their pharmaceutically tolerable salts.

20

Very particularly preferred is the use of compounds of the formula I in which:

R₁ and R₅

independently of one another are F, Cl, Br, CN, methyl, ethyl, isopropyl,

CF₃, cyclopropyl, OH, O-methyl, O-ethyl, O-isopropyl, OCF₃, O-acetyl, NH₂,

25 NMe₂, NEt₂, N-pyrrolidino, N-piperidino, N-morpholino, N-(N'-methyl)-

piperazino, NHSO₂Me, acetyl, COOH, COOR₁₄, CONR₁₁R₁₂, SO₂R₁₅ or O-phenyl,

R₁₁ and R₁₂ independently of one another are H, methyl or ethyl;

30 R₁₄ is methyl or ethyl,

R₁₅ is CH₃, CF₃, OH, OCH₃, OCF₃ or NR₂₁R₂₂;

R₂₁ and R₂₂

independently of one another are H or methyl;

but R1 and R5 are not simultaneously Cl or CH₃, and at most one of the substituents

R1 and R5 is hydrogen,

R2, R3 and R4

5 are H;

R6 and R9

independently of one another are H, F, Cl, CN, CH₃, CF₃, cyclopropyl, OH,

OCH₃, OCF₃, O-acetyl or NR₂₅R₂₆;

R₂₅ and R₂₆

10 independently of one another are H, methyl or acetyl;

R7 and R8

independently of one another are H, F or OH;

and of their pharmaceutically tolerable salts.

15 Very particularly especially preferred is the use of compounds of the formula I, which are:

1: (1H-benzimidazol-2-yl)-(2,6-dichlorophenyl)amine;

2: 2-(2,6-dichlorophenylamino)-1H-benzimidazol-4-ol;

3: (1H-benzimidazol-2-yl)-(2,6-dimethylphenyl)amine;

20 4: (1H-benzimidazol-2-yl)-(2-chloro-6-methylphenyl)amine;

5: (2,6-dichlorophenyl)-(5,6-difluoro-1H-benzimidazol-2-yl)amine;

6: (2,6-dichlorophenyl)-(4-methyl-1H-benzimidazol-2-yl)amine;

7: (1H-benzimidazol-2-yl)-(2-chloro-6-fluorophenyl)amine;

8: (1H-benzimidazol-2-yl)-(2,6-dibromophenyl)amine;

25 9: 2-(2,6-dichlorophenylamino)-5-fluorobenzimidazole;

10: 2-(2,6-dichlorophenylamino)-4-fluorobenzimidazole;

11: 2-(2-trifluoromethyl-6-chlorophenylamino)benzimidazole;

12: 2-(2,6-dichlorophenylamino)-4,5-difluorobenzimidazole;

13: 2-(2,6-dichlorophenylamino)-5 hydroxybenzimidazole;

30 14: 2-(2,6-dichlorophenylamino)-4,5,6,7-tetrafluorobenzimidazole;

15: 2-(2,6-dichlorophenylamino)-4,6-difluorobenzimidazole;

16: (1H-benzimidazol-2-yl)-(2-chlorophenyl)amine;

17: (1H-benzimidazol-2-yl)-(2-trifluoromethylphenyl)amine;

18: (1H-benzimidazol-2-yl)-(2-bromophenyl)amine; and

19: (1H-benzimidazol-2-yl)-o-tolylamine;

and of their pharmaceutically tolerable salts.

- 5 If the compounds of the formula I contain one or more centers of asymmetry, these can have either the S or the R configuration. The compounds can be present as optical isomers, as diastereomers, as racemates or as mixtures thereof.

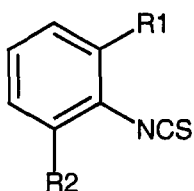
- 10 The compounds of the formula I can furthermore be present as tautomers or as a mixture of tautomeric structures. In the case of substitution on the corresponding N atoms of the benzimidazole structure, the compounds can be present in the form of the various double bond isomers or as a mixture of the double bond isomers.

- 15 The designated alkyl radicals or partially or completely fluorinated alkyl radicals can be either straight-chain or branched.

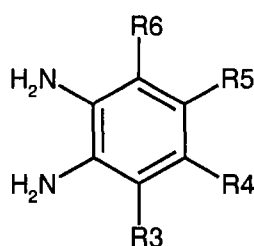
CH₂ units are also the terminal CH₃ groups in an alkyl chain, which are interpreted in this connection as CH₂-H groups.

- 20 Methods for the preparation of the compounds used are also described.

Thus substances described by formula I can be prepared in the manner known to the person skilled in the art from the underlying isothiocyanates II and the corresponding phenylenediamines III.



II



III

25

The thiourea intermediately formed here is cyclized to the corresponding benzimidazole I by means of mercury(II) oxide (J. Med. Chem., 1975, 18, 90 - 99), methyl iodide (Synthesis, 1974, 41 - 42) or carbodiimide (Synthesis, 1977, 864 - 865). The isothiocyanates II used here, if not commercially obtainable, can be

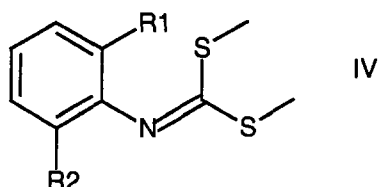
prepared in the manner known from the literature from the corresponding anilines by the methods known to the person skilled in the art, e.g. by treating with thiophosgene (J. Med. Chem., 1975, 18, 90-99) or thiocarbonyldiimidazole (Justus Liebigs Ann. Chem., 1962, 657).

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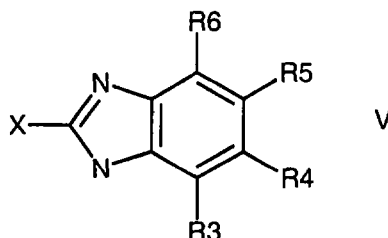
Likewise, starting from the anilines, by treating with NaOH, carbon disulphide and methyl iodide in processes which are already known from the literature, it is possible to prepare the corresponding N-aryldithiocarbamates (Synthesis, 1981, 961) and, from these in turn, the N-aryldithiocarboximidates IV (Synthesis, 1983, 375), which

10

can be reacted in the presence of the phenylenediamines III at elevated temperatures to give the desired benzimidazoles I.



15 Finally, the described compounds I can be prepared starting from the anilines and the corresponding 2-substituted benzimidazoles V by heating.



X in this case is a leaving group, such as, for example, Cl, Br, or SO₃H (J. Org. Chem., 1986, 51, 1882).

20

British patent specification 1 171 904 describes a general formula which would even allow o,o-disubstitution in the aniline moiety. However, there is no indication of compounds of type I actually taken into consideration which have an o,o-

25

disubstitution pattern, let alone an experimental description. The compounds described in this British patent specification 1 174 904 are protected therein as substances having antibacterial activity. In the case of the compounds according to

the invention, it was not possible with the aid of an exemplary compound to detect any antibacterial action, such that the substance class according to GB 1 171 904 can be differentiated clearly from the compounds according to the invention, both structurally and in its pharmacological properties.

5

Furthermore, some of the benzimidazoles according to the invention could be constructed from WO 9808818, which are described therein as phospholipase inhibitors. However, no single representative of this class of compound is described therein, neither experimentally nor pharmacologically.

10

It was possible to show that compounds of the formula I are outstanding inhibitors of the sodium-hydrogen exchanger (NHE) - in particular of the sodium-hydrogen exchanger of subtype 3 (NHE3).

