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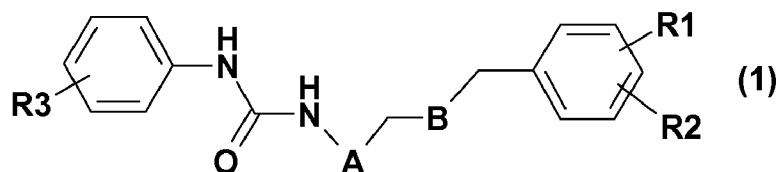
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(54) Title: PYRAN DERIVATIVES AS CCR3 MODULATORS



(57) Abstract: The compounds of formula (1) wherein A, B, R1, R2 and R3 have the meanings as given in the description, the stereoisomers, as well as the salts of the stereoisomers thereof are effective CCR3 modulators.

Description

Pyran derivatives as CCR3 modulators

5 Field of application of the invention

The invention relates to novel pyran derivatives, processes for their preparation, pharmaceutical compositions comprising said pyran derivatives and the use thereof in the treatment or prophylaxis of diseases.

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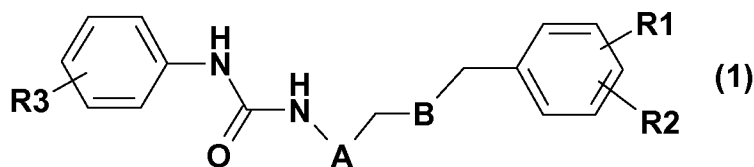
Known technical background

In the international patent application WO0202525 N-ureidoheterocycloalkyl-piperidines are described as modulators of CC chemokine receptor 3 (CCR3) activity, whereby the central
15 heterocyclic ring can be inter alia an optionally substituted pyran ring. In the international patent applications WO0035452, WO0198270 and WO2004110993 N-ureidocycloalkyl-piperidines are described as modulators of CC chemokine receptor 3 (CCR3) activity. In Bioorganic and Medicinal Chemistry Letters 17 (2000), 2992-2997, James R. Britt et al describe CC chemokine receptor 3 (CCR3) antagonists with inter alia a central pyran ring. Takeda et al. disclose CCR3 as a possible
20 target for age-related macular degeneration diagnosis and therapy in Nature Vol. 460, 225-230 (2009).

Description of the invention

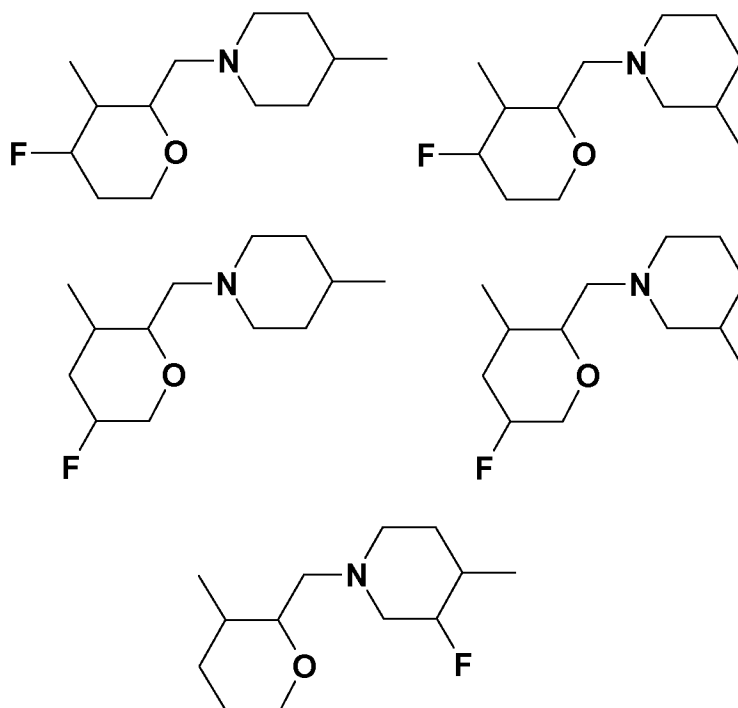
25 It has now been found that the pyran derivatives, which are described in detail below, have surprising and advantageous properties.

The invention relates to compounds of formula (1)



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wherein the group $-\text{A}-\text{CH}_2-\text{B}-$ is selected from



- R1 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
- R2 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine, and
- 5 R3 is hydrogen, halogen, cyano, hydroxycarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl, 1-4C-alkoxy-carbonyl, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylamino-carbonyl,
- 10 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

1-4C-Alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms. Examples are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

- 15 1-4C-Alkoxy is a group which, in addition to the oxygen atom, contains a straight-chain or branched alkyl group having 1 to 4 carbon atoms. Alkoxy groups having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy groups.
- 20 1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy group, of which the difluoromethoxy group is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

“Halogen” within the meaning of the present invention includes fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

- 5 1-4C-Alkylcarbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkyl group is bonded. An example is the acetyl group $[\text{CH}_3\text{C}(\text{O})-]$.

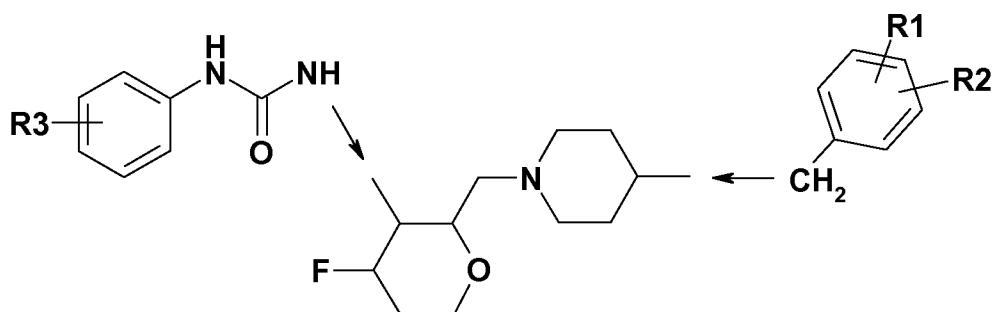
An 1-4C-Alkylcarbonylamino group is, for example, the propionylamino $[\text{C}_3\text{H}_7\text{C}(\text{O})\text{NH}-]$ and the acetylamino group $[\text{CH}_3\text{C}(\text{O})\text{NH}-]$.

10

1-4C-Alkoxy carbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy groups is bonded. Examples are the methoxycarbonyl $[\text{CH}_3\text{O}-\text{C}(\text{O})-]$, the ethoxycarbonyl $[\text{CH}_3\text{CH}_2\text{O}-\text{C}(\text{O})-]$ and the tert-butoxycarbonyl $[(\text{CH}_3)_3\text{CO}-\text{C}(\text{O})-]$ group.

- 15 Mono- or Di-1-4C-alkylaminocarbonyl groups contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino groups. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropyl-aminocarbonyl group.

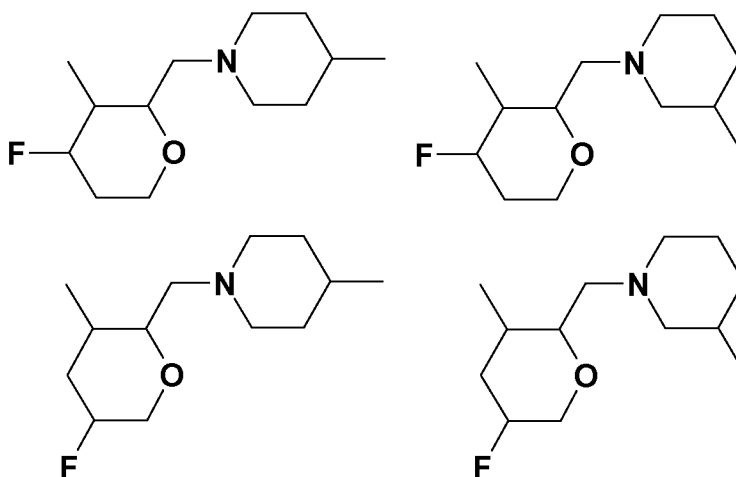
- 20 In the groups $-\text{A}-\text{CH}_2-\text{B}-$ shown in the description and the claims the urea group is attached to the indicated free valence at the pyran ring and the benzyl group is attached to the indicated free valence on the piperidiny ring. For example:



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In a preferred embodiment, the invention relates to compounds of formula (1), wherein the group $-\text{A}-\text{CH}_2-\text{B}-$ is selected from

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R1 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

5 R2 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine, and

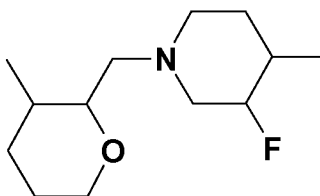
R3 is hydrogen, halogen, cyano, hydroxycarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl, 1-4C-alkoxy-carbonyl, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylamino-

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carbonyl,

the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

In a further preferred embodiment, the invention relates to compounds of formula (1), wherein the group $-A-CH_2-B-$ is selected from



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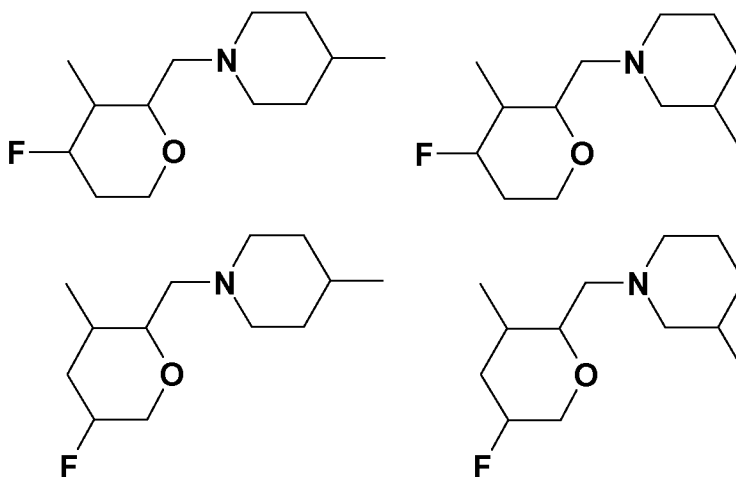
R1 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

20 R2 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine, and

R3 is hydrogen, halogen, cyano, hydroxycarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl, 1-4C-alkoxy-carbonyl, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylamino-carbonyl,

25 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

In a further preferred embodiment, the invention relates to compounds of formula (1), wherein the group -A-CH₂-B- is selected from

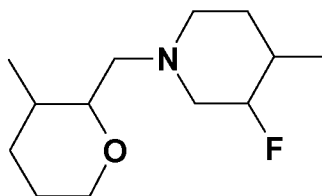


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- R1 is fluorine, chlorine, methoxy or difluoromethoxy,
 R2 is hydrogen, fluorine, chlorine, methyl or difluoromethoxy, and
 R3 is cyano, fluorine, methyl, methoxy, ethoxy, difluoromethoxy or acetyl,
 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

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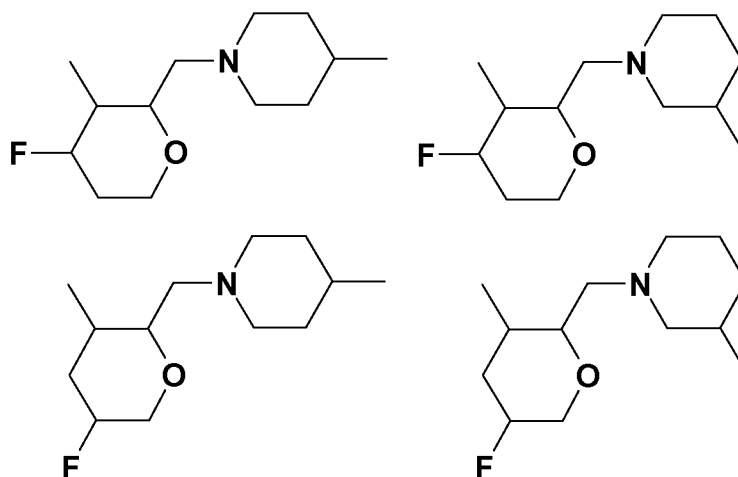
In a further preferred embodiment, the invention relates to compounds of formula (1), wherein the group -A-CH₂-B- is selected from



- 15 R1 is fluorine, chlorine, methoxy or difluoromethoxy,
 R2 is hydrogen, fluorine, chlorine, methyl or difluoromethoxy, and
 R3 is cyano, fluorine, methyl, methoxy, ethoxy, difluoromethoxy or acetyl,
 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

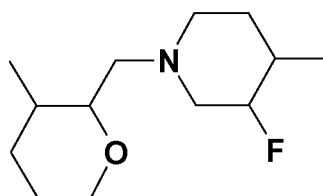
- 20 In a further preferred embodiment, the invention relates to compounds of formula (1), wherein the group -A-CH₂-B- is selected from

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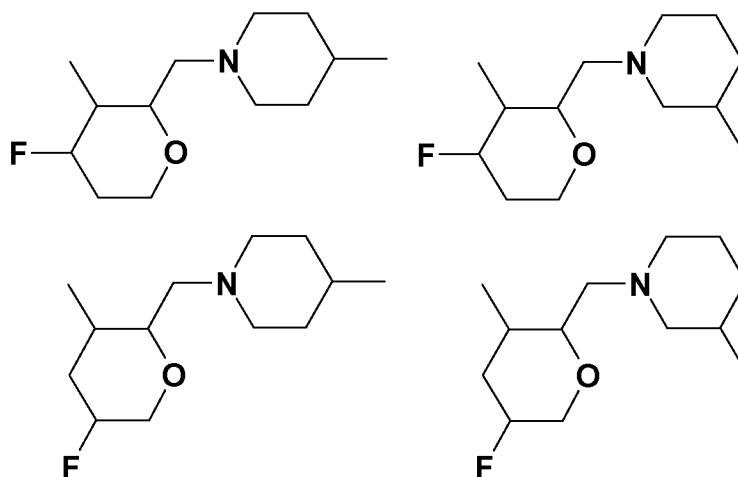
- R1 is 2-fluorine or 4-fluorine,
 R2 is hydrogen or 2-methyl, and
 5 R3 is 3-cyano, 4-cyano, 3-fluorine, 4-fluorine, 3-methyl, 4-methyl, 3-methoxy, 4-methoxy, 3-difluoromethoxy, 4-difluoromethoxy, 3-acetyl or 4-acetyl,
 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

In a further preferred embodiment, the invention relates to compounds of formula (1), wherein
 10 wherein the group -A-CH₂-B- is selected from



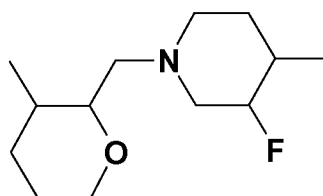
- R1 is 4-fluorine,
 R2 is hydrogen, and
 15 R3 is 3-cyano, 4-cyano, 3-fluorine, 4-fluorine, 3-methyl, 4-methyl, 3-methoxy, 4-methoxy, 3-ethoxy, 4-ethoxy, 3-difluoromethoxy, 4-difluoromethoxy, 3-acetyl or 4-acetyl,
 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

In a further preferred embodiment, the invention relates to compounds of formula (1),
 20 wherein the group -A-CH₂-B- is selected from



- R1 is 4-fluorine,
 R2 is hydrogen, and
 5 R3 is 4-cyano, 4-fluorine, 4-methyl, 4-methoxy, 4-ethoxy, 4-difluoromethoxy, 3-acetyl or 4-acetyl,
 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

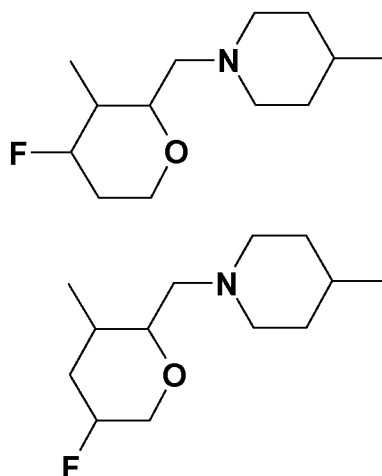
- In a further preferred embodiment, the invention relates to compounds of formula (1),
 10 wherein the group -A-CH₂-B- is selected from



- R1 is 4-fluorine,
 R2 is hydrogen, and
 R3 is 3-methoxy, 4-methoxy, 3-ethoxy, 4-difluoromethoxy, 3-acetyl or 4-acetyl,
 15 the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

A special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group -A-CH₂-B- is selected from

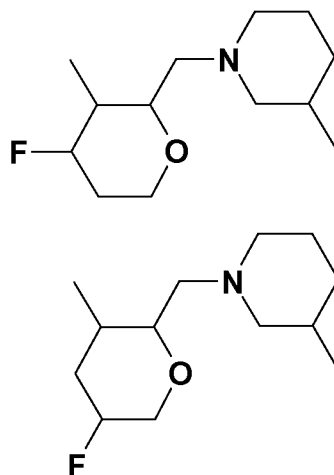
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and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

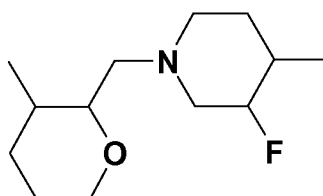
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A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is selected from



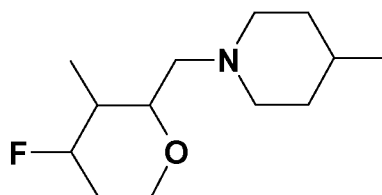
10 and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

A further special embodiment of the compounds of the present invention includes those compounds of formula (1) wherein the group $-A-CH_2-B-$ is



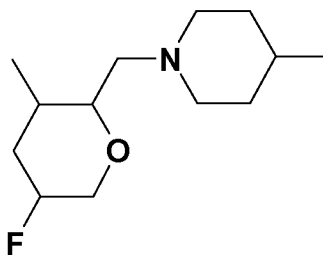
and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

A further special embodiment of the compounds of the present invention includes those
5 compounds of formula (1), wherein the group $-A-CH_2-B-$ is



and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

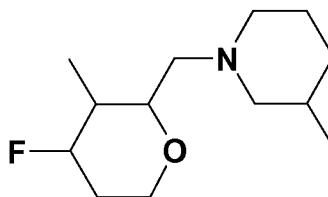
10 A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is



and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

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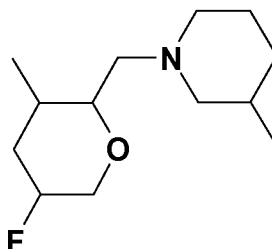
A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is



20 and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is

10



and R1, R2 and R3 are as defined above, the stereoisomers thereof, as well as the salts of these compounds and stereoisomers.

