

Description

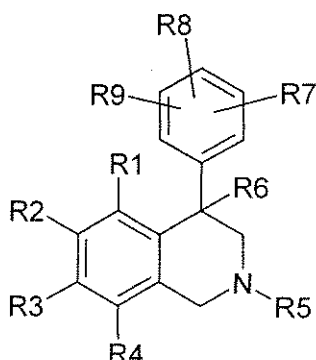
Substituted 4-phenyltetrahydroisoquinolines, method for production thereof, the use of the same as medicaments, and medicament containing such compounds

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The invention relates to compounds of the substituted 4-phenyltetrahydroisoquinoline type. Medicaments which comprise compounds of this type are useful in the prevention or treatment of various disorders. For instance, the compounds can be used, among other uses, in the event of renal disorders such as acute or chronic renal failure, in the event of disorders of biliary function, in the event of respiratory disorders such as snoring or sleep apneas or in the event of stroke.

10

The invention relates to compounds of the formula I



I

15 where:

R1, R2, R3 and R4

are each independently H, F, Cl, Br, I, CN, NO₂, OH, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, O-alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, O_k-(CH₂)_l-phenyl, heteroaryl having 1, 2, 3 or 4 nitrogen atoms or 1 oxygen atom or 1 sulfur atom, O_n-SO_j-R10, NR14R15, CONR16R17, COOR18 or OCOR18;

k is 0 or 1;

l is 0, 1, 2, 3 or 4;

25

h is 0 or 1;

j is 0, 1 or 2;

R10 is alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, OH, O-alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated or NR11R12;

R11 and R12

are each independently hydrogen, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be

fluorinated and one or more CH₂ groups may be replaced by O, NR13, CO or CS,

R13 is H or alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated,

or

R11 and R12

together with the nitrogen atom which bonds them together may form a 5- or 6-membered ring;

R14 and R15

are each independently H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated and one or more CH₂ groups may be replaced by O, CO, CS or NR19,

or

R14 and R15

together with the nitrogen atom which bonds them together may form a 5- or 6-membered ring;

R16 and R17

are each independently H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated and one or more CH₂ groups may be replaced by O, CO, CS or NR19,

or

R16 and R17

together with the nitrogen atom which bonds them together may form a 5- or 6-membered ring;

R19 is H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

5 R18 is H or alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

R5 is H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, COR20 or SO₂R20;

10 R20 is H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R6 is H, OH, F, Cl, Br, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, O-alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, or O-acyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

R7, R8 and R9

are each independently H, F, Cl, Br, I, OH, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, O-alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, O_v-SO_w-R47, COR47, COOR60, NR51R52 or a -L-G group;

v is 0 or 1;

w is 2 or 3;

25 R47 is H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated or NR48R49;

R48 and R49

are each independently H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated and one or more CH₂ groups may be replaced by O, CO, CS or NR50,

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R50 is H or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

or

R48 and R49

5 together with the nitrogen atom which bonds them together form a 5, 6, 7 or 8-membered ring;

R60 is H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

R51 and R52

10 are each independently H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated, acyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated and one or more CH₂ groups may be replaced by O or NR₅₃,

15 R53 is H or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

or

R51 and R52

20 together with the nitrogen atom which bonds them together form a 5, 6, 7 or 8-membered ring;

L is -CH₂-, -O-, -NR₃₀-, -OCO-, -NR₃₀CO-, -NR₃₀CS-, -NR₃₀SO₂-, -CONR₃₀-, -COO-, -CSNR₃₀-, -SO₂NR₃₀-, -NR₃₀CONR₃₁-, -NR₃₀COO-, -NR₃₀CSNR₃₁- or -NR₃₀SO₂NR₃₁-;

R30 and R31

25 are each independently H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated or cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

30 G is a C_a(OR₃₂)_xH_{2a+1-x} group where one or more CH₂ groups may be replaced by O or NR₃₃,

$C_b(OR_{32})_yH_{2b-1-y}$ where one or more CH_2 groups may be replaced by O or NR_{33} , C_cH_{2c+1} where two or more CH_2 groups are replaced by O or NR_{33} ,

$-(CH_2)_z-COOR_{34}$, $-(CH_2)_z-SO_3R_{34}$, $-(CH_2)_z-N^+R_{35}R_{36}R_{37}$

5 where one or more hydrogen atoms of the $-(CH_2)_z$ units may be replaced by OR_{32} groups, $-CR_{38}R_{39}-COOR_{40}$ or -

$CR_{38}R_{39}NR_{41}R_{42}$,

a is 2, 3, 4, 5, 6, 7 or 8;

x is 2, 3, 4, 5, 6, 7 or 8;

10 R_{32} is H, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated or acyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

15 R_{33} is H or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

b is 3, 4, 5, 6 or 7;

y is 2, 3, 4, 5, 6 or 7;

c is 3, 4, 5, 6, 7 or 8;

z is 0, 1, 2, 3 or 4;

20 R_{34} , R_{35} , R_{36} and R_{37}

are each independently H or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

R_{38} is $-(CH_2)_n-Y$;

25 n is 0, 1, 2, 3 or 4;

Y is H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated and one or more CH_2 groups may be replaced by O, S or NR_{43} , or is $-COOR_{44}$, $-CONR_{45}R_{46}$, $-NHC(NH)NH_2$,

30 phenyl or heteroaryl, and the phenyl and heteroaryl radicals may be substituted by up to three

substituents selected from the group of CH₃, CF₃,

OH, OCH₃ and NH₂;

R43, R44, R45 and R46

are each independently H or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

R39 is H or alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

R40 is H or alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

R41 and R42

are each independently H, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated or acyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms of which some or all may be fluorinated;

in which at least one of the R7, R8 or R9 radicals has to be defined by the –L-G group, and also its pharmaceutically acceptable salts and trifluoroacetates.

20 Preference is given to compounds of the formula I where R1, R2, R3 and R4,

are each independently H, F, Cl, Br, I, CN, NO₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated, O-alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, O-phenyl, SO₂R10, NR14R15, CONR16R17, COOR18 or OCOR18;

R10 is alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, OH or NR11R12;

R11 and R12

are each independently hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be

fluorinated, or acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated,

or

R11 and R12

5 together with the nitrogen atom which bonds them together form a 5- or 6-membered ring, from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholiny;

R14 and R15

10 are each independently H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated or acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated,

or

R14 and R15

15 together with the nitrogen atom which bonds them together form a 5- or 6-membered ring, from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholiny;

R16 and R17

20 are each independently H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated,

or

R16 and R17

25 together with the nitrogen atom which bonds them together form a 5- or 6-membered ring, from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholiny;

R18 is H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R5 is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, or cycloalkyl having 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

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R6 is H, OH, F, Cl, Br, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5 or 6 carbon atoms of which some or

all may be fluorinated, O-alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, or O-acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R7, R8 and R9

5 are each independently H, F, Cl, Br, I, OH, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, cycloalkyl having 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated, O-alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, O_v-SO_w-R47, COR47, COOR60, NR51R52 or a -L-G group;

10 v is 0 or 1;

w is 2 or 3;

R47 is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, or NR48R49;

R48 and R49

15 are each independently H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated,

or

20 R48 and R49

together with the nitrogen atom which bonds them together form a 5- or 6-membered ring, from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholinyl;

25 R60 is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R51 and R52

30 are each independently H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated,

or

R51 and R52

together with the nitrogen atom which bonds them together form a 5- or 6-membered ring, from the group of 1-pyrrolyl, 1-piperidinyl, 1-piperazinyl, 1-N-methylpiperazinyl and 4-morpholinyl;

L is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NR}_{30}-$, $-\text{OCO}-$, $-\text{NR}_{30}\text{CO}-$, $-\text{NR}_{30}\text{CS}-$, $-\text{NR}_{30}\text{SO}_2-$, $-\text{CONR}_{30}-$, $-\text{COO}-$, $-\text{CSNR}_{30}-$, $-\text{SO}_2\text{NR}_{30}-$, $-\text{NR}_{30}\text{CONR}_{31}-$, $-\text{NR}_{30}\text{COO}-$, $-\text{NR}_{30}\text{CSNR}_{31}-$ or $-\text{NR}_{30}\text{SO}_2\text{NR}_{31}-$;

where R_{30} and R_{31}

are each independently H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated or cycloalkyl having 3, 4, 5 or 6 carbon atoms of which some or all may be fluorinated;

G is a $\text{C}_a(\text{OR}_{32})_x\text{H}_{2a+1-x}$ group where one or more CH_2 groups may be replaced by O or NR_{33} ,

$\text{C}_b(\text{OR}_{32})_y\text{H}_{2b-1-y}$ where one or more CH_2 groups may be replaced by O or NR_{33} , $\text{C}_c\text{H}_{2c+1}$ where two or more CH_2 groups are replaced by O or NR_{33} ,

$-(\text{CH}_2)_z-\text{COOR}_{34}$, $-(\text{CH}_2)_z-\text{SO}_3\text{R}_{34}$, $-(\text{CH}_2)_z-\text{N}^+\text{R}_{35}\text{R}_{36}\text{R}_{37}$

where one or more hydrogen atoms of the $-(\text{CH}_2)_z$ units may be replaced by OR_{32} groups, $-\text{CR}_{38}\text{R}_{39}-\text{COOR}_{40}$ or $-\text{CR}_{38}\text{R}_{39}\text{NR}_{41}\text{R}_{42}$;

a is 2, 3, 4, 5, 6, 7 or 8;

x is 2, 3, 4, 5, 6, 7 or 8;

R_{32} is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated or acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R_{33} is H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

b is 3, 4, 5, 6 or 7;

y is 2, 3, 4, 5, 6 or 7;

c is 3, 4, 5, 6, 7 or 8;

z is 0, 1, 2, 3 or 4;

R34, R35, R36 and R37

are each independently H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R38 is $-(CH_2)_n-Y$;

n is 0, 1, 2, 3 or 4;

Y is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated and one or more CH_2 groups may be replaced by O, S or NR_{43} , or is $COOR_{44}$, $CONR_{45}R_{46}$, $NHC(NH)NH_2$, phenyl or heteroaryl, and the phenyl and heteroaryl radicals may be substituted by up to three substituents selected from the group of CH_3 , CF_3 , OH, OCH_3 and NH_2 ;

R43, R44, R45 and R46

are each independently H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R39 is H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R40 is H or alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

R41 and R42

are each independently H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated, or acyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated;

in which at least one of the R7, R8 or R9 radicals has to be defined by the $-L-G$ group, and also its pharmaceutically acceptable salts and trifluoroacetates.

Particular preference is given to compounds of the formula I where where:

R1, R2, R3 and R4,

are each independently H, F, Cl, Br, CN, NO₂, OH, CH₃, CH₂CH₃, CF₃,

CH₂CF₃, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, SO₂R₁₀, NR₁₄R₁₅,

5 CONR₁₆R₁₇, COOR₁₈ or OCOR₁₈,

R₁₀ is CH₃, CH₂CH₃, CF₃, CH₂CF₃, OH, NR₁₁R₁₂,

R₁₁ and R₁₂

are each independently H, CH₃, CH₂CH₃, CF₃,

CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or

10 COCH₂CF₃,

or

R₁₁ and R₁₂

together with the nitrogen atom which bonds them together

form a 5- or 6-membered ring from the group of 1-pyrrolyl,

15 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholinyl;

R₁₄ and R₁₅

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃,

COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃,

20 or

R₁₄ and R₁₅

together with the nitrogen atom which bonds them together form a

5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidiny, 1-

piperaziny, 1-N-methylpiperaziny and 4-morpholinyl;

25 R₁₆ and R₁₇

are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃,

or

R₁₆ and R₁₇

together with the nitrogen atom which bonds them together form a

30 5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholinyl;

R18 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R5 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R6 is H, OH, CH₃, CH₂CH₃, CF₃, CH₂CF₃, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, OCOCH₃, OCOCH₂CH₃, OCOCF₃ or OCOCH₂CF₃;

5 R7, R8 and R9

are each independently H, F, Cl, Br, I, OH, CH₃, CH₂CH₃, CF₃, CH₂CF₃,

OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, SO₂R47, SO₃R60, COR47, COOR60,

NR51R52 or a -L-G group;

R47 is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃ or NR48R49;

10 R48 and R49

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃,

COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃,

or

R48 and R49

15 together with the nitrogen atom which bonds them together form a 5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidinyll, 1-piperazinyll, 1-N-methylpiperazinyll and 4-morpholinyl;

R60 is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃;

20 R51 and R52

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃,

COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃,

or

R51 and R52

25 together with the nitrogen atom which bonds them together form a 5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidinyll, 1-piperazinyll, 1-N-methylpiperazinyll and 4-morpholinyl;

L is -CH₂-, -O-, -NR30-, -OCO-, -NR30CO-, -NR30CS-, -NR30SO₂-, -CONR30-, -COO-, -CSNR30-, -SO₂NR30-, -NR30CONR31-, -NR30COO-, -NR30CSNR31- or -NR30SO₂NR31-;

30

R30 and R31

are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

G is a C_a(OR32)_xH_{2a+1-x} group where one or more CH₂ groups may be replaced by O or NR33,

C_b(OR32)_yH_{2b-1-y} where one or more CH₂ groups may be replaced by O or NR33, C_cH_{2c+1} where two or more CH₂ groups are replaced by O or NR33,

-(CH₂)_z-COOR34, -(CH₂)_z-SO₃R34, -(CH₂)_z-N⁺R35R36R37

where 1 or 2 hydrogen atoms of the -(CH₂)_z units may be replaced by OR32 groups, -CR38R39-COOR40 or -CR38R39NR41R42;

a is 2, 3, 4, 5, 6, 7 or 8;

x is 2, 3, 4, 5, 6, 7 or 8;

R32 is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃;

R33 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

b is 3, 4, 5, 6 or 7;

y is 2, 3, 4, 5, 6 or 7;

c is 3, 4, 5, 6, 7 or 8;

z is 1 or 2;

R34, R35, R36 and R37

are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R38 is -(CH₂)_n-Y;

n is 0, 1, 2, 3 or 4;

Y is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated and one or more CH₂ groups may be replaced by O, S or NR43, or is COOR44, CONR45R46, NHC(NH)NH₂, phenyl or

heteroaryl, and the phenyl and heteroaryl radicals may be substituted by up to 3 substituents selected from the group of CH₃, CF₃, OH, OCH₃ or NH₂;

R43, R44, R45 and R46 are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R39 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R40 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R41 and R42 are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃;

in which at least one of the R7, R8 or R9 radicals has to be defined by the -L-G group, and also its pharmaceutically acceptable salts and trifluoroacetates.

In a first aspect, there are provided compounds of the formula I where R1, R2, R3 and R4, are each independently H, F, Cl, Br, CN, NO₂, OH, CH₃, CH₂CH₃, CF₃, CH₂CF₃, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, SO₂R10, NR14R15, CONR16R17, COOR18 or OCOR18;

R10 is CH₃, CH₂CH₃, CF₃, CH₂CF₃, OH or NR11R12;

R11 and R12 are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃;

R14 and R15 are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃;

R16 and R17 are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R18 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R5 is CH₃;

R6 is H;

R7, R8 and R9

are each independently H, F, Cl, Br, I, OH, CH₃, CH₂CH₃, CF₃, CH₂CF₃,
 5 OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, SO₂R₄₇, SO₃R₆₀, COR₄₇, COOR₆₀,
 NR₅₁R₅₂ or a -L-G group;

R₄₇ is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃ or NR₄₈R₄₉;

R₄₈ and R₄₉

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃,
 10 COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃,

or

R₄₈ and R₄₉

together with the nitrogen atom which bonds them together
 form a 5- or 6-membered ring from the group of 1-pyrrolyl,
 15 1-piperidinyl, 1-piperazinyl, 1-N-methylpiperazinyl and 4-
 morpholinyl;

R₆₀ is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃;

R₅₁ and R₅₂

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃,
 20 COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃

or

R₅₁ and R₅₂

together with the nitrogen atom which bonds them together form a
 5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidinyl, 1-
 25 piperazinyl, 1-N-methylpiperazinyl and 4-morpholinyl;

L is -CH₂-, -O-, -NR₃₀-, -OCO-, -NR₃₀CO-, -NR₃₀CS-, -NR₃₀SO₂-,
 -CONR₃₀-, -COO-, -CSNR₃₀-, -SO₂NR₃₀-, -NR₃₀CONR₃₁-,
 -NR₃₀COO-, -NR₃₀CSNR₃₁- or -NR₃₀SO₂NR₃₁;

R₃₀ and R₃₁

are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

G is a group C_a(OR₃₂)_xH_{2a+1-x} where one or more CH₂ groups may be replaced by O or NR₃₃,

5 C_b(OR₃₂)_yH_{2b-1-y} where one or more CH₂ groups may be replaced by O or NR₃₃, C_cH_{2c+1} where two or more CH₂ groups are replaced by O or NR₃₃,

10 -(CH₂)_z-COOR₃₄, -(CH₂)_z-SO₃R₃₄, -(CH₂)_z-N⁺R₃₅R₃₆R₃₇ where 1 or 2 hydrogen atoms of the -(CH₂)_z units may be replaced by OR₃₂ groups, -CR₃₈R₃₉-COOR₄₀ or -CR₃₈R₃₉NR₄₁R₄₂;

a is 2, 3, 4, 5, 6, 7 or 8;

x is 2, 3, 4, 5, 6, 7 or 8;

R₃₂ is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃;

15 R₃₃ is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

b is 3, 4, 5, 6 or 7;

y is 2, 3, 4, 5, 6 or 7;

c is 3, 4, 5, 6, 7 or 8;

z is 1 or 2;

20 R₃₄, R₃₅, R₃₆ and R₃₇

are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R₃₈ is -(CH₂)_n-Y;

n is 0, 1, 2, 3 or 4;

25 Y is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated and one or more CH₂ groups may be replaced by O, S or NR₄₃, or is COOR₄₄, CONR₄₅R₄₆, NHC(NH)NH₂, phenyl or heteroaryl, and the phenyl and heteroaryl radicals

may be substituted by up to 3 substituents selected from the group of CH₃, CF₃, OH, OCH₃ or NH₂;

R43, R44, R45 and R46

are each independently H, CH₃, CH₂CH₃,
CF₃ or CH₂CF₃,

R39 is H;

R40 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

R41 and R42

are each independently H, CH₃, CH₂CH₃, CF₃,
CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or
COCH₂CF₃;

in which at least one of the R7, R8 or R9 radicals has to be defined by the -L-G group, and also its pharmaceutically acceptable salts and trifluoroacetates.

In one embodiment, preference is given to compounds of the formula I in which R1 and R3 are described by H.