15 On account of these properties, the compounds are suitable for the treatment of diseases which are caused by oxygen deficiency. As a result of their pharmacological properties, the compounds are outstandingly suitable as antiarrhythmic medicaments having a cardioprotective component for infarct prophylaxis and infarct treatment and for the treatment of angina pectoris, which also
20 preventively inhibit or greatly decrease the pathophysiological processes in the formation of ischemically induced damage, in particular in the triggering of ischemically induced cardiac arrhythmias. Because of their protective actions against pathological hypoxic and ischemic situations, the compounds of the formula I used according to the invention can be used, as a result of the inhibition of the cellular
25 Na^+/H^+ exchange mechanism, as medicaments for the treatment of all acute or chronic damage caused by ischemia or diseases induced primarily or secondarily thereby. This relates to their use as medicaments for surgical interventions, e.g. in organ transplants, where the compounds can be used both for the protection of the organs in the donor before and during removal, for the protection of removed organs,
30 for example during treatment with or storage thereof in physiological fluids, and during transfer to the recipient's body. The compounds are likewise valuable, protectively acting medicaments when carrying out angioplastic surgical interventions, for example on the heart and on peripheral vessels. Corresponding to

their protective action against ischemically induced damage, the compounds are also suitable as medicaments for the treatment of ischemias of the nervous system, in particular of the CNS, where they are suitable, for example, for the treatment of stroke or of cerebral edema. Moreover, the compounds of the formula I used according to the invention are likewise suitable for the treatment of forms of shock, such as, for example, of allergic, cardiogenic, hypovolemic and of bacterial shock.

Furthermore, the compounds induce an improvement in the respiratory drive and are therefore used for the treatment of respiratory conditions in the following clinical conditions and diseases: disturbed central respiratory drive (e.g. central sleep apneas, sudden infant death, postoperative hypoxia), muscular-related respiratory disorders, respiratory disorders after long-term respiration, respiratory disorders during adaptation in a high mountainous area, obstructive and mixed forms of sleep apnea, acute and chronic lung diseases with hypoxia and hypercapnia.

The compounds additionally increase the muscle tone of the upper airways such that snoring is suppressed.

A combination of an NHE inhibitor with a carboanhydrase inhibitor (e.g. acetazolamide), where the latter produces a metabolic acidosis and thereby even increases the respiratory activity, proves advantageous due to increased action and decreased use of active substance.

It has been shown that the compounds used according to the invention have a mild laxative action and accordingly can be used advantageously as laxatives or in the case of threatening intestinal blockage, where the prevention of ischemic damage accompanying blockages in the intestinal area is particularly advantageous.

The possibility furthermore exists of preventing gallstone formation.

Moreover, the compounds of the formula I used according to the invention are distinguished by strongly inhibitory action on the proliferation of cells, for example fibroblast cell proliferation and the proliferation of the vascular smooth muscle cells. Therefore, the compounds of the formula I are suitable as valuable therapeutics for diseases in which cell proliferation is a primary or secondary cause, and can

therefore be used as antiatherosclerotic agents against diabetic late complications, cancers, fibrotic diseases such as pulmonary fibrosis, fibrosis of the liver or fibrosis of the kidneys, organ hypertrophies and hyperplasias, in particular in prostate hyperplasia or prostate hypertrophy.

5

The compounds used according to the invention are effective inhibitors of the cellular sodium-proton antiporter (Na/H exchanger), which is raised in numerous diseases (essential hypertension, atherosclerosis, diabetes etc.) even in those cells which are accessible to measurements, such as, for example, in erythrocytes, platelets or leukocytes. The compounds used according to invention are therefore suitable as outstanding and simple scientific tools, for example in their use as diagnostics for the determination and differentiation of certain forms of hypertension, but also of atherosclerosis, diabetes, proliferative diseases etc. Moreover, the compounds of the formula I are suitable for preventive therapy for the prevention of the genesis of high blood pressure, for example of essential hypertension.

10
15

It has additionally been found that NHE inhibitors exhibit a favorable influence on the serum lipoproteins. It is generally recognized that for the formation of arteriosclerotic vascular changes, in particular of a heart disease, excessively high blood lipid levels, 'hyperlipoproteinemia' is a significant risk factor. For the prophylaxis and the regression of atherosclerotic changes, the lowering of raised serum lipoproteins therefore assumes extreme importance. The compounds used according to the invention can therefore be used for the prophylaxis and for the regression of atherosclerotic changes, by excluding a causal risk factor. With this protection of the vessels against the syndrome of endothelial dysfunction, compounds of the formula I are valuable medicaments for the prevention and for the treatment of coronary vasospasms, atherogenesis and atherosclerosis, left-ventricular hypertrophy and dilated cardiomyopathy, and thrombolytic diseases.

20
25

The compounds mentioned are therefore advantageously used for the production of a medicament for the prevention and treatment of sleep apneas and muscle-related respiratory disorders; for the production of a medicament for the prevention and treatment of snoring; for the production of a medicament for lowering blood pressure; for the production of a medicament for the prevention and treatment of

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diseases which are induced by ischemia and reperfusion of central and peripheral organs, such as acute kidney failure, stroke, endogenous states of shock, intestinal diseases etc.; for the production of a medicament for the treatment of diabetic late damage and chronic kidney diseases, in particular of all kidney inflammations (nephritides) which are associated with increased protein/albumin excretion; for the production of a medicament for the treatment of attack by ectoparasites in human and veterinary medicine; for the production of a medicament for the treatment of the diseases mentioned in combination with blood pressure-lowering substances, preferably with angiotensin-converting enzyme (ACE) inhibitors, with diuretics and saluretics such as furosemide, hydrochlorothiazide, pseudoaldosterone antagonists and aldosterone antagonists, and with angiotensin receptor antagonists.

The administration of sodium-proton exchange inhibitors of the formula I as novel medicaments for the lowering of raised blood lipid levels is claimed, and the combination of sodium-proton exchange inhibitors with medicaments having blood pressure-lowering and/or hypolipidemic action.

Preferably, the compounds mentioned are advantageously used for the production of a medicament for the prevention and treatment of sleep apneas and muscle-related respiratory disorders; for the production of a medicament for the prevention and treatment of snoring; for the production of a medicament for lowering blood pressure; for the production of a medicament for the prevention and treatment of diseases which are induced by ischemia and reperfusion of central and peripheral organs, such as acute kidney failure, intestinal diseases etc.; for the production of a medicament for the treatment of diabetic late damage and chronic kidney diseases, in particular of all kidney inflammations (nephritides) which are associated with increased protein/albumin excretion; for the production of a medicament for the treatment of attack by ectoparasites in human and veterinary medicine; for the production of a medicament for the treatment of the diseases mentioned in combination with blood pressure-lowering substances, preferably with angiotensin-converting enzyme (ACE) inhibitors, with diuretics and saluretics such as furosemide, hydrochlorothiazide, pseudoaldosterone antagonists and aldosterone antagonists; with adenosine receptor modulators, in particular with adenosine receptor activators (A2 agonists), and with angiotensin receptor antagonists.

Pharmaceuticals which contain a compound I can in this case be administered orally, parenterally, intravenously, rectally, transdermally or by inhalation, the preferred administration being dependent on the particular clinical picture of the disease. The compounds I can in this case be administered on their own or together with pharmaceutical excipients, namely both in veterinary and in human medicine.