5 Salts of the compounds or stereoisomers according to the invention, include all inorganic and organic acid addition salts and salts with bases, especially all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases, particularly all pharmaceutically acceptable inorganic and organic acid addition salts and salts with bases customarily used in pharmacy.

10

Examples of acid addition salts include, but are not limited to, hydrochlorides, hydrobromides, phosphates, nitrates, sulfates, acetates, citrates, D-gluconates, benzoates, 2-(4-hydroxybenzoyl)-benzoates, butyrates, sulfosalicylates, maleates, laurates, malates, fumarates, succinates, oxalates, tartrates, stearates, toluenesulfonates, methanesulfonates, 3-hydroxy-2-naphthoates and

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trifluoroacetates.

Examples of salts with bases include, but are not limited to, lithium, sodium, potassium, calcium, aluminum, magnesium, titanium, ammonium, meglumine and guanidinium salts.

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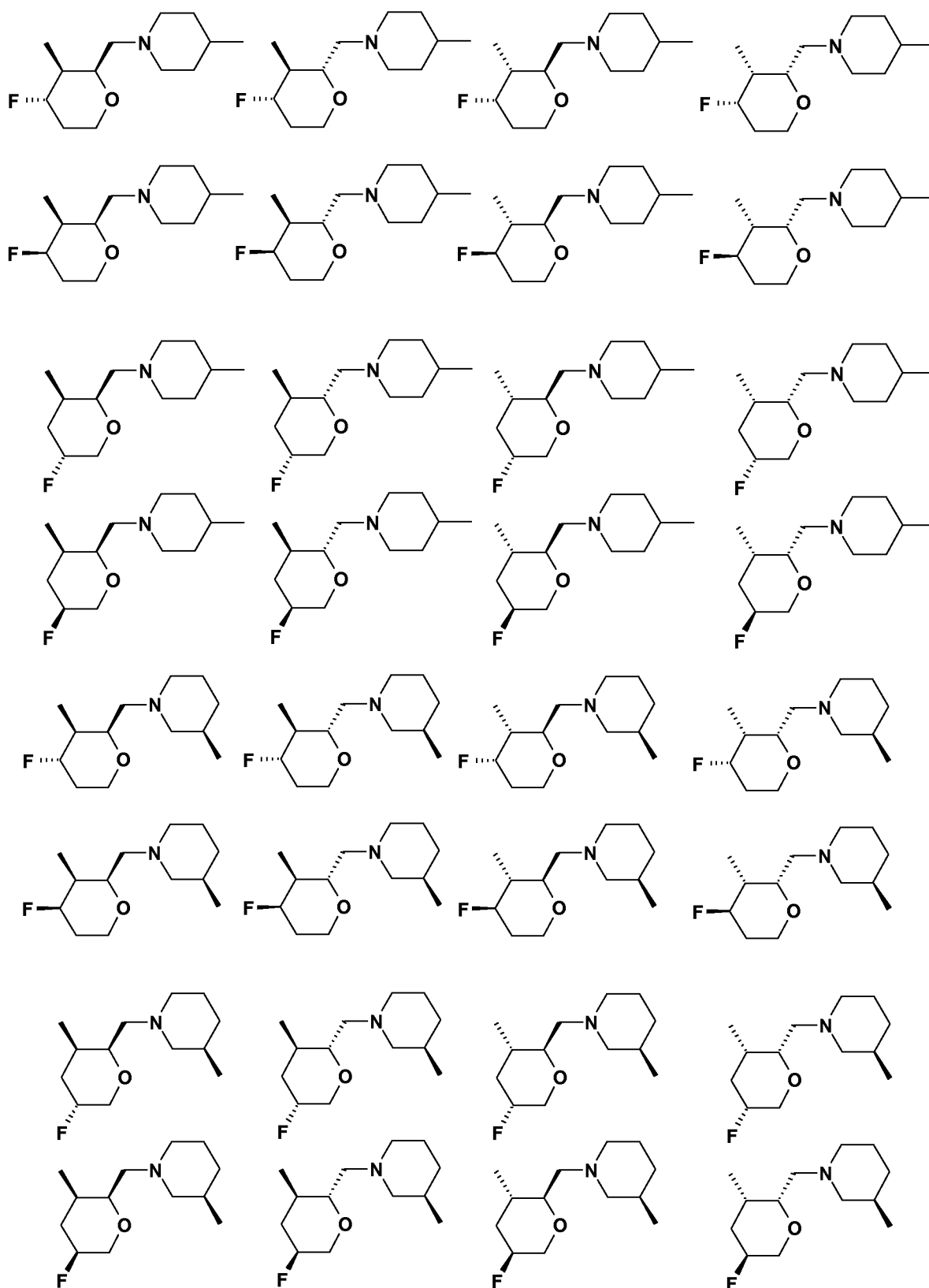
The salts include water-insoluble and, particularly, water-soluble salts.

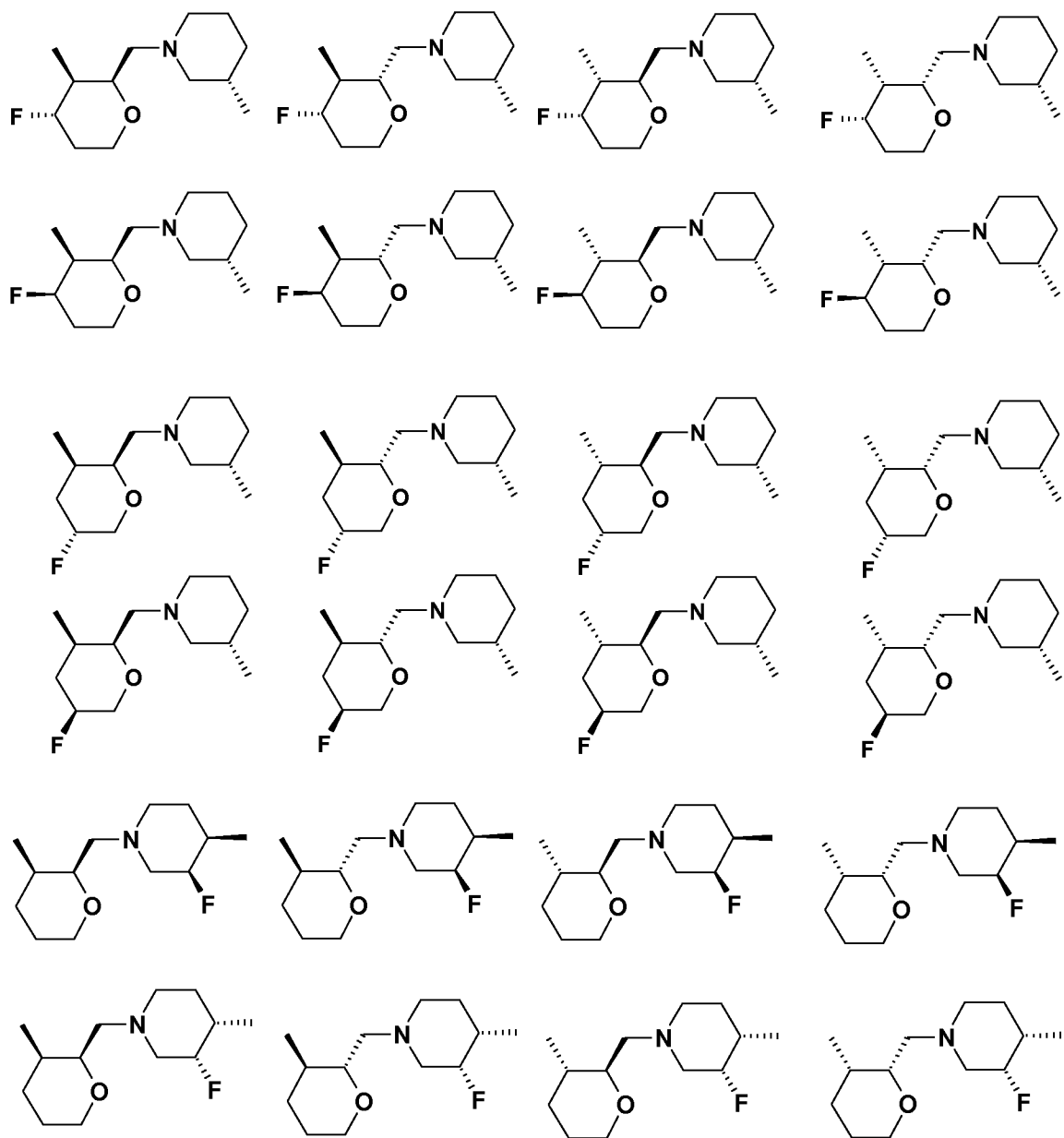
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The compounds of the invention, the salts thereof, the stereoisomers of the compounds of the invention and the salts thereof may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore, all solvates of the compounds of the invention, of the salts thereof, of the stereoisomers of the compounds of the invention and of the salts of the stereoisomers. Hydrates are a preferred example of said solvates.

The compounds according to the invention and the salts thereof include stereoisomers. In the compounds of formula (1) stereogenic centers exist in the group –A-CH₂-B-:

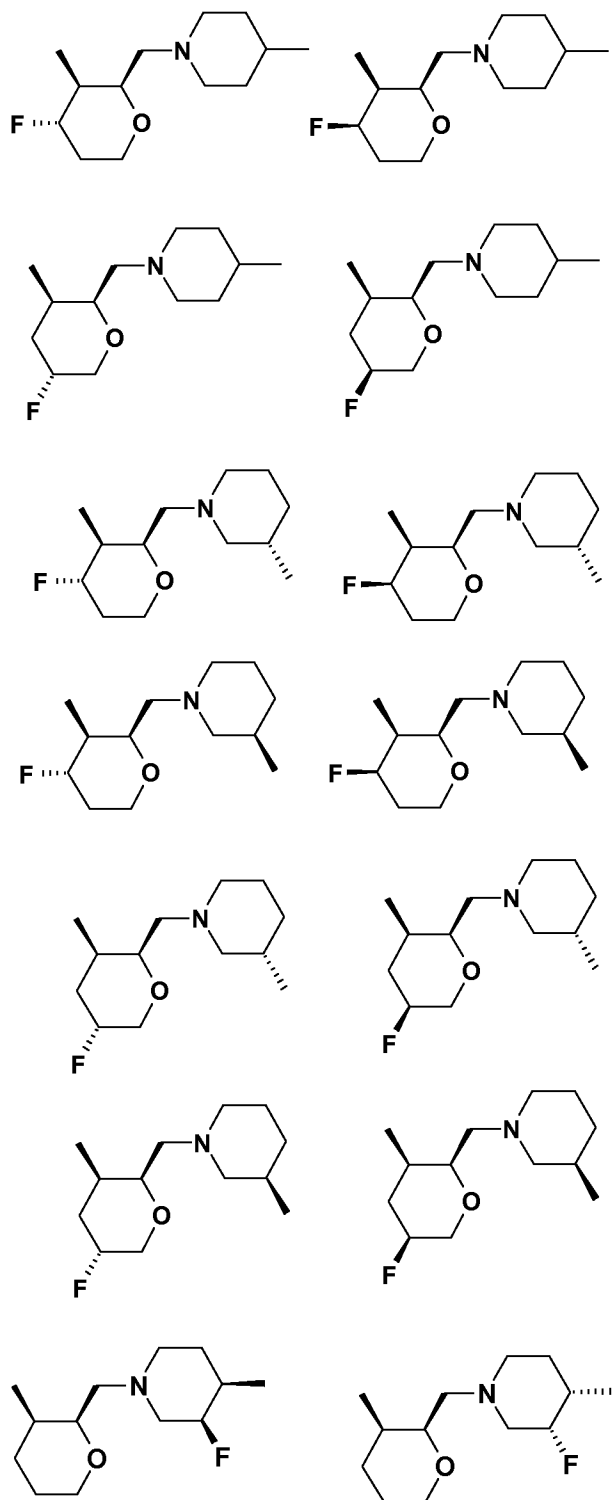
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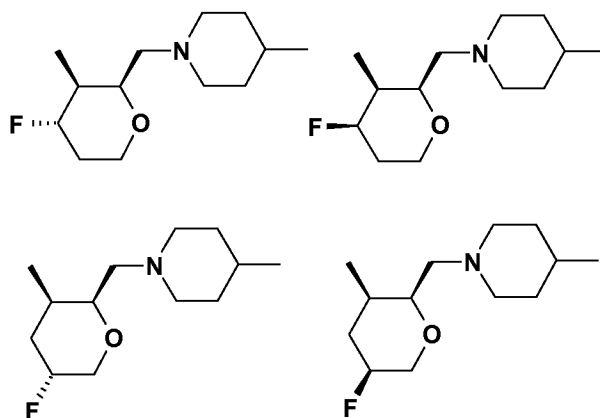


- 5 Preferred compounds of formula (1) are those wherein the group $-A-CH_2-B-$ shows one of the following stereochemistries:

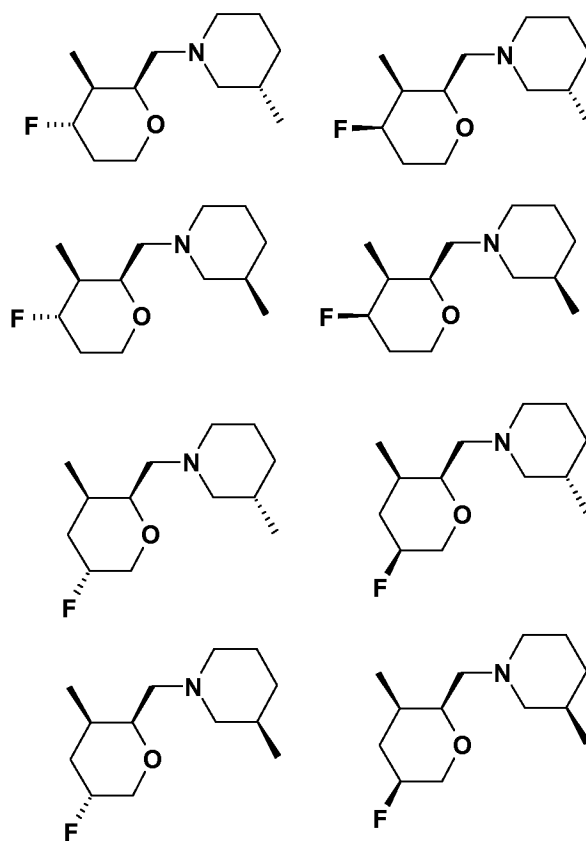
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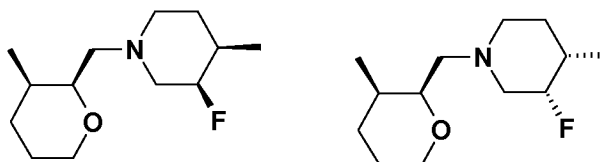
One group of particularly preferred compounds of formula (1) are those wherein the group -A-CH₂-B- shows one of the following stereochemistries:



- 5 Another group of particularly preferred compounds of formula (1) are those wherein the group -A-CH₂-B- shows one of the following stereochemistries:

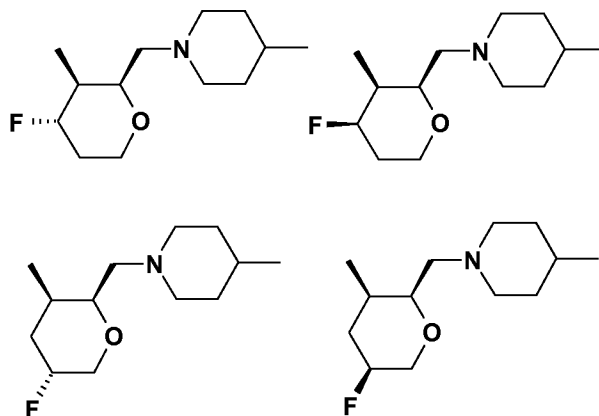


A further group of particularly preferred compounds of formula (1) are those wherein the group -A-CH₂-B- shows one of the following stereochemistries:



- 5 The invention includes each of the possible stereoisomers indicated above in pure form as well as any mixture of these stereoisomers independent of the ratio.

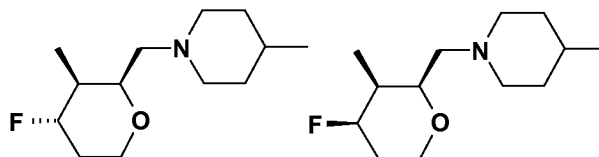
Accordingly a further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group -A-CH₂-B- is selected from



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and R₁, R₂ and R₃ are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group -A-CH₂-B- is selected from

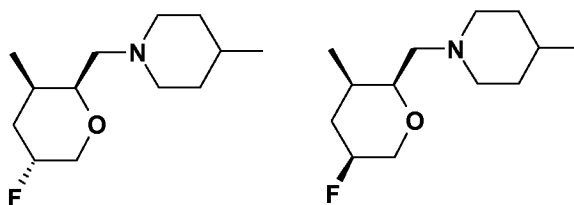


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and R₁, R₂ and R₃ are as defined above, and the salts of these compounds.

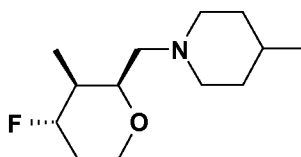
A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group -A-CH₂-B- is selected from

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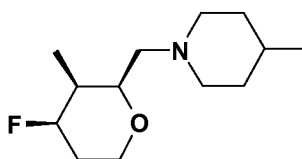
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
 5 compounds of formula (1), wherein the group $-A-CH_2-B-$ is



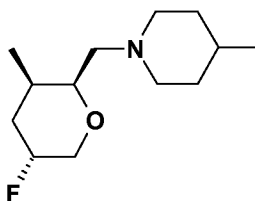
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
 10 compounds of formula (1), wherein the group $-A-CH_2-B-$ is



and R1, R2 and R3 are as defined above, and the salts of these compounds.

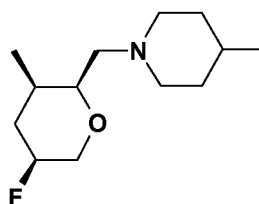
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and R1, R2 and R3 are as defined above, and the salts of these compounds.