In a further embodiment, preference is given to compounds of the formula I in which R2 and R4 are described by Cl.

In one embodiment, preference is given to compounds of the formula I in which R5 is described by H, CH₃ or CF₃.

In another embodiment, preference is given to compounds of the formula I in which R6 is described by H, OH, CH₃, CF₃, OCH₃ or OCOCH₃, and preference is given to compounds in which R6 is described by H.

In one embodiment, preference is given to compounds of the formula I in which R7, R8 and R9 are each independently described by H, OH, CH₃, CF₃, OCH₃, SO₂R47,

SO₃R60, COR47, COOR60, NR51R52 or a -L-G group, where

R47 is H, CH₃ or NR₄₈R₄₉;

R₄₈ and R₄₉

are each independently H, CH₃ or COCH₃;

R₆₀ is H, CH₃;

5

R₅₁ and R₅₂

are each independently H, CH₃, CH₂CH₃ or COCH₃;

L is -NR₃₀CO-, -CONR₃₀- or -NR₃₀CONR₃₁-;

R₃₀ and R₃₁

are each H;

10

G is a group of the form C_a(OR₃₂)_xH_{2a+1-x}, C_b(OR₃₂)_yH_{2b-1-y} where one CH₂ group may be replaced by O, C_cH_{2c+1} where two or more CH₂ groups are replaced by O or NR₃₃, -(CH₂)₂-COOH, -(CH₂)₂-SO₃H, -(CH₂)₂-N⁺(CH₃)₃ where 1 or 2 hydrogen atoms of the -(CH₂)₂ units may be replaced by OH groups, -CR₃₈R₃₉-COOR₄₀ or -CR₃₈R₃₉NR₄₁R₄₂

15

a is 3, 4, 5 or 6;

x is 2, 3, 4 or 5;

R₃₂ is H;

b is 5 or 6;

20

y is 2, 3, 4 or 5;

c is 6, 7 or 8;

R₃₃ is H or CH₃;

R₃₈ is H, alkyl having 1, 2, 3 or 4 carbon atoms, CH₂OH,

CH₂SH, CH₂NH₂, CH(OH)CH₃, CH₂CH₂SCH₃,

25

CH₂CH₂CH₂NH₂, CH₂CH₂CH₂CH₂NH₂,

CH₂CH₂CH₂NHC(NH)NH₂, CH₂COOH,

CH₂CONH₂, CH₂CH₂COOR₄₄, CH₂CH₂CONH₂,

COOH, phenyl, 4-hydroxyphenyl, 4-imidazolyl or 3-indolyl;

30

R₃₉ is H;

R40 is H, CH₃ or CH₂CH₃;

R41 and R42

are each independently H, CH₃ or COCH₃;

R44 is H, CH₃ or CH₂CH₃;

5 in which at least one of the R7, R8 or R9 radicals has to be defined by the -L-G group.

In one embodiment, preference is given to compounds of the formula I in which one of the R7, R8 or R9 radicals is described by LG and the other R7, R8, R9 radicals by H, OH, CH₃, CF₃, OCH₃, SO₂R47, SO₃R60, COR47, COOR60 or NR51R52, in

10 particular by hydrogen or COOH; particular preference is given to compounds of the formula I, in which one of the R7, R8 or R9 radicals is described by LG and the other R7, R8, R9 radicals are each described by H.

In one embodiment, preference is given to compounds of the formula I in which two of
15 the R7, R8 or R9 radicals are each described by LG and one of the R7, R8 or R9 radicals by hydrogen.

Epecially preferred are compounds of the formula I selected from the group of
20 N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-pentahydroxyhexanamide,

N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-pentahydroxyhexanamide,

N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-pentahydroxyhexanamide,

25 N-[3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-pentahydroxyhexanamide,

N-[3-((R)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-pentahydroxyhexanamide,

30 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-hydroxymethylethyl)urea,

1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,

- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2,3,4,5,6-pentahydroxyhexyl)urea,
- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2,4,5-trihydroxy-6-hydroxymethyltetrahydropyran-3-yl)urea,
- 5 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-sulfo-2-ethyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(ethyl-2-trimethylammonium)}urea chloride,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-10 hydroxy-2-propyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2-butyl)}urea,
- 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2,3,4,5,6-pentahydroxyhexyl)benzamide,
- 15 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1-hydroxymethylethyl)benzamide,
- 2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
- 2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinic 20 acid,
- 2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamic acid,
- N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-[1-carboxy-5-guanidino-2-pentyl]urea,
- 25 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2-butyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2-propyl)}urea,
- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
- 30 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2,3,4,5,6-pentahydroxyhexyl)urea,

- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1-hydroxymethylethyl)isophthalamide,
 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,
- 5 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,
 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2,3,4,5,6-pentahydroxyhexyl)isophthalamide,
 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2,3,4,5,6-
- 10 pentahydroxyhexyl)isophthalamide,
 2-[3-(1-carboxy-2-hydroxyethylcarbamoyl)-5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
 N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
- 15 N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
 2-amino-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide,
 2-amino-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-
- 20 imidazol-4-yl)propionamide,
 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
- 25 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
 {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic
- 30 acid,
 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,

- ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
acetate,
- ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-
acetate,
- 5 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
acetate,
- ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-
acetate,
- 10 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
acetate,
- ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-
acetate,
- {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic
acid,
- 15 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic
acid,
- {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic
acid,
- {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic
20 acid,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic
acid,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic
acid,
- 25 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-
carbamate,
- 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-
carbamate,
- 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-
30 carbamate,
- and

2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-carbamate;

and their pharmaceutically acceptable salts and trifluoroacetates.

- 5 Very especially preferred are compounds of the formula I selected from the group of
N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-
2,3,4,5,6-pentahydroxyhexanamide,
N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-
2,3,4,5,6-pentahydroxyhexanamide,
- 10 N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-
2,3,4,5,6-pentahydroxyhexanamide,
N-[3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
N-[3-((R)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
15 (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-
hydroxymethylethyl)urea,
1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-
bishydroxymethylethyl)urea,
- 20 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-
((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea,
1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((4R,5S,6R)-
2,4,5-trihydroxy-6-hydroxymethyltetrahydropyran-3-yl)urea,
{N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-sulfo-2-
25 ethyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(ethyl-2-
trimethylammonium)}urea chloride,
{N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-
hydroxy-2S-propyl)}urea,
- 30 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-
aminocarboxy-2S-butyl)}urea,

- 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)benzamide,
 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1-hydroxymethylethyl)benzamide,
- 5 2-(S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
 2-(S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinic acid,
 2-(S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-
- 10 succinamic acid,
 N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-[1-carboxy-5-guanidino-2S-pentyl]urea,
 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R)-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea,
- 15 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(S)-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea,
 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R)-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea,
 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(S)-yl)phenyl]-N'-(1-
- 20 carboxy-3-hydroxy-2S-propyl)}urea,
 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R)-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(S)-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
- 25 1-[3-((R)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea,
 1-[3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea,
 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1-
- 30 hydroxymethylethyl)isophthalamide,
 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,

- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,
 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)isophthalamide,
 5 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)isophthalamide,
 (S)-2-[3-((S)-1-carboxy-2-hydroxyethylcarbamoyl)-5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
 (S)-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-
 10 guanidinopentanamide,
 (S)-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
 (S)-2-amino-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide,
 15 (S)-2-amino-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide,
 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-
 20 acetate,
 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
 {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
 25 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
 30 acetate,
 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,

- ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
acetate,
- ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-
acetate,
- 5 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
acetate,
- ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-
acetate,
- {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic
10 acid,
- {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic
acid,
- {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic
acid,
- 15 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic
acid,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic
acid,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic
20 acid,
- 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-
carbamate,
- 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-
carbamate,
- 25 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-
carbamate
- and
- 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-
carbamate;
- 30 and their pharmaceutically acceptable salts and trifluoroacetates.

The groups of the form $C_a(OR_{32})_xH_{2a+1-x}$ described under G may be either straight-chain or branched. This results in polyhydroxylated alkyl chains, as derived, for example, from monosaccharide building blocks, which are bonded to the phenyl radical via a linker unit L. Correspondingly, the formula $C_b(OR_{32})_yH_{2b-1-y}$ preferably describes polyhydroxylated, cyclic alkyl substituents. Exchange of a CH_2 unit for O results, for example, in the class of the pyranoside or furanoside carbohydrate building blocks, as realized in example 9. G may equally derive from the group of the amino acids, which are bonded via the amino acid amino or amino acid carboxyl function, in which case the amino or carbonyl function is included in the linker unit L. The amino acid side chains then occur in R38.

When the compounds of the formula I contain one or more centers of asymmetry, these may each independently have either the S or R configuration. The compounds may be present as optical isomers, as enantiomers, as diastereomers, as racemates or as mixtures in any ratios thereof.

The present invention includes all tautomeric forms of the compounds of the formula I.

Alkyl radicals may be straight-chain or branched. This also holds when they bear substituents or occur as substituents of other radicals, for example in fluoroalkyl radicals or alkoxy radicals. Examples of alkyl radicals are methyl, ethyl, n-propyl, isopropyl (= 1-methylethyl), n-butyl, isobutyl (= 2-methylpropyl), sec-butyl (= 1-methylpropyl), tert-butyl (= 1,1-dimethylethyl), n-pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, heptyl, octyl. Preferred alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-pentyl, n-hexyl. In the alkyl radicals, one or more, for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17, hydrogen atoms may be substituted by fluorine atoms. Examples of such fluoroalkyl radicals are trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, heptafluoroisopropyl. Substituted alkyl radicals may be substituted in any desired positions, for example by hydroxyl. In the alkyl radicals, one or more CH_2 groups may be replaced by O, NH or N-alkyl.

Alkenyl radicals may be straight-chain or branched. This also holds when they bear substituents, for example in fluoroalkenyl radicals. The alkenyl radicals may be unsaturated in different positions. Examples of alkenyl radicals are propenyl, butenyl, pentenyl, hexenyl or heptenyl. In alkenyl radicals, one or more, for example 1, 2, 3, 4, 5, 5, 6, 7, 8, 9, 10, 11, 12 or 13, hydrogen atoms may be substituted by fluorine atoms. Substituted alkenyl radicals may be substituted in any desired positions, for example by hydroxyl. In the alkenyl radicals, one or more CH₂ groups may be replaced by O, NH or N-alkyl.

- 10 Acyl radicals may be straight-chain or branched. This is also true when they bear substituents. Examples of acyl radicals are formyl, acetyl, propionyl or butyryl. In acyl radicals, one or more, for example 1, 2, 3, 4, 5, 6 or 7, hydrogen atoms may be substituted by fluorine atoms.
- 15 Examples of cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. In cycloalkyl radicals, one or more, for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, hydrogen atoms may be substituted by fluorine atoms. Substituted cycloalkyl radicals may be substituted in any desired positions, for example by hydroxyl. The cycloalkyl radicals may also be in branched form as alkylcycloalkyl or
- 20 cycloalkylalkyl, for example methylcyclohexyl or cyclohexylmethyl. In the cycloalkyl radicals, one or more CH₂ groups may be replaced by O, NH or N-alkyl.

- Phenyl radicals may be unsubstituted or singly or multiply, for example singly, doubly or triply, substituted by identical or different radicals. When a phenyl radical is
- 25 substituted, it preferably bears one or two identical or different substituents. This applies equally to substituted phenyl radicals in groups such as phenylalkyl, phenylcarbonyl, etc. Phenylalkyl radicals are, for example, benzyl, 1-phenylethyl or 2-phenylethyl. In monosubstituted phenyl radicals, the substituent may be in the 2-position, the 3-position or the 4-position. Disubstituted phenyl may be substituted in the
- 30 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl radicals, the substituents may be in the 2,3,4-position, 2,3,5-position, 2,4,5-position, 2,4,6-position, 2,3,6-position or 3,4,5-position.

Heteroaryl radicals are aromatic ring compounds in which one or more ring atoms are oxygen atoms, sulfur atoms or nitrogen atoms, for example 1, 2, 3 or 4 nitrogen atoms, 1 or 2 oxygen atoms, 1 or 2 sulfur atoms or are combinations of different heteroatoms.

5 The heteroaryl radicals may be bonded via all positions, for example via the 1-position, 2-position, 3-position, 4-position, 5-position, 6-position, 7-position or 8-position.

Heteroaryl radicals may be unsubstituted or singly or multiply, for example singly, doubly or triply, substituted by identical or different radicals. Heteroaryls are, for example, 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-,
 10 3-, 4- or 5-pyrazolyl, 1, 2, 3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-oxadiazol-2-yl or -5-yl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, 1-,
 15 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-indazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 3-, 5-, 6-, 7- or 8-quinoxaliny, 1-, 4-, 5-, 6-, 7- or 8-phthalazinyl. Also included are the corresponding N-oxides of these compounds, i.e., for example, 1-oxy-2-, 3- or 4-pyridyl. Preference is
 20 given to the 5- or 6-membered heterocycles, for example imidazolyl, pyrazolyl, pyrrolyl, triazolyl, tetrazolyl, thiazolyl and oxazolyl and pyridyl.

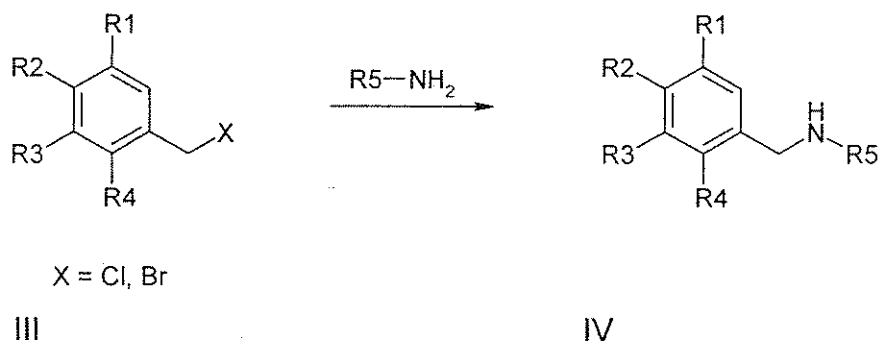
Also included as CH_2 units are the CH_3 groups which terminate an alkyl chain, which are interpreted in this context as $\text{CH}_2\text{-H}$ groups.

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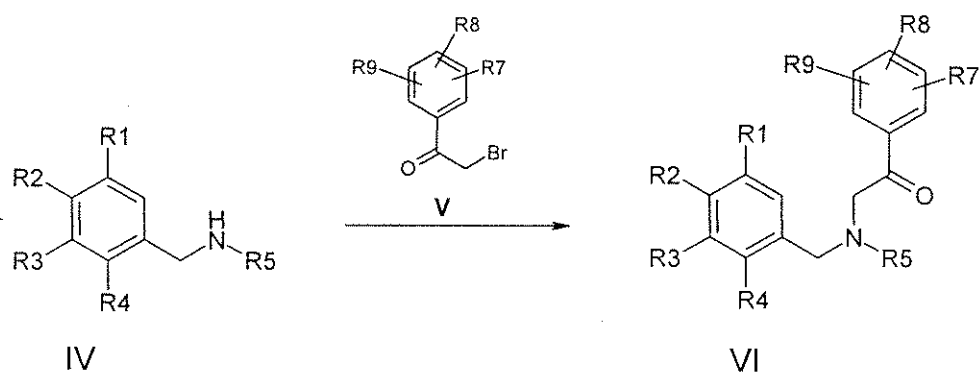
Also described are methods for preparing the compounds of the formula I.

The compounds of the formula I described here can be prepared starting from the benzylamine precursors IV. If not commercially obtainable, these can in turn be
 30 synthesized by standard methods known to those skilled in the art from the corresponding benzyl chlorides or bromides III and the corresponding amine.

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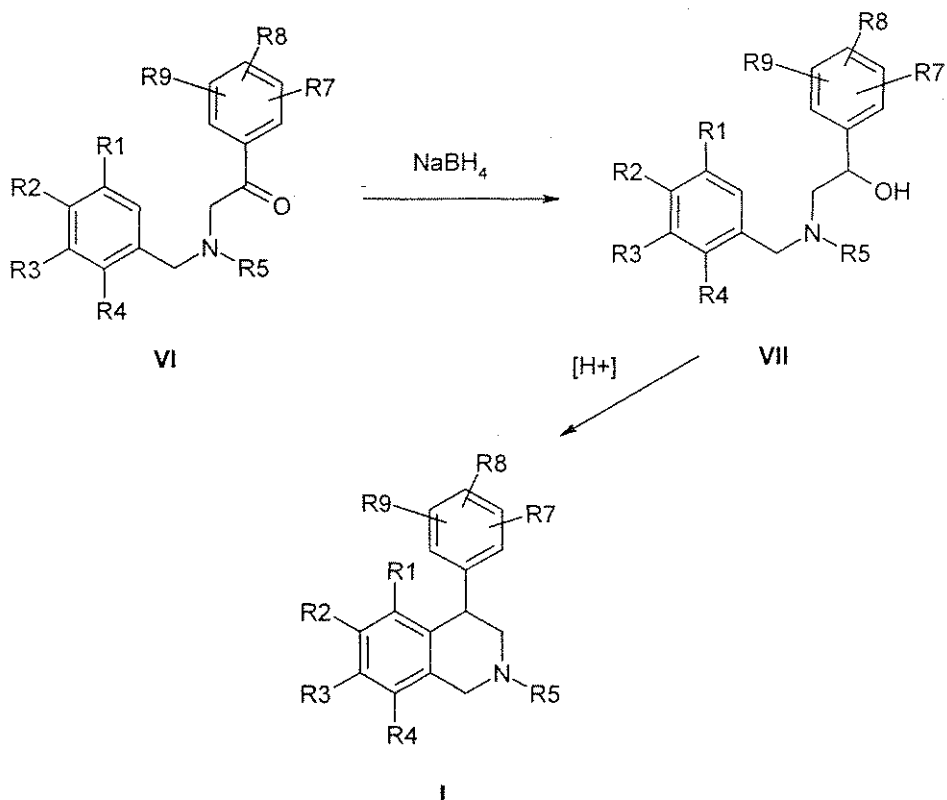
5 The benzylamines IV obtained in this way are alkylated in a manner known to those skilled in the art with the appropriately substituted alpha-bromoacetophenone compounds V.