The person skilled in the art is familiar on the basis of his/her expert knowledge with excipients which are suitable for the desired pharmaceutical formulation. In addition to solvents, gel formers, suppository bases, tablet excipients, and other active compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers or colorants.

For an oral administration form, the active compounds are mixed with the additives suitable therefor, such as vehicles, stabilizers or inert diluents, and brought by the customary methods into the suitable administration forms, such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions. Inert excipients which can be used are, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular cornstarch. In this case, preparation can be carried out both as dry and moist granules. Suitable oily vehicles or solvents are, for example, vegetable or animal oils, such as sunflower oil or cod liver oil.

For subcutaneous or intravenous administration, the active compounds used, if desired with the substances customary therefor, such as solubilizers, emulsifiers or further excipients, are brought into solution, suspension or emulsion. Possible solvents are, for example: water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively a mixture of the various solvents mentioned.

Pharmaceutical formulations which are suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active compound of the formula I in a pharmaceutically acceptable solvent, such as, in particular, ethanol or water, or a mixture of such solvents.

If required, the formulation can also contain yet other pharmaceutical excipients such as surfactants, emulsifiers and stabilizers, and a propellant. Such a preparation customarily contains the active compound in a concentration of approximately 0.1 to 10, in particular of approximately 0.3 to 3, % by weight.

The dose of the active compound of the formula I to be administered and the frequency of administration depend on the potency and duration of action of the compounds used; moreover also on the nature and severity of the illness to be treated and on the sex, age, weight and individual responsiveness of the mammal to be treated.

On average, the daily dose of a compound of the formula I in the case of a patient weighing approximately 75 kg is at least 0.001 mg/kg, preferably 0.01 mg/kg, to at most 10 mg/kg, preferably 1 mg/kg, of body weight. In the case of acute episodes of the disease, for example immediately after suffering a cardiac infarct, even higher and especially more frequent doses may also be necessary, e.g. up to 4 individual doses per day. In particular in the case of i.v. administration, for example in the case of an infarct patient in the intensive care unit, up to 200 mg per day may be necessary.

Experimental descriptions and examples:

List of abbreviations used:

EA	Ethyl acetate	
R _t	Retention time	RT Room temperature
TFA	Trifluoroacetic acid	THF Tetrahydrofuran
LCMS	Liquid chromatography-mass spectroscopy	
MS	Mass spectroscopy	
CI	Chemical Ionization	

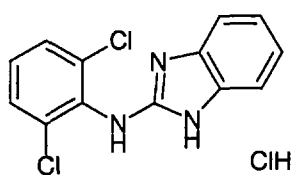
General:

The retention times (R_t) indicated below relate to LCMS measurements having the following parameters:

stationary phase: Merck Purospher $3\mu 2 \times 55$ mm

5 mobile phase: 95% H_2O (0.05% TFA) $\rightarrow$ 95% acetonitrile; 4 min; 95% acetonitrile; 1.5 min $\rightarrow$ 5% acetonitrile; 1 min; 0.5 ml/min.

Example 1: (1H-Benzimidazol-2-yl)-(2,6-dichlorophenyl)amine hydrochloride

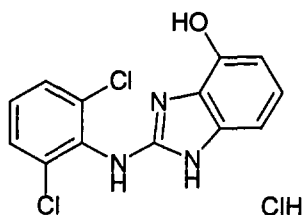


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(1H-Benzimidazol-2-yl)-(2,6-dichlorophenyl)amine can be prepared according to methods known from the literature (J. Med. Chem., 1975, 18, 90). Recrystallization from hot, dilute hydrochloric acid yields the corresponding hydrochloride as a

15 colorless solid . (MS-Cl: 278.2, 280.0; LCMS- R_t = 3.605 min).

Example 2: 2-(2,6-Dichlorophenylamino)-1H-benzimidazol-4-ol hydrochloride



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Intermediate 1: 1-(2-Amino-6 hydroxyphenyl)-3-(2,6-dichlorophenyl)thiourea

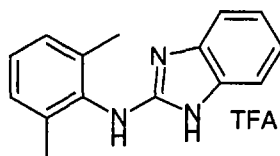
1.0 equivalent of 2,6-dichlorophenyl isothiocyanate is treated with 1.0 equivalent of 2,3-diaminophenol and heated to reflux for 1 h. After cooling to room temperature, the precipitate is filtered off with suction, washed with ether and dried. The desired

25 thiourea is obtained in a yield of 61%. (M.p. 202-204°C).

2-(2,6-Dichlorophenylamino)-1H-benzimidazol-4-ol hydrochloride

Intermediate 1 is dissolved in ethanol and treated with 8 equivalents of methyl iodide. The mixture is heated to reflux for 8 h. After it has cooled to room temperature, the reaction solution is filtered through activated carbon and the filtrate is concentrated in vacuo. The residue is treated with 0.5 N HCl and the precipitate is filtered off with suction after 30 min. The residue is stirred once more with ethyl acetate and dried, it being possible to isolate the title compound in a yield of 47%. (M.p.: 333-335°C; MS(Cl⁺): 294.1; 296.1).

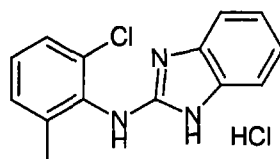
Example 3: (1H-Benzimidazol-2-yl)-(2,6-dimethylphenyl)amine trifluoroacetate



2,6-Dimethylaniline (0.5 g) and 2-chlorobenzimidazole (0.63 g) were mixed in a flask and then kept at 200°C for 2 h. After cooling, the residue was dissolved out of the flask with 1 N HCl at boiling heat. The material dissolved out was then stirred at RT for 30 min, then the insoluble material was filtered off with suction and the filtrate was evaporated. The residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined, concentrated and then recrystallized from acetonitrile/water. 500 mg of white crystals were obtained.

LCMS-R_t: 3.30 min; MS (ES⁺, M+H⁺): 238.1

Example 4: (1H-Benzimidazol-2-yl)-(2-chloro-6-methylphenyl)amine hydrochloride



2-Chloro-6-methylaniline (0.46 g) and 2-chlorobenzimidazole (0.5 g) were mixed in a flask and then kept at 170°C for 30 min. After cooling, the residue was dissolved out

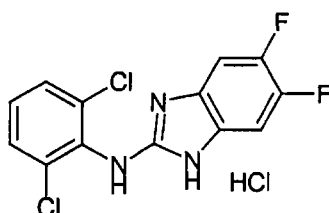
of the flask with 1 N HCl and 10% ethanol at boiling heat. The material dissolved out was then stirred at RT for 30 min, then the insoluble material was filtered off with suction and the filtrate was evaporated. The residue was purified by means of

5 fractions were combined, the acetonitrile was stripped off, the residue was adjusted to pH 10 with potassium carbonate solution, extracted three times with EA and then the combined phases were dried, filtered and concentrated. The residue was taken up using HCl/water and freeze-dried. 227 mg of the title compound were obtained.