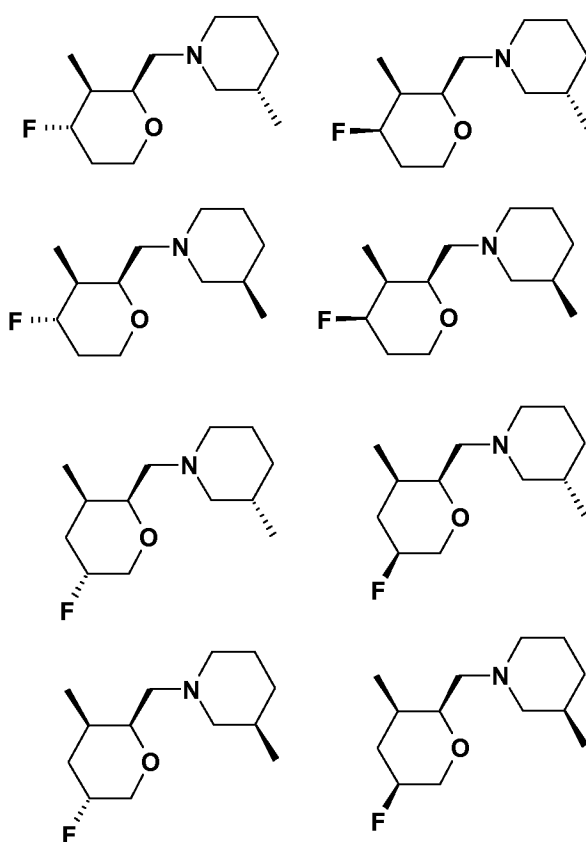
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 20 compounds of formula (1), wherein the group $-A-CH_2-B-$ is

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and R1, R2 and R3 are as defined above, and the salts of these compounds.

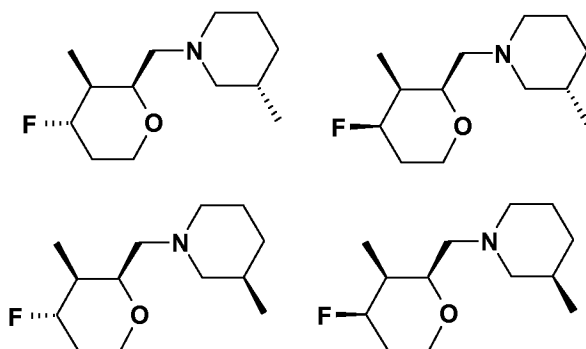
A further special embodiment of the compounds of the present invention includes those
 5 compounds of formula (1), wherein the group $-A-CH_2-B-$ is selected from



and R1, R2 and R3 are as defined above, and the salts of these compounds.

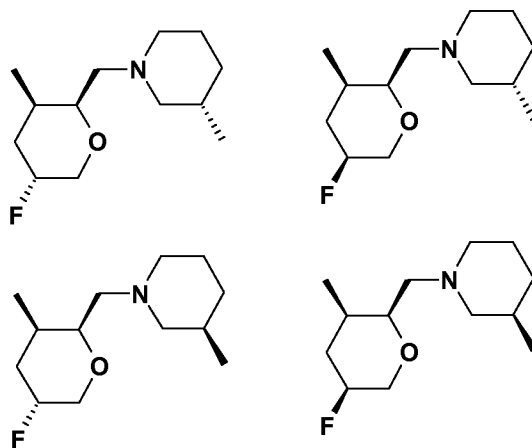
A further special embodiment of the compounds of the present invention includes those
 10 compounds of formula (1), wherein the group $-A-CH_2-B-$ is selected from

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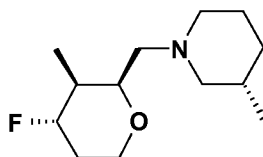
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
 5 compounds of formula (1), wherein the group $-A-CH_2-B-$ is selected from



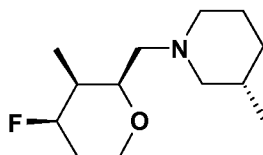
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
 10 compounds of formula (1), wherein the group $-A-CH_2-B-$ is



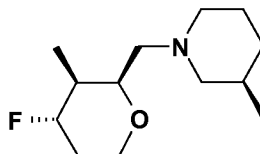
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
 15 compounds of formula (1), wherein the group $-A-CH_2-B-$ is



and R1, R2 and R3 are as defined above, and the salts of these compounds.

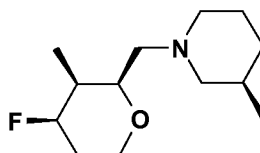
A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is



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and R1, R2 and R3 are as defined above, and the salts of these compounds.

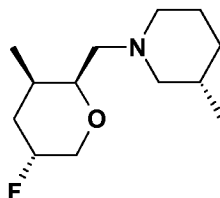
A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is



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and R1, R2 and R3 are as defined above, and the salts of these compounds.

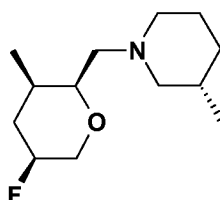
A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is



15

and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is

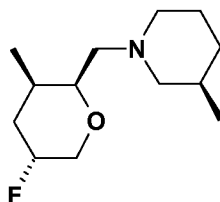


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and R1, R2 and R3 are as defined above, and the salts of these compounds.

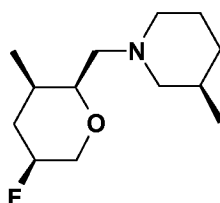
A further special embodiment of the compounds of the present invention includes those compounds of formula (1), wherein the group $-A-CH_2-B-$ is

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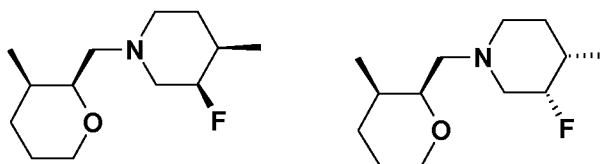
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
5 compounds of formula (1), wherein the group $-A-CH_2-B-$ is



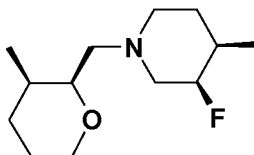
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
10 compounds of formula (1) wherein the group $-A-CH_2-B-$ is selected from



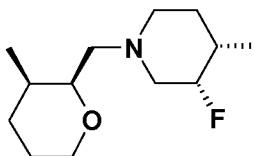
and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
15 compounds of formula (1) wherein the group $-A-CH_2-B-$ is



and R1, R2 and R3 are as defined above, and the salts of these compounds.

A further special embodiment of the compounds of the present invention includes those
20 compounds of formula (1) wherein the group $-A-CH_2-B-$ is



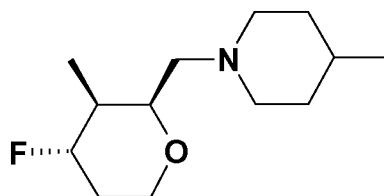
21

and R1, R2 and R3 are as defined above, and the salts of these compounds.

Some of the compounds, salts, stereoisomers and salts of the stereoisomers according to the invention may exist in different crystalline forms (polymorphs), which are within the scope of the invention.

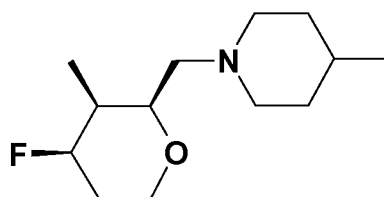
The compounds according to the invention can be prepared as follows:

The compounds of formula (1), wherein group $-A-CH_2-B-$ stands for



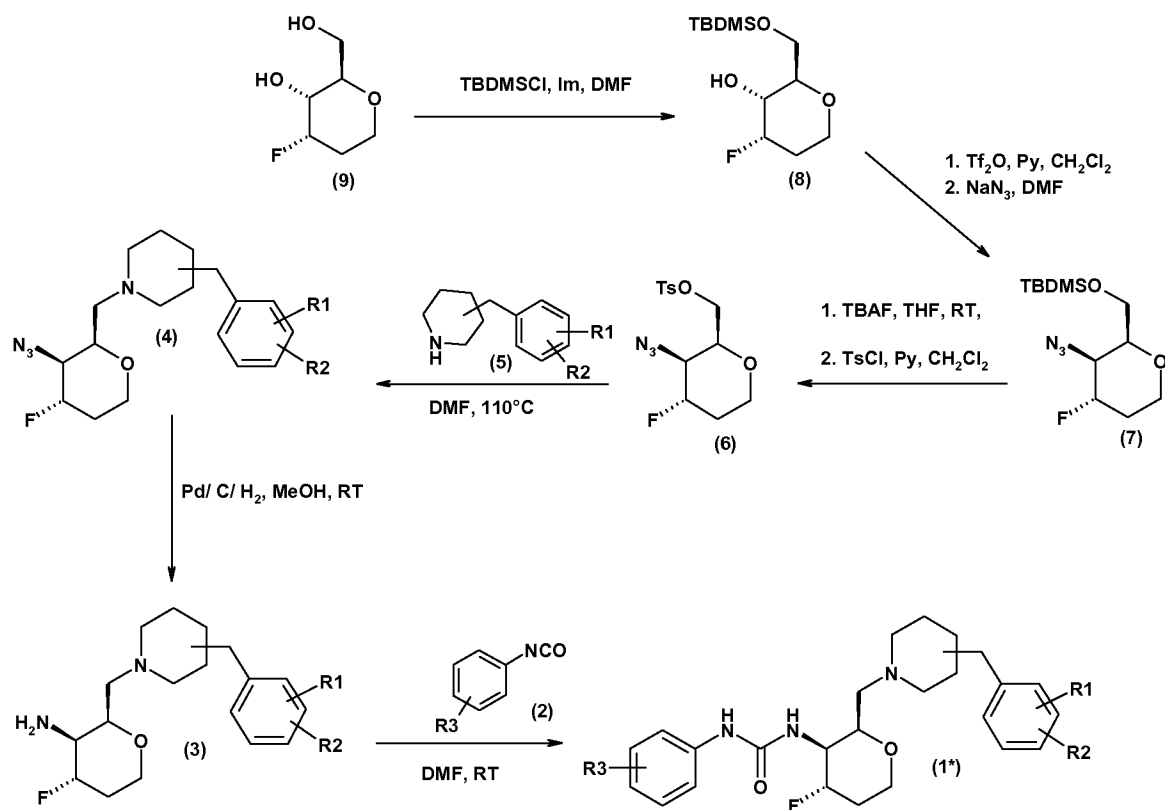
and R1, R2 and R3 have the abovementioned meanings can be prepared, for example, as shown in reaction Scheme 1.

Compounds of formula (1), wherein the group $-A-CH_2-B-$ stands for

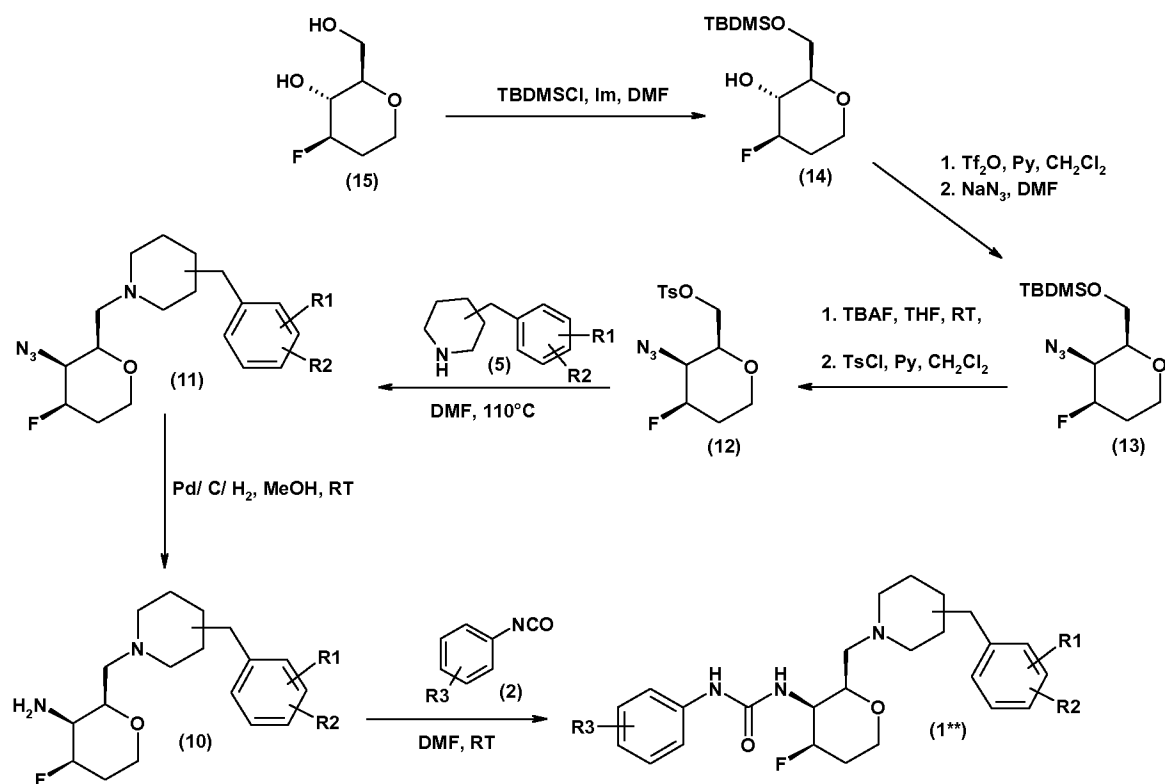


and R1, R2 and R3 have the abovementioned meanings can be prepared, for example, as shown in reaction Scheme 2.

Scheme 1:



Scheme 2:



23

As shown in Scheme 1 compounds of formula (1*) wherein R1, R2 and R3 have the abovementioned meanings can be prepared by reaction of compounds of formula (3), wherein R1 and R2 have the abovementioned meanings with an isocyanate of formula (2), wherein R3 has the abovementioned meanings. The reaction is preferably carried out in an anhydrous inert solvent, such as, for example, but not limited to dichloromethane, trichloromethane, tetrahydrofuran, dioxane, toluene, ethyl acetate or dimethylformamide at a temperature between 0°C and the boiling point of the solvent being used, preferably between 20 and 30°C.

The amino-compounds of formula (3) wherein R1 and R2 have the abovementioned meanings can be prepared from the corresponding azido-compounds of formula (4) by a reduction process. Suitable reduction systems are for example zinc in acetic acid, hydrogen over Pd/C in an inert solvent, P(OEt)₃ / HCl, Ph₃P / H₂O; preferably the conversion is carried out as a catalytic reduction with hydrogen over Pd/C in an inert solvent, such as for example, but not limited to methanol, ethanol or glacial acetic acid at room temperature.

The azido-compounds of formula (4), wherein R1 and R2 have the abovementioned meanings can be prepared by reaction of compounds of formula (6), wherein a suitable leaving group is attached to the 6-position, such as, for example TsO, MsO or iodine, with a benzyl-piperidine of formula (5), wherein R1 and R2 have the abovementioned meanings. Preferably the leaving group is TsO. The reaction is preferably carried out in an anhydrous inert solvent, such as, for example dimethylformamide, dimethylacetamide or N-methylpyrrolidone at a temperature between 0°C and the boiling point of the solvent being used.

Compounds of formula (6) with a suitable leaving group (LG) can be prepared from compounds of formula (7) wherein PG is a suitable hydroxyl protective group, such as, for example, tert-butyltrimethylsilyl (TBDMS), triisopropylsilyl (TIPS) or dimethylhexylsilyl (TDS) by a PG cleavage/LG introduction reaction sequence. Reaction conditions for the cleavage of the suitable hydroxyl protective group and the introduction of the suitable leaving group depend on the particular hydroxyl protective group, respectively the particular leaving group; such reaction conditions are known to the person skilled in the art and can be found for example in Theodora V. Greene, Peter G. M. Wuts (eds.) Protective groups in Organic Synthesis 4th ed 2007, John Wiley & Sons. Furthermore, suitable reaction conditions for the cleavage of the hydroxyl protective group TBDMS and the introduction of the tosylate leaving group are described in the experimental part of the present application.

The azido-group of the compounds of formula (7) wherein PG is a suitable hydroxyl protective group can be prepared from corresponding hydroxyl-compounds of formula (8) by a nucleophilic substitution reaction. In a first reaction step the hydroxyl group of the compounds of formula (8) is activated by reaction with, for example, trifluoromethanesulfonic anhydride in the presence of a

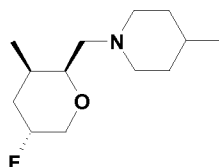
base, such as for example pyridine, triethylamine, ethyldiisopropylamine or lutidine in an inert anhydrous solvent like dichloromethane, trichloromethane, tetrahydrofuran or toluene at low temperatures between -50°C and $+10^{\circ}\text{C}$. In a second reaction step the activated hydroxyl group is replaced in a nucleophilic substitution reaction by the azido-group; the nucleophilic substitution
5 reaction is carried out with sodium azide in an inert anhydrous solvent, such as, for example, dimethylformamide, dimethylacetamide or N-methylpyrrolidon, preferably at temperatures between 0°C and room temperature.

The hydroxyl compounds of formula (8), wherein PG is a suitable hydroxyl protective group, such
10 as, for example tert-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS) or dimethylthexylsilyl (TDS) can be prepared from the corresponding compounds of formula (9), wherein the primary hydroxyl group is unprotected. Hydroxyl protective groups, which are suitable to protect a primary hydroxyl group in the presence of a secondary hydroxyl group and the reaction conditions for their introduction are known to the person skilled in the art and can be found for example in Theodora V.
15 Greene, Peter G. M. Wuts (eds.) Protective groups in Organic Synthesis 4rd ed 2007, John Wiley & Sons. Reaction conditions for the introduction of the TBDMS protective group are described in the experimental part of the present application.

The preparation of compounds of formula (1**) starting from compounds of formula (15) as
20 described in scheme 2, the preparation of compounds of formula (1***) starting from compounds of formula (21) as described in scheme 3, the preparation of compounds of formula (1****) starting from compounds of formula (27) as described in scheme 4 and the preparation of compounds of formula (1*****) starting from compounds of formula (33) as described in scheme 5 follows a similar reaction sequence as described above for the compounds of formula (1*) starting from the
25 compounds of formula (9). Therefore, the above described reaction conditions can also be used for the preparation of these compounds.