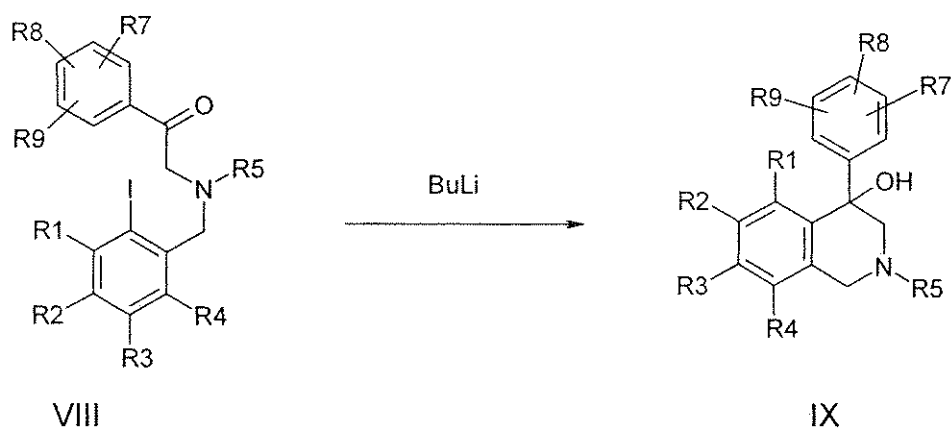
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The alpha-bromoacetophenone compounds V can be obtained in literature methods from the corresponding acetophenone precursors by bromination.

15 By reduction of the carbonyl groups in VI and subsequent acid-catalyzed cyclization of the resulting alcohols VII (cf. Tetrahedron Lett.; 1989, 30, 5837; Org. Prep. Proced. Int.; 1995, 27, 513) the desired tetrahydroisoquinolines I can be obtained by known methods.

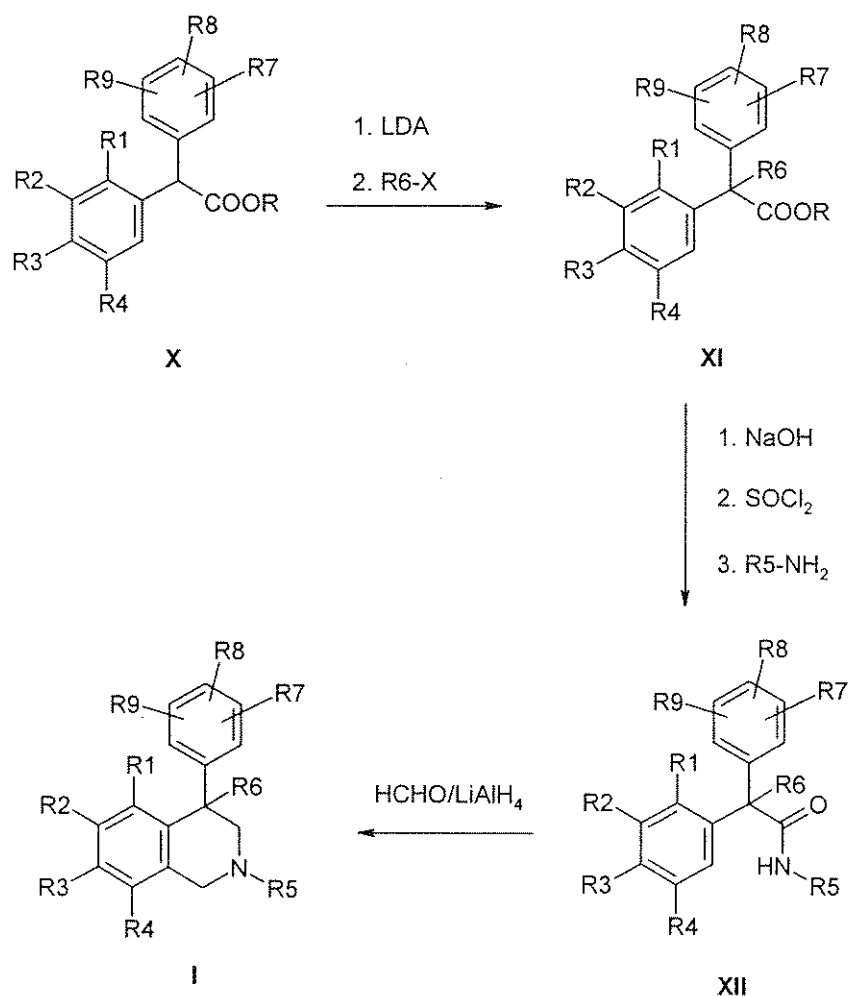


When R6 is not H, the desired compounds of the formula I can be prepared, for example, from the iodides VIII (cf. Chem. Pharm. Bull.; 1994, 42, 67) by halogen-metal exchange and subsequent nucleophilic attack of the intermediate organolithium species on the carbonyl group (cf. Chem. Pharm. Bull.; 1995, 43, 1543).



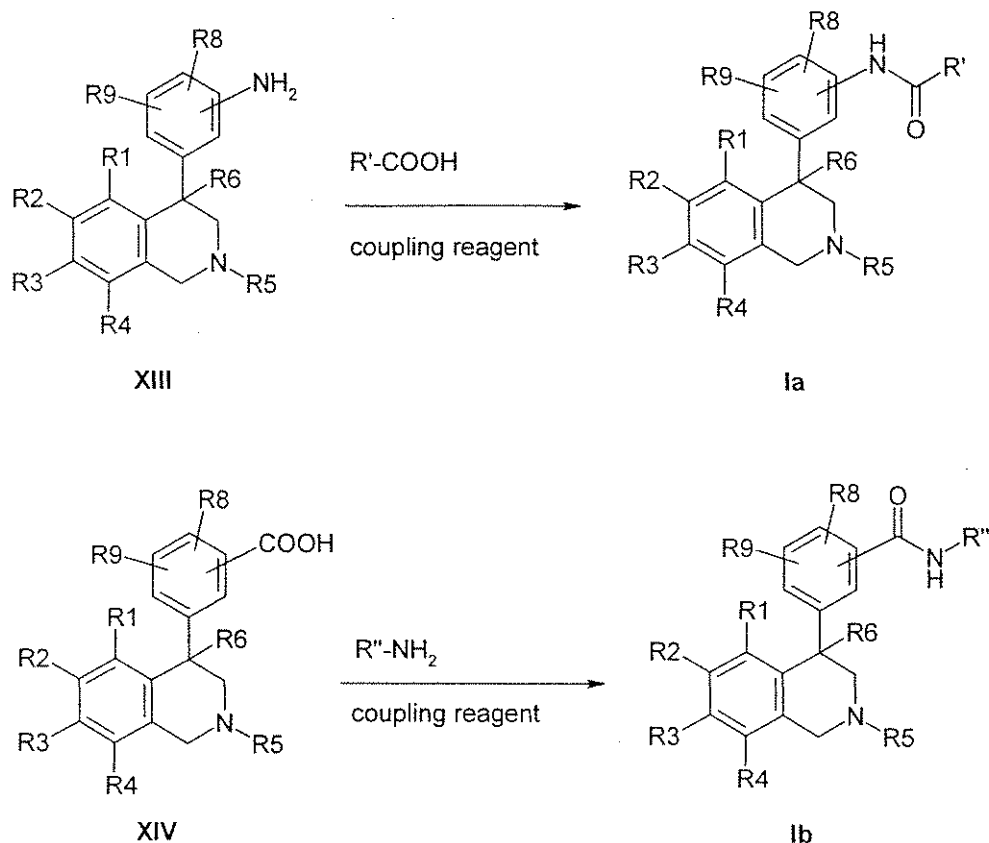
The tertiary alcohols IX synthesized in this way can be converted by known methods to further derivatives, for example the ethers or esters derived therefrom.

To prepare alkyl-branched analogs (I), the appropriate diphenylacetic esters X can be alkylated in the alpha-position with R6 by known methods. The desired products XI can be converted by standard methods to the corresponding amides XII which are converted to the desired tetrahydroisoquinolines I in a Pictet-Spengler-like reaction (cf. 5 Tetrahedron; 1987, 43, 439; Chem. Pharm. Bull.; 1985, 33, 340).



The bonding of the L-G substituents to the R7, R8 or R9 positions may, for example, be via an amide bond. In this case, the above-described synthetic routes ensure that at least one of the R7, R8 or R9 radicals is present as an NH₂ or COOH group. A polar radical can be bonded in a manner known to those skilled in the art by coupling polar carboxylic acids (for example gluconic acid which has to be appropriately protected) to the NH₂ compound XIII or by coupling polar amines (for example glucamine) to the

corresponding $-\text{COOH}$ compound XIV, resulting in the carboxanilides Ia or the carboxamides Ib.



5

In the compounds of the formulae II to XIV, the R_1 to R_9 radicals are each as defined above or they are functional groups in protected form or in precursor stages.

10 The urea or else thiourea compounds derived from the precursor molecules XIII can likewise be prepared therefrom in a manner known to those skilled in the art.

It has been possible to show that compounds of the formula I constitute outstanding inhibitors of the sodium-hydrogen exchanger (NHE), especially of the sodium-hydrogen exchanger of the subtype 3 (NHE3).

15

Tetrahydroisoquinolines as inhibitors of the sodium-hydrogen exchanger of the subtype 3 (NHE3) have already been described in the patent application WO03048129. The patent application WO03055880 describes the related compound

class of the tetrahydroisoquinolinium salts as NHE3 inhibitors. However, the properties of these compounds are not yet satisfactory in various respects, and there is still a need for compounds having a more favorable pharmacodynamic or pharmacokinetic property profile, and suitable for treating highly differing disorders.

The NHE3 is found in the body of various species, preferably in the gallbladder, the intestines and in the kidneys (Larry Fliegel et al., *Biochem. Cell. Biol.* 76: 735-741, 1998), but could also be found in the brain (E. Ma et al., *Neuroscience* 79: 591-603).

As a consequence of their unexpected NHE-inhibitory properties, the compounds of the formula I are suitable for preventing and treating disorders which are caused by activation and/or by an activated NHE. The use of the compounds disclosed herein relates to the prevention and treatment of acute and chronic disorders in veterinary medicine and human medicine.

Thus, the inventive inhibitors of NHE are suitable for treating disorders which are caused by ischemia and/or by reperfusion.

In a second aspect, there is provided a compound of the formula I and its pharmaceutically acceptable salts as defined above for use as a medicament.

In a third aspect, there is provided use of a compound of the formula I and the pharmaceutically acceptable salts thereof as defined above for preparing a medicament for the treatment or prophylaxis of disorders of respiratory drive, of respiratory disorders, sleep-related respiratory disorders, sleep apneas, of snoring, of acute and chronic renal disorders, of acute renal failure and of chronic renal failure, of disorders of intestinal function, of high blood pressure, of essential hypertension, of disorders of the central nervous system, of disorders resulting from CNS overexcitability, epilepsy and centrally induced convulsions or of anxiety states, depressions and psychoses, of ischemic states of the peripheral or central nervous system and of stroke, of acute and chronic damage to and disorders of peripheral organs or limbs caused by ischemic or by reperfusion

events, of atherosclerosis, of disorders of lipid metabolism, of thromboses, of disorders of biliary function, of infestation by ectoparasites, of disorders resulting from endothelial dysfunction, of protozoal disorders, of malaria, for the preservation and storage of transplants for surgical procedures, for use in surgical operations and organ transplantations or for the treatment of states of shock or of diabetes and late damage from diabetes or of diseases in which cellular proliferation represents a primary or secondary cause, and for maintaining health and prolonging life.

In a fourth aspect, there is provided use of a compound of the formula I and the pharmaceutically acceptable salts thereof as defined above in combination with other medicaments or active ingredients for preparing a medicament for the treatment or prophylaxis of disorders of respiratory drive, of respiratory disorders, sleep-related respiratory disorders, sleep apneas, of snoring, of acute and chronic renal disorders, of acute renal failure and of chronic renal failure, of disorders of intestinal function, of high blood pressure, of essential hypertension, of disorders of the central nervous system, of disorders resulting from CNS overexcitability, epilepsy and centrally induced convulsions or of anxiety states, depressions and psychoses, of ischemic states of the peripheral or central nervous system and of stroke, of acute and chronic damage to and disorders of peripheral organs or limbs caused by ischemic or by reperfusion events, of atherosclerosis, of disorders of lipid metabolism, of thromboses, of disorders of biliary function, of infestation by ectoparasites, of disorders resulting from endothelial dysfunction, of protozoal disorders, of malaria, for the preservation and storage of transplants for surgical procedures, for use in surgical operations and organ transplantations or for the treatment of states of shock or of diabetes and late damage from diabetes or of diseases in which cellular proliferation represents a primary or secondary cause, and for maintaining health and prolonging life.

As a consequence of their pharmacological properties, the compounds described here are outstandingly suitable as antiarrhythmic medicaments having a cardioprotective component for prophylaxis of infarction and for treatment of infarction, and also for treatment of angina pectoris, in which case they also inhibit or greatly reduce, in a preventative manner, the pathophysiological events in the development of ischemia-induced damage, in particular in

the induction of ischemia-induced cardiac arrhythmias. Owing to their protective effects against pathological hypoxic and ischemic situations, the compounds of the formula I used in accordance with the invention can, as a consequence of inhibition of the cellular Na^+/H^+ exchange mechanism, be used as a medicament for treating all acute or chronic damage induced by ischemia or disorders induced primarily or secondarily thereby. This relates to the use thereof as medicaments for surgical interventions, for example in organ transplants, in which case the compounds can be used both for the protection of the organs in the donor and during the removal, to protect removed organs, for example in

the course of treatment with or storage thereof in physiological bath fluids, and also in the course of transfer into the recipient organism. The compounds are likewise valuable medicaments having a protective action when carrying out angioplastic surgical interventions, for example on the heart or else on peripheral vessels.

In accordance with their protective action against ischemia-induced damage, the compounds are also suitable as medicaments for treating ischemias of the nervous system, especially of the CNS, in which case they are suitable, for example, for treating stroke or cerebral edema.

In addition, the compounds of the formula I used in accordance with the embodiments disclosed herein are likewise suitable for treating forms of shock, for example allergic, cardiogenic, hypovolemic and bacterial shock.

In addition, the compounds induce an improvement in the respiratory drive and are therefore used for treating respiratory conditions in the event of the following clinical conditions and disorders: disrupted central respiratory drive (for example central sleep apneas, sudden infant death, postoperative hypoxia), muscle-related respiratory disorders, breathing disorders after long-term ventilation, breathing disorders in the course of adaptation in high mountains, obstructive and mixed form of sleep apneas, acute and chronic pulmonary disorders with hypoxia and hypercapnia.

The compounds may additionally increase the muscle tone of the upper airways, so that snoring is suppressed.

The compounds mentioned are therefore advantageously used to prepare a medicament for the prevention and treatment of sleep apneas and muscle-related respiratory disorders and to prepare a medicament for the prevention and treatment of snoring.

A combination of an NHE inhibitor with a carbonic anhydrase inhibitor (for example acetazolamide), in which case the latter brings about metabolic acidosis and thus itself increases respiratory activity, is found to be advantageous as a result of enhanced action and reduced use of active ingredient.

In addition, the compounds described here are suitable as medicaments for therapy and prophylaxis of diseases and disorders which are induced by hyperexcitability of the central nervous system, in particular for treating diseases of the epileptic type, centrally induced clonic and tonic spasms, states of psychological depression, anxiety disorders and psychoses. The NHE inhibitors described here may be employed alone or in combination with other antiepileptic substances or antipsychotic active ingredients, or carbonate dehydratase inhibitors, for example with acetazolamide, and also with further inhibitors of NHE or of the sodium-dependent chloride-bicarbonate exchanger (NCBE).

It has been found that the compounds used in accordance with the embodiments disclosed herein have a mild laxative effect and can accordingly be used advantageously as laxatives or in the event of risk of constipation.

In addition, the compounds disclosed herein can advantageously be used for the prevention and therapy of acute and chronic disorders of the intestinal tract which are induced by ischemic states in the intestinal region and/or by subsequent reperfusion. Such complications may be caused, for example, by inadequate bowel peristalsis as frequently observed, for example, after surgical interventions, in the event of constipation or greatly reduced bowel activity.

There is also the possibility of preventing gallstone formation.

In addition, the compounds of the formula I used in accordance with the embodiments disclosed herein feature strong inhibiting action on the proliferation of cells, for example on fibroblast cell proliferation and the proliferation of smooth vascular muscle cells. The compounds of the formula I are therefore useful as valuable therapeutic agents for disorders in which cell proliferation constitutes a primary or secondary cause, and can therefore be used as antiatherosclerotic agents, agents against diabetic late complications, agents against chronic kidney failure, cancers, fibrotic disorders of the heart and also as pulmonary fibrosis, hepatic fibrosis, or renal fibrosis, organ hypertrophies and

hyperplasias, for example of the heart and the prostate, and thus for the prevention and treatment of congestive heart failure or in the event of prostate hyperplasia or prostate hypertrophy.

The compounds disclosed herein are effective inhibitors of the cellular sodium-proton antiporter (Na/H exchanger) which is elevated in numerous disorders (essential hypertension, atherosclerosis, diabetes, etc.), also in those cells which are readily amenable to measurements, for example in erythrocytes, thrombocytes or leucocytes. The compounds used in accordance with the invention are therefore suitable as outstanding and simple scientific tools, for example in their use as diagnostic agents for determining and differentiating different forms of hypertension, but also of atherosclerosis, diabetes and diabetic late complications, proliferative disorders, etc.

In addition, the compounds of the formula I are suitable for preventive therapy for preventing development of, and treating, high blood pressure, for example of essential hypertension, since they reduce or fully inhibit the reabsorption of NaCl in the tubular system of the kidneys. Accordingly, they are also outstandingly suitable as combination and formulation partners for medicaments which are used to treat high blood pressure. For example, they may be combined with diuretics having thiazide-like action, loop diuretics, aldosterone and pseudoaldosterone antagonists such as hydrochlorothiazide, indapamide, polythiazide, furosemide, piretanide, torasemide, bumetanide, amiloride, triamterene. In addition, the NHE inhibitors of the present invention may be used in combination with ACE inhibitors, for example ramipril, enalapril or captopril.

Further favorable combination partners are also β -blockers.

The NHE inhibitors described may likewise be used in the prevention of, and for treating, thrombotic disorders, since, as NHE inhibitors, they can both inhibit platelet aggregation itself and additionally inhibit or prevent the excessive release of coagulation mediators, in particular of von Willebrand's factor. The NHE inhibitors of the present invention can therefore be combined with further anticoagulant active ingredients, for example acetylsalicylic acid, thrombin antagonists, factor Xa

antagonists, medicaments having fibrinolytic action, factor VIIa antagonists, etc. Combined application of the present NHE inhibitors with NCBE inhibitors is particularly beneficial.