LCMS- R_t : 3.71 min; MS (ES^+ , $M+H^+$): 258.0

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Example 5: (2,6-Dichlorophenyl)-(5,6-difluoro-1H-benzimidazol-2-yl)amine hydrochloride



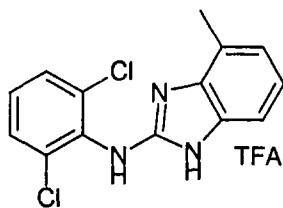
2,6-Dichlorophenyl isothiocyanate (0.3 g) and 4,5-difluoro-1,2-phenylenediamine (0.21 g) were stirred at RT for 4 h in THF (15 ml) and then concentrated and dried in a high vacuum. The foamy residue was dissolved in ethanol and heated to 70°C with stirring. Methyl iodide (0.73 ml) was then added dropwise. After three hours, the heating was stopped and the batch was allowed to stand overnight. After concentration, it was taken up using water and EA, and the EA phase was separated

20 off, dried with magnesium sulfate, filtered and concentrated. The residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined, the acetonitrile was stripped off, the residue was adjusted to pH 10 with potassium carbonate solution, extracted three times with EA and then the combined phases were dried, filtered and concentrated.

25 The residue was taken up using 2 N HCl and freeze-dried. 55 mg of the title compound were obtained.

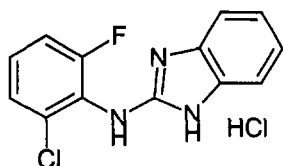
LCMS- R_t : 3.83 min; MS (CI^+ , $M+H^+$): 314.1

Example 6: (2,6-Dichlorophenyl)-(4-methyl-1H-benzimidazol-2-yl)amine trifluoroacetate



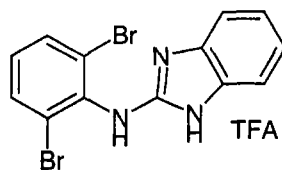
2,6-Dichlorophenyl isothiocyanate (0.15 g) and 2,3-diaminotoluene (0.09 g) were dissolved in THF (15 ml), the solution was stirred at RT for 4 h and then treated with N,N'-dicyclohexylcarbodiimide (0.23 g) and the mixture was boiled under reflux for 6 h. After allowing to stand overnight, the reaction mixture was concentrated, treated with acetonitrile/water (80:20), the undissolved material was filtered off and the solution was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The product-containing fractions were combined and brought to dryness. Crystallization from EA/ether/heptane yielded 85 mg of the title compound. LCMS-R_t: 3.81 min; MS (ES⁺, M+H⁺): 292.0

Example 7: (1H-Benzimidazol-2-yl)-(2-chloro-6-fluorophenyl)amine hydrochloride



2-Chloro-6-fluoroaniline (0.48 g) and 2-chlorobenzimidazole (0.5 g) were mixed in a flask and then kept at 170°C for 30 min. After cooling, the residue was dissolved out of the flask at boiling heat using 1 N HCl and 10% ethanol. The material dissolved out was then stirred at RT for 30 min, then the insoluble material was filtered off with suction and the filtrate was evaporated. The residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined, the acetonitrile was stripped off, the residue was adjusted to pH 10 with potassium carbonate solution, extracted three times with EA and then the combined phases were dried, filtered and concentrated. The residue was taken up using HCl/water and freeze-dried. 27 mg of the title compound were obtained. LCMS-R_t: 3.45 min; MS (ES⁺, M+H⁺): 262.0

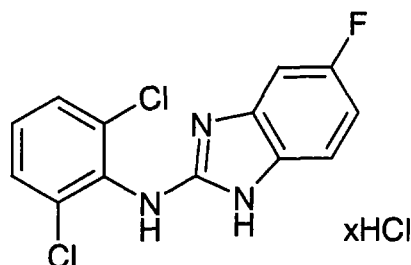
Example 8: (1H-Benzimidazol-2-yl)-(2,6-dibromophenyl)amine trifluoroacetate



2,6-Dibromaniline (0.5 g) was dissolved in absolute dioxane (5 ml), trimethylsilyl chloride (0.22 g) was added dropwise through a septum and the mixture was then stirred at RT for 2 h. 2-Chlorobenzimidazole (0.3 g) dissolved in dioxane was then added and the mixture was boiled under reflux. After 4 h, it was cooled, the dioxane was stripped off and the residue was heated at 190°C for 10 min. After cooling, the residue was dissolved out of the flask using 1 N HCl at boiling heat. The insoluble material was then filtered off and the filtrate was evaporated. The residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined and freeze-dried. 2.4 mg of the title compound were obtained.

LCMS- R_t : 3.74 min; MS (ES⁺, M+H⁺): 369.2

Example 9: 2-(2,6-Dichlorophenylamino)-5-fluorobenzimidazole hydrochloride



a) 1-(2-Amino-5-fluorophenyl)-3-(2,6-dichlorophenyl)thiourea

A mixture of 4.37 g (0.0346 mol) of 4-fluoro-1,2-diaminobenzene and 7.07 g (0.0346 mol) of 2,6-dichlorophenyl isothiocyanate in 150 ml of ethyl acetate is boiled under reflux for 3 hours. After distilling off the solvent, the residue is dissolved in methanol, treated with activated carbon, 2/3 of the solvent volume is distilled off and the thiourea is allowed to crystallize in an ice bath for a number of hours, 8.9 g of the desired product being obtained. Colorless crystals, 1st m.p. 175-178°C; 2nd m.p.

294-296°C. MS (ES⁺, M+ H⁺): 329.9

b) 2-(2,6-Dichlorophenylamino)-5-fluorobenzimidazole hydrochloride

1-(2-Amino-5-fluorophenyl)-3-(2,6-dichlorophenyl)-thiourea is dissolved in ethanol and treated with 8 equivalents of methyl iodide. The mixture is heated to reflux for 6 h. The solvent is distilled off, the residue is treated with water, then the mixture is

5 rendered weakly alkaline by addition of saturated aqueous sodium hydrogencarbonate solution and extracted. After distilling off the solvent, the residue is purified by column chromatography on silica gel using a mixture of methylene chloride and methanol (10:1). After distilling off the solvent under reduced pressure, the residue is dissolved using ethyl acetate, and the solution is treated with excess
10 ethereal hydrochloric acid. The mixture is stirred at room temperature for approximately 30 minutes, and the crystalline substance is filtered off and recrystallized from a mixture of ethyl acetate and ethanol. Colorless crystalline product, m.p.: 294-296 °C; MS: (Cl⁺, M⁺ H⁺), 296

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Example 10: 2-(2,6-Dichlorophenylamino)-4-fluorobenzimidazole hydrochloride

a) 3-Fluoro-2-nitro-phenylhydrazine

A mixture of 0.01 M 2,6-difluoronitrobenzene and 0.01 M hydrazine hydrate (99%
20 strength) in 30 ml of tetrahydrofuran is stirred overnight at room temperature (exothermic reaction) and the residue is brought to crystallization after distilling off the solvent by treating with diisopropyl ether. Crystalline substance, m.p. 93-95°C. MS (Cl⁺, M⁺ H⁺), 172.1

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b) 2,3-Diaminofluorobenzene

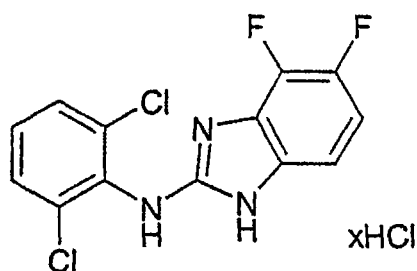
is obtained by hydrogenation of 0.0038 mol of 3-fluoro-2-nitrophenylhydrazine in 50 ml of methanol using palladium on carbon (10% strength) as a catalyst until the absorption of hydrogen has ended. After filtration, 2,3-diaminofluorobenzene is
30 obtained as a yellow oily substance.