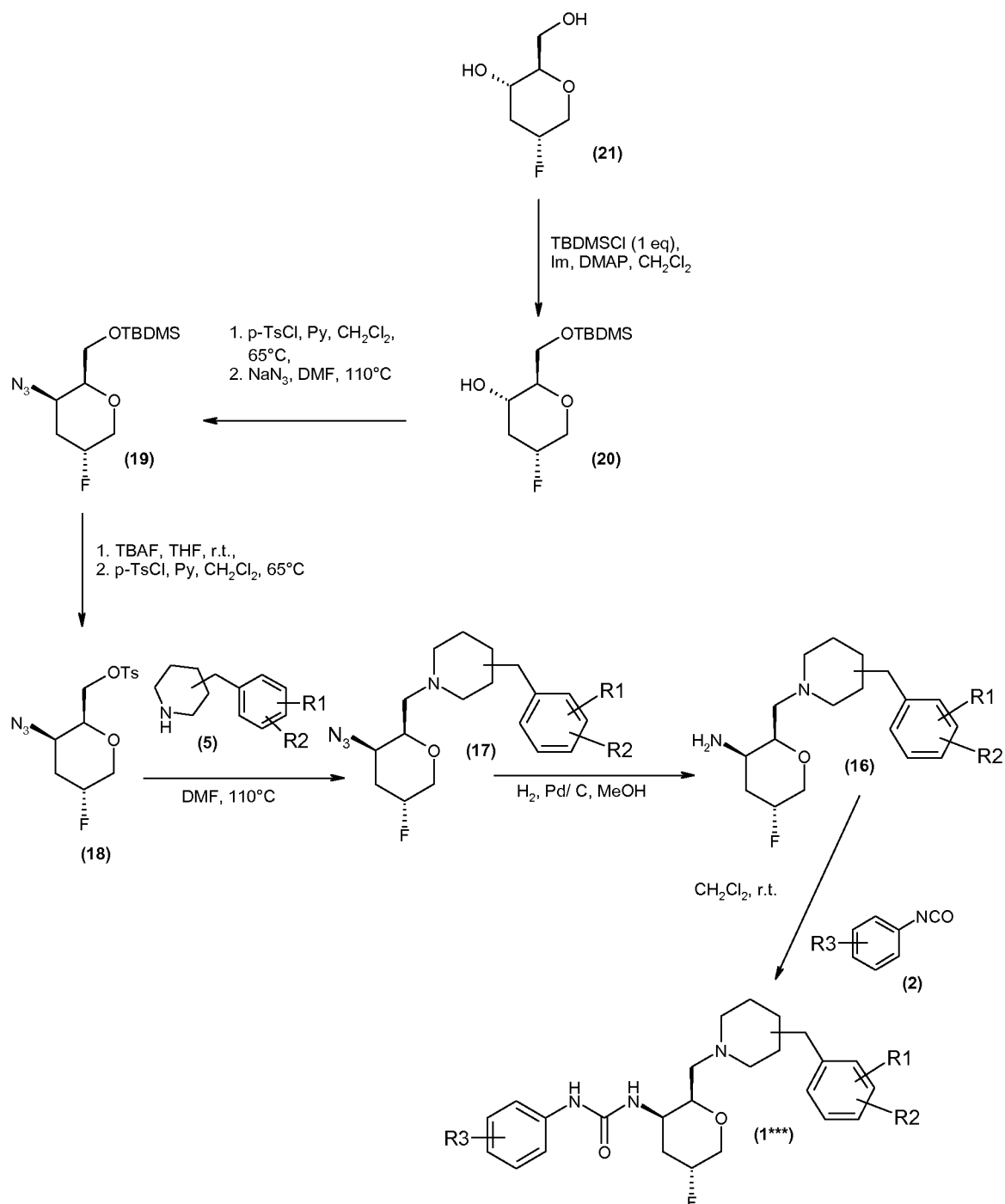
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The compounds of formula (1), wherein group $-A-CH_2-B-$ stands for



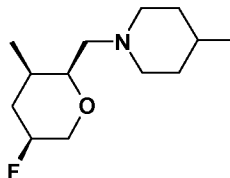
and R1, R2 and R3 have the abovementioned meanings can be prepared, for example, as described in reaction scheme 3.

5 **Scheme 3:**



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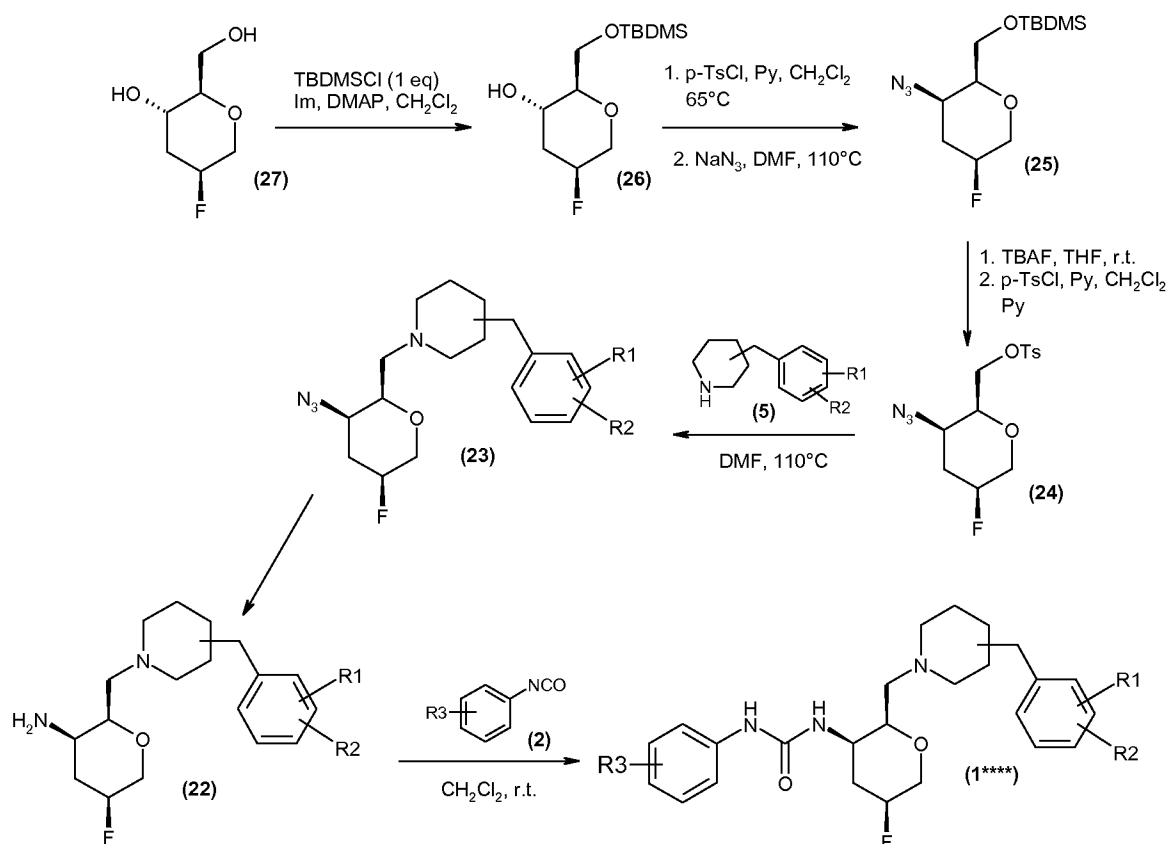
The compounds of formula (1), wherein group –A-CH₂-B- stands for



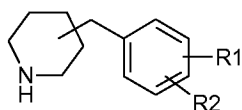
and R₁, R₂ and R₃ have the abovementioned meanings can be prepared, for example, as described in reaction scheme 4:

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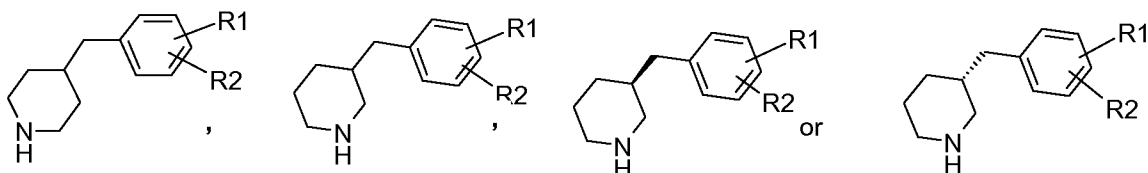
Scheme 4:



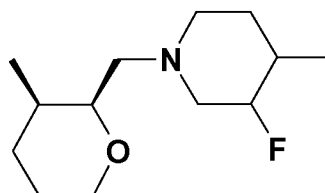
In reaction schemes 1 to 4 the formula



10 stands for



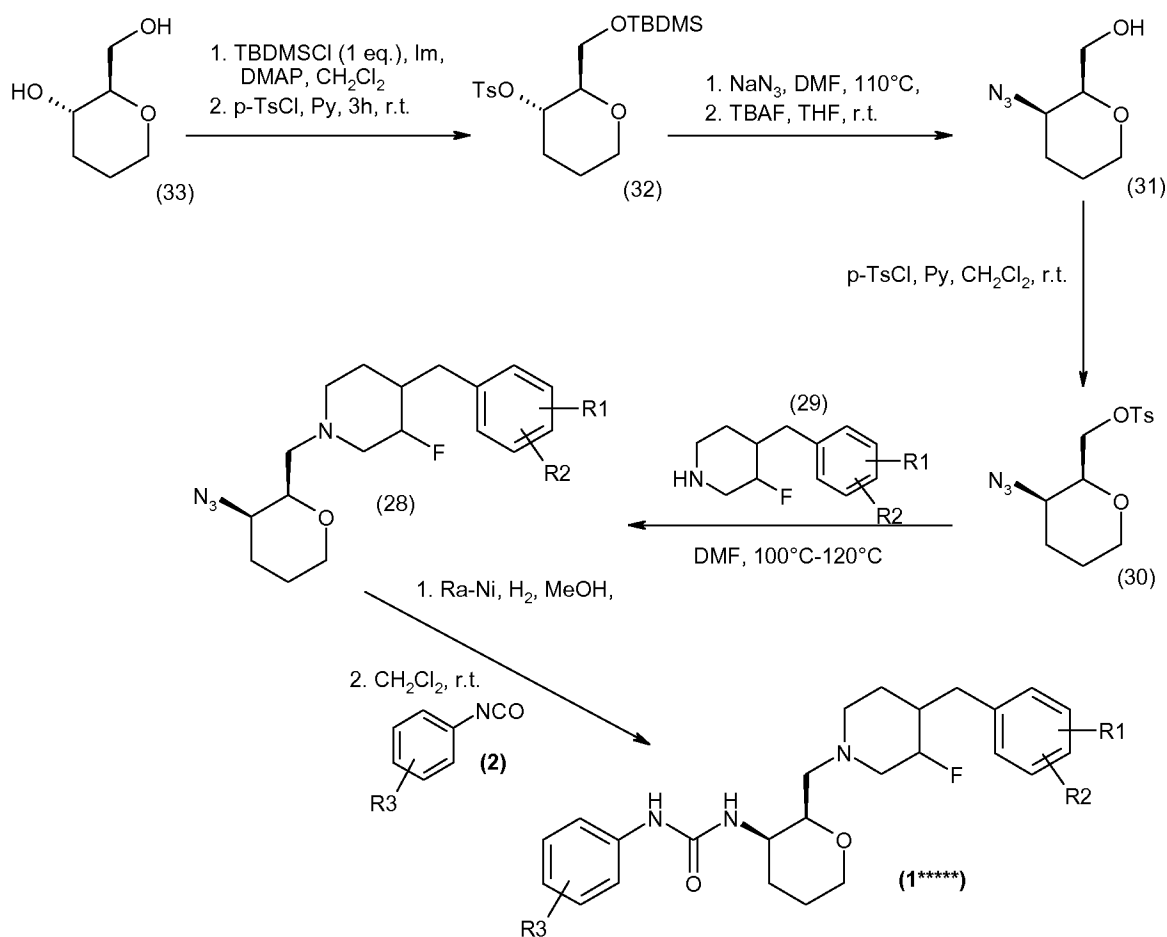
The compounds of formula (1) wherein the group $-A-CH_2-B-$ stands for



and R1, R2 and R3 have the abovementioned meanings can be prepared as described in reaction scheme 5.

5

Scheme 5:



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The preparation of the compounds of formulae (9), (15), (21) and (27) is described below, respectively in the experimental part of the present application.

The preparation of 4-(4-Fluorobenzyl)piperidine is described for example in J. R. Shanklin et al. *J. Med. Chem.* **1991**, 34 (10), 3011-3022, J. Pabel et al. *Bioorg. Med. Chem. Lett.* **2000**, 10(12), 1377-1380, J. A. McCauly et al. *J. Med. Chem.* **2004**, 47 (8), 2089-2096 and P. C. Ting et al. *Bio-*

org. Med. Chem. Lett. **2005**, 15(5), 1375-1378. Other 4-benzyl-piperidines substituted in the benzyl moiety by R1 and/or R2 can be prepared in an analogous way.

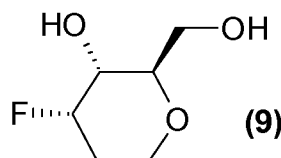
The preparation of (3R)- and (3S)-3-(4-Fluorobenzyl)piperidine is described for example in T.-Y. Yue et al. *Organic Process Research & Development* **2006**, 10, 262-271 and in J. Med Chem. **2005**, 48, 2194-2211. Other (3R)- and (3S)-3-(benzyl)piperidines substituted in the benzyl moiety by R1 and/or R2 can be prepared in an analogous way.

The preparation of (3R,4R)- respectively (3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine is described below in the Examples. Other (3R,4R)- respectively (3S,4S)-3-fluoro-4-(benzyl)piperidines substituted in the benzyl moiety by R1 and/or R2 can be prepared in an analogous way.

The invention further relates to compounds of formulae (9), (15), (21) and (27) shown below, which are important intermediates in the process of preparing the compounds of formula (1) according to the invention as described above.

A further aspect of the present invention therefore is to provide novel intermediate compounds of formulae (9), (15), (21) and (27) as well as a process for their preparation.

The invention therefore also relates to a compound of formula (9)

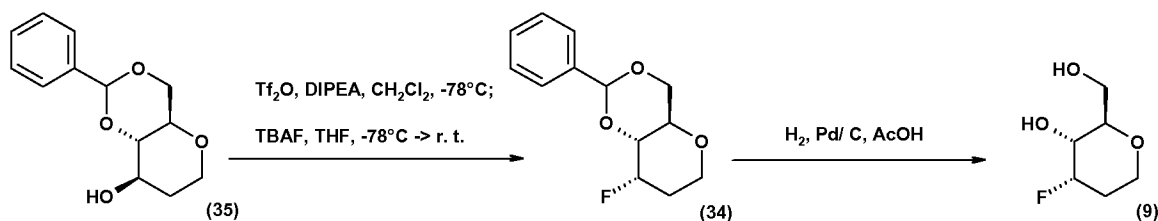


or a salt thereof.

The compound of formula (9) can be prepared as described in reaction scheme 6.

25

Scheme 6:

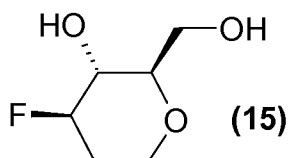


The preparation of the compound of formula (35), 1,5-Anhydro-2-deoxy-4,6-O-(phenylmethylidene)-D-arabino-hexitol, is described, for example in Foster et al. *Acta Chem. Scand.* 1958, 12, 1819, 1823, Sasaki, M. et al. *Tetrahedron Letters* 2006, 47(32), 5687-5691 and Thonia, G. et al. *J. Med. Chem.* 1999, 42(23), 4909-4913.

A detailed description of the preparation of the compound of formula (9), 1,5-Anhydro-2,3-dideoxy-3-fluoro-4,6-O-(phenylmethylidene)-D-ribo-hexitol, is given in the part "Examples" - starting materials A1 to A3.

5

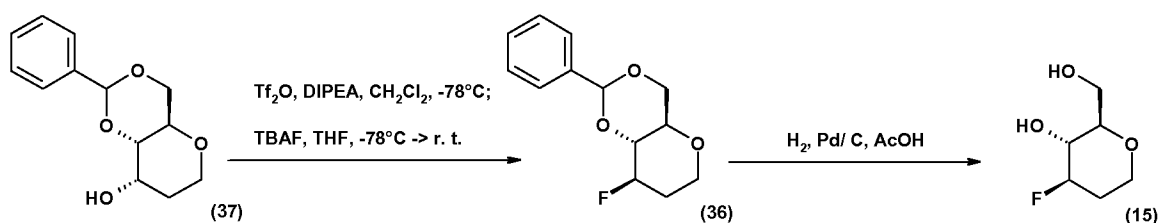
The invention as well relates to a compound of formula (15)



or a salt thereof.

10 The compound of formula (15) can be prepared as described in reaction scheme 7.

Scheme 7:

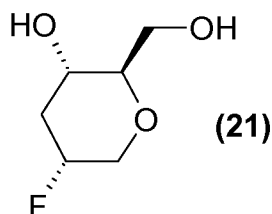


15 The preparation of the compound of formula (37), 1,5-Anhydro-2-deoxy-4,6-O-(phenylmethylidene)-D-ribo-hexitol, is described, for example in Angew. Chem (int Ed.) 1996, 108(15), 1782-1785 or in Angew. Chem (int. Ed.) 2004, 116(21), 2894-2897.

A detailed description of the preparation of the compound of formula (15), 1,5-Anhydro-2,3-dideoxy-3-fluoro-D-arabino-hexitol, is given in the part "Examples" - starting materials A57 to A59.

20

Additional the invention relates to a compound of formula (21)



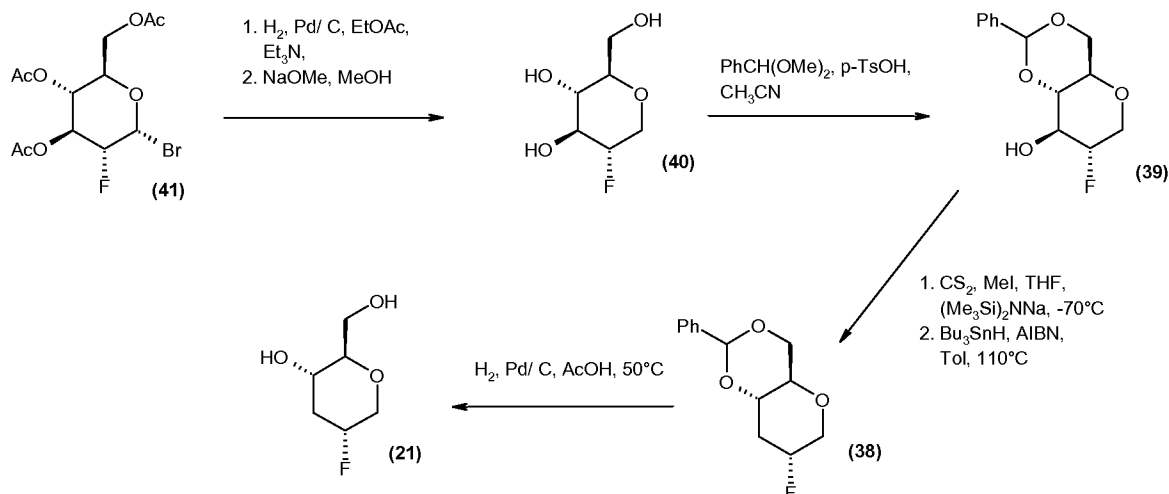
or a salt thereof.