- 5 It has also been found that NHE inhibitors exhibit a beneficial influence on serum lipoproteins. It is generally acknowledged that excessively high blood lipid levels, known as hyperlipoproteinemias, constitute a significant risk factor for the development of arteriosclerotic vascular lesions, especially of coronary heart disease. The reduction in elevated serum lipoproteins is therefore exceptionally important for the prophylaxis and the regression of atherosclerotic lesions. The compounds used in accordance with the invention can therefore be used for prophylaxis and for regression of atherosclerotic lesions by eliminating a causal risk factor. The inventive inhibitors of NHE can also advantageously be combined with other antiarteriosclerotic active ingredients, such as a substance from the class of the fibrates, an upregulator of LD2
10 receptor activity, such as MD-700 and LY295427, or a cholesterol or bile acid resorption inhibitor or an antihypercholesterolemic from the class of the statins, such as, for example, pravastatin, lovastatin, simvastatin. This protection of the vessels against the syndrome of endothelial dysfunction makes compounds of the formula I viable medicaments for preventing and for treating coronary vasospasms, peripheral
15 vascular disorders, such as claudicatio intermittens, atherogenesis and atherosclerosis, left-ventricular hypertrophy and dilated cardiomyopathy, and thrombotic disorders.

The compounds mentioned may likewise be used for treating diseases which are caused by protozoa and are especially suitable as antimalarials.

25 In addition, the compounds are suitable for controlling sucking parasites such as mosquitoes, ticks, fleas and plant pests.

In accordance with their protective actions, the compounds are also suitable as
30 medicaments for maintaining health and prolonging life.

Generally, the NHE inhibitors described here may advantageously be combined with other compounds which regulate the intracellular pH, and useful combination partners are inhibitors of the enzyme group of carbonate dehydratase, inhibitors of bicarbonate ion-transporting systems such as the sodium-bicarbonate cotransporter or the sodium-
5 dependent chloride-bicarbonate exchanger, and also other NHE inhibitors, for example having inhibitory action on other NHE subtypes, because they may strengthen the pharmacologically relevant pH-regulating effects of the NHE inhibitors described here.

The compounds mentioned therefore advantageously find use for preparing a
10 medicament for preventing and treating sleep apneas and muscle-related respiratory disorders; for preparing a medicament for preventing and treating snoring; for preparing a medicament for blood pressure reduction; for preparing a medicament having a laxative effect for preventing and treating intestinal blockages; for preparing a medicament for preventing and treating disorders which are induced by ischemia and
15 reperfusion of central and peripheral organs such as acute renal failure, stroke, endogenous states of shock, intestinal disorders, etc.; for preparing a medicament for treating diabetic late damage and chronic renal disorders, in particular all renal inflammations (nephritides) which are associated with increased protein/albumin excretion; for preparing a medicament for treating hypercholesterinemia; for preparing
20 a medicament for preventing atherogenesis and atherosclerosis; for preparing a medicament for preventing and treating disorders which are induced by elevated cholesterol levels; for preparing a medicament for preventing and treating disorders which are induced by endothelial dysfunction; for preparing a medicament for treating infection by ectoparasites; for preparing a medicament for treating the diseases
25 mentioned in combinations with blood pressure-reducing substances, preferably with angiotensin converting enzyme (ACE) inhibitors, with diuretics, aldosterone antagonists or angiotensin receptor antagonists. It has been found that a combination of an NHE inhibitor of the formula I with a blood lipid level-reducing active ingredient, preferably with an HMG-CoA reductase inhibitor (for example lovastatin or
30 pravastatin), the latter bringing about hypolipidemic action and thus increasing the hypolipidemic properties of the NHE inhibitor of the formula I, is a beneficial combination having enhanced action and reduced use of active ingredient.

The administration of sodium-proton exchange inhibitors of the formula 1 as novel medicaments for reducing elevated blood lipid level is claimed, as is the combination of sodium-proton exchange inhibitors with blood pressure-reducing and/or hypolipidemic medicaments.

In a fifth aspect, there are provided curative compositions for human, veterinary or phytoprotective use, comprising an effective amount of a compound of the formula I and/or of a pharmaceutically acceptable salt thereof.

In a sixth aspect, there are provided curative compositions for human, veterinary or phytoprotective use, comprising an effective amount of a compound of the formula I and/or of a pharmaceutically acceptable salt thereof alone or in combination with one or more other pharmacological active ingredients or medicaments.

Medicaments which comprise a compound of the formula I or the pharmaceutically acceptable salts thereof can be administered, for example, orally, parenterally, intramuscularly, intravenously, rectally, nasally, by inhalation, subcutaneously or by a suitable transcutaneous dosage form, the preferred administration depending on the particular characteristics of the disorder. The compounds of the formula I can be used alone or together with pharmaceutical excipients, in veterinary or in human medicine and in plant protection. The medicaments comprise active ingredients of the formula I and/or their pharmaceutically acceptable salts in general in an amount of from 0.01 mg to 1 g per dose unit.

The excipients which are suitable for the desired pharmaceutical formulation are familiar to those skilled in the art on the basis of their expert knowledge. In addition to solvents, gel formers, suppository bases, tablet excipients and other active ingredient carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavorings, preservatives, solubilizers or colorings.

For an oral administration form, the active compounds are mixed with the additives suitable for this purpose, such as carriers, stabilizers or inert diluents and converted by

customary methods to the suitable dosage forms, such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions. Examples of useful inert carriers include gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch. The preparation may be either in the form of dry granules or in the form of moist granules. Examples of useful oily carriers or useful solvents are vegetable or animal oils, such as sunflower oil or cod liver oil.

For subcutaneous, percutaneous or intravenous administration, the active compounds used, if desired with the substances customary for this purpose such as solubilizers, emulsifiers or further excipients are converted to solution, suspension or emulsion. Examples of useful solvents are: water, physiological saline or alcohols, for example ethanol, propanol, glycerol and additionally also sugar solutions such as glucose or mannitol solutions, or else a mixture of the different solvents mentioned.

Examples of suitable pharmaceutical formulations for administration in the form of aerosols or sprays are solutions, suspensions or emulsions of the active ingredient of the formula I in a pharmaceutically acceptable solvent, in particular ethanol or water, or a mixture of such solvents. If required, the formulation may also comprise other pharmaceutical excipients such as surfactants, emulsifiers and stabilizers, and also a propellant gas. Such a preparation typically contains the active ingredient in a concentration of from about 0.1 to 10% by weight, in particular from about 0.3 to 3% by weight.

The dosage of the active ingredient of the formula I to be administered and the frequency of administration depend on the potency and duration of action of the compounds used; additionally also on the nature and severity of the disease to be treated, and also on the gender, 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 about 75 kg is at least 0.001 mg/kg, preferably 0.1 mg/kg, up to at most 30 mg/kg, preferably 1 mg/kg, of body weight. In the event of acute episodes of the

disease, for instance immediately after suffering apnetic states in high mountains, even higher dosages may be necessary. Especially in the case of i.v. administration, for instance in a heart attack patient in the intensive care unit, up to 300 mg/kg per day may be necessary. The daily dose can be divided into one or more, for example up to 5 4, individual doses.

When the compounds of the formula I contain one or more acidic or basic groups and/or one or more basic heterocycles, the corresponding physiologically or toxicologically acceptable salts are also included in the invention, in particular the salts 10 which can be used pharmaceutically. For instance, the compounds of the formula I can be deprotonated at an acidic group and be used, for example, as alkali metal salts, preferably sodium or potassium salts, or as ammonium salts, for example as salts with ammonia or organic amines or amino acids. Compounds of the formula I which contain a basic group can also be used in the form of their physiologically acceptable acid 15 addition salts with inorganic or organic acids, for example as hydrochlorides, phosphates, sulfates, methanesulfonates, acetates, lactates, maleates, fumarates, malates, gluconates, etc.

Experimental descriptions and examples

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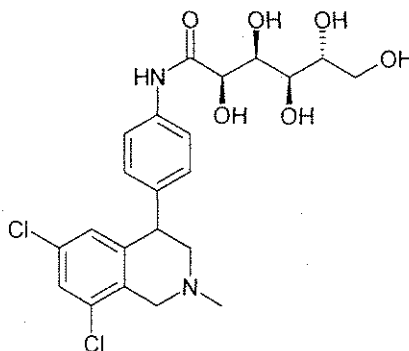
List of abbreviations used:

	R _t	Retention time
	TFA	Trifluoroacetic acid
25	HPLC	High Performance Liquid Chromatography
	eq	equivalents
	LCMS	Liquid Chromatography Mass Spectroscopy
	MS	Mass Spectroscopy
	ESI	Electrospray ionization
30	RT	Room temperature
	THF	Tetrahydrofuran

	TOTU	O-[(Ethoxycarbonyl)cyanomethyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate
	DMSO	Dimethyl sulfoxide
	abs.	absolute
5	decomp.	decomposition
	DMF	Dimethylformamide
	DMAP	4-Dimethylaminopyridine
	HOBt	1-Hydroxybenzotriazole
	DIC	Diisopropylcarbodiimide
10	ACN	Acetonitrile
	DEA	Diethylamine

Example 1: N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide

15



Intermediate 1: 2,4-dichlorobenzylmethylamine
was prepared by literature methods (J. Med. Chem.; 1984, 27, 1111).

20

Intermediate 2: N-[4-(2-bromoacetyl)phenyl]acetamide
was synthesized in a manner known to those skilled in the art by brominating N-(4-acetylphenyl)acetamide.

25

The starting compound (0.256 mol) is initially charged in 300 ml of acetic acid and a solution of 39.9 g of bromine (1.0 eq) in 60 ml of acetic acid was added dropwise at 60°C. After 1.5 hours, the mixture was cooled to room temperature and the reaction

mixture was added to 1 l of ice-water. The precipitate was filtered off with suction, washed with water and dried to isolate 60 g of the title compound (m.p.: 192°C).

Intermediate 3: N-{4-[2-(2,4-dichlorobenzylamino)acetyl]phenyl}acetamide

- 5 37.1 g (0.195 mol) of intermediate 1 were initially charged in 400 ml of dioxane and admixed with a solution of 60 g (0.234 mol) of intermediate 2 in 600 ml of dioxane. 134 ml of triethylamine were added and the mixture was stirred at room temperature for 4 h. After standing overnight, the precipitate was filtered off and the filtrate concentrated in vacuo. The residue was taken up in ethyl acetate, washed with NaHCO₃ and H₂O,
10 dried with MgSO₄ and concentrated. The resulting oily residue was triturated with an ethyl acetate/ether mixture to obtain 36 g of intermediate 3 in the form of a crystalline solid (m.p.: 115-117°C).

Intermediate 4: N-{4-[2-(2,4-dichlorobenzylamino)-1-hydroxyethyl]phenyl}acetamide

- 15 36 g (0.099 mol) of intermediate 3 were dissolved in 500 ml of methanol and admixed at 0°C with 7.8 g (2 eq) of sodium borohydride. The mixture was stirred at 0°C for another 30 min and at room temperature for a further hour. For workup, the reaction mixture was concentrated and the residue partitioned between 1 N HCl and ethyl acetate. The aqueous phase was removed, adjusted to pH 9 and extracted twice with
20 ethyl acetate. The combined organic phases were dried with MgSO₄ and concentrated. The crude product obtained in this way could be used further without further purification.

Intermediate 5: N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]acetamide

- 25 20 g (0.054 mol) of intermediate 4 were dissolved in 250 ml of dichloromethane and admixed dropwise at 0°C with 250 ml of conc. H₂SO₄. The mixture was stirred at 0°C for 2 h and at room temperature for 1 h. For workup, the reaction mixture was added to ice-water and the precipitate was filtered off with suction. The precipitate was taken up
30 in 300 ml of 1 N NaOH and extracted 3 times with ethyl acetate. Drying of the organic phases and concentration afforded a crude product which was triturated with

diisopropyl ether to isolate 11.7 g of the title compound as a crystalline solid (m.p.: 205-206°C).

Intermediate 6: 4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine
 5 3.0 g (8.6 mmol) of N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]acetamide (intermediate 5) were dissolved in 100 ml of 20% sodium ethoxide solution and heated to reflux for 4 hours. A further 2.0 g (29.4 mmol) of solid sodium ethoxide were added and the mixture was heated to reflux for another 3 hours. For workup, the solvent was removed in vacuo, and the residue was taken up in 200 ml of
 10 H₂O and extracted twice with dichloromethane. The combined organic phases were dried with MgSO₄ and concentrated. For further purification, chromatography was effected on silica gel (1:1 ethyl acetate/heptane) to obtain the aniline as a yellowish oil in quantitative yield.

15 Intermediate 7: 2,3,4,5,6-penta-O-acetylgluconyl chloride
 The title compound was synthesized by literature methods (Org. Syntheses, 1961, 41, 79-82).

Intermediate 8: N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
 20 (2R,3S,4R,5R)-2,3,4,5,6-penta-O-acetylhexanamide
 614 mg (2.0 mmol) of 4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (intermediate 6) were initially charged in 20 ml of pyridine and admixed at 0°C with a solution of 1.28 g (3.0 mmol) of 2,3,4,5,6-penta-O-acetylgluconyl chloride in 10 ml of dichloromethane. The mixture was stirred at 0°C for 15 minutes and at
 25 room temperature for 1 hour. For workup, the mixture was concentrated and the residue taken up in dichloromethane. Washing was effected once with H₂O, once with saturated NaHCO₃ solution, twice with 1 N HCl and once more with H₂O, followed by drying over MgSO₄ and concentration. The crude product obtained in this way (1.12 g) could be used in the next reaction without further purification.

30

1: N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
 (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide;

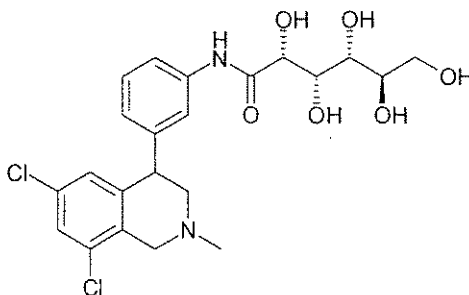
The crude product obtained in intermediate 8 was dissolved in 30 ml of methanol and admixed in portions at room temperature with 452 mg (8.4 mmol) of sodium methoxide. After one to two hours at room temperature, the pH was adjusted to about 7 using 1 N HCl and the solvent removed in vacuo. The residue was taken up in sat.

5 NaHCO_3 solution and extracted twice with ethyl acetate. The combined organic phases were dried over MgSO_4 and concentrated. Chromatography on silica gel using a dichloromethane/methanol mixture afforded 373 mg of the title compound as a pale yellow solid.

10 1a: N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide hydrochloride; 201 mg (0.4 mmol) of [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide (example compound 1) were taken up in 75 ml of H_2O and admixed at room temperature with 4.14 ml of 0.1 M
15 HCl. The mixture was stirred for 15 minutes, filtered and freeze-dried to obtain 177 mg of the desired hydrochloride.

Example 2: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide

20



Intermediate 1: 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine
Starting from 2,4-dichlorobenzylmethylamine (Example 1, intermediate 1) and N-[3-(2-bromoacetyl)phenyl]acetamide (cf. Example 1, intermediate 2), the aniline derivative 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (cf. Example 1, intermediate 6) was prepared in a similar manner to the synthetic route described in Example 1.

25

Intermediate 2: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-penta-O-acetylhexanamide

3.1 g (10 mmol) of 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (intermediate 1) were dissolved in 100 ml of pyridine and admixed at 0°C with a solution of 1.2 equivalents of 2,3,4,5,6-penta-O-acetylgluconyl chloride in 60 ml of dichloromethane. The mixture was stirred at room temperature. Once the monitoring of the reaction indicated complete conversion, the mixture was concentrated and the residue taken up in dichloromethane. Washing was effected once with H₂O, once with saturated NaHCO₃ solution, twice with 1 N HCl and once more with H₂O, followed by drying over MgSO₄ and concentration. The crude product obtained in this way (6.91 g) could be used in the next reaction without further purification.

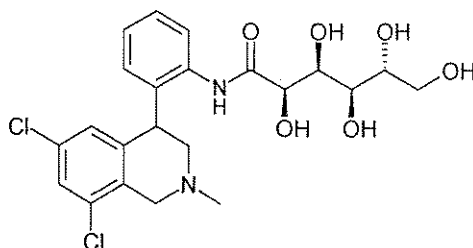
2: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide

6.91 g of the crude product from intermediate 2 were admixed into 200 ml of methanol at room temperature with 2.79 g (51.7 mmol) of sodium methoxide. After 1 to 2 hours at room temperature, the pH was adjusted to about 7 using 1 N HCl and the solvent was removed in vacuo. The residue was taken up in sat. NaHCO₃ solution and extracted twice with ethyl acetate. The combined organic phases were dried over MgSO₄ and concentrated. Chromatography on silica gel using a dichloromethane/methanol mixture afforded 2.05 g of the title compound as a pale yellow solid.

2a: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide hydrochloride

300 mg (0.6 mmol) of N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide (example compound 2) were taken up in 100 ml of H₂O and admixed at room temperature with 6.18 ml of 0.1 M HCl. The mixture was stirred for 15 minutes, filtered and freeze-dried to obtain 294 mg of the desired hydrochloride.

Example 3: N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide



5

Intermediate 1: N-[2-(2-bromoacetyl)phenyl]acetamide

31 g (0.175 mol) of N-(2-acetylphenyl)acetamide (prepared by acylating 2-aminoacetophenone with acetyl chloride according to Fuerstner, Alois; Jumbam, Denis
10 N.; Tetrahedron; 48; 29; 5991-6010, (1992)) were dissolved in 200 ml of glacial acetic acid. 127 ml of 33% HBr in glacial acetic acid were added and then 8.75 ml (0.175 mol) of bromine were added slowly at room temperature. The mixture was stirred at room temperature overnight. The mixture was stirred into 1.5 l of ice-water, and the precipitated product was filtered off with suction, washed thoroughly with ice-water and
15 dried in vacuo. According to HPLC and NMR, the crude product contained some reactant and dibrominated product, but was clean enough for the further reaction (approx. 85%).

Yield: 43 g

20 Intermediate 2: N-(2-{2-[(2,4-dichlorobenzyl)methylamino]acetyl}phenyl)acetamide
12.4 g (65.24 mmol) of 2,4-dichlorobenzylmethylamine (Example 1, intermediate 1) were dissolved in 200 ml of dioxane. To this were added 19.96 g of the crude product of the above bromination, likewise dissolved in 200 ml of dioxane, and 45 ml of triethylamine. The mixture was stirred at room temperature overnight and then filtered.
25 The filtrate was evaporated, and the residue was taken up in ethyl acetate and washed with saturated sodium hydrogen carbonate and sodium chloride solution, dried over sodium sulfate and concentrated by rotary evaporation. According to NMR, the crude product (20.4 g) was clean enough for the further reaction.