MS (Cl⁺, M⁺ H⁺), 127.2

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distilling off the phosphorus oxychloride under reduced pressure, the oily residue is treated with water, slow crystallization taking place. The crystals are filtered off and chromatographed on silica gel using a mixture of 10 parts of dichloromethane and 1 part of methanol. After distilling off the solvent, the residue is dissolved in ethyl acetate and rendered strongly acidic using a saturated solution of hydrogen chloride gas in diethyl ether. The crystalline precipitate is filtered off. Colorless to slightly yellowish crystals. M.p. 255-288°C. MS (Cl^+ , M^+ H^+): 312.2

- 10 Example 12: 2-(2,6-Dichlorophenylamino)-4,5-difluorobenzimidazole hydrochloride
SO100308, 32902-001-15834



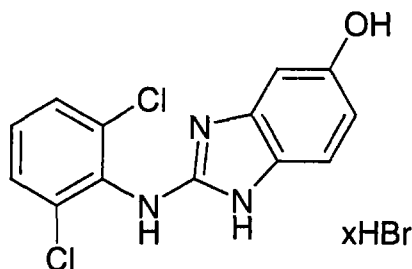
- 15 a) 1-(2-Amino-5,6-difluorophenyl)-3-(2,6-dichlorophenyl)thiourea
is obtained by boiling a mixture of 0.01 M 1,2-diamino-3,4-difluorobenzene with 0.01 M 2,6-dichlorophenyl isothiocyanate in 50 ml of ethyl acetate for 4 hours. After distilling off the solvent, the thiourea is brought to crystallization under diisopropyl ether. Crystalline solid. M.p. >310°C.

20 MS (Cl^+ , M^+ H^+): 348.0

- b) 2-(2,6-Dichlorophenylamino)-4,5-difluorobenzimidazole hydrochloride
is obtained analogously to the procedure described in example 9.b) from 3.2 g of 1-(2-amino-5,6-difluorophenyl)-3-(2,6-dichlorophenyl)thiourea and 10.6 g of methyl iodide.

25 Crystalline solid, m.p. 228-230°C. MS (Cl^+ , M^+ H^+): 314.0

Example 13: 2-(2,6-Dichlorophenylamino)-5-hydroxybenzimidazole hydrobromide



a) 1-(2-Amino-5-methoxyphenyl)-3-(2,6-dichlorophenyl)thiourea

5 is obtained analogously to the procedure described in example 12a) from 0.005 M 1,2-diamino-4-methoxybenzene and 0.005 M 2,6-dichlorophenyl isothiocyanate. Crystalline solid. M.p.: 164-166°C and fresh crystallization; decomposition point: 200°C.

MS (ES⁺, M⁺): 342.0

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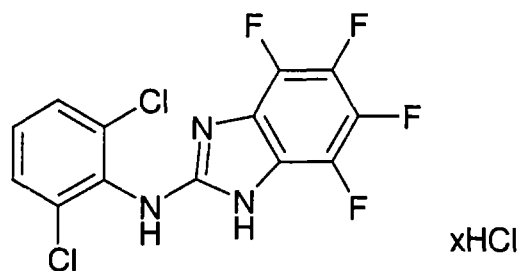
b) 2-(2,6-Dichlorophenylamino)-5-methoxybenzimidazole hydrochloride

is obtained analogously to the procedure described in example 9 by reaction of 0.0025 M 1-(2-amino-5-methoxyphenyl)-3-(2,6-dichlorophenyl)thiourea with 0.0205 M methyl iodide in 20 ml of ethanol. After distilling off the solvent, the residue
15 is dissolved in a little ethyl acetate, the solution is rendered strongly acidic using a saturated solution of hydrogen chloride gas in diethyl ether and the crystals are filtered off after a few hours. M.p. 172-174°C, MS (Cl⁺, M⁺ H⁺): 308.0

c) 2-(2,6-Dichlorophenylamino)-5-hydroxybenzimidazole hydrobromide

20 A mixture of 0.05 g of 2-(2,6-dichlorophenylamino)-5-methoxybenzimidazole hydrochloride, 0.5 ml of glacial acetic acid and 0.5 ml of hydrobromic acid (48% strength) are boiled under reflux for 3 hours and the solvent is then distilled off. The solid residue is brought to crystallization under a little ethyl acetate. 0.02 g of 2-(2,6-dichlorophenylamino)-5-hydroxybenzimidazole hydrobromide is obtained of m.p.
25 265-269°C, MS (Cl⁺, M⁺ H⁺): 294.1

Example 14: 2-(2,6-Dichlorophenylamino)-4,5,6,7-tetrafluorobenzimidazole hydrochloride



a) 1-(2-Amino-3,4,5,6-tetrafluorophenyl)-3-(2,6-dichlorophenyl)thiourea

is obtained by boiling a mixture of 1 g of 1,2-diamino-3,4,5,6-tetrafluorobenzene with 1.13 g of 2,6-dichlorophenyl isothiocyanate in 30 ml of anhydrous tetrahydrofuran for 4 hours. After distilling off the solvent, the thiourea is brought to crystallization under diisopropyl ether and 1.88 g of 1-(2-amino-3,4,5,6-tetrafluorophenyl)-3-(2,6-dichlorophenyl)thiourea are obtained as a crystalline solid. M.p. >300°C. MS (ES+, M+ H⁺): 384.06

b) 2-(2,6-Dichlorophenylamino)-4,5,6,7-tetrafluorobenzimidazole hydrochloride is obtained analogously to the procedure described in example 9.b) from 1.5 g of 1-(2-amino-3,4,5,6-tetrafluorophenyl)-3-(2,6-dichlorophenyl)thiourea and 4.4 g of methyl iodide and subsequent column chromatography on silica gel using a mixture of 10 parts of ethyl acetate, 5 parts of n-heptane, 5 parts of dichloromethane, 5 parts of methanol and 1 part of aqueous concentrated ammonia. Crystalline solid, m.p. 220-222°C.

MS (Cl⁺, M+ H⁺): 350.2

Example 15: 2-(2,6-Dichlorophenylamino)-4,6-difluorobenzimidazole hydrochloride

a) 1,2-Diamino-3,5-difluorobenzene

is obtained by hydrogenation of 5 g of 2-amino-3,5-difluoronitrobenzene with 0.8 g of palladium catalyst on carbon at room temperature and normal pressure. After distilling off the solvent, a dark partially crystalline oil is obtained, which is used without further purification for the preparation of stage b).