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The compound of formula (21) can be prepared as described in reaction scheme 8.

30

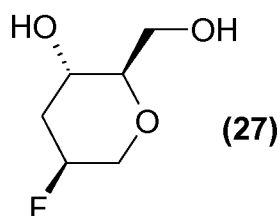
Scheme 8:



The preparation of the compound of formula (41), 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro- α -D-glucopyranosyl bromide, is described, for example in Boyd, E. et al. Tetrahedr. Lett. 2006, 47(45), 7983-7986, McCarter, S. et al. J. Am. Chem. Soc. 1997, 119(25), 5792-5797 and Maschauer, S. et al. J. Labelled Compd. Radiopharm. 2005, 48(10), 701-719.

A detailed description of the preparation of the compound of formula (21), 1,5-Anhydro-2,3-dideoxy-2-fluoro-D-ribo-hexitol, is given in the part "Examples" - starting materials A27 to A33.

Furthermore the invention relates to a compound of formula (27)



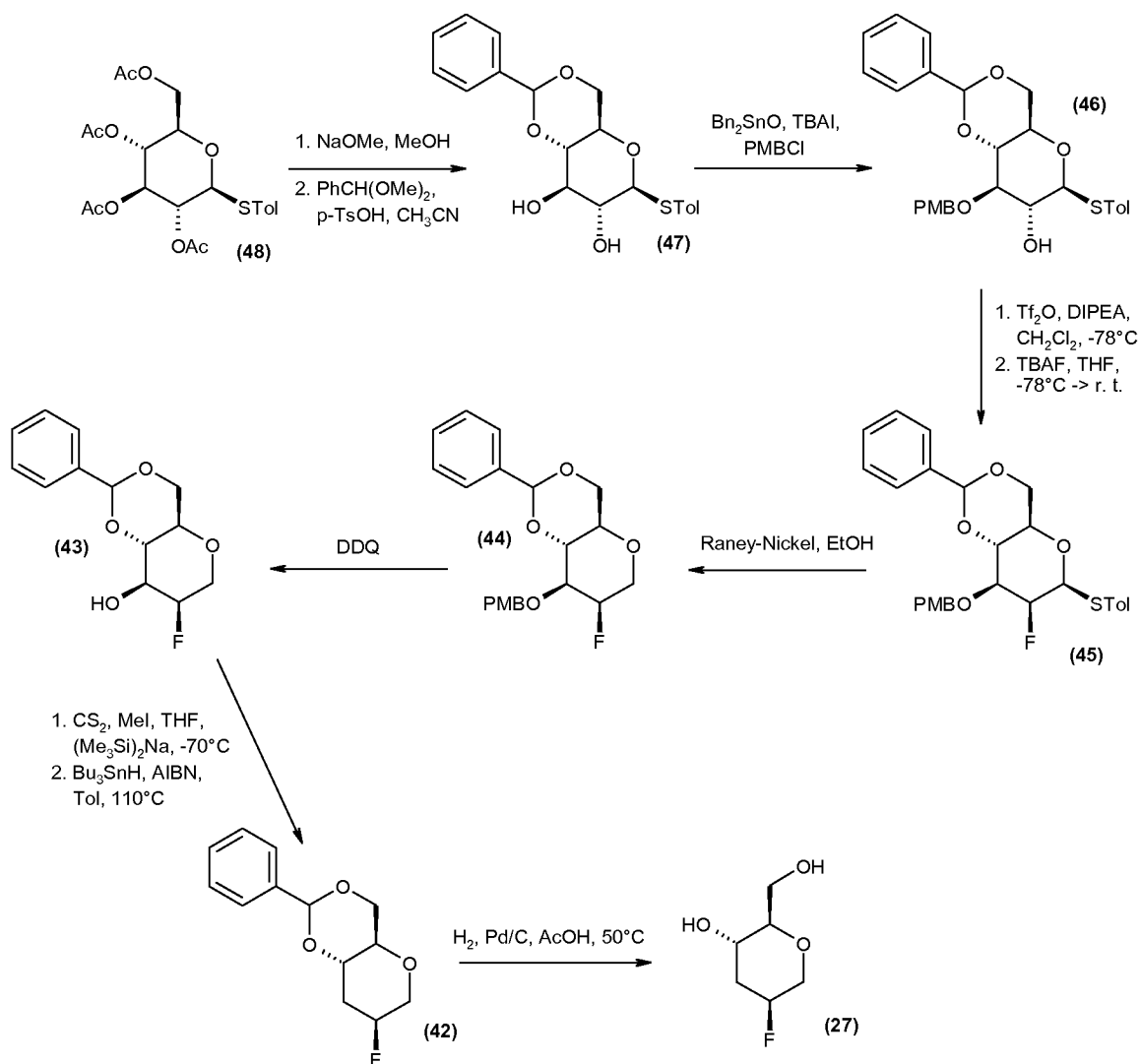
or a salt thereof.

15

The compound of formula (27) may be prepared as described in reaction scheme 9.

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Scheme 9:



The preparation of the compound of formula (46), 4-methylphenyl 4,6-O-benzylidene-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside, is described, for example in Aust. J. Chem. 1999, 52(9), 895-904, J. Am. Chem. Soc. 1949, 71, 3679-3681 and Can. J. Chem. 1955, 33, 109, 116-117.

The preparation of the compound of formula (48), 4-methylphenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside, is described, for example in Tetrahedron 1993, 49(33), 7301-7316.

10

It is known to the person skilled in the art that, if there are a number of reactive centers on a starting or intermediate compound, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center.

15

The compounds according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

5

Salts of the compounds of formula (1) and the salts of the stereoisomers of the compounds of formula (1) according to the invention can be obtained by dissolving the free compound in a suitable solvent (for example a ketone such as acetone, methylethylketone or methylisobutylketone, an ether such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon such as methylene chloride or chloroform, a low molecular weight aliphatic alcohol such as methanol, ethanol or isopropanol, a low molecular weight aliphatic ester such as ethyl acetate or isopropyl acetate, or water) which contains the desired acid or base, or to which the desired acid or base is then added. The acid or base can be employed in salt preparation, depending on whether a mono- or polybasic acid or base is concerned and depending on which salt is desired, in an equimolar quantitative ratio or one differing therefrom. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the salt or by evaporating the solvent. Salts obtained can be converted into the free compounds, which, in turn, can be converted into salts. In this manner, pharmaceutically unacceptable salts, which can be obtained, for example, as process products in the manufacturing on an industrial scale, can be converted into pharmaceutically acceptable salts by processes known to the person skilled in the art.

20

Pure stereoisomers of the compounds of formula (1) and the salts thereof according to the invention can be obtained e.g. by asymmetric synthesis, by using chiral starting compounds in synthesis and by splitting up enantiomeric and diastereomeric mixtures obtained in synthesis.

25

Preferably, the pure stereoisomers of the invention are obtained by using chiral starting compounds in synthesis.

30

Alternatively, stereoisomeric mixtures can be split up into the pure stereoisomers by methods known to a person skilled in the art. Preferably, diastereomeric mixtures are separated by crystallization, in particular fractional crystallization, or chromatography. Enantiomeric mixtures can be separated e.g. by forming diastereomers with a chiral auxiliary agent, resolving the diastereomers obtained and removing the chiral auxiliary agent. As chiral auxiliary agents, for example, chiral acids can be used to separate enantiomeric bases and chiral bases can be used to separate enantiomeric acids via formation of diastereomeric salts. Furthermore, diastereomeric derivatives such as diastereomeric esters can be formed from enantiomeric mixtures of alcohols or enantiomeric mixtures of acids, respectively, using chiral acids or chiral alcohols, respectively, as chiral auxiliary agents. Additionally, diastereomeric complexes or diastereomeric clathrates may be used for separating enantiomeric mixtures. Alternatively, enantiomeric mixtures can be split up

35

using chiral separating columns in chromatography. Another suitable method for the isolation of enantiomers is the enzymatic separation.

As will be appreciated by persons skilled in the art, the invention is not limited to the particular
5 embodiments described herein, but covers all modifications of said embodiments that are within the spirit and scope of the invention as defined by the appended claims.

All patents, patent applications, publications, test methods and other materials cited herein are
10 incorporated by reference in their entireties.

The following examples illustrate the invention in greater detail, without restricting it. Further
compounds according to the invention, of which the preparation is not explicitly described, can be
prepared in an analogous way.

15 The compounds which are mentioned in the examples, the salts, the stereoisomers and the salts of the stereoisomers thereof represent preferred embodiments of the invention.

Examples

The following abbreviations are used:

5	Ac:	Aceton
	calc:	calculated
	DIPEA:	N,N-Di-isopropylethylamine
	DMAP:	4-Dimethylamino-pyridine
	DMF:	N,N-Dimethyl formamide
10	EA:	Ethyl Acetate
	EF:	Empirical Formula
	fnd:	found
	m.p.:	Melting Point
	MW:	Molecular Weight
15	PE:	Petrolether
	TBAF:	Tetrabutylammoniumfluoride
	TBDMSCl:	tert-Butyl-dimethylsilylchloride
	THF:	Tetrahydrofuran
	TLC:	Thin Layer Chromatography
20	Tol:	Toluene
	(v/v):	Volume/Volume

The chemical names of the Final Products and Intermediates have been generated using the software ACD/NAME Library DLL 9.6.0.7481. They were accepted without further verification.

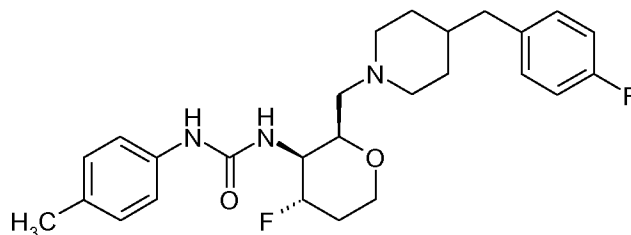
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General method:

To a solution of any of the compounds A10, A12, A26, A40, A43, A46, A49, A52, A54, A56, A66 and A68 (1.0 mmol) in 6 ml anhydrous dichloromethane the respective isocyanate (1.2 mmol) is added. After the mixture is stirred for 1 – 12 h at room temperature 1 ml MeOH is dropped to the solution. For workup, the mixture is concentrated in vacuo. The resulting products 1–32 are purified as follows.

35

1. **1,5-Anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-4-[(4-methylphenyl)carbamoyl]amino}-D-xylo-hexitol**



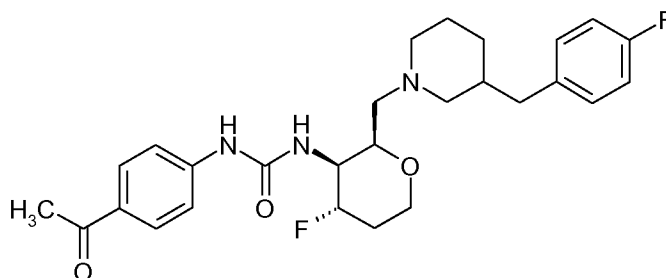
0.34 g (1.04 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(4-(4-fluorobenzyl)-piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.11 g (0.58 mmol) p-Tolyl-isocyanate by general method for 7 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (97:3 → 96:4; (v/v))] as colourless solid foam of m. p. 87°C.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.2

EF: C₂₆ H₃₃ N₃ O₂ F₂; MW: calc.: 457.57

MS: fnd.: 458.2 (MH⁺)

2. **4-[(4-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



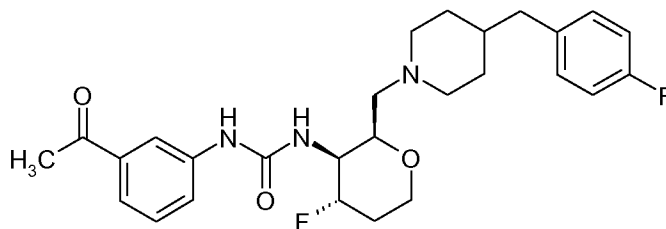
0.14 g (0.43 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A12) is reacted with 0.83 g (0.52 mmol) 4-Acetylphenyl-isocyanate by general method for 1.5 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (98:2 → 96:4; (v/v))] as yellow solid of m. p. 84.6°C.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.3

EF: C₂₇ H₃₃ N₃ O₃ F₂; MW: calc.: 485.58

MS: fnd.: 486.5 (MH⁺)

3. **4-[(3-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



0.16 g (0.49 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[4-(4-fluorobenzyl)-

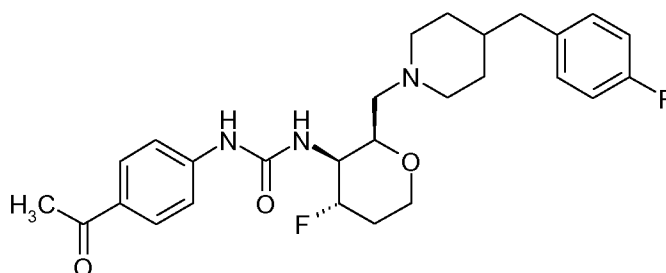
5 piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.094 g (0.58 mmol) 3-Acetylphenyl-isocyanate by general method for 12 h. The title compound is isolated after silica gel chromatogra-
phy [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (97:3 $\rightarrow$ 96:4; (v/v))] as colourless solid foam of m. p. 75°C.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5, (v/v))], $R_f=0.36$

EF: C27 H33 N3 O3 F2; MW: calc.: 485.58

10 MS: fnd.: 486.2 (MH^+)

4. **4-[(4-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



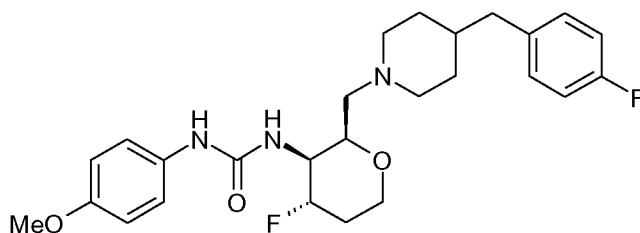
15 0.92 g (2.83 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.55 g (3.4 mmol) 4-Acetylphenyl-isocyanate by general method for 1 h. The title compound is isolated after silica gel chromatogra-
phy [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2 $\rightarrow$ 95:5; (v/v))] as colourless solid foam of m. p. 98°C.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5, (v/v))], $R_f=0.27$

20 EF: C27 H33 N3 O3 F2; MW: calc.: 485.58

MS: fnd.: 486.1 (MH^+)

5. **1,5-Anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-4-[(4-methoxyphenyl)carbamoyl]amino}-D-xylo-hexitol**



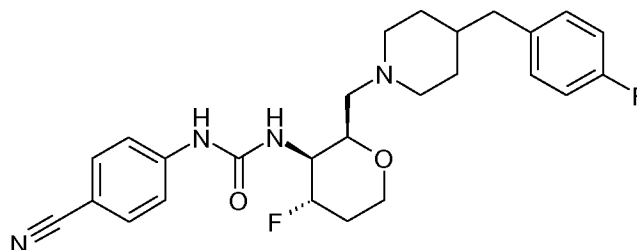
0.146 g (0.45 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(4-(4-fluorobenzyl)-
 5 piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.08 g (0.54 mmol) 4-Methoxyphenyl-
 isocyanate by general method for 4 h. The title compound is isolated after silica gel chroma-
 tography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], as colourless solid foam of m. p. 83°C.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.2$

EF: $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3\text{F}_2$; MW: calc.: 473.57

10 MS: fnd.: 474.1 (MH^+)

6. **1,5-Anhydro-4-[(4-(4-cyanophenyl)carbamoyl]amino}-2,3,4,6-tetradeoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



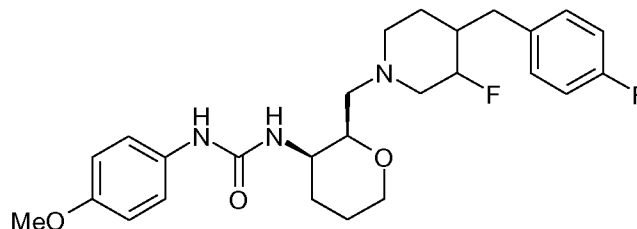
15 0.142 g (0.44 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(4-(4-fluorobenzyl)-
 piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.076 g (0.53 mmol) 4-cyanophenyl-
 isocyanate by general method for 6 h. The title compound is isolated after silica gel chromatogra-
 phy [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2 → 95:5; (v/v))], as colourless solid of m. p. 112°C.