Intermediate 3: N-(2-{2-[(2,4-dichlorobenzyl)methylamino]-1-hydroxyethyl}-phenyl)acetamide

20 g of the crude product of the preceding stage (approx. 50 mmol) were dissolved in
5 200 ml of methanol and cooled to $< 5^{\circ}\text{C}$ in an ice bath. 4.3 g (109 mmol) of sodium borohydride were added with good stirring in portions, in such a way that the internal temperature did not exceed 10°C . Subsequently, stirring was continued in the ice bath for another 30 min and at room temperature for 1 hour. After standing overnight, the mixture was evaporated, and the residue was taken up in ethyl acetate, washed 3x
10 with water and 1x with sodium chloride solution, dried over sodium sulfate and concentrated by rotary evaporation. The crude product (19.4 g) was used further without purification.

Intermediate 4: 1-(2-aminophenyl)-2-[(2,4-dichlorobenzyl)methylamino]ethanol

15 10 g of the crude product from the preceding stage were dissolved in 300 ml of methanol. 200 ml of concentrated hydrochloric acid were added and the mixture was stirred at 50°C for 10 hours. The mixture was allowed to cool and poured into water, and the pH was adjusted to 10-12 using 20% NaOH. The product was extracted with ethyl acetate, and the combined extracts were washed with sodium chloride solution,
20 dried over sodium sulfate and evaporated. The crude product (9.9 g) contained a little sodium chloride, which did not, however, disrupt the further reaction.

Intermediate 5: 2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine

9.9 g of the crude product from the preceding stage were dissolved in 350 ml of
25 chloroform. With cooling in an ice bath, 123 ml of concentrated sulfuric acid were added dropwise. Stirring was carried out in the ice bath for 2 hours, then the mixture was gradually warmed to room temperature and finally heated to 50°C overnight. The cooled mixture was poured onto ice and made alkaline using sodium hydroxide solution ($\text{pH} > 10$). The organic phase was removed, the aqueous phase was extracted
30 twice with methylene chloride, and the combined organic phases were washed with water and NaCl, dried over sodium sulfate and evaporated.

Intermediate 6: N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-penta-O-acetylhexanamide

614 mg (2.0 mmol) of 2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (intermediate 5) were dissolved in 20 ml of pyridine and admixed at 0°C with a solution of 1.5 equivalents of 2,3,4,5,6-penta-O-acetylgluconyl chloride in 10 ml of dichloromethane. The mixture was stirred at room temperature. Once the monitoring of the reaction indicated complete conversion, the mixture was concentrated and the residue taken up in dichloromethane. Washing was effected once with H₂O, once with saturated NaHCO₃ solution, twice with 1 N HCl and once more with H₂O, followed by drying over MgSO₄ and concentration. The crude product obtained in this way (1.27 g) was able to be used in the next reaction without further purification.

3: N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide;

1.27 g of the crude product from intermediate 6 were admixed in 30 ml of methanol at room temperature with 513 mg (9.5 mmol) of sodium methoxide. After 1 to 2 hours at room temperature, the pH was adjusted to about 7 using 1 N HCl and the solvent removed in vacuo. The residue was taken up in sat. NaHCO₃ solution and extracted twice with ethyl acetate. The combined organic phases were washed once more with H₂O, dried over MgSO₄ and concentrated. Chromatography on silica gel using a dichloromethane/methanol mixture afforded 313 mg of the title compound as a pale yellow solid.

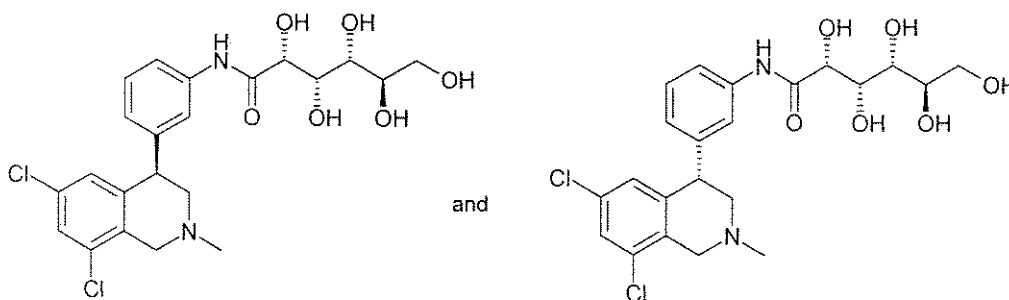
3a: N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide hydrochloride

145.5 mg (0.3 mmol) of N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxygluconamide (example compound 3) were taken up in 75 ml of H₂O and admixed at room temperature with 3.0 ml of 0.1 M HCl. The mixture was stirred for 15 minutes, filtered and freeze-dried to obtain 149 mg of the desired hydrochloride.

Example 4:

4a: N-[(R)-3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide and

5 4b: N-[(S)-3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-
(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide



10 2.0 g of the example compound 2 were separated on a chiral phase into the two diastereomers.

Preparative separation conditions for baseline separation:

Chiral column: Chiralpak AD9 250 x 50 mm + Chiralpak AD2 250 x 50 mm

15 Solvent: 2:1:1 heptane:ethanol:methanol

Flow rate: 150 ml/min

Analytical data on a chiral phase:

Chiral column: Chiralpak ADH/40 250 x 4,6

20 Solvent: 2:1:1 heptane:ethanol:methanol

Flow rate: 1 ml/min

Temperature: 30 °C

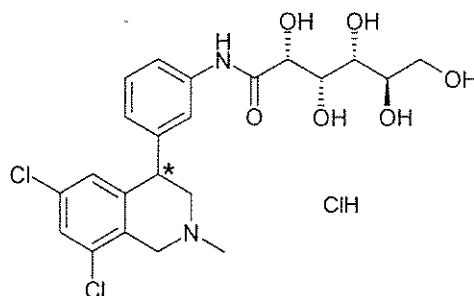
Retention time of diastereomer A: 4.5 minutes,

Yield of diastereomer A: 988 mg;

25 Retention time of diastereomer B: 7.5 minutes,

Yield of diastereomer B: 942 mg.

Example 5: N-[(R or S)-3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide hydrochloride

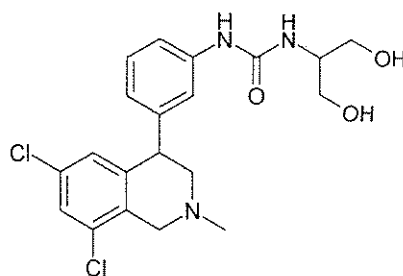


5

300 mg (0.6 mmol) of N-[(R or S)-3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide (Example compound 4a or 4b; diastereomer B) were taken up in 20 ml of H₂O and admixed at room temperature with 6.18 ml of 0.1 M HCl. The mixture is stirred for 15 minutes, filtered and freeze-dried to obtain 297 mg of the desired hydrochloride.

10

Example 6: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-hydroxymethylethyl)urea



15

Intermediate 1: 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride

350 mg (1.1 mmol) of 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (Example compound 2, intermediate 1) were dissolved in 17.5 ml of dichloromethane and admixed with stirring with 230 mg (1.1 mmol) of 4-nitrophenyl chloroformate. After 4.5 hours, a further 0.1 equivalent (23 mg) of 4-nitrophenyl chloroformate was added and the solution was stirred overnight. For workup, the

20

resulting precipitate was filtered off and washed with dichloromethane. The crude product obtained in this way could be reacted further without further purification.

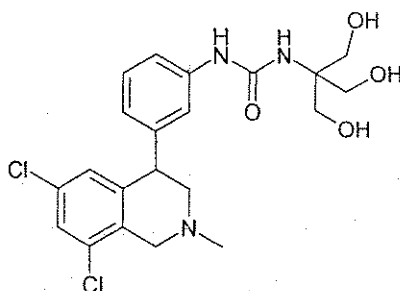
6: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-hydroxymethylethyl)urea

1.02 g (2.0 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1) were dissolved in 30 ml of abs. DMF and admixed at 0°C with a solution of 200.5 mg (2.2 mmol) of 2-amino-1,3-propanediol in 25 ml of abs. DMF. The mixture was stirred at room temperature for 3 hours. After standing overnight, the solvent was removed in vacuo and the residue partitioned between ethyl acetate and saturated NaHCO₃ solution. The organic phase was removed and the aqueous extracted twice more with ethyl acetate. The combined organic phases were washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated. Chromatography of the crude product obtained in this way on silica gel (dichloromethane/methanol mixture) afforded 500 mg of the desired urea.

6a: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-hydroxymethylethyl)urea hydrochloride

200 mg of 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-hydroxymethylethyl)urea (Example compound 6) were dissolved in 40 ml of 0.1 M HCl, filtered and freeze-dried to obtain 194 mg of the desired hydrochloride.

Example 7: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea



1.02 g (2.0 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were reacted with 2-amino-2-hydroxymethylpropane-1,3-diol in a similar manner to that described in Example 6. Similar workup afforded 395 mg of the title compound.

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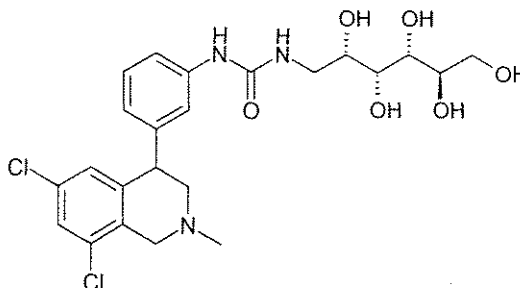
7a: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea hydrochloride

A similar procedure to the method described in Example 6a starting from 200 mg of 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea (Example compound 7) afforded 195 mg of the desired hydrochloride.

10

Example 8: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea

15



1.02 g (2.0 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were reacted with D-glucamine in a similar manner to the way described in Example 6. Similar workup afforded 273 mg of the title compound.

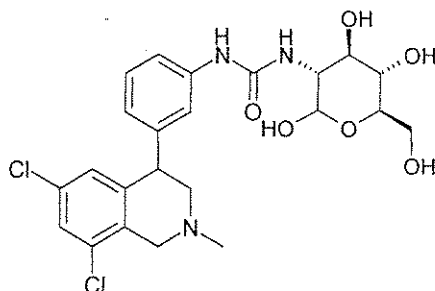
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8a: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea hydrochloride

25

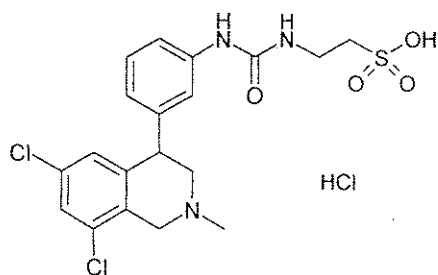
A similar procedure to the method described in Example 6a starting from 200 mg of 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-6-pentahydroxyhexyl)urea (Example compound 8) afforded 181 mg of the desired hydrochloride.

Example 9: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((4R,5S,6R)-2,4,5-trihydroxy-6-hydroxymethyltetrahydropyran-3-yl)urea



- 5 254 mg (0.5 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were initially charged in 7 ml of abs. DMF and admixed at 0°C with a suspension of 119 mg (0.55 mol) of D-glucosamine hydrochloride in 5 ml of abs. DMF. A similar procedure to the method described in Example 6 afforded, after chromatography on
10 silica gel, 87 mg of the title compound.

Example 10: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-sulfo-2-ethyl)}urea hydrochloride

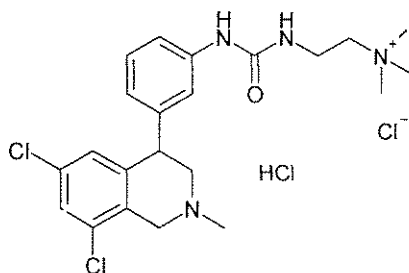


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- 1.02 g (2.0 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were admixed in 30 ml of abs. DMF at 0°C with 275 mg (2.2 mmol) of 2-aminoethanesulfonic acid, and also 0.83 ml (6.0 mmol) of triethylamine and stirred at
20 room temperature for 2 hours. After standing overnight, the liquid was filtered off from the precipitate which had formed and was concentrated in vacuo. The residue was taken up in saturated NaHCO₃ solution, filtered and neutralized with 1 N HCl, and a

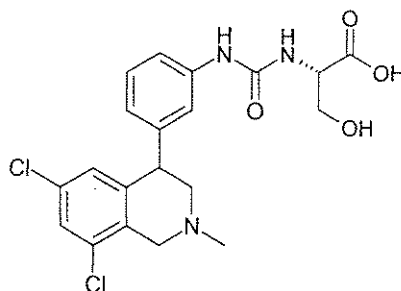
solid precipitated out. Filtering off and drying afforded 356 mg of the title compound as a crude product. The mother liquor was freeze-dried and the residue triturated with dichloromethane. The insoluble residue (634 mg) was combined with the precipitate (356 mg) which had already been obtained and chromatographed on silica gel. After a further purification on a preparative HPLC, the product fractions were combined and freeze-dried. The product obtained in this way was dissolved in 1 N HCl and freeze-dried once again to obtain the desired hydrochloride. Repeated dissolution in H₂O and further freeze-drying afforded 271 mg of the title compound.

- Example 11: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(ethyl-2-trimethylammonium))urea chloride hydrochloride



- 1.02 g (2.0 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were dissolved in 30 ml of abs. DMF and admixed at 0°C with a solution of 333 mg (1.9 mmol) of 2-aminoethyltrimethylammonium chloride hydrochloride in 5 ml of DMF. After addition of 0.277 ml (2.0 mmol) of triethylamine, the mixture was stirred at room temperature for 4 hours. After standing overnight, the mixture was filtered and concentrated in vacuo. The residue was taken up in H₂O and freeze-dried to obtain 1.77 g of crude product. Purification on a preparative HPLC afforded the desired product which could be converted to the title compound by dissolution in 1 N HCl and freeze-drying. After repeated dissolution in H₂O and further freeze-drying, 544 mg of the desired hydrochloride were obtained.

- Example 12: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl))urea



Intermediate 1: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-ethoxycarbonyl-3-hydroxy-2S-propyl)}urea

- 5 254 mg (0.5 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were dissolved in 7 ml of abs. DMF and admixed at 0°C with a solution of 93 mg (0.55 mol) of (S)-serine ethyl ester hydrochloride in 5 ml of abs. DMF. After adding 104 µl (0.75 mmol) of triethylamine, the mixture was stirred at room temperature. After
10 standing overnight, workup was effected in the manner described in Example 6 to obtain 184 mg of the title compound.

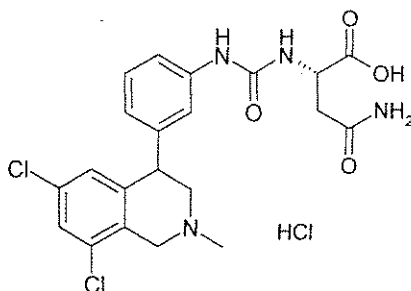
12: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea

- 15 170 mg (0.36 mmol) of {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-ethoxycarbonyl-3-hydroxy-2S-propyl)}urea (intermediate 1) were dissolved in 2 ml of methanol and admixed with 2 ml of 2 M KOH. After 3 hours at room temperature, the mixture was concentrated and the residue was taken up in H₂O. Once the pH of approx. 7 was attained by adding dilute HCl, the liquid was filtered off
20 from the precipitate which had formed. Drying afforded 89 mg of the title compound.

12a: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea hydrochloride

- 51 mg of {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea (Example compound 12) were dissolved in 20 ml of
25 0.1 M HCl and freeze-dried to obtain 52 mg of the desired hydrochloride.

Example 13: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea hydrochloride



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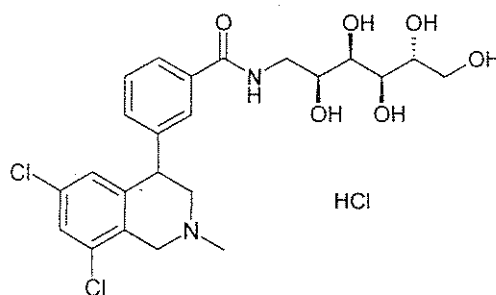
Intermediate 1: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-tert-butoxycarbonyl-4-aminocarboxy-2S-butyl)}urea

254 mg (0.5 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were reacted with 124 mg (0.55 mmol) of (S)-asparagine tert-butyl ester hydrochloride in a similar manner to the method described in Example 12 to obtain 220 mg of the title compound.

13: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea hydrochloride

210 mg (0.4 mmol) of intermediate 1 were dissolved in 3 ml of trifluoroacetic acid and left to stand at room temperature for 3 hours. Subsequently, the mixture was concentrated, and the residue was triturated with ether and filtered off with suction to obtain 230 mg of the corresponding trifluoroacetate. This was converted to the desired hydrochloride by dissolution in 0.1 N HCl and subsequent freeze-drying.

Example 14: 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)benzamide hydrochloride



Intermediate 1: 3-acetylbenzoic acid

The title compound was prepared in a manner known to those skilled in the art from 3-acetylbenzonitrile by hydrolyzing the nitrile group.

Intermediate 2: ethyl 3-acetylbenzoate

The title compound was prepared in a manner known to those skilled in the art by acid-catalyzed esterification of 3-acetylbenzoic acid (intermediate 1).

Intermediate 3: ethyl 3-(2-bromoacetyl)benzoate

The title compound is synthesized from ethyl 3-acetylbenzoate (intermediate 2) in a similar manner to the method described in Example 1, intermediate 2.

Intermediate 4: ethyl 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoate

In a similar manner to the synthetic route described under Example 1, the process was continued starting from ethyl 3-(2-bromoacetyl)benzoate (intermediate 3) and 2,4-dichlorobenzylmethylamine (Example 1, intermediate 1) to obtain ethyl 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoate after alkylation reaction, reduction and ring closure reaction.

Intermediate 5: 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoic acid

3.3 g of ethyl 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoate (intermediate 4) were dissolved in 60 ml of methanol and admixed with 60 ml of 2 N KOH. After two hours at 50°C, the mixture was concentrated in vacuo and the residue partitioned between water and ether. The water phase was adjusted to a pH of approx.

6 using 2 N HCl and the precipitate which formed was filtered off with suction. Drying afforded 1.7 g of the title compound as a colorless solid.

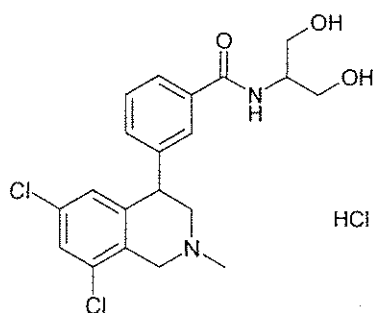
14: 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)benzamide hydrochloride

300 mg (0.9 mmol) of 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoic acid (intermediate 5) were initially charged in 10 ml of DMF and admixed at 0°C with 0.137 ml (1.0 mmol) of triethylamine, and also 354 mg (1.1 mmol) TOTU. The mixture was stirred at 0°C for 15 minutes and at room temperature for 30 minutes.