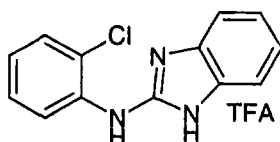
b) 1-(2-Amino-4,6-difluorophenyl)-3-(2,6-dichlorophenyl)thiourea

is obtained by allowing a mixture of 0.01 M 1,2-diamino-3,5-difluorobenzene with 0.01 M 2,6-dichlorophenyl isothiocyanate in 60 ml of anhydrous THF to stand over

the weekend at room temperature. After distilling off the solvent, the thiourea is brought to crystallization under diisopropyl ether. Crystalline solid. M.p. 310-314°C. MS (Cl⁺, M+ H⁺): 348.1

- 5 c) 2-(2,6-Dichlorophenylamino)-4,5-difluorobenzimidazole hydrochloride is obtained analogously to the procedure described in example 9.b) from 2 g of 1-(2-amino-4,6-difluorophenyl)-3-(2,6-dichlorophenyl)thiourea and 6.4 g of methyl iodide. Crystalline solid, m.p. 232-234°C. MS (Cl⁺, M+ H⁺): 314.2

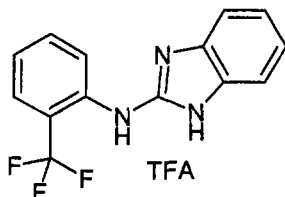
10 Example 16: (1H-Benzimidazol-2-yl)-(2-chlorophenyl)amine trifluoroacetate



- 2-Chloraniline (0.5 g) and 2-chlorobenzimidazole (0.6 g) were mixed in a flask and then kept at 225°C for 2 h. After cooling, the residue was dissolved out of the flask at boiling heat using 1 N HCl, the insoluble material was filtered off with suction, and the filtrate was adjusted to pH 9-10 using potassium carbonate and concentrated. The residue was treated with hot methanol, the insoluble material was filtered off, the mother liquor was treated with ether and the precipitate was filtered off again. The mother liquor was concentrated and the residue was crystallized again from methanol/ether. After filtering off the crystals with suction, the mother liquor was concentrated and the residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined and freeze-dried. 100 mg of the title compound were obtained.

LCMS-R_t: 3.16 min; MS (Cl⁺, M+H⁺): 244.0

25 Example 17: (1H-Benzimidazol-2-yl)-(2-trifluoromethylphenyl)amine trifluoroacetate

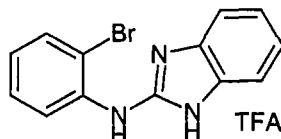


2-Aminobenzotrifluoride (0.5 g) and 2-chlorobenzimidazole (0.47 g) were mixed in a flask and then kept at 225°C for 2 h. After cooling, the residue was dissolved out of

the flask at boiling heat using 1 N HCl and the insoluble matter was filtered off with suction after cooling. The filtrate was concentrated and the residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined and freeze-dried. 52 mg of the title compound were obtained.

LCMS- R_t : 3.65 min; MS (Cl^+ , $M+H^+$): 278.1

Example 18: (1H-Benzimidazol-2-yl)-(2-bromophenyl)amine trifluoroacetate

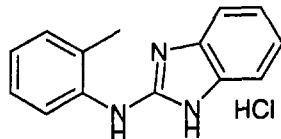


2-Bromoaniline (0.5 g) and 2-chlorobenzimidazole (0.44 g) were reacted according to example 17.

117 mg of the title compound were obtained.

LCMS- R_t : 3.55 min; MS (ES^+ , $M+H^+$): 288.0

Example 19: (1H-Benzimidazol-2-yl)-o-tolylamine hydrochloride



2-Methylaniline (0.5 g) and 2-chlorobenzimidazole (0.71 g) were mixed in a flask and then kept at 250°C for 2 h. After cooling, the residue was dissolved out of the flask at boiling heat using 1 N HCl, then the insoluble material was filtered off with suction and the filtrate was evaporated. The residue was purified by means of preparative HPLC on RP-18 using acetonitrile/water (0.05% TFA). The clean fractions were combined, the acetonitrile was stripped off, the residue was rendered alkaline using potassium carbonate solution, extracted three times with EA and the combined phases were then dried, filtered and concentrated. The residue was taken up using 2 N HCl and the solution was freeze-dried. 110 mg of the title compound were obtained.

LCMS- R_t : 3.54 min; MS (Cl^+ , $M+H^+$): 224.1

Pharmacological data:

Test description:

- 5 In this test, the recovery of the intracellular pH (pH_i) after an acidification was determined which commences with functional NHE even under bicarbonate-free conditions. For this, the pH_i was determined using the pH-sensitive fluorescent dye BCECF (Calbiochem, the precursor BCECF-AM is employed). The cells were first loaded with BCECF. The BCECF fluorescence was determined in a "Ratio
- 10 Fluorescence Spectrometer" (Photon Technology International, South Brunswick, N.J., USA) at excitation wavelengths of 505 and 440 nm and an emission wavelength of 535 nm and converted into the pH_i by means of calibration curves. The cells were incubated in NH_4Cl buffer (pH 7.4) even in the case of BCECF loading (NH_4Cl buffer: 115 mM NaCl, 20 mM NH_4Cl , 5 mM KCl, 1 mM CaCl_2 , 1 mM
- 15 MgSO_4 , 20 mM Hepes, 5 mM glucose, 1 mg/ml of BSA; a pH of 7.4 is set using 1 M NaOH). The intracellular acidification was induced by addition of 975 μl of an NH_4Cl -free buffer (see below) to 25 μl aliquots of the cells incubated in NH_4Cl buffer. The subsequent rate of pH recovery was recorded for two minutes in the case of NHE1, for five minutes in the case of NHE2 and for three minutes in the case of NHE3. For
- 20 the calculation of the inhibitory potency of the substances tested, the cells were first investigated in buffers in which a complete pH recovery or no pH recovery at all took place. For the complete pH recovery (100%), the cells were incubated in Na^+ -containing buffer (133.8 mM NaCl, 4.7 mM KCl, 1.25 mM CaCl_2 , 1.25 mM MgCl_2 , 0.97 mM Na_2HPO_4 , 0.23 mM Na_2HPO_4 , 5 mM Hepes, 5 mM glucose, a pH of 7.0 is
- 25 set using 1 M NaOH). For the determination of the 0% value, the cells were incubated in an Na^+ -free buffer (133.8 mM choline chloride, 4.7 mM KCl, 1.25 mM CaCl_2 , 1.25 mM MgCl_2 , 0.97 mM K_2HPO_4 , 0.23 mM KH_2PO_4 , 5 mM Hepes, 5 mM glucose, a pH of 7.0 is set using 1 M NaOH). The substances to be tested were applied in the Na^+ -containing buffer. The recovery of the intracellular pH at each
- 30 tested concentration of a substance was expressed in percent of the maximum recovery. The IC value of the respective substance for the individual NHE subtypes

was calculated from the percentage values of the pH recovery by means of the program Sigma-Plot.

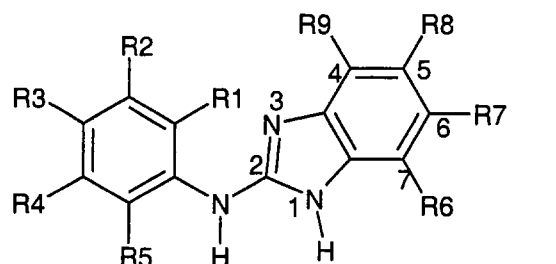
Results:

5

Example	IC ₅₀ [μ M], (rNHE3)
1	0.53
2	0.47
3	0.64
4	0.49
5	0.78
6	0.39
7	0.52
8	0.65
9	1.0
10	3.2
11	0.83
12	2.9
13	1.1
14	5.6
15	1.6
16	0.63
17	3.5
18	1.2
19	3.5

Patent claims

1. A substituted benzimidazole of the formula I



5 in which:

R1 and R5

independently of one another are F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by
fluorine,

or

R1 and R5

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or partially or completely substituted by
fluorine,

or

R1 and R5

are OH, O-alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by
fluorine,

or

R1 and R5

are OCOR₁₀, NR₁₁R₁₂, COR₁₃, COOH, COOR₁₄, CONR₁₁R₁₂, -(O)_n-
SO_mR₁₅,

n is zero or 1;

m is zero, 1 or 2;

or

R1 and R5

are O-phenyl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, Br, I, alkyl having 1 to 4 carbon atoms, OH, O-alkyl having 1 to 4 carbon atoms, NR₁₆R₁₇, CN or (C₁-C₄)-alkylsulfonyl,