20 TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.42$

EF: $\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_2\text{F}_2$; MW: calc.: 468.55

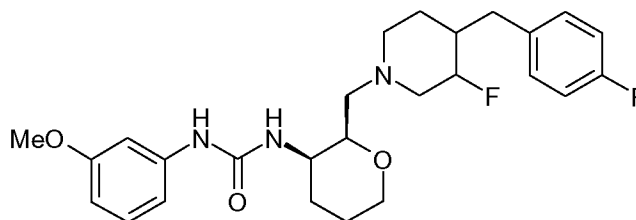
MS: fnd.: 469.1 (MH^+)

7. **Diastereomeric mixture of 2,6-Anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidin-1-yl]-3-[[4-methoxyphenyl]carbamoyl]amino}-D-threo-hexitol**



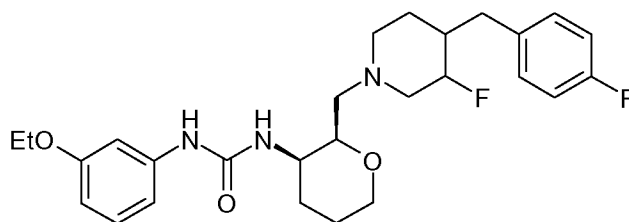
- 0.155 g (0.48 mmol) diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol (Compound A26) is reacted with 0.072 g (0.48 mmol) 4-Methoxyphenyl-isocyanate by general method for 1 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (95:5; (v/v))], as yellow solid. TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.40
- EF: C₂₆ H₃₃ N₃ O₃ F₂; MW: calc.: 473.56
- MS: fnd.: 474.1 (MH⁺)

8. **Diastereomeric mixture of 2,6-Anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidin-1-yl]-3-[[3-methoxyphenyl]carbamoyl]amino}-D-threo-hexitol**



- 0.15 g (0.46 mmol) diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol (Compound A26) is reacted with 0.069 g (0.46 mmol) 3-Methoxyphenyl-isocyanate by general method for 1 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (98:2 → 97:3; (v/v))], as colourless solid.
- TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.42
- EF: C₂₆ H₃₃ N₃ O₃ F₂; MW: calc.: 473.56
- MS: fnd.: 474.2 (MH⁺)

9. **Diastereomeric mixture of 2,6-Anhydro-1,3,4,5-tetradexoxy-1-[(3*R*,4*R*)/(3*S*,4*S*)-3-fluoro-4-(4-fluorobenzyl)piperidin-1-yl]-3-[[3-ethoxyphenyl]carbamoyl]amino}-D-threo-hexitol**



0.15 g (0.46 mmol) diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-

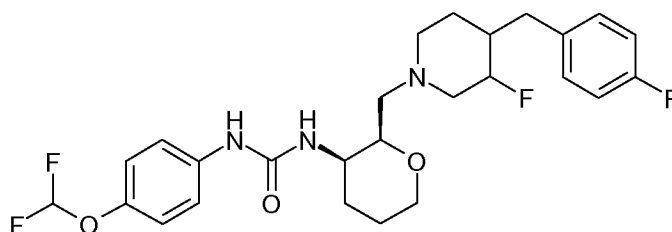
5 [(3*R*,4*R*)/(3*S*,4*S*)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol (Compound A26) is reacted with 0.078 g (0.46 mmol) 3-Ethoxyphenyl-isocyanate by general method for 1 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (98:2 → 97:3; (v/v))] as colourless solid.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.40

10 EF: C₂₇ H₃₅ N₃ O₃ F₂; MW: calc.: 487.59

MS: fnd.: 488.2 (MH⁺)

10. **Diastereomeric mixture of 2,6-Anhydro-1,3,4,5-tetradexoxy-3-([4-difluoromethoxy]phenyl)carbamoyl]amino)-1-[(3*R*,4*R*)/(3*S*,4*S*)-3-fluoro-4-(4-fluorobenzyl)piperidin-1-yl]-D-threo-hexitol**



0.15 g (0.46 mmol) diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-

[(3*R*,4*R*)/(3*S*,4*S*)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol (Compound A26) is

reacted with 0.087 g (0.46 mmol) 4-(Difluoromethoxy)phenyl-isocyanate by general method for 1 h.

20 The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (98:2 → 97:3; (v/v))] as colourless solid.

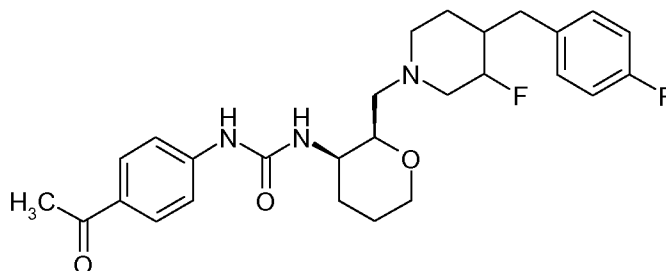
TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.40

EF: C₂₆ H₃₁ N₃ O₃ F₄; MW: calc.: 509.54

MS: fnd.: 510.2 (MH⁺)

25

11. **Diastereomeric mixture of 3-[(4-Acetylphenyl)carbamoyl]amino}-2,6-anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidin-1-yl]-D-threo-hexitol**



0.2 g (0.61 mmol) diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-

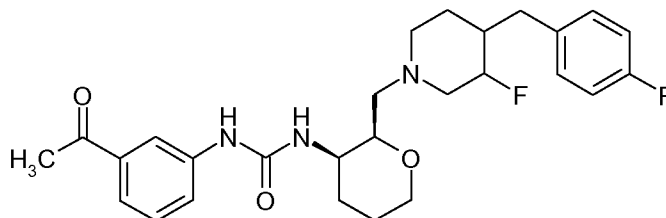
- 5 [(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-*threo*-hexitol (Compound A26) is reacted with 0.12 g (0.74 mmol) 4-Acetylphenyl-isocyanate by general method for 12 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (95:5; (v/v))] as colourless solid of m. p. 82°C.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.30

- 10 EF: C27 H33 N3 O3 F2; MW: calc.: 485.58

MS: fnd.: 486.2 (MH⁺)

12. **Diastereomeric mixture of 3-[(3-Acetylphenyl)carbamoyl]amino}-2,6-anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidin-1-yl]-D-threo-hexitol**



15

0.155 g (0.48 mmol) diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-

- 20 [(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-*threo*-hexitol (Compound A26) is reacted with 0.078 g (0.48 mmol) 3-Acetylphenyl-isocyanate by general method for 1 h. The title compound is isolated after silica gel chromatography [CH₂Cl₂/MeOH (98:2; (v/v))] as colourless solid.

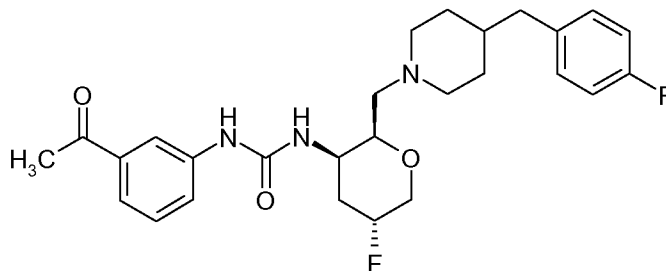
TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.40

EF: C27 H33 N3 O3 F2; MW: calc.: 485.58

MS: fnd.: 486.1 (MH⁺)

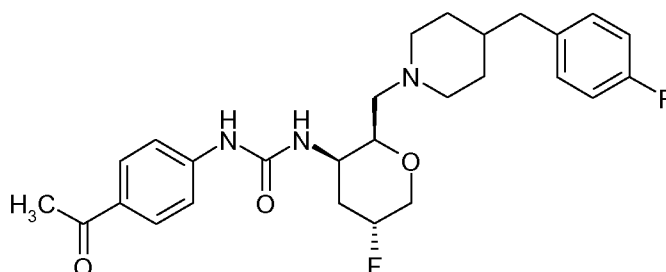
25

13. 4-[(3-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



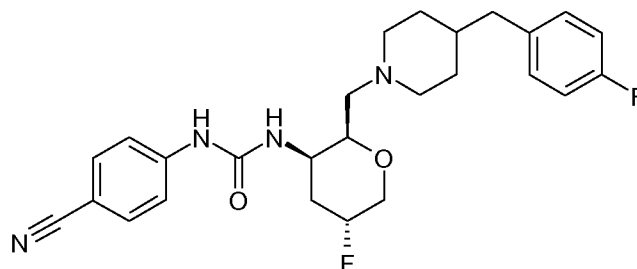
- 5 0.27 g (0.81 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A40) is reacted with 0.16 g (0.99 mmol) 3-Acetylphenyl-isocyanate by general method for 1 h. The title compound is isolated after silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2; (v/v))] as colourless solid of m. p. 82°C.
TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.20$
10 EF: C27 H33 N3 O3 F2; MW: calc.: 485.58
MS: fnd.: 486.2 (MH^+)

14. 4-[(4-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



- 15 0.26 g (0.80 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A40) is reacted with 0.154 g (0.96 mmol) 4-Acetylphenyl-isocyanate by general method for 3 h. The title compound is isolated after silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2; (v/v))] as colourless solid of m. p. 89°C.
20 TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.25$
EF: C27 H33 N3 O3 F2; MW: calc.: 485.58
MS: fnd.: 486.3 (MH^+)

15. **4-[[[(4-Cyanophenyl)carbamoyl]amino]-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



0.26 g (0.80 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(4-(4-

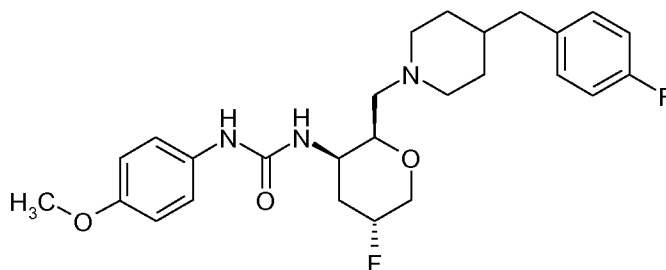
5 fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A40) is reacted with 0.137 g (0.95 mmol) 4-Cyanophenyl-isocyanate by general method for 1.5 h. The title compound is isolated after silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2; (v/v))] as colourless foam.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.40$

EF: $\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_2\text{F}_2$; MW: calc.: 468.55

10 MS: fnd.: 469.2 (MH^+)

16. **4-[[[(4-Methoxyphenyl)carbamoyl]amino]-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



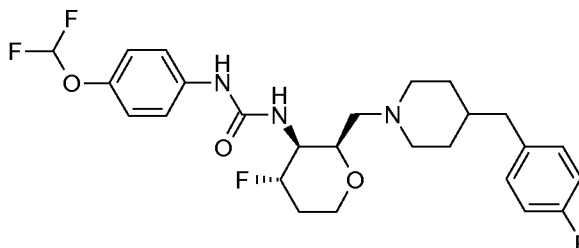
15 0.21 g (0.64 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A40) is reacted with 0.115 g (0.77 mmol) 4-Methoxyphenyl-isocyanate by general method for 2 h. The title compound is isolated after silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2; (v/v))] as colourless foam.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.2$

20 EF: $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3\text{F}_2$; MW: calc.: 473.57

MS: fnd.: 474.2 (MH^+)

17. **1,5-Anhydro-2,3,4,6-tetradeoxy-4-([4-(difluoromethoxy)phenyl]carbamoyl)amino}-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



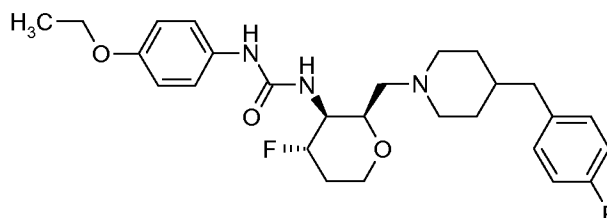
0.148 g (0.46mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.077 ml (0.55mmol) 4-(Difluoromethoxy)-phenylisocyanate by general method for 2 h. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2; (v/v))] and subsequent crystallisation from EA/ n-pentane as a colourless solid of m. p. 166-168°C.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.42

EF: C₂₆H₃₁F₄N₃O₃; MW: calc.: 509.54

MS: fnd.: 510.2 (MH⁺)

18. **1,5-Anhydro-2,3,4,6-tetradeoxy-4-([4-(ethoxyphenyl)carbamoyl]amino)-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



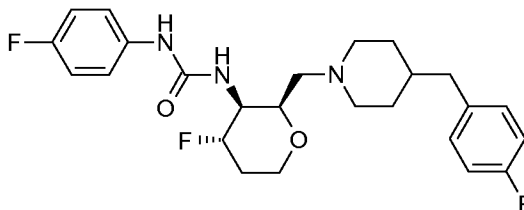
0.154 g (0.47mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.077 ml (0.52mmol) 4-Ethoxyphenylisocyanate by general method for 1 h. The title compound is obtained after purification by HPLC as a colourless lyophilisate.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.43

EF: C₂₇ H₃₅ F₂ N₃ O₃; MW: calc.: 487.59

MS: fnd.: 488.2 (MH⁺)

19. **1,5-Anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-4-[(4-fluorophenyl)carbamoyl]amino}-D-xylo-hexitol**



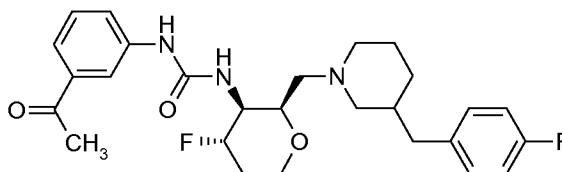
0.14 g (0.43 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A10) is reacted with 0.058 ml (0.52 mmol) 4-Fluorophenylisocyanate by general method for 12 h. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2)] and subsequent crystallisation from EA/ n-pentane as a colourless solid of m.p. 89-92°C

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.46

EF: C₂₅ H₃₀ F₃ N₃ O₂; MW: calc.: 461,53

MS: fnd.: 462.1 (MH⁺)

20. **4-[(3-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



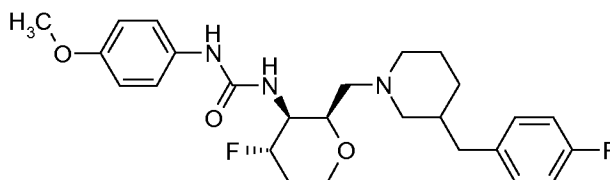
0.139 g (0.43 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A12) is reacted with 0.071 ml (0.51 mmol) 3-Acetylphenyl-isocyanate by general method for 1 h. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2; (v/v))], purification with charcoal and subsequent crystallisation from EA/ n-pentane as a colourless solid of m.p. 76-79°C.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.38

EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.1 (MH⁺)

21. **1,5-Anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-4-[[4-methoxyphenyl]carbamoyl]amino}-D-xylo-hexitol**



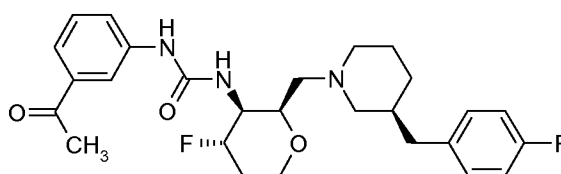
0.137 g (0.42 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A12) is reacted with 0.066 ml (0.51 mmol) 4-Methoxyphenylisocyanate by general method for 1.5 h. The title compound is obtained after silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2; (v/v))] and subsequent crystallisation from EA/ n-pentane as a colourless solid.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.18$

EF: $\text{C}_{26} \text{H}_{33} \text{F}_2 \text{N}_3 \text{O}_3$; MW: calc.: 473,56

MS: fnd.: 474.1 (MH^+)

22. **4-[(3-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



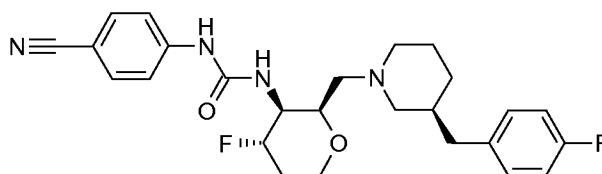
0.205 g (0.63 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A43) is reacted with 0.121 ml (0.88 mmol) 3-Acetylphenyl-isocyanat by general method for 2 h. The title compound is obtained after silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2; (v/v))] and subsequent crystallisation from EA/ n-pentane as a colourless solid of m.p. 86-88°C.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5; (v/v))], $R_f=0.35$

EF: $\text{C}_{27} \text{H}_{33} \text{F}_2 \text{N}_3 \text{O}_3$; MW: calc.: 485,57

MS: fnd.: 486.2 (MH^+)

23. **1,5-Anhydro-4-[(4-cyanophenyl)carbamoyl]amino}-2,3,4,6-tetradeoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



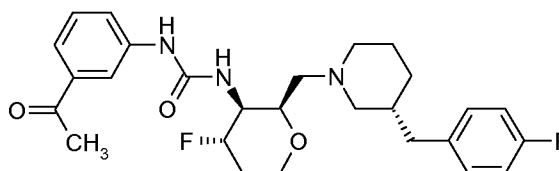
0.203 g (0.62 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A43) is reacted with 0.097 g (0.68 mmol) 4-Cyanophenyl-isocyanate by general method for 40 min. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2 → 96:4; (v/v))] and subsequent crystallisation from EA/ n-

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.4

EF: C₂₆ H₃₀ F₂ N₄ O₂; MW: calc.: 468,55

MS: fnd.: 469.2 (MH⁺)

24. 4-[(3-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3R)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



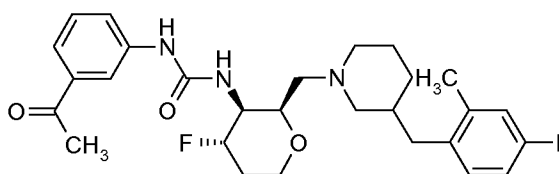
0.187 g (0.57 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3R)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A46) is reacted with 0.095 ml (0.69mmol) 3-Acetylphenyl-isocyanate by general method for 1 h. The title compound is obtained after purification by HPLC as a colourless lyophilisate.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.35

EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.2 (MH⁺)

25. 4-[(3-Acetylphenyl)carbamoyl]amino}-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3RS)-3-(4-fluoro-2-methylbenzyl)piperidin-1-yl]-D-xylo-hexitol



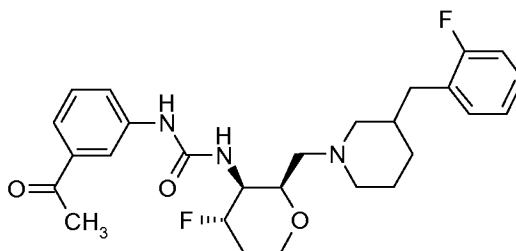
0.171 g (0.51mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3RS)-3-(4-fluoro-2-methylbenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A49) is reacted with 0.103 ml (0.74 mmol) 3-Acetylphenyl-isocyanate by general method for 30 min. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2; (v/v))] and subsequent purification by HPLC as a colourless lyophilisate.

TLC: [CH₂Cl₂/MeOH (98:2; (v/v))], R_f=0.35

EF: C₂₈ H₃₅ F₂ N₃ O₃; MW: calc.: 499,59

MS: fnd.: 500.2 (MH⁺)

26. **4-[[[(3-Acetylphenyl)carbamoyl]amino]-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3RS)-3-(2-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



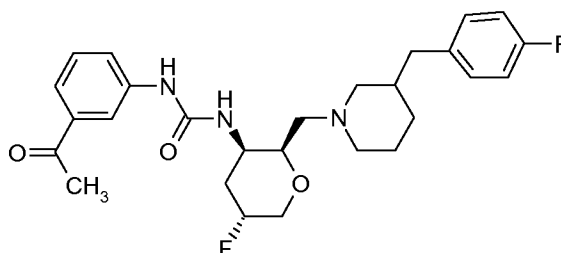
0.25 g (0.77 mmol) 4-[[[(3-Acetylphenyl)carbamoyl]amino]-1,5-anhydro-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3R)-3-(2-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A52) is reacted with 0.175 g (1.1 mmol) 3-Acetylphenyl-isocyanate by general method for 1 h. The title compound is obtained after purification by HPLC as a colourless lyophilisate.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))]

EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.1 (MH⁺)

27. **4-[[[(3-Acetylphenyl)carbamoyl]amino]-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



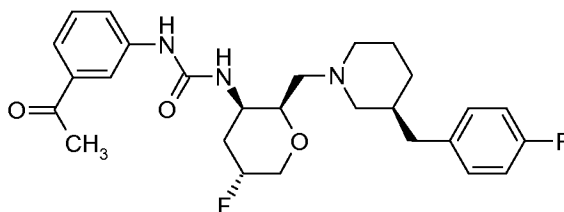
0.144 g (0.44 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A54) is reacted with 0.097ml (0.71 mmol) 3-Acetylphenyl-isocyanat by general method for 2.5 h. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2; (v/v))] and subsequent crystallisation from ethyl acetate/ n-pentane as a colourless solid of m. p. 69-72°C.

TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.37

EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.1 (MH⁺)

28. **4-[(3-Acetylphenyl)carbamoylamino]-1,5-anhydro-2,3,4,6-tetradeoxy-2-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



0.221 g (0.68 mmol) 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-2-fluoro-6-[(3S)-3-(4-

5 fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A56) is reacted with 0.112 ml (0.82 mmol) 3-Acetylphenyl-isocyanat by general method for 45 minutes. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (98:2; (v/v))] and subsequent crystallisation from ethyl acetate/ n-pentane as a colourless solid of m. p. 77-79°C.

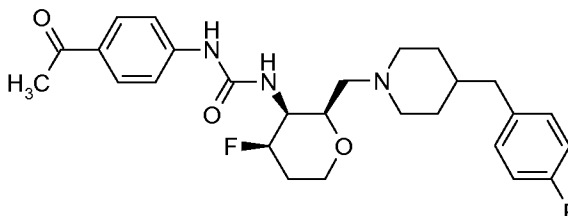
TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.27

10 EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.2 (MH⁺)

29. **3-[(4-Acetylphenyl)carbamoylamino]-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[4-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol**

15



0.199 g (0.61 mmol) 3-Amino-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[4-(4-fluorobenzyl)- piperidin-1-yl]-D-arabino-hexitol (Compound A66) is reacted with 0.118 ml (0.74mmol) 4-Acetylphenyl-isocyanate by general method for 1 h. The title compound is obtained after silica gel chromatography [CH₂Cl₂/MeOH (96:4, (v/v))] and subsequent crystallization from ethyl- acetate/ n-pentane as a colourless solid of m.p. 102-103°C.

20

TLC: [CH₂Cl₂/MeOH (95:5, (v/v))] R_f=0.3

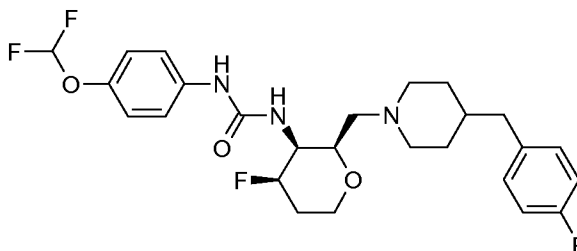
EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.2 (MH⁺)

25

30

30. **2,6-Anhydro-1,3,4,5-tetradeoxy-3-([4-(difluoromethoxy)phenyl]carbamoyl)amino)-4-fluoro-1-[4-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol**



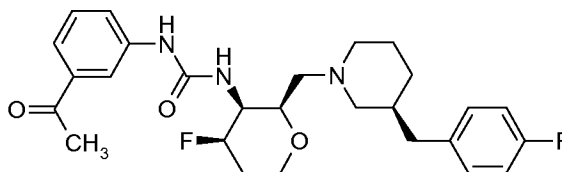
0.171 g (0.53 mmol) 3-Amino-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[4-(4-fluorobenzyl)-piperidin-1-yl]-D-arabino-hexitol (Compound A66) is reacted with 0.093 ml (0.63mmol) 4-(Difluoromethoxy)-phenylisocyanate by general method for 1 h. The title compound is obtained after purification by HPLC as a colourless lyophilisate.

TLC: [CH₂Cl₂/MeOH (95:5, (v/v))] R_f=0.3

EF: C₂₆ H₃₁ F₄ N₃ O₃; MW: calc.: 509,54

MS: fnd.: 510.3 (MH⁺)

31. **3-([3-Acetylphenyl]carbamoyl)amino)-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol**



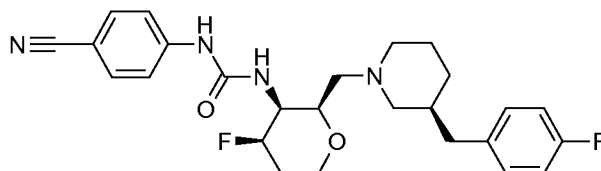
0.23 g (0.71 mmol) 3-Amino-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)-piperidin-1-yl]-D-arabino-hexitol (Compound A68) is reacted with 0.117 ml (0.85 mmol) 3-Acetylphenylisocyanate by general method for 1 h. The title compound is obtained after purification by HPLC as a colourless lyophilisate.

TLC: [CH₂Cl₂/MeOH (95:5, (v/v))] R_f=0.3

EF: C₂₇ H₃₃ F₂ N₃ O₃; MW: calc.: 485,57

MS: fnd.: 486.4 (MH⁺)

32. **2,6-Anhydro-3-([4-cyanophenyl]carbamoyl)amino)-1,3,4,5-tetradeoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol**



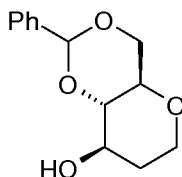
0.156 g (0.48 mmol) 3-Amino-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)-piperidin-1-yl]-D-arabino-hexitol (Compound A68) is reacted with 0.09 ml (0.63mmol)

4-Cyanophenyl-isocyanate by general method for 1 h. The title compound is obtained after purification by HPLC as a colourless lyophilisate.

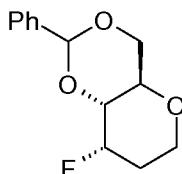
TLC: [CH₂Cl₂/MeOH (95:5, (v/v))] R_f=0.3

EF: C₂₆ H₃₀ F₂ N₄ O₂; MW: calc.: 468,55

5 MS: fnd.: 469.4 (MH⁺)

Starting materials:**A1. 1,5-Anhydro-2-deoxy-4,6-O-(phenylmethylidene)-D-arabino-hexitol**

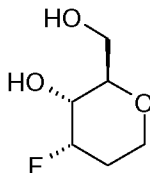
- 5 **Lit.:** Foster et al. *Acta Chem. Scand.* **1958**, 12, 1819, 1823
 Sasaki, M. et al. *Tetrahedron Letters* **2006**, 47(32), 5687-5691
 Thonia, G. et al. *J. Med. Chem.* **1999**, 42(23), 4909-4913

A2. 1,5-Anhydro-2,3-dideoxy-3-fluoro-4,6-O-(phenylmethylidene)-D-ribo-hexitol

10

To a solution of 12 g (51 mmol) 1,5-Anhydro-2-deoxy-4,6-O-(phenylmethylidene)-D-arabino-hexitol (compound A1) in 300 ml anhydrous dichloromethane 27 ml DIPEA and 12 ml (72 mmol) triflic anhydride are slowly added one after another under stirring at -70°C . After stirring for 15 min. 300 ml (300 mmol, 1 M solution in anhydrous THF) TBAF is added to the reaction solution between a range of -70°C and -55°C . After stirring over night at room temperature the solution is diluted with 500 ml water and extracted with 500 ml dichloromethane (3 x). The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude product is subsequently purified by silica gel chromatography [PE/EA (9:1 $\rightarrow$ 8:2; (v/v))] affording the title compound as light yellow oil. The mass spectrum shows the molecular peak M^+ of 238.2 Da.

- 15
 20 **TLC:** [PE/EA (8:2; (v/v))], $R_f=0.35$
EF: $\text{C}_{13}\text{H}_{15}\text{O}_3\text{F}$; MW: calc.: 238.26
MS: fnd.: 238.2 (M^+)

A3. 1,5-Anhydro-2,3-dideoxy-3-fluoro-D-ribo-hexitol

25

A solution of 8.8 g (37 mmol) 1,5-Anhydro-2,3-dideoxy-3-fluoro-4,6-O-(phenylmethylidene)-D-ribo-hexitol (compound A2) in 95 ml acetic acid is hydrogenated at room temperature over 0.95 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo and coevaporated with toluene (2 x). Further purifi-

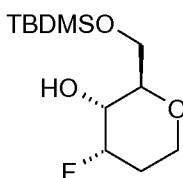
cation of the crude material by silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5 $\rightarrow$ 93:7; (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular peak M^+ of 150.1 Da.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5)], $R_f=0.26$

5 EF: $\text{C}_6\text{H}_{11}\text{O}_3\text{F}$; MW: calc.: 150.15

MS: fnd.: 150.1 (M^+), 132.1 ($\text{M}^+ - 18$)

A4. 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-D-ribo-hexitol



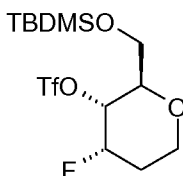
10 5.8 g (85 mmol) imidazole and 5.6 g (37.4 mmol) TBDMSCI are added to a solution of 5.1 g (34 mmol) 1,5-Anhydro-2,3-dideoxy-3-fluoro-D-ribo-hexitol (compound A3) in 160 ml anhydrous dichloromethane. After subsequent addition of 150 mg DMAP the solution is stirred for 1.5 h at room temperature. For workup, the mixture is poured into a half saturated aqueous NH_4Cl solution and then extracted three times with CH_2Cl_2 . The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. Subsequent purification by silica gel chromatography [PE/EA (9:1 $\rightarrow$ 85:15; (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular peak $\text{M}^+ - 57$ of 321.4 Da.

TLC: [PE/EA (9:1; (v/v))], $R_f=0.3$

EF: $\text{C}_{12}\text{H}_{25}\text{O}_3\text{SiF}$; MW: calc.: 264.46

20 MS: fnd.: 321.4 ($\text{M}^+ - 57$)

A5. 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-4-O-[(trifluoromethyl)sulfonyl]-D-ribo-hexitol

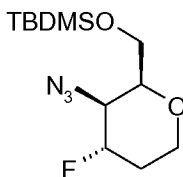


25 2.43 ml (14.6 mmol) trifluoromethanesulfonic acid anhydride is added dropwise to a solution of 3.65 g (13.8 mmol) 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-D-ribo-hexitol (compound A4) in 11.1 ml pyridine and 87 ml dry dichloromethane at -50°C . The reaction solution is stirred for 0.5 h till the temperature is warmed-up to about $+10^\circ\text{C}$. After the reaction solution is cooled to -30°C , 1 ml methanol is added and the stirring is continued for 5 min. For workup, the mixture is poured into a half saturated aqueous NaCl solution and then extracted three times with CH_2Cl_2 . The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting residue is coevaporated with toluene (2 x) and dried in vacuo for 1 h to give the title compound as a yellow oil, which is used for the next step without further purification.

TLC: [PE/EA (9:1; (v/v))], $R_f=0.55$

EF: C13 H24 O5 S Si F4; MW: calc.: 396.48

A6. 1,5-Anhydro-4-azido-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-D-xylo-hexitol

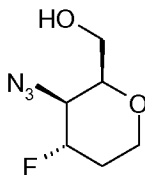


2.69 g (41.4 mmol) sodium azide is added to a solution of 5.58 g (13.8 mmol) 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-4-O-[(trifluoromethyl)sulfonyl]-D-ribo-hexitol (compound A5) in 70 ml dry DMF at 0°C. First, the mixture is stirred at 0°C for 4 h and again at room temperature over night. For workup, a half saturated aqueous NaCl solution is poured to the mixture and afterwards it is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo affording the title compound as colourless oil. The compound is used for the next step without further purification.

TLC: [PE/EA (9:1; (v/v))], $R_f=0.6$

EF: C12 H24 N3 O3 Si F; MW: calc.: 289.43

A7. 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-D-xylo-hexitol



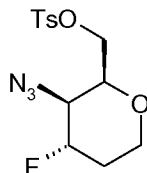
To a solution of 4 g (13.8 mmol) 1,5-Anhydro-4-azido-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-D-xylo-hexitol (compound A6) in 65 ml absolute THF 12.9 ml (12.9 mmol, 1 M solution in anhydrous THF) TBAF is added at room temperature under stirring. After continuous stirring still at room temperature for 2 h, 80 ml of a half saturated aqueous NaCl solution is poured into the reaction mixture. The resulting solution is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (7:3→ 1:1; (v/v))] and [Tol/Ac (92:8→ 88:12; (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular peak M^+ of 175.1 Da.

TLC: [PE/EA (6:4; (v/v))], $R_f=0.35$

EF: C6 H16 N3 O2 F; MW: calc.: 175.16

MS: fnd.: 175.1 (M^+)

A8. 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol



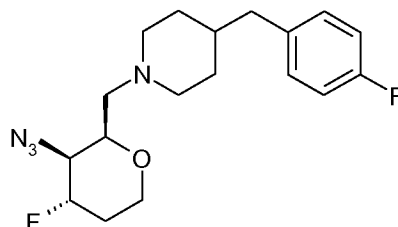
To a solution of 1.1 g (6.3 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-D-xylo-hexitol (compound A7) in 3 ml pyridine and 25 ml dry dichloromethane 2.44 g (12.8 mmol) p-toluenesulfonyl chloride is added at room temperature under stirring. After continuous stirring at room temperature over night the reaction solution is refluxed for 2 h. Thereafter 30 ml of a half saturated aqueous NaCl solution is poured into the reaction solution and the resulting mixture is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (8:2; (v/v))] affords the title compound as colourless liquid. The mass spectrum shows the molecular peak M⁺ of 175.1 Da.

TLC: [PE/EA (7:3; (v/v))], R_f=0.6

EF: C₁₃ H₁₆ N₃ O₄ S F; MW: calc.: 329.35

MS: fnd.: 155.3 (tosyl fragment)

A9. 1,5-Anhydro-4-azido-2,3,4,6-tetradexo-3-fluoro-6-[(4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



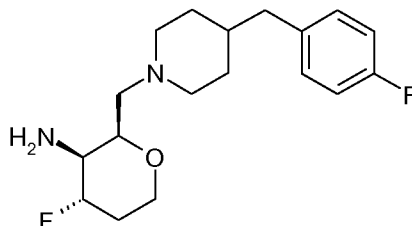
A solution of 2.0 g (6.1 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (compound A8) and 2.85 g (6.1 mmol) 4-(4-Fluorobenzyl)piperidine (compound A14) in 30 ml absolute DMF is stirred at 110°C for 4 h. After stirring at room temperature over night, 30 ml of a half saturated aqueous NaCl solution is poured into the reaction solution and the resulting mixture is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (95:5; (v/v))] and [Tol/Ac (96:4; (v/v))] affords the title compound (1.4 g) as yellow oil. The mass spectrum shows the molecular peak MH⁺ of 351.1 Da.

TLC: [Tol/Ac (9:1; (v/v))], R_f=0.33

EF: C₁₈ H₂₄ N₄ O F₂; MW: calc.: 350.41

MS: fnd.: 351.1 (MH⁺)

A10. 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



5 A solution of 1.4 g (0.4 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-3-fluoro-6-[(4-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (compound A9) in 88 ml methanol is hydrogenated at room temperature over 0.44 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as colourless oil. The mass spectrum shows the molecular peak MH^+ at 325.3 Da. The compound is used for the next step without further purification.

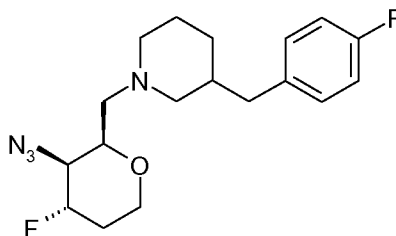
TLC: [$CH_2Cl_2/MeOH$ (95:5; (v/v))], $R_f=0.11$

EF: $C_{18}H_{26}N_2O_2F_2$; MW: calc.: 324.42

MS: fnd.: 325.3 (MH^+)

15

A11. 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



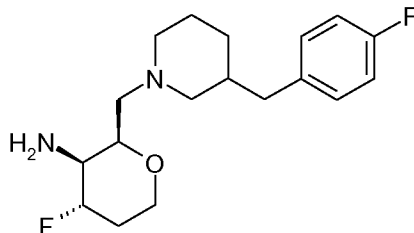
20 A solution of 0.367 g (1.11 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (compound A8) and 0.26 g (1.34 mmol) (3RS)-3-(4-Fluorobenzyl)piperidine (compound A13) in 6 ml absolute DMF is stirred at 110°C for 4.5 h. After stirring at room temperature over night, 10 ml of a half saturated aqueous NaCl solution is poured into the reaction solution and the resulting mixture is extracted three times with CH_2Cl_2 . The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (95:5; (v/v))] affords the title compound (0.17 g) as light yellow oil. The mass spectrum shows the molecular peak MH^+ of 351.0 Da.

TLC: [Tol/Ac (8:2; (v/v))], $R_f=0.6$

EF: $C_{18}H_{24}N_4O_2F_2$; MW: calc.: 350.41

30 MS: fnd.: 351.0 (MH^+)

A12. 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol

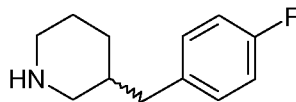


- 5 A solution of 0.164 g (0.47 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-3-fluoro-6-[(3S,3R)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (compound A11) in 10 ml methanol is hydrogenated at room temperature over 0.05 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as colourless oil. The mass spectrum shows the molecular peak MH^+ at 325.2 Da. The
- 10 compound is used for the next step without further purification.