Subsequently, this solution was added dropwise to a second solution consisting of 196 mg (1.08 mmol) of D-glucamine and 0.137 ml (1.0 mmol) of triethylamine in 10 ml of DMF and 3 ml of H₂O, and stirred at room temperature. After 2 hours, the mixture was concentrated in vacuo and the residue purified on silica gel. After a further purification on a preparative HPLC, the desired benzamide was obtained as the trifluoroacetate.

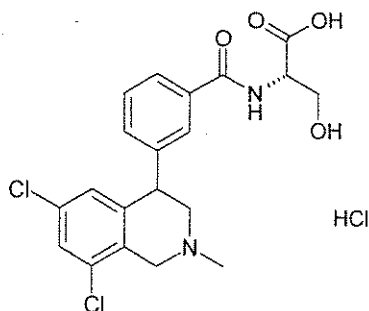
Dissolution in 0.1 N HCl and subsequent freeze-drying afforded the desired hydrochloride as a colorless solid.

Example 15: 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1-hydroxymethylethyl)benzamide hydrochloride



The title compound was prepared in a similar manner to the method described in Example 14 starting from 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoic acid (Example 14, intermediate 5) and 2-amino-1,3-propanediol.

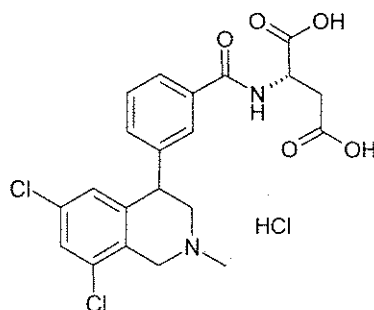
Example 16: (S)-2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid hydrochloride



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The title compound was prepared in a similar manner to the method described in Example 14 starting from 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoic acid (Example 14, intermediate 5) and L-(+)-serine.

10 Example 17: (S)-2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinic acid hydrochloride



Intermediate 1: Di-tert-butyl (S)-2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinate

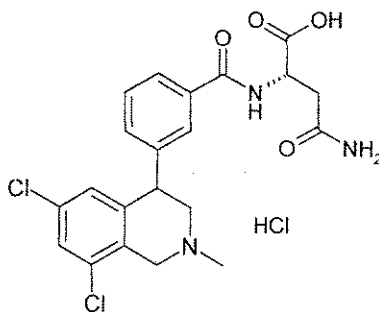
15 300 mg (0.9 mmol) of 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoic acid (Example 14, intermediate 5) were reacted in a similar manner to the method described in Example 14 with 304 mg (1.0 mmol) of di-tert-butyl aspartate in a TOTU-mediated coupling reaction to obtain 170 mg of the title compound as the

20 trifluoroacetate after purification on a preparative HPLC.

17: 2S-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinic acid hydrochloride

170 mg of di-tert-butyl 2S-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinate (intermediate 1) were dissolved in 15 ml of dichloromethane and admixed with 5 ml of trifluoroacetic acid. After 1 hour at room temperature, the mixture was concentrated in vacuo, and the residue was taken up in 30 ml of 0.1 N HCl and freeze-dried. After repeated dissolution in H₂O and further freeze-drying, 130 mg of the title compound were obtained.

10 Example 18: (S)-2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamic acid hydrochloride



Intermediate 1: tert-butyl (S)-2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamate

15 300 mg (0.9 mmol) of 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoic acid (Example 14, intermediate 5) were reacted in a similar manner to the method described in Example 14 with 242 mg (1.08 mmol) of tert-butyl aspartate in a TOTU-mediated coupling reaction to obtain 550 mg of the title compound after purification on silica gel.

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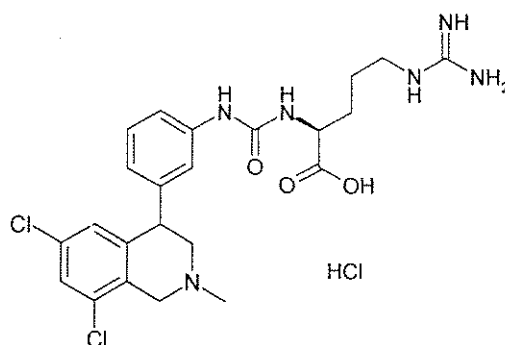
18: (S)-2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamic acid hydrochloride

550 mg of tert-butyl 2S-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamate (intermediate 1) were dissolved in 20 ml of dichloromethane and admixed at room temperature with 5 ml of trifluoroacetic acid. After 3 hours, the mixture was concentrated in vacuo and codistillation with toluene was effected once. The residue was dissolved in 0.1 N HCl with heating, filtered and

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concentrated in vacuo. The residue was dissolved in H₂O and freeze-dried to obtain 322 mg of the title compound.

Example 19: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-[1-carboxy-5-guanidino-2S-pentyl]urea hydrochloride



Intermediate 1: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-[1-tert-butoxycarbonyl-5-N'-(2,2,5,7,8-pentamethylchromyl-6-sulfonyl)guanidino-2S-pentyl]urea

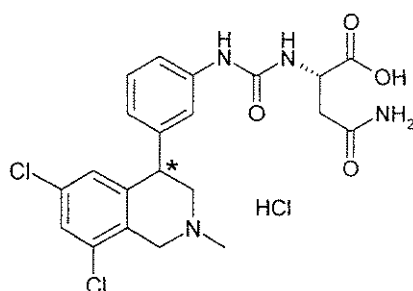
373 mg (0.73 mmol) of 4-nitrophenyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 1, Example 6) were dissolved in 10 ml of abs. DMF and reacted at 0°C with 400 mg (0.8 mmol) of tert-butyl S-2-amino-5-(N'-(2,2,5,7,8-pentamethylchromyl-6-sulfonyl)guanidinopentanoate in a similar manner to the method described in Example 6 to obtain 657 mg of the title compound after chromatography on silica gel.

19: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-[1-carboxy-5-guanidino-2S-pentyl]urea hydrochloride

590 mg of 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-[1-tert-butoxycarbonyl-5-N'-(2,2,5,7,8-pentamethylchromyl-6-sulfonyl)guanidino-2S-pentyl]urea were taken up in 25 ml of trifluoroacetic acid and stirred at room temperature for 1 hour. Afterwards, the mixture was concentrated in vacuo, and the residue was triturated with ether and filtered off with suction. The resulting crude product was taken up in 1 N HCl, filtered and freeze-dried. After purification on a preparative HPLC, the product fractions were concentrated, dissolved in 0.1 N HCl and

freeze-dried. Afterwards, dissolution in H₂O was repeated and was followed by further freeze-drying to obtain 170 mg of the title compound.

Example 20: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea hydrochloride



Intermediate 1:

10 1a: (R)-3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine and
1b: (S)-3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine
10 g of 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine
(Example 2, intermediate 1) were separated into the enantiomers on a chiral phase.

15 Preparative separation conditions in baseline separation:

Chiral column: Chiralpak AD10 50 x 10 cm, base-preconditioned;
Solvent: 45:4:1 acetonitrile:ethanol:methanol
Flow rate: 300 ml/min

20 Analytical data on a chiral phase:

Chiral column: Chiralpak ADH/33 250 x 4.6, base-preconditioned;
Solvent: 45:4:1 acetonitrile:ethanol:methanol
Flow rate: 1 ml/min
Temperature: 30°C

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Retention time of enantiomer A: 4.498 minutes,

Yield of enantiomer A: 4.0 g;

Retention time of enantiomer B: 5.480 minutes,

Yield of enantiomer B: 4.5 g.

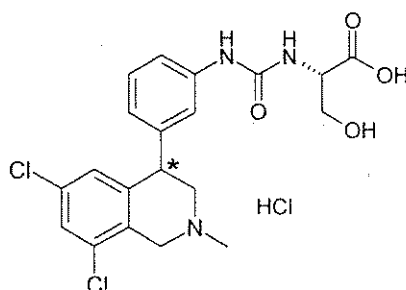
Intermediate 2: 4-nitrophenyl (R or S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride

- 5 1.54 g (5.0 mmol) of enantiomer B of intermediate 1 were reacted with 1.1 equivalents of 4-nitrophenyl chloroformate in a similar manner to the method described in Example 6, intermediate 1 to obtain 1.87 g of the title compound.

10 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea hydrochloride

Starting from 4-nitrophenyl (R or S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 2) and tert-butyl (S)-aspartate hydrochloride, the title compound was prepared in diastereomerically pure form in a similar manner to the synthetic route specified in
15 Example 13.

Example 21: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea hydrochloride



20 Intermediate 1: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-N'-(1-tert-butoxycarbonyl-3-butoxy-2S-propyl)}urea

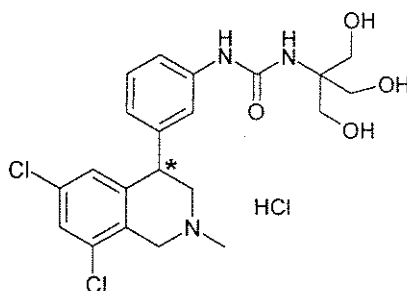
- 509 mg (1.0 mmol) of 4-nitrophenyl (R or S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 2, Example
25 20) were reacted with 280 mg (1.1 mmol) of tert-butyl (S)-2-amino-3-tert-butoxypropionate hydrochloride in a similar manner to that described in Example 12, intermediate 1 to obtain 460 mg of the title compound.

21: {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea hydrochloride

270 mg (0.49 mmol) of {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-N'-(1-tert-butoxycarbonyl-3-butoxy-2S-propyl)}urea (intermediate 1) were stirred in 12 ml of trifluoroacetic acid at room temperature for 1 hour.

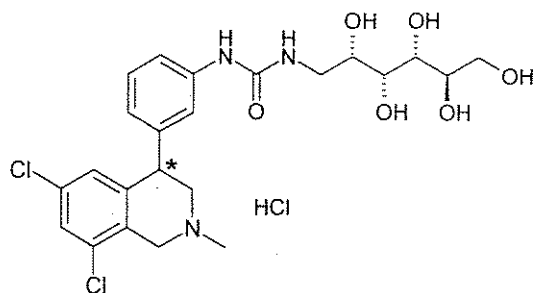
Subsequently, the mixture was concentrated. The residue was triturated with ether and filtered off with suction to obtain 247 mg of the trifluoroacetate. This was dissolved in 30 ml of H₂O/30 ml of 1 N HCl and freeze-dried. Repeated dissolution in H₂O and subsequent freeze-drying afforded 182 mg of the title compound.

Example 22: 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R or S)-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea hydrochloride



Starting from 509 mg (1.0 mmol) of 4-nitrophenyl (R or S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 2, Example 20) and 2-amino-2-hydroxymethylpropane-1,3-diol, a similar procedure to the method described in example 77a afforded 101 mg of the desired enantiomerically pure hydrochloride.

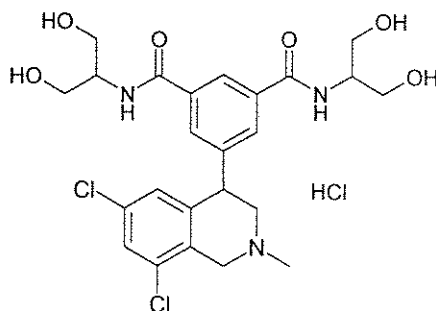
Example 23: 1-[3-((R or S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea hydrochloride



Starting from 509 mg (1.0 mmol) of 4-nitrophenyl (R or S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]carbamate hydrochloride (intermediate 2,
 5 Example 20) and D-glucamine, a similar procedure to the method described in Example 8/8a afforded 169 mg of the desired diastereomerically pure hydrochloride.

Example 24: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1-hydroxymethylethyl)isophthalamide hydrochloride

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Intermediate 1: 1-(3,5-bis(trifluoromethyl)phenyl)ethanone

5.16 g (20 mmol) of 3,5-bis(trifluoromethyl)benzoic acid were dissolved in 100 ml of
 15 abs. THF and admixed at 0°C with 31.25 ml of a 1.6 M solution of methyllithium in diethyl ether. After the mixture had been stirred at room temperature for 5 hours, excess methyllithium was hydrolyzed by adding H₂O and the solvent was removed in vacuo. The residue was taken up in dichloromethane and washed with saturated
 NaHCO₃ solution. The organic phase was removed, dried over MgSO₄ and
 20 concentrated. Chromatography on silica gel afforded 3.97 g of the title compound.

Intermediate 2: 1-(3,5-bis(trifluoromethyl)phenyl)-2-bromoethanone

2.97 g (11.6 mmol) of 1-(3,5-bis(trifluoromethyl)phenyl)ethanone (intermediate 1) were dissolved in 15 ml of glacial acetic acid and admixed at 0°C with 1.82 g (11.4 mmol) of Br₂ and stirred at 50°C for 2.5 hours. After standing overnight, the reaction mixture was added to ice and extracted twice with ethyl acetate. The combined ethyl acetate phases were washed twice more with H₂O, dried over Na₂SO₄ and concentrated to obtain 4 g of the title compound.

Intermediate 3: 4-(3,5-bis(trifluoromethyl)phenyl)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinoline

The process was continued in a similar manner to the synthetic route described under Example 1 starting from 1-(3,5-bis(trifluoromethyl)phenyl)-2-bromoethanone (intermediate 2) and 2,4-dichlorobenzylmethylamine (Example 1, intermediate 1) to obtain the 4-(3,5-bis(trifluoromethyl)phenyl)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinoline after alkylation reaction, reduction and ring closure reaction.

Intermediate 4: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)isophthalic acid

800 mg (1.9 mmol) of 4-(3,5-bis(trifluoromethyl)phenyl)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinoline (intermediate 3) were introduced into a mixture of 6 ml of chlorosulfonic acid and 5 ml of conc. H₂SO₄ and subsequently heated to 100°C for 6 hours. For workup, the mixture was added to ice, and the precipitate was filtered off with suction and dried to obtain 772 mg of the desired isophthalic acid as the hydrogen sulfate.

24: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1-hydroxymethylethyl)isophthalamide hydrochloride

95 mg of intermediate 4 were dissolved in 4 ml of DMF and a solution of 75.9 mg (0.75 mmol) of triethylamine and 164 mg (0.5 mmol) of TOTU in 3 ml of DMF was added at 0°C. The mixture was stirred at 0°C for 30 minutes and at room temperature for 30 minutes. The resulting solution was added to a solution of 46 mg (0.5 mmol) of 2-amino-1,3-propanediol in 5 ml of DMF. After adding a further 50.6 mg (0.5 mmol) of

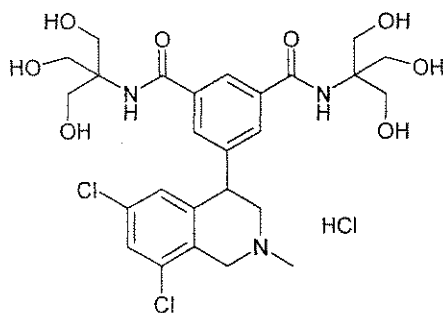
triethylamine, the mixture was stirred at room temperature. For workup, the solvent was removed in vacuo and the residue purified on silica gel. After a further purification on a preparative HPLC, the product fractions were concentrated, dissolved in 1 N HCl and freeze-dried to isolate 48 mg of the title compound.

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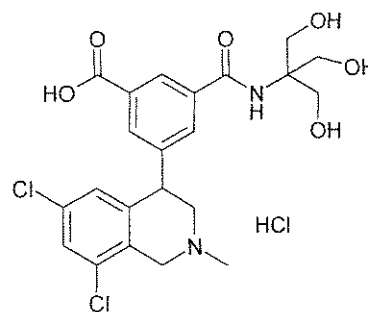
Example 25: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide hydrochloride and

Example 26: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide hydrochloride

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95 mg of 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)isophthalic acid (intermediate 4, Example 24) were reacted with 2-amino-2-hydroxymethylpropane-1,3-diol in a TOTU-mediated reaction in a similar manner to the method described in Example 24. In the subsequent purification on silica gel, 2 fractions could be isolated which were both subjected to a further purification on a preparative HPLC.

15

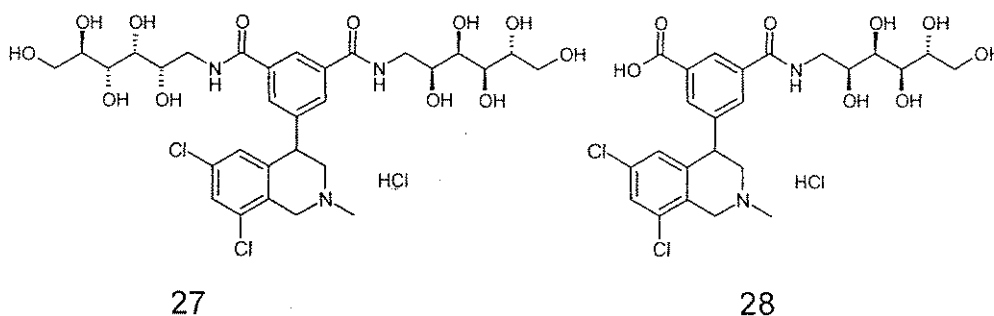
Concentration of the product fractions, dissolution in dilute HCl and subsequent freeze-drying afforded 17 mg of the title compound for Example 25, and also 33 mg of the title compound for Example 26.

20

Example 27: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)isophthalamide hydrochloride and

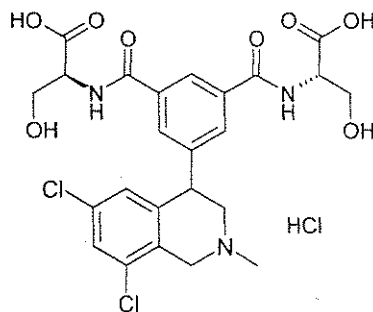
Example 28: 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)isophthalamide hydrochloride

25



Starting from 95 mg of 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)isophthalic acid (intermediate 4, Example 24), a similar procedure to the method described in Examples 25/26 afforded 11 mg of Example compound 27, and also 29 mg of Example compound 28.

Example 29: (S)-2-[3-((S)-1-carboxy-2-hydroxyethylcarbamoyl)-5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid hydrochloride



Intermediate 1: tert-butyl (S)-3-tert-butoxy-2-[3-((S)-2-tert-butoxy-1-tert-butoxycarbonyl-3-hydroxypropionate)-5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]propionate

95 mg of 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)isophthalic acid (intermediate 4, Example 24) were reacted in a similar manner to the TOTU coupling described in Example 24 with 127 mg of tert-butyl (S)-2-amino-3-tert-butoxypropionate hydrochloride to obtain 200 mg of the title compound after chromatography on silica gel.