5 which is unsubstituted or partially or wholly fluorinated,
R₁₆ and R₁₇

are H or alkyl having 1 to 4 carbon atoms,

where the alkyl groups are unsubstituted or partially
or wholly fluorinated,

10 R₁₀ is H or alkyl having 1 to 4 carbon atoms,
 which is unsubstituted or partially or completely substituted
 by fluorine,

R₁₁ and R₁₂

15 independently of one another are H, alkyl having 1 to 4 carbon
atoms, which may be partially or completely fluorinated and any
desired CH₂ group may be replaced by O or NR₁₈

or R₁₁ and R₁₂

together are a 5-, 6- or 7-membered ring;

or R₁₁ and R₁₂

20 are COR₁₉ or SO₂R₂₀;

R₁₈, R₁₉ and R₂₀

independently of one another are H or alkyl having 1 to 4
carbon atoms,

25 which is unsubstituted or partially or completely
substituted by fluorine;

R₁₃ and R₁₄

are alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted
by fluorine;

30 R₁₅

is alkyl or O-alkyl having 1 to 4 carbon atoms,

where the alkyl groups are unsubstituted or partially or
wholly fluorinated,

or

R15 is OH or NR₂₁R₂₂;

R₂₁ and R₂₂

independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine, in which any desired CH₂ group can be replaced by O or NR₂₃;

R₂₃

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

or

R₂₁ and R₂₂

together form a 5-, 6- or 7-membered ring;

but R₁ and R₅ must not simultaneously be Cl or CH₃;

R₂, R₃ and R₄

are H or one of the radicals R₂, R₃ or R₄ may be F;

R₆, R₇, R₈ and R₉

independently of one another are H, F, Cl, Br, I, CN, alkyl or O-alkyl having 1 to 4 carbon atoms,

which are unsubstituted or wholly or completely substituted by fluorine,

or R₆, R₇, R₈ and R₉

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,

or R₆, R₇, R₈ and R₉

are OH, OCOR₂₄ or NR₂₅R₂₆;

R₂₄

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine;

R₂₅ and R₂₆

independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,

or

R25 and R26

are COR27;

or R25 and R26

together with the nitrogen atom to which they are bonded,

form a 5-, 6- or 7-membered ring, in which any desired CH₂

group can be replaced by O or NR18;

R27

is H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or wholly or completely

substituted by fluorine,

or its pharmaceutically tolerable salts or trifluoroacetates.

2. A compound of the formula I as claimed in claim 1, in which:

R1 and R5

independently of one another are F, Cl, Br, CN, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, cycloalkyl having 3 to 7 carbon atoms, O-alkyl having 1 to 4 carbon atoms, OH, OCF₃, OCH₂CF₃, OCF₂CF₃, OCOR10, NR11R12, COR13, COOH, COOR14, CONR11R12, -O_m-SO₂R15 or O-phenyl;

m is zero or 1;

R10

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃,

R11 and R12

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, where any desired CH₂ group may be replaced by O or NR18 and where R11 and R12, together with

the nitrogen to which they are bonded, may form a 5-, 6- or 7-membered ring,

or R11 and R12

are COR19 or SO₂R20;

5 R18, R19 and R20

independently of one another are H or alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃,

R13 and R14

are alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

10 R15

is alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, OH, O-alkyl, having 1 to 4 carbon atoms, OCF₃, OCH₂CF₃, OCF₂CF₃ or NR21R22;

R21 and R22

15 independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

or

R21 and R22, together with the nitrogen atom to which they are bonded, are -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂- or -(CH₂)₂-

20 NR30-(CH₂)₂;

R30

is H, CH₃ or CF₃;

but R1 and R5 must not simultaneously be Cl or CH₃,

R2, R3 and R4

25 are H or one of the radicals R2, R3 or R4 may be F;

R6, R7, R8 and R9

independently of one another are H, F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, cycloalkyl having 3 to 7 carbon atoms, OH, O-alkyl having 1 to 4 carbon atoms, OCF₃, OCH₂CF₃,

30 OCF₂CF₃, OCOR24 or NR25R26;

R24

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or CF₂CF₃;

R25 and R26

independently of one another are H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃, CF₂CF₃, COR₂₇;

or

5 R25 and R26

together with the nitrogen to which they are bonded, are a 5-, 6- or 7-membered ring;

R27

is H, alkyl having 1 to 4 carbon atoms, CF₃, CH₂CF₃ or

10 CF₂CF₃

or its pharmaceutically tolerable salts or trifluoroacetates.

3. A compound of the formula I as claimed in claim 1, in which:

R1 and R5

15 independently of one another are F, Cl, Br, CN, methyl, ethyl, isopropyl, CF₃, cyclopropyl, OH, O-methyl, O-ethyl, O-isopropyl, OCF₃, O-acetyl, NH₂, NMe₂, NEt₂, N-pyrrolidino, N-piperidino, N-morpholino, N-(N'-methyl)-piperazino, NHSO₂Me, acetyl, COOH, COOR₁₄, CONR₁₁R₁₂, SO₂R₁₅ or O-phenyl,

20

R11 and R12 independently of one another are H, methyl or ethyl;

R14 is methyl or ethyl,

R15 is CH₃, CF₃, OH, OCH₃, OCF₃ or NR₂₁R₂₂;

R21 and R22

25 independently of one another are H or methyl;

but R1 and R5 are not simultaneously Cl or CH₃,

R2, R3 and R4

are H;

R6, R7, R8 and R9

30 independently of one another are H, F, Cl, CN, CH₃, C₂H₅, isopropyl, CF₃, cyclopropyl, OH, OCH₃, OCF₃, O-acetyl or NR₂₅R₂₆;

R25 and R26

independently of one another are H, methyl or acetyl;
or its pharmaceutically tolerable salts or trifluoroacetates.

4. A compound of the formula I as claimed in claim 1, in which:

5 R1 and R5

independently of one another are F, Cl, Br, CN, methyl, ethyl, isopropyl,
CF₃, cyclopropyl, OH, O-methyl, O-ethyl, O-isopropyl, OCF₃, O-acetyl, NH₂,
NMe₂, NEt₂, N-pyrrolidino, N-piperidino, N-morpholino, N-(N'-methyl)-
piperazino, NHSO₂Me, acetyl, COOH, COOR₁₄, CONR₁₁R₁₂, SO₂R₁₅ or
10 O-phenyl,

R₁₁ and R₁₂ independently of one another are H, methyl or ethyl;

R₁₄ is methyl or ethyl,

R₁₅ is CH₃, CF₃, OH, OCH₃, OCF₃ or NR₂₁R₂₂;

15 R₂₁ and R₂₂

independently of one another are H or methyl;

but R₁ and R₅ are not simultaneously Cl or CH₃,

R₂, R₃ and R₄

are H;

20 R₆ and R₉

independently of one another are H, F, Cl, CN, CH₃, CF₃, cyclopropyl, OH,
OCH₃, OCF₃, O-acetyl or NR₂₅R₂₆;

R₂₅ and R₂₆

independently of one another are H, methyl or acetyl;

25 R₇ and R₈

independently of one another are H, F or OH;

or its pharmaceutically tolerable salts or trifluoroacetates.