TLC: [$CH_2Cl_2/MeOH$ (95:5, (v/v))], $R_f=0.16$

EF: $C_{18}H_{26}N_2O_2F_2$; MW: calc.: 324.42

A13. (3RS)-3-(4-Fluorobenzyl)piperidine



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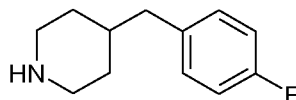
Lit.: De Lucca G. V. et al. *J. Med. Chem.* **2005**, 48, 2194-2211

Emmett G. C. et al. *Synthesis* **2005**, 1, 92-96

Yue T.-Y. et al. *J. Am. Chem. Soc.* **2002**, 124 (46), 13692-13693

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A14. 4-(4-Fluorobenzyl)piperidine



Lit.: Shanklin J. R. et al. *J. Med. Chem.* **1991**, 34 (10), 3011-3022

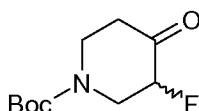
Pabel J. et al. *Bioorg. Med. Chem. Lett.* **2000**, 10(12), 1377-1380

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McCauly J. A. et al. *J. Med. Chem.* **2004**, 47 (8), 2089-2096

Ting P. C. et al. *Bioorg. Med. Chem. Lett.* **2005**, 15(5), 1375-1378

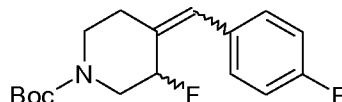
A15. tert-Butyl(3RS)-3-fluoro-4-oxopiperidine-1-carboxylate



- Lit.:** Sun, A. et al. *Chem. Europ. J.* **2005**, 11(5), 1579-1591
 Beeler, A.B. et al. *Bioorg. Med. Chem.* **2003**, 11(23), 5229-5234
 Castro, J.L. et al. *J. Med. Chem.* **1998**, 41, 2667-2670
 Van Niel, M.B. et al. *J. Med. Chem.* **1999**, 42, 2087-2104

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A16. tert-Butyl-(4E/Z)-(3RS)-3-fluoro-4-[(4-fluorophenyl)methylidene]piperidine-1-carboxylate



A solution of 22.8 g (54.9 mmol) 4-Fluorobenzyl-triphenylphosphoniumchloride, 1 ml (4.9 mmol) 15-Crown-5 and 2.16 g (54.0 mmol) NaH in 100 ml anhydrous THF is stirred at 0°C for 45 min. Then, a solution of 10.7 g (49.1 mmol) *tert*-Butyl(3RS)-3-fluoro-4-oxopiperidine-1-carboxylate (compound A15) in 53 ml anhydrous THF is slowly added to the reaction mixture at 0°C. After stirring for 10 min at 0°C and 1 h at room temperature 150 ml of a half saturated aqueous NaHCO₃ solution is poured into the reaction solution and the resulting mixture is extracted three times with ethyl acetate. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (95:5→85:15, (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular peak MH⁺-Boc of 209.9 Da.

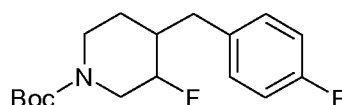
TLC: [PE/EA (8:2; (v/v))], R_f=0.55

EF: C₁₇ H₂₁ O₂ N F₂; MW: calc.: 309.36

MS: fnd.: 209.9 (MH⁺-Boc)

20

A17. Racemic mixture of tert-Butyl[(3R,4R)/(3S,4S)]-3-fluoro-4-(4-fluorobenzyl)piperidine-1-carboxylate



25

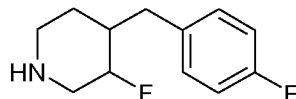
A solution of 18.0 g (58.2 mmol) *tert*-Butyl(4E/Z)-(3RS)-3-fluoro-4-[(4-fluorophenyl)methylidene]piperidine-1-carboxylate (compound A16) in 300 ml methanol is hydrogenated at room temperature over 0.5 g of Raney-Nickel (B113W) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (95:5→8:2; (v/v))] affords the title compound (8.4 g) as light yellow crystals. The mass spectrum shows the molecular peak MNH₄⁺ of 328.9 Da.

TLC: [PE/EA (8:2)], R_f=0.65

EF: C₁₇ H₂₃ N O₂ F₂; MW: calc.: 311.37

MS: fnd.: 328.9 (MNH₄⁺)

35

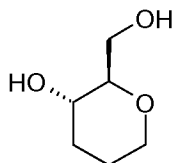
A18. Racemic mixture of (3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine

A suspension of 8.4 g (26.9 mmol) of the racemic mixture of *tert*-Butyl[(3*R*,4*R*)/(3*S*,4*S*)]-3-fluoro-4-(4-fluorobenzyl)piperidine-1-carboxylate (compound A17) in 105 ml HCl/ diethyl ether is stirred at room temperature for 3 h. The resulting precipitate is filtered off, suspended in 200 ml of an aqueous 2N NaOH solution and extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound as light yellow oil. The mass spectrum shows the molecular peak MH⁺ of 212.1 Da. The compound is used for the next step without further purification.

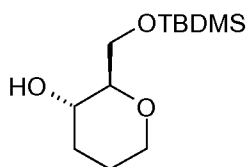
TLC: [CH₂Cl₂/MeOH (95:5; (v/v))], R_f=0.35

EF: C₁₂ H₁₅ N F₂; MW: calc.: 211.25

MS: fnd.: 212.1 (MH⁺)

A19. 1,5-Anhydro-2,3-dideoxy-D-erythro-hexitol

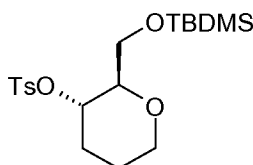
Lit.: Nicolaou, K.C. et al. *J. Am. Chem. Soc.* **1990**, 112(8), 3040-3054

A20. 1,5-Anhydro-6-O-[*tert*-butyl(dimethyl)silyl]-2,3-dideoxy-D-erythro-hexitol

Lit.: Delgado, M. et al. *J. Org. Chem.* **1999**, 64(13), 4798-4816

59

A21. 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-4-O-[(4-methylphenyl)sulfonyl]-D-erythro-hexitol



To a solution of 18.7 g (75.9 mmol) 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-D-
 5 *erythro*-hexitol (compound A20) in 250 ml pyridine 30.4 g (159.4 mmol) p-toluenesulfonyl chloride
 is added at room temperature under stirring. After the reaction solution is stirred at 60°C for 6 h,
 300 ml of a half saturated aqueous NaHCO₃ solution is slowly poured into the reaction solution and
 the resulting mixture is extracted three times with ethyl acetate (3x). The combined organic phases
 are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting
 10 residue by silica gel chromatography [PE/EA (95:5→ 9:1; (v/v))] affords the title compound as light
 yellow oil. The mass spectrum shows the molecular peak M⁺ - 57 of 343.2 Da.

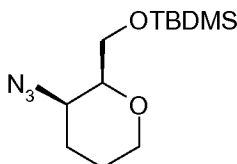
TLC: [PE/EA (9:1; (v/v))], R_f=0.4

EF: C₁₉ H₃₂ O₅ S Si; MW: calc.: 400.61

MS: fnd.: 343.2 (M⁺ - 57)

15

A22. 2,6-Anhydro-3-azido-1-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3,4,5-trideoxy-D-threo-hexitol



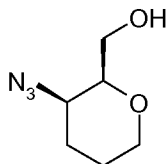
5.3 g (81.4 mmol) sodium azide is added to a solution of 25.1 g (62.6 mmol) 1,5-Anhydro-6-O-[tert-
 20 butyl(dimethyl)silyl]-2,3-dideoxy-4-O-[(4-methylphenyl)sulfonyl]-D-*erythro*-hexitol (compound A21)
 in 275 ml dry DMF under stirring. The reaction mixture is stirred at 110°C for 2.5 h. For workup, a
 half saturated aqueous NaCl solution is poured to the mixture and afterwards it is extracted three
 times with Et₂O. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in
 vacuo affording the crude title compound as colourless oil. The compound is used for the next step
 25 without further purification.

TLC: [PE/EA (9:1; (v/v))], R_f=0.8

EF: C₁₂ H₂₄ N₃ O₂ Si F; MW: calc.: 289.43

30

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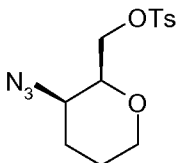
A23. 1,5-Anhydro-4-azido-2,3,4-trideoxy-D-threo-hexitol

To a solution of 6.3 g (23.2 mmol) 2,6-Anhydro-3-azido-1-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3,4,5-trideoxy-D-threo-hexitol (compound A22) in 192 ml absolute THF 17.4 ml (17.4 mmol, 1 M solution in anhydrous THF) TBAF is added at room temperature under stirring. After continuous stirring still at room temperature for 1 h, 150 ml of a half saturated aqueous NaCl solution is poured into the reaction mixture. The resulting solution is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (7:3→ 3:7; (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular peak M⁺ of 157.0 Da.

TLC: [PE/EA (6:4, (v/v))], R_f=0.35

EF: C₆ H₁₁ N₃ O₂; MW: calc.: 157.17

MS: fnd.: 157.0 (M⁺)

A24. 2,6-Anhydro-3-azido-3,4,5-trideoxy-1-O-[(4-methylphenyl)sulfonyl]-D-threo-hexitol

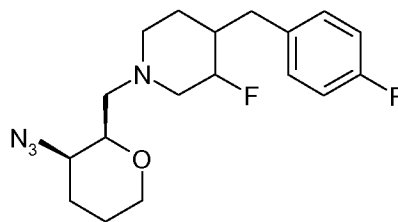
To a solution of 2.8 g (17.6 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-D-threo-hexitol (compound A23) in 5.7 ml pyridine and 68 ml dry dichloromethane 4.0 g (21.1 mmol) p-toluenesulfonyl chloride is added at room temperature under stirring. After continuous stirring at room temperature over night the reaction solution is refluxed for 4 h. Thereafter 50 ml of a half saturated aqueous NH₄Cl solution is poured into the reaction solution and the resulting mixture is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (85:15→ 8:2, (v/v))] affords the title compound as yellow oil. The mass spectrum shows the molecular peak MNH₄⁺ of 328.9 Da.

TLC: [PE/EA (7:3; (v/v))], R_f=0.48

EF: C₁₃ H₁₇ N₃ O₄ S; MW: calc.: 311.36

MS: fnd.: 328.9 (MNH₄⁺)

A25. Diastereomeric mixture of 2,6-Anhydro-3-azido-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol



A solution of 6.0 g (19.25 mmol) 2,6-Anhydro-3-azido-3,4,5-trideoxy-1-O-[(4-methylphenyl)sulfonyl]-D-threo-hexitol (compound A24) and 4.9 g (23.1 mmol) of the racemic mixture of (3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine (compound A18) in 76 ml absolute DMF is stirred at 85°C over night. Thereafter 80 ml of a half saturated aqueous Na₂CO₃ solution is poured into the reaction solution and the resulting mixture is extracted three times with ethyl acetate. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo.

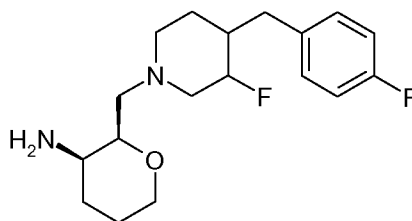
Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (8:2 → 6:4; (v/v))] affords the title compound as yellow oil. The mass spectrum shows the molecular peak MH⁺ of 351.1 Da.

TLC: [Tol/Ac (7:3; (v/v))], R_f=0.35

EF: C₁₈ H₂₄ N₄ O F₂; MW: calc.: 350.41

MS: fnd.: 351.1 (MH⁺)

A26. Diastereomeric mixture of 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol

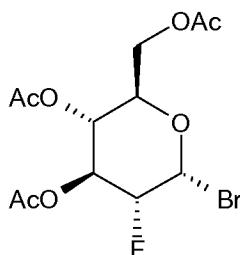


A solution of 2.24 g (6.4 mmol) of the diastereomeric mixture of 2,6-Anhydro-3-azido-1,3,4,5-tetradexoxy-1-[(3R,4R)/(3S,4S)-3-fluoro-4-(4-fluorobenzyl)piperidine-1-yl]-D-threo-hexitol (compound A25) in 140 ml methanol is hydrogenated at room temperature over 0.5 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as colourless oil. The mass spectrum shows the molecular peak MH⁺ at 325.2 Da. The compound is used for the next step without further purification.

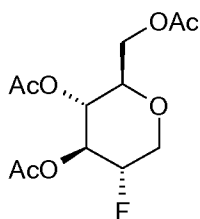
TLC: [CH₂Cl₂/MeOH (95:5, (v/v))], R_f=0.15

EF: C₁₈ H₂₆ N₂ O F₂; MW: calc.: 324.42

MS: fnd.: 325.3 (MH⁺)

A27. 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro- α -D-glucopyranosyl bromide

- 5 **Lit.:** Boyd, E. et al. *Tetrahedr. Lett.* **2006**, 47(45), 7983-7986
 McCarter, S. et al. *J. Am. Chem. Soc.* **1997**, 119(25), 5792-5797
 Maschauer, S. et al. *J. Labelled Compd. Radiopharm.* **2005**, 48(10), 701-719

A28. 3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-2-fluoro-D-glucitol

10

A solution of 64.9 g (175 mmol) 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro- α -D-glucopyranosyl bromide (compound A27) in 350 ml ethyl acetate and 35 ml Et₃N is hydrogenated at room temperature over 5.5 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo. Subsequent purification by silica gel chromatography [PE/EA (8:2; (v/v))] affords the title compound as colourless solid of m. p. 80.2°C. The mass spectrum shows the molecular peak MH⁺ at 293.0 Da.

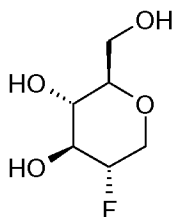
15

TLC: [PE/EA (7:3, (v/v))], R_f=0.40

EF: C₁₂ H₁₇ O₇ F; MW: calc.: 292.26

MS: fnd.: 293.0 (MH⁺)

20

A29. 1,5-Anhydro-2-deoxy-2-fluoro-D-glucitol

25

To a solution of 25 g (85.5 mmol) 3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-2-fluoro-D-glucitol (compound A28) in 150 ml methanol 3.1 ml (85.5 mmol) NaOMe (25% solution in MeOH) is slowly dropped at room temperature under stirring. After continuous stirring at room temperature for 2.5 h the reaction solution is neutralized with ion exchange resin Amberlite IR120 (treated with 1 N HCl).

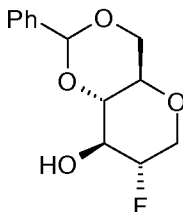
After the ion exchanger is filtered off, the solution is then concentrated in vacuo. The resulting colourless residue is the title compound, which is used for the next step without further purification.

TLC: [CH₂Cl₂/MeOH (9:1; (v/v))], R_f=0.25

EF: C₆ H₁₁ O₄ F; MW: calc.: 166.15

5 MS: fnd.: 135.1 (M⁺-31)

A30. 1,5-Anhydro-2-deoxy-2-fluoro-4,6-O-(phenylmethyldene)-D-glucitol



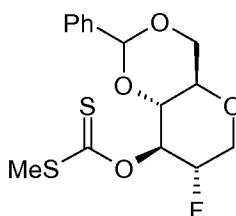
15.0 g (90.3 mmol) 1,5-Anhydro-2-deoxy-2-fluoro-D-glucitol (compound A29) is suspended in 300 mL CH₃CN under stirring. 22.3 mL (148 mmol) Benzaldehyde dimethylacetal and 1.47 g (7.7 mmol) PTSA are added and the reaction mixture is stirred for 12 h at room temperature. For workup, K₂CO₃ (1.65 g, 20 mmol) is added to the clear solution. After 10 min the solids are filtered off, the solvent is removed, and the resulting residue is subjected to silica gel flash chromatography [PE/EA (8:2; (v/v))]. The title compound is isolated as a colorless solid of m. p. 146°C.

15 TLC: [PE/EA (7:3, (v/v))], R_f=0.45

EF: C₁₃ H₁₅ O₄ F; MW: calc.: 254.26

MS: fnd.: 254.2 (M⁺)

A31. 1,5-Anhydro-2-deoxy-2-fluoro-3-O-[(methylsulfanyl)carbonothioyl]-4,6-O-(phenylmethyldene)-D-glucitol



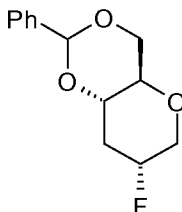
A solution of 13.3 g (52.3 mmol) 1,5-Anhydro-2-deoxy-2-fluoro-4,6-O-(phenylmethyldene)-D-glucitol (compound A30) in 400 ml dry THF is cooled to -70°C. One after another 3.2 ml (52.3 mmol) CS₂ and 55.2 ml (55.2 mmol) (Me₃Si)₂NNa (1 M solution in THF) is slowly dropped at -70°C under stirring. After stirring for 20 min 11.6 ml (177.5 mmol) MeI is added to the reaction mixture and the solution is stirred for another 5 min at -70°C and for 1 h at room temperature.

For workup, a half saturated aqueous NaCl solution is poured to the mixture and afterwards it is extracted three times with ethyl acetate. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo affording the title compound as yellow solid. The compound is used for the next step without further purification.

30 TLC: [PE/EA (8:2, (v/v))], R_f=0.55

EF: C₁₅ H₁₇ O₄ S₂ F; MW: calc.: 344.43

A32. 1,5-Anhydro-2,3-dideoxy-2-fluoro-4,6-O-(phenylmethylidene)-D-ribo-hexitol



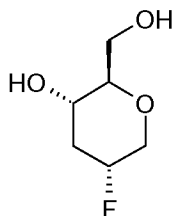
To a solution of 21.1 g (52.3 mmol) crude 1,5-Anhydro-2-deoxy-2-fluoro-3-O-[(methylsulfanyl)carbonothioyl]-4,6-O-(phenylmethylidene)-D-glucitol (compound A31) in 500 ml toluene 35 ml (53.3 mmol) Bu₃SnH and 0.26 g (52.3 mmol) AIBN are added and the mixture is stirred under reflux for 0.5 h. Thereafter the reaction mixture is concentrated in vacuo, the resulting residue is dissolved in CH₃CN and kieselguhr is added. The mixture is filtered and the filtrate is then concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (95:5; (v/v))] affords the title compound as colourless solid. The mass spectrum shows the molecular peak M⁺ at 238.2 Da.

TLC: [PE/EA (8:2; (v/v))], R_f=0.62

EF: C₁₃ H₁₅ O₃ F; MW: calc.: 238.26

MS: fnd.: 238.2 (M⁺)

A33. 1,5-Anhydro-2,3-dideoxy-2-fluoro-D-ribo-hexitol



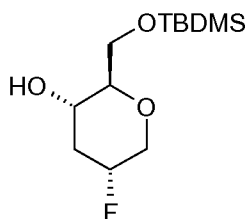
A solution of 7.35 g (30.8 mmol) 1,5-Anhydro-2,3-dideoxy-2-fluoro-4,6-O-(phenylmethylidene)-D-ribo-hexitol (compound A32) in 74 ml acetic acid is hydrogenated at 55°C over 1.36 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo and coevaporated with toluene (2 x). Further purification of the crude material by silica gel chromatography [CH₂Cl₂/MeOH (95:5, (v/v))] affords the title compound as colourless oil.

TLC: [PE/EA (8:2; (v/v))], R_f=0.62

EF: C₆ H₁₁ O₃ F; MW: calc.: 150.15

MS: fnd.: 132.1 (M⁺ -18), 119.1 (M⁺ -31)

65

A34. 1,5-Anhydro-6-O-[*tert*-butyl(dimethyl)silyl]-2,3-dideoxy-2-fluoro-D-ribo-hexitol

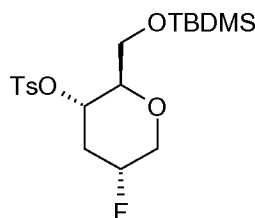
4.3 g (25.9 mmol