29: (S)-2-[3-((S)-1-carboxy-2-hydroxyethylcarbamoyl)-5-(6,8-dichloro-2-methyl-1,2,3,4-

tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid hydrochloride

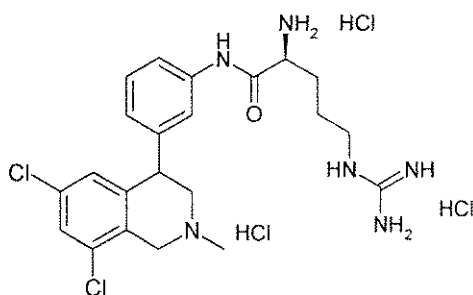
200 mg of intermediate 1 were stirred in 5 ml of trifluoroacetic acid at room

temperature for 1 hour. Subsequently, the solvent was removed in vacuo, and the

5 residue was triturated with ether and filtered off with suction. The trifluoroacetate obtained in this way was dissolved in dilute HCl and freeze-dried to obtain 109 mg of the title compound.

Example 30: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(S)-

10 2-amino-5-guanidinopentanamide hydrochloride



Intermediate 1: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-

15 2S-tert-butoxycarbonylamino-5-(N',N''-di-tert-butoxycarbonyl)-guanidinopentanamide

570 mg (1.2 mmol) of (S)-5-(N',N''-di-tert-butoxycarbonylguanidino)-2-tert-

butoxycarbonylamino-pentanoic acid were initially charged in 10 ml of DMF and 405 mg

(4.0 mmol) of triethylamine were added. After cooling to 0°C, 406 mg (3.0 mmol) of

HOBt, 379 mg (3.0 mmol) of DIC and 61 mg (0.5 mmol) of DMAP were added.

20 Afterwards, the mixture was admixed at 0°C with a solution of 307 mg (1.0 mmol) of 3-

(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (Example 2,

intermediate 1) in 6 ml of DMF and stirred at room temperature. For workup, the

solvent was removed in vacuo, and the residue was taken up in ethyl acetate and

washed with saturated NaHCO₃ solution. The organic phase was removed and the

25 aqueous extracted once more with ethyl acetate. The combined organic phases were

washed once with 2 N HCl and once with H₂O, dried over MgSO₄ and concentrated by

rotary evaporation. After subsequent chromatography on silica gel, 237 mg of the title

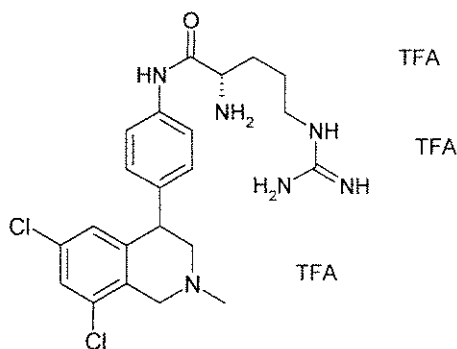
compound were obtained.

30: N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(S)-2-amino-5-guanidinopentanamide hydrochloride

237 mg of intermediate 1 were dissolved in 5 ml of dichloromethane and admixed at 0°C with 1 ml of trifluoroacetic acid. The mixture was allowed to warm to room temperature and was stirred for 24 hours. Afterwards, the mixture was freed of solvents and codistilled once with toluene. The product obtained in this way was dissolved in 25 ml of 0.1 N HCl, filtered and freeze-dried. Repeated dissolution in H₂O and subsequent freeze-drying afforded 162 mg of the title compound.

10

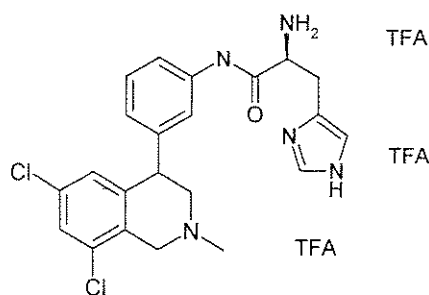
Example 31: N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(S)-2-amino-5-guanidinopentanamide trifluoroacetate



15 Starting from 4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (Example 1, intermediate 6) and (S)-5-(N',N''-di-tert-butoxycarbonylguanidino)-2-tert-butoxycarbonylaminopentanoic acid, a similar procedure to the method described in Example 30 with subsequent treatment with trifluoroacetic acid afforded the title compound as the trifluoroacetate.

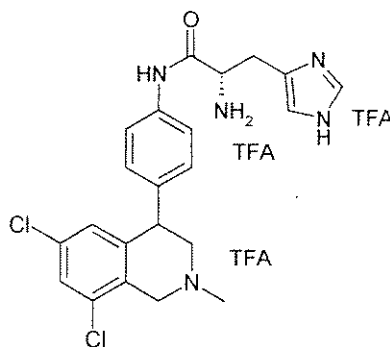
20

Example 32: (S)-2-amino-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide trifluoroacetate



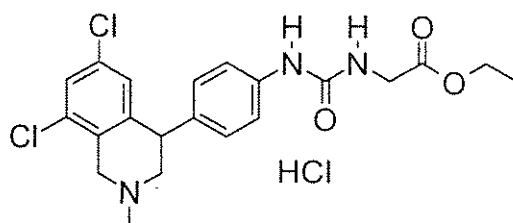
The title compound was prepared in a similar manner to the procedure described in Example 30 starting from 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (Example 2, intermediate 1) and tert-butyl 4-((S)-2-tert-butoxycarbonylamino-2-carboxyethyl)imidazole-1-carboxylate with subsequent treatment with trifluoroacetic acid.

Example 33: (S)-2-amino-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propanamide trifluoroacetate



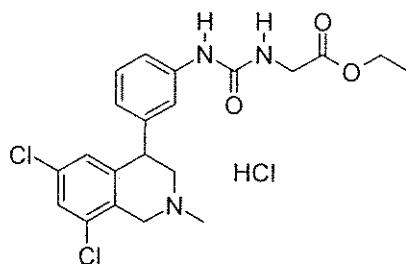
The title compound was prepared in a similar manner to the procedure described in Example 30 starting from 4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (Example 1, intermediate 6) and tert-butyl 4-((S)-2-tert-butoxycarbonylamino-2-carboxyethyl)imidazole-1-carboxylate with subsequent treatment with trifluoroacetic acid.

Example 34: Ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido} acetate hydrochloride



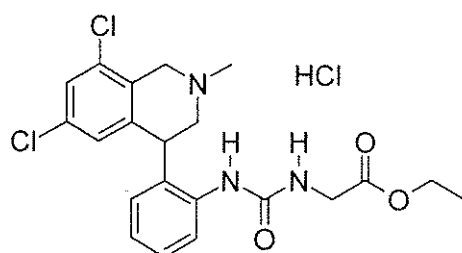
4-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (95 mg, example 1, intermediate 6) was dissolved in acetonitrile (2 ml) and ethyl isocyanatoacetate (30 mg) was added dropwise with stirring. After four hours, the solution was concentrated and the residue purified by means of preparative HPLC. The product-containing fractions were combined, the acetonitrile was removed on a rotary evaporator, and the aqueous residue was neutralized with potassium carbonate and extracted three times with ethyl acetate. Drying over magnesium sulfate was followed by drying. The residue was taken up with aqueous hydrochloric acid and freeze-dried. 107 mg of the desired compound were obtained.

Example 35: Ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-phenyl]ureido} acetate hydrochloride



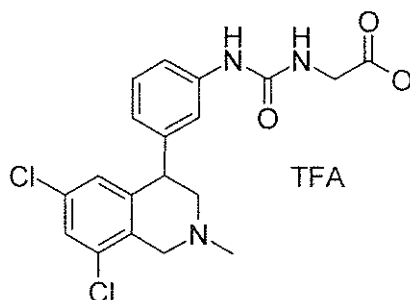
In a similar manner to example 34, 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (example 2, intermediate 1) and ethyl isocyanatoacetate were reacted.

Example 36: Ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-phenyl]ureido} acetate hydrochloride



In a similar manner to example 34, 2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine (example 3, intermediate 5) and ethyl isocyanatoacetate were reacted.

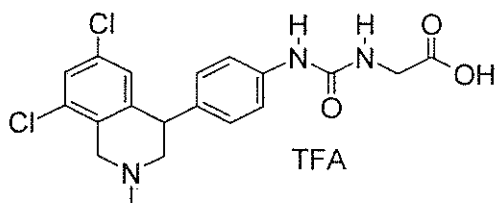
Example 37: {3-[3-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-ureido} acetic acid, trifluoroacetic acid salt



10 Ethyl 3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido} acetate hydrochloride (9 mg, example 35) was admixed with water (2 ml) and saturated potassium carbonate solution (0.25 ml) and stirred for 48 h. Aqueous 2 N hydrochloric acid was used to adjust the pH to 2, the solvent was removed and the residue purified by means of preparative HPLC. The product-containing fractions were
15 combined, the acetonitrile removed on a rotary evaporator and the residue freeze-dried. 6 mg of the desired compound were obtained.

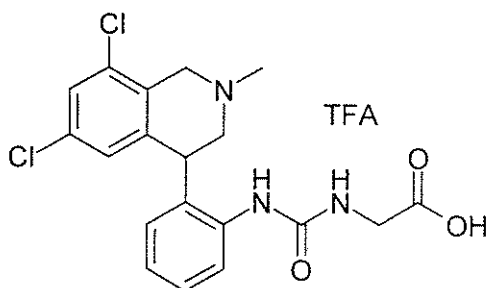
Example 38: {3-[4-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-ureido} acetic acid, trifluoroacetic acid salt

76



In a similar manner to example 4, ethyl 3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido} acetate hydrochloride was hydrolyzed.

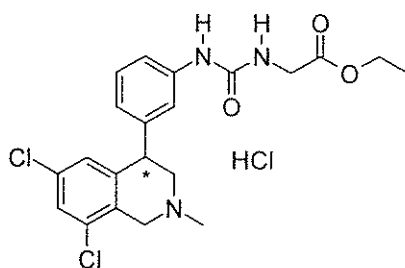
- 5 Example 39: {3-[2-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-ureido} acetic acid, trifluoroacetic acid salt



In a similar manner to example 4, ethyl 3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido} acetate hydrochloride (example 36) was hydrolyzed.

10

- Example 40: Ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]ureido} acetate

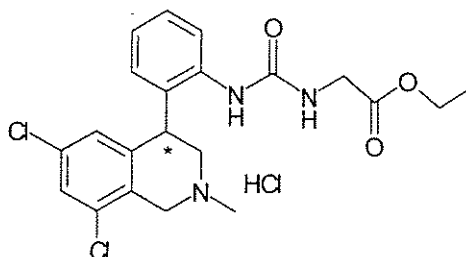


15

In a similar manner to example 34, 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenylamine (example 20, intermediate 1, enantiomer B) and ethyl isocyanatoacetate were reacted, except that dichloromethane was used as the solvent instead of acetonitrile.

20

Example 41: Ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]ureido} acetate



5

Intermediate 1:

(R)-2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine and

(S)-2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine

2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-phenylamine (example 3,

10 intermediate 5) was separated into the enantiomers on a chiral phase.

Preparative separation conditions:

Chiral column: Chiralpak AD10 35 x 10 cm

Solvent: acetonitrile

15 Flow rate: 300 ml/min

Analytical data on a chiral phase:

Chiral column: Chiralpak ADH 250 x 4.6 mm ,

Solvent: acetonitrile

20 Flow rate: 1 ml/min

Temperature: 30°C

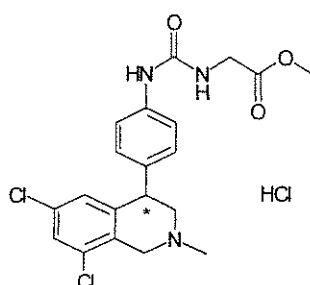
Retention time of enantiomer A: 5.1 min

Retention time of enantiomer B: 7.3 min

25

In a similar manner to example 40, 2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4(R or S)-yl)phenylamine (enantiomer B) and ethyl isocyanatoacetate were reacted.

Example 42: Ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]ureido} acetate



5

Intermediate 1:

(R)-4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine and

(S)-4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenylamine

10 4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-phenylamine (example 1, intermediate 6) was separated into the enantiomers on a chiral phase.

Preparative separation conditions:

Chiral column: Chiralpak AD10 35 x 10 cm

15 Solvent: MeOH/0.1% DEA

Flow rate: 300 ml/min

Analytical data on a chiral phase:

Chiral column: Chiralpak ADH 250 x 4.6 mm ,

20 Solvent: MeOH/0.1% DEA

Flow rate: 1 ml/min

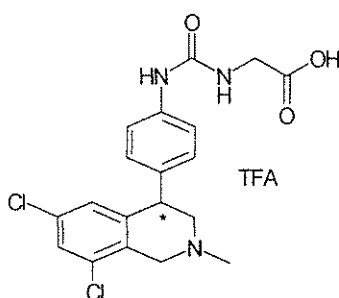
Temperature: 30°C

Retention time of enantiomer A: 4.8 min

25 Retention time of enantiomer B: 7.6 min

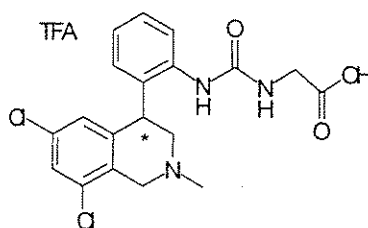
In a similar manner to example 40, 4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenylamine (enantiomer B) and ethyl isocyanatoacetate were reacted.

- 5 Example 43: {3-[4-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)-phenyl]ureido} acetic acid, trifluoroacetic acid salt



- 10 In a similar manner to example 4, ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]ureido} acetate hydrochloride (example 42) was hydrolyzed, except that ethanol served as the solvent and aqueous sodium hydroxide solution as the base.

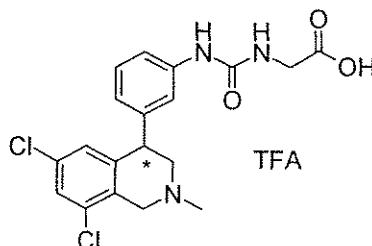
- 15 Example 44: {3-[2-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)-phenyl]ureido} acetic acid, trifluoroacetic acid salt



- 20 Ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]ureido} acetate hydrochloride (430 mg, example 41) was initially charged in water (35 ml) and admixed with 10% hydrochloric acid with stirring. After 3 hours under reflux, the mixture was hydrolyzed. The solvent was removed and the residue purified by means of preparative HPLC. The product-containing fractions were combined, and the solvent removed on a rotary evaporator. The residue was further purified using silica gel (1:1 ethyl acetate/methanol), the product-containing fractions were combined,

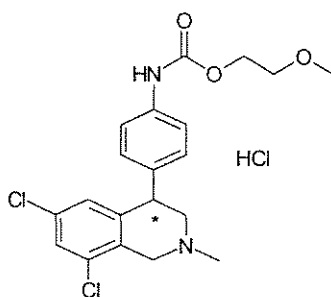
the solvent was removed on a rotary evaporator and the residue was freeze-dried. 45 mg of the desired compound were obtained.

Example 45: {3-[3-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)-phenyl]ureido} acetic acid, trifluoroacetic acid salt



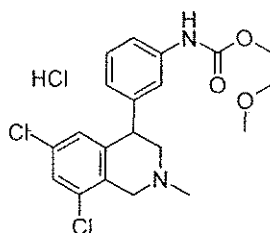
In a similar manner to example 4, ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]ureido} acetate hydrochloride (example 40) was hydrolyzed, except that the acetonitrile solvent was dispensed with.

Example 46: 2-Methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]carbamate



4-(6,8-Dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenylamine (70 mg, example 20, intermediate 1, enantiomer B) was dissolved in methylene chloride (4.5 ml) and a solution of 2-methoxyethyl chloroformate (39 mg) in methylene chloride (0.5 ml) was slowly added dropwise with stirring. After leaving to stand overnight, the solvent was removed and the residue purified by means of preparative HPLC. The product-containing fractions were combined, the acetonitrile removed on a rotary evaporator, and the residue admixed with hydrochloric acid and freeze-dried. 80 mg of the desired compound were obtained.

Example 47: 2-Methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R or S)-yl)phenyl]carbamate



In a similar manner to example 13, 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydro-
isoquinolin-4-yl)phenylamine (example 2, intermediate 1) was reacted with 2-methoxy-
ethyl chloroformate. However, chromatography could be dispensed with.

Conditions

Prep. HPLC:

Unless stated otherwise, the preparative HPLC was carried out under the following
conditions:

stationary phase: Merck Purospher RP18 (10 μ M) 250 x 25 mm

mobile phase: 90% H₂O (0.05% TFA) → 90% acetonitrile; 40 min; 25 ml/min

LCMS methods:

Method A:

Stationary phase: YMC, J'sphere ODS, H80 20 x 2.4 μ m;

Mobile phase: 0 min, 90% H₂O (0.05% TFA); 2.5 min, 95% ACN; 3.3 min, 95%
ACN; 3.35 min, 90% H₂O; 1 ml/min; 30°C.

Method B:

Stationary phase: Merck Purosphere 3 μ m 2 x 55 mm;

Mobile phase: 0 min, 95% H₂O (0.05% TFA); 4 min, 95% ACN; 5.5 min, 95%
ACN; 6.5 min, 95% H₂O; 0.5 ml/min; 30°C.

Method C:

Stationary phase: Merck Purosphere 5 μ 2 x 55 mm;

Mobile phase: 0 min, 95% H₂O (0.05% TFA); 3 min, 95% ACN; 4.5 min, 95% ACN; 5.5 min, 95% H₂O; 0.5 ml/min; 30°C.

5 Method D:

Stationary phase: YMC, J'sphere ODS, H80 20 x 2.4 μ ;

Mobile phase: 0 min, 90% H₂O (0.05% TFA); 1.9 min, 95% ACN; 2.4 min, 95% ACN; 2.45 min, 90% H₂O; 1 ml/min; 30°C.

10 Method E:

Stationary phase: Merck Purosphere 5 μ 2 x 55 mm;

Mobile phase: 0 min, 95% H₂O (0.05% TFA); 3.5 min, 95% ACN; 4.5 min, 95% ACN; 5.5 min, 95% H₂O; 0.5 ml/min; 30°C.

15 Method F:

Stationary phase: YMC J'sphere ODS H80 20 x 2.1 mm

Mobile phase: 90% H₂O (0.05% TFA) → 95% acetonitrile; 1.9 min; 95% acetonitrile; 0.5 min → 10% acetonitrile; 0.05 min; 1 ml/min.

20 Method G:

Stationary phase: YMC J'sphere ODS H80 20 x 2.1 mm

Mobile phase: 96% H₂O (0.05% TFA) → 95% acetonitrile; 2.0 min; 95% acetonitrile; 0.4 min → 4% acetonitrile; 0.05 min; 1 ml/min.

25 Table 1: Analytical data of the example compounds

Example No.	Retention time*)	Method	M+H ⁺	Method
1	1.402	A	485.1	ESI
1a	1.774	C	485.3	ESI
2	1.469	A	485.1	ESI

2a	3.420	B	485.1	ESI
3	1.512	A	485.1	ESI
3a	1.519	A	485.1	ESI
4a	1.828	C	485.2	ESI
4b	1.806	C	485.3	ESI
5	0.879	D	485.1	ESI
6	0.933	D	424.2	ESI
6a	0.937	D	424.2	ESI
7	0.951	D	454.2	ESI
7a	0.958	D	454.1	ESI
8	0.902	D	514.2	ESI
8a	0.9121	D	514.2	ESI
9	0.891	D	512.1	ESI
10	0.979	D	458.1	ESI
11	0.883	D	435.2	ESI
12	0.973	D	438.1	ESI
12a	0.970	D	438.2	ESI
13	0.945	D	465.2	ESI
14	0.834	D	499.1	ESI
15	0.887	D	409.1	ESI
16	0.959	D	423.1	ESI
17	2.081	E	451.1	ESI
18	2.027	E	450.1	ESI
19	0.925	D	507.2	ESI
20	0.959	D	465.1	ESI
21	0.982	D	438.1	ESI
22	0.971	D	454.2	ESI
23	0.925	D	514.2	ESI
24	0.633	D	526.1	ESI
25	0.711	D	586.2	ESI
26	0.853	D	483.1	ESI

27	0.402	D	706.1	ESI
28	0.803	D	543.1	ESI
29	0.820	D	554.1	ESI
30	0.772	D	463.2	ESI
31	1.805	E	463.2	ESI
32	1.917	E	444.1	ESI
33	1.817	E	444.1	ESI
34	1.14	F	436.5	ESI
35	1.15	F	436.5	ESI
36	1.13	F	436.5	ESI
37	1.08	F	408.4	ESI
38	1.00	F	408.4	ESI
39	1.04	F	408.4	ESI
40	1.15	F	436.5	ESI
41	1.13	F	436.5	ESI
42	1.05	G	436.5	ESI
43	0.94	G	408,1	ESI
44	0.95	G	408,1	ESI
45	0.96	G	408,1	ESI
46	1.10	G	409.1	ESI
47	1.13	F	409,1	ESI

*) The retention times relate to the mass spectra.

Pharmacological data:

5 Test description:

This test determines the recovery of the intracellular pH (pH_i) after acidification, and this recovery occurs in the case of functional NHE even under bicarbonate-free conditions. To this end, the pH_i was determined using the pH-sensitive fluorescent dye BCECF (Calbiochem, the BCECF-AM precursor was used). The cells were initially loaded with BCECF. The BCECF fluorescence was determined in a Ratio

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 to the pH_i by means of calibration curves. The cells had already been incubated in NH_4Cl buffer (pH 7.4) in the course of the BCECF loading (NH_4Cl buffer: 115 mM NaCl, 20 mM NH_4Cl , 5 mM KCl, 1 mM CaCl_2 , 1 mM MgSO_4 , 20 mM Hepes, 5 mM glucose, 1 mg/ml BSA; a pH of 7.4 was established using 1 M NaOH). The intracellular acidification was induced by adding 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 the pH recovery was registered at 2 minutes for NHE1, at 5 minutes for NHE2 and at three minutes for NHE3. For the calculation of the inhibitory potency of the tested substances, the cells were initially investigated in buffers in which complete or absolutely no pH recovery took place. For 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 NaH_2PO_4 , 5 mM Hepes, 5 mM glucose, a pH of 7.0 was established 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 was established using 1 M NaOH). The substances to be tested were made up in the Na^+ -containing buffer. The recovery of the intracellular pH at each tested concentration of a substance was expressed in percent of the maximum recovery. The percentages of the pH recovery were used to calculate the IC_{50} value of the particular substance for the individual NHE subtypes by means of the program Sigma-Plot.

The inhibitory data of some example compounds were shown by way of example in Table 2.

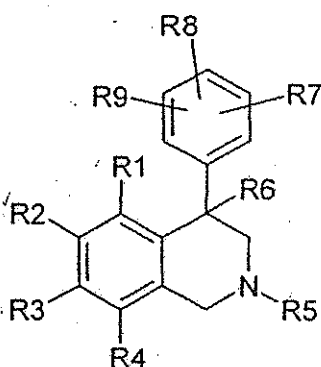
Table 2: Inhibitory data of some example compounds on NHE3

Example compound	IC_{50} value (μM)
2	0.0036

13	0.0176
16	0.1594
31	0.0291

CLAIMS:

1. A compound of the formula I



where: R1, R2, R3 and R4,

are each independently H, F, Cl, Br, CN, NO₂, OH, CH₃, CH₂CH₃, CF₃, CH₂CF₃, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, SO₂R10, NR14R15, CONR16R17, COOR18 or OCOR18;

R10 is CH₃, CH₂CH₃, CF₃, CH₂CF₃, OH or NR11R12;

R11 and R12

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃;

R14 and R15

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃,

87a

COCH_3 , COCH_2CH_3 , COCF_3 or COCH_2CF_3 ;

R16 and R17

are each independently H, CH_3 , CH_2CH_3 , CF_3 or CH_2CF_3 ;

R18 is H, CH_3 , CH_2CH_3 , CF_3 or CH_2CF_3 ;

R5 is CH_3 ;

R6 is H;

R7, R8 and R9

are each independently H, F, Cl, Br, I, OH, CH₃, CH₂CH₃, CF₃, CH₂CF₃, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, SO₂R₄₇, SO₃R₆₀, COR₄₇, COOR₆₀, NR₅₁R₅₂ or a -L-G group;

R₄₇ is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃ or NR₄₈R₄₉;

R₄₈ and R₄₉

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃,

or

R₄₈ and R₄₉

together with the nitrogen atom which bonds them together form a 5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholiny;

R₆₀ is H, CH₃, CH₂CH₃, CF₃, CH₂CF₃;

R₅₁ and R₅₂

are each independently H, CH₃, CH₂CH₃, CF₃, CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or COCH₂CF₃

or

R₅₁ and R₅₂

together with the nitrogen atom which bonds them together form a 5- or 6-membered ring from the group of 1-pyrrolyl, 1-piperidiny, 1-piperaziny, 1-N-methylpiperaziny and 4-morpholiny;

L is -CH₂-, -O-, -NR₃₀-, -OCO-, -NR₃₀CO-, -NR₃₀CS-, -NR₃₀SO₂-, -CONR₃₀-, -COO-, -CSNR₃₀-, -SO₂NR₃₀-, -NR₃₀CONR₃₁-, -NR₃₀COO-, -NR₃₀CSNR₃₁- or -NR₃₀SO₂NR₃₁-;

R₃₀ and R₃₁

are each independently H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

G is a group C_a(OR₃₂)_xH_{2a+1-x} where one or more CH₂ groups may be replaced by O or NR₃₃,

$C_b(OR_{32})_yH_{2b-1-y}$ where one or more CH_2 groups may be replaced by O or NR_{33} , C_cH_{2c+1} where two or more CH_2 groups are replaced by O or NR_{33} ,

$-(CH_2)_z-COOR_{34}$, $-(CH_2)_z-SO_3R_{34}$, $-(CH_2)_z-N^+R_{35}R_{36}R_{37}$

where 1 or 2 hydrogen atoms of the $-(CH_2)_z$ units may be replaced by OR_{32} groups, $-CR_{38}R_{39}-COOR_{40}$ or $-CR_{38}R_{39}NR_{41}R_{42}$;

a is 2, 3, 4, 5, 6, 7 or 8;

x is 2, 3, 4, 5, 6, 7 or 8;

R_{32} is H, CH_3 , CH_2CH_3 , CF_3 , CH_2CF_3 , $COCH_3$, $COCH_2CH_3$, $COCF_3$ or $COCH_2CF_3$;

R_{33} is H, CH_3 , CH_2CH_3 , CF_3 or CH_2CF_3 ;

b is 3, 4, 5, 6 or 7;

y is 2, 3, 4, 5, 6 or 7;

c is 3, 4, 5, 6, 7 or 8;

z is 1 or 2;

R_{34} , R_{35} , R_{36} and R_{37}

are each independently H, CH_3 , CH_2CH_3 , CF_3 or CH_2CF_3 ;

R_{38} is $-(CH_2)_n-Y$;

n 0, 1, 2, 3 or 4;

Y is H, alkyl having 1, 2, 3 or 4 carbon atoms of which some or all may be fluorinated and one or more CH_2 groups may be replaced by O, S or NR_{43} , or is $COOR_{44}$, $CONR_{45}R_{46}$, $NHC(NH)NH_2$, phenyl or heteroaryl, and the phenyl and heteroaryl radicals may be substituted by up to 3 substituents selected from the group of CH_3 , CF_3 , OH, OCH_3 or NH_2 ;

R_{43} , R_{44} , R_{45} and R_{46}

are each independently H, CH₃, CH₂CH₃,
CF₃ or CH₂CF₃,

R39 is H;

R40 is H, CH₃, CH₂CH₃, CF₃ or CH₂CF₃;

5 R41 and R42

are each independently H, CH₃, CH₂CH₃, CF₃,
CH₂CF₃, COCH₃, COCH₂CH₃, COCF₃ or
COCH₂CF₃;

10 in which at least one of the R7, R8 or R9 radicals has to be defined by the -L-G group,
and also its pharmaceutically acceptable salts and trifluoroacetates.

2. A compound of the formula I as claimed in claim 1, selected from the group of
N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-
15 pentahydroxyhexanamide,
N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-
pentahydroxyhexanamide,
N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-
pentahydroxyhexanamide,
20 N-[3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-
pentahydroxyhexanamide,
N-[3-((R)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2,3,4,5,6-
pentahydroxyhexanamide,
1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-
25 hydroxymethylethyl)urea,
1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-
bishydroxymethylethyl)urea,
1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2,3,4,5,6-
pentahydroxyhexyl)urea,
30 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2,4,5-
trihydroxy-6-hydroxymethyltetrahydropyran-3-yl)urea,

- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-sulfo-2-ethyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(ethyl-2-trimethylammonium)}urea chloride,
- 5 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2-propyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2-butyl)}urea,
- 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2,3,4,5,6-
- 10 pentahydroxyhexyl)benzamide,
- 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1-hydroxymethylethyl)benzamide,
- 2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
- 15 2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinic acid,
- 2-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamic acid,
- N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-[1-carboxy-5-
- 20 guanidino-2-pentyl]urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2-butyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2-propyl)}urea,
- 25 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2,3,4,5,6-pentahydroxyhexyl)urea,
- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1-
- 30 hydroxymethylethyl)isophthalamide,
- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,

- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,
- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2,3,4,5,6-pentahydroxyhexyl)isophthalamide,
- 5 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2,3,4,5,6-pentahydroxyhexyl)isophthalamide,
- 2-[3-(1-carboxy-2-hydroxyethylcarbamoyl)-5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
- N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
- 10 N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
- 2-amino-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide,
- 15 2-amino-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide,
- ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
- ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
- 20 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
- 25 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
- {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
- ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-acetate,
- 30 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,

- ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-acetate,
- ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,
- 5 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-acetate,
- ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,
- 10 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic acid,
- {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic acid,
- {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic acid,
- 15 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic acid,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic acid,
- {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic acid,
- 20 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-carbamate,
- 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-carbamate,
- 25 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-carbamate,
- and
- 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-carbamate;
- 30 and their pharmaceutically acceptable salts and trifluoroacetates.

3. A compound of the formula I as claimed in claim 1 or 2, selected from the group of
 - N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
 - N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
 - N-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
 - N-[3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
 - N-[3-((R)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-(2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanamide,
 - 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1-hydroxymethylethyl)urea,
 - 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
 - 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea,
 - 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((4R,5S,6R)-2,4,5-trihydroxy-6-hydroxymethyltetrahydropyran-3-yl)urea,
 - {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-sulfo-2-ethyl)}urea,
 - {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(ethyl-2-trimethylammonium)}urea chloride,
 - {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea,
 - {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea,
 - 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)benzamide,
 - 3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1-hydroxymethylethyl)benzamide,

- 2-(S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
- 2-(S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]succinic acid,
- 5 2-(S)-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-4-succinamic acid,
- N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-N'-[1-carboxy-5-guanidino-2S-pentyl]urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R)-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea,
- 10 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(S)-yl)phenyl]-N'-(1-carboxy-4-aminocarboxy-2S-butyl)}urea,
- {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R)-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea,
- 15 {N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(S)-yl)phenyl]-N'-(1-carboxy-3-hydroxy-2S-propyl)}urea,
- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(R)-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
- 1-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-(S)-yl)phenyl]-3-(2-hydroxy-1,1-bishydroxymethylethyl)urea,
- 20 1-[3-((R)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea,
- 1-[3-((S)-6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)urea,
- 25 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1-hydroxymethylethyl)isophthalamide,
- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,
- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-(2-hydroxy-1,1-bishydroxymethylethyl)isophthalamide,
- 30 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N,N'-bis((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)isophthalamide,

- 5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)isophthalamide,
 (S)-2-[3-((S)-1-carboxy-2-hydroxyethylcarbamoyl)-5-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)benzoylamino]-3-hydroxypropionic acid,
- 5 (S)-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
 (S)-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-2-amino-5-guanidinopentanamide,
 (S)-2-amino-N-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-
- 10 (1H-imidazol-4-yl)propionamide,
 (S)-2-amino-N-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]-3-(1H-imidazol-4-yl)propionamide,
 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
- 15 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}-acetate,
 {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic
- 20 acid,
 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)phenyl]ureido}acetic acid,
- 25 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-acetate,
 ethyl {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,
 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-
- 30 acetate,
 ethyl {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,

ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}-acetate,
 ethyl {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}-acetate,
 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic acid,
 {3-[4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic acid,
 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic acid,
 {3-[2-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic acid,
 {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]ureido}acetic acid,
 {3-[3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]ureido}acetic acid,
 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-carbamate,
 2-methoxyethyl [4-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-carbamate,
 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(R)-yl)phenyl]-carbamate,
 and
 2-methoxyethyl [3-(6,8-dichloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-4(S)-yl)phenyl]-carbamate;
 and their pharmaceutically acceptable salts and trifluoroacetates.

4. A compound of the formula I and its pharmaceutically acceptable salts as claimed in any one of claims 1 to 3 for use as a medicament.
5. Use of a compound of the formula I and the pharmaceutically acceptable salts thereof as claimed in any one of claims 1 to 4 for preparing a medicament for the

treatment or prophylaxis of disorders of respiratory drive, of respiratory disorders, sleep-related respiratory disorders, sleep apneas, of snoring, of acute and chronic renal disorders, of acute renal failure and of chronic renal failure, of disorders of intestinal function, of high blood pressure, of essential hypertension, of disorders of the central nervous system, of disorders resulting from CNS overexcitability, epilepsy and centrally induced convulsions or of anxiety states, depressions and psychoses, of ischemic states of the peripheral or central nervous system and of stroke, of acute and chronic damage to and disorders of peripheral organs or limbs caused by ischemic or by reperfusion events, of atherosclerosis, of disorders of lipid metabolism, of thromboses, of disorders of biliary function, of infestation by ectoparasites, of disorders resulting from endothelial dysfunction, of protozoal disorders, of malaria, for the preservation and storage of transplants for surgical procedures, for use in surgical operations and organ transplantations or for the treatment of states of shock or of diabetes and late damage from diabetes or of diseases in which cellular proliferation represents a primary or secondary cause, and for maintaining health and prolonging life.

6. Use of a compound of the formula I and the pharmaceutically acceptable salts thereof as claimed in any one of claims 1 to 4 in combination with other medicaments or active ingredients for preparing a medicament for the treatment or prophylaxis of disorders of respiratory drive, of respiratory disorders, sleep-related respiratory disorders, sleep apneas, of snoring, of acute and chronic renal disorders, of acute renal failure and of chronic renal failure, of disorders of intestinal function, of high blood pressure, of essential hypertension, of disorders of the central nervous system, of disorders resulting from CNS overexcitability, epilepsy and centrally induced convulsions or of anxiety states, depressions and psychoses, of ischemic states of the peripheral or central nervous system and of stroke, of acute and chronic damage to and disorders of peripheral organs or limbs caused by ischemic or by reperfusion events, of atherosclerosis, of disorders of lipid metabolism, of thromboses, of disorders of biliary function, of infestation by ectoparasites, of disorders resulting from endothelial dysfunction, of protozoal disorders, of malaria, for the preservation and storage of transplants for surgical procedures, for use in surgical operations and organ

transplantations or for the treatment of states of shock or of diabetes and late damage from diabetes or of diseases in which cellular proliferation represents a primary or secondary cause, and for maintaining health and prolonging life.

7. Use of a compound of the formula I and/or the pharmaceutically acceptable salts thereof as claimed in any one of claims 1 to 4 alone or in combination with other medicaments or active ingredients for preparing a medicament for the treatment or prophylaxis of disorders of respiratory drive and/or of sleep-related respiratory disorders such as sleep apneas.
8. Use of a compound of the formula I and/or the pharmaceutically acceptable salts thereof as claimed in any one of claims 1 to 4 alone or in combination with other medicaments or active ingredients for preparing a medicament for the treatment or prophylaxis of snoring.
9. Use of a compound of the formula I and/or the pharmaceutically acceptable salts thereof as claimed in any one of claims 1 to 4 alone or in combination with other medicaments or active ingredients for preparing a medicament for the treatment or for the prophylaxis of acute or chronic renal disorders, of acute renal failure and of chronic renal failure.
10. Use of a compound of the formula I and/or the pharmaceutically acceptable salts thereof as claimed in any one of claims 1 to 4 alone or in combination with other medicaments or active ingredients for preparing a medicament for the treatment or prophylaxis of disorders of intestinal function.
11. A curative composition for human, veterinary or phytoprotective use comprising an effective amount of a compound of the formula I and/or of a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 4.
12. A curative composition for human, veterinary or phytoprotective use comprising an effective amount of a compound of the formula I and/or a pharmaceutically

acceptable salt thereof as claimed in any one of claims 1 to 4, in combination with other pharmacological active ingredients or medicaments.