5. A compound of the formula I as claimed in claim 1, which is

30 (1H-benzimidazol-2-yl)-(2,6-dichlorophenyl)amine;

2-(2,6-dichlorophenylamino)-1H-benzimidazol-4-ol;

(1H-benzimidazol-2-yl)-(2,6-dimethylphenyl)amine;

(1H-benzimidazol-2-yl)-(2-chloro-6-methylphenyl)amine;

- (2,6-dichlorophenyl)-(5,6-difluoro-1H-benzimidazol-2-yl)amine;
 (2,6-dichlorophenyl)-(4-methyl-1H-benzimidazol-2-yl)amine;
 (1H-benzimidazol-2-yl)-(2-chloro-6-fluorophenyl)amine;
 (1H-benzimidazol-2-yl)-(2,6-dibromophenyl)amine;
 5 2-(2,6-dichlorophenylamino)-5-fluorobenzimidazole;
 2-(2,6-dichlorophenylamino)-4-fluorobenzimidazole;
 2-(2-trifluoromethyl-6-chlorophenylamino)benzimidazole;
 2-(2,6-dichlorophenylamino)-4,5-difluorobenzimidazole;
 2-(2,6-dichlorophenylamino)-5 hydroxybenzimidazole;
 10 2-(2,6-dichlorophenylamino)-4,5,6,7-tetrafluorobenzimidazole;
 2-(2,6-dichlorophenylamino)-4,6-difluorobenzimidazole;
 (1H-benzimidazol-2-yl)-(2-chlorophenyl)amine;
 (1H-benzimidazol-2-yl)-(2-trifluoromethylphenyl)amine;
 (1H-benzimidazol-2-yl)-(2-bromophenyl)amine; or
 15 (1H-benzimidazol-2-yl)-o-tolylamine;
 or their pharmaceutically tolerable salts or trifluoroacetates.

6. The use of compounds of the formula I, in which:

R1 and R5

- 20 independently of one another are H, F, Cl, Br, I, CN, alkyl having 1 to 4 carbon atoms,
 which is unsubstituted or partially or completely substituted by fluorine,

or

- 25 R1 and R5

are cycloalkyl having 3 to 7 carbon atoms,
 which is unsubstituted or partially or completely substituted by fluorine,

or

- 30 R1 and R5

are OH, O-alkyl having 1 to 4 carbon atoms,
 which is unsubstituted or partially or completely substituted by fluorine,

or

R1 and R5

are OCOR₁₀, NR₁₁R₁₂, COR₁₃, COOH, COOR₁₄, CONR₁₁R₁₂, -(O)_nSO_mR₁₅,

n is zero or 1;

5 m is zero, 1 or 2;

or

R1 and R5

are O-phenyl,

10 which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, Br, I, alkyl having 1 to 4 carbon atoms, OH, O-alkyl having 1 to 4 carbon atoms, NR₁₆R₁₇, CN or (C₁-C₄)-alkylsulfonyl,

which is unsubstituted or partially or wholly fluorinated,

R₁₆ and R₁₇

15 are H or alkyl having 1 to 4 carbon atoms,

where the alkyl groups are unsubstituted or partially or wholly fluorinated,

R₁₀ is H or alkyl having 1 to 4 carbon atoms,

20 which is unsubstituted or partially or completely substituted by fluorine,

R₁₁ and R₁₂

independently of one another are H, alkyl having 1 to 4 carbon atoms, which may be partially or completely fluorinated and any desired CH₂ group may be replaced by O or NR₁₈

25 or R₁₁ and R₁₂

together are a 5-, 6- or 7-membered ring;

or R₁₁ and R₁₂

are COR₁₉ or SO₂R₂₀;

R₁₈, R₁₉ and R₂₀

30 independently of one another are H or alkyl having 1 to 4 carbon atoms,

which is unsubstituted or partially or completely substituted by fluorine;

R13 and R14

are alkyl having 1 to 4 carbon atoms,
which is unsubstituted or partially or completely substituted
by fluorine;

5 R15

is alkyl or O-alkyl having 1 to 4 carbon atoms,
where the alkyl groups are unsubstituted or partially or
wholly fluorinated,

or

10 R15 is OH or NR²¹R²²;

R²¹ and R²²

independently of one another are H or alkyl having 1 to 4
carbon atoms,

15 which is unsubstituted or partially or completely substituted
by fluorine, in which any desired CH₂ group can be replaced
by O- or NR²³;

R²³

is H or alkyl having 1 to 4 carbon atoms,
which is unsubstituted or partially or
completely substituted by fluorine;

20

or

R²¹ and R²²

together form a 5-, 6- or 7-membered ring;

but R¹ and R⁵ must not simultaneously be Cl or CH₃;

25 R², R³ and R⁴

are H or F;

R⁶, R⁷, R⁸ and R⁹

independently of one another are H, F, Cl, Br, I, CN, alkyl or O-alkyl having 1
to 4 carbon atoms,

30 which are unsubstituted or wholly or completely substituted by
fluorine,

or R⁶, R⁷, R⁸ and R⁹

are cycloalkyl having 3 to 7 carbon atoms,

which is unsubstituted or wholly or completely substituted by fluorine,
or R6, R7, R8 and R9

are OH, OCOR₂₄ or NR₂₅R₂₆;

R₂₄

5 is H or alkyl having 1 to 4 carbon atoms,
which is unsubstituted or wholly or completely substituted by fluorine;

R₂₅ and R₂₆

independently of one another are H or alkyl having 1 to 4 carbon
atoms,

10 which is unsubstituted or wholly or completely substituted by
fluorine,

or

R₂₅ and R₂₆

are COR₂₇;

15 or R₂₅ and R₂₆

together with the nitrogen atom to which they are bonded,
form a 5-, 6- or 7-membered ring, in which any desired CH₂
group can be replaced by O or NR₁₈;

R₂₇

20 Is H or alkyl having 1 to 4 carbon atoms,
which is unsubstituted or wholly or completely
substituted by fluorine,

or of their pharmaceutically tolerable salts,

for the production of a medicament for the treatment of diseases which are

25 influenced by inhibition of the Na⁺/H⁺ exchanger.

7. The use of a compound I as claimed in claim 6 for the production of a medicament
for the treatment or prophylaxis of disorders of the respiratory drive.

30 8. The use of a compound I as claimed in claim 6 for the production of a medicament
for the treatment or prophylaxis of respiratory disorders, in particular sleep-related
respiratory disorders such as sleep apneas.

9. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of snoring.

10. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of acute and chronic kidney diseases, particularly acute kidney failure and chronic kidney failure.

11. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of disorders of intestinal function.

12. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of disorders of bile function.

13. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of the peripheral and central nervous system and of stroke.

14. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of peripheral organs and limbs.

15. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment of states of shock.

16. The use of a compound I as claimed in claim 6 for the production of a medicament for use in surgical operations and organ transplantations.

17. The use of a compound I as claimed in claim 6 for the production of a medicament for the preservation and storage of transplants for surgical measures.

18. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment of illnesses in which cell proliferation is a primary or secondary cause.

19. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment or prophylaxis of disorders of lipid metabolism.

5 20. The use of a compound I as claimed in claim 6 for the production of a medicament for the treatment of attack by ectoparasites in human and veterinary medicine.

21. A medicament comprising a compound of formula I as claimed in claim 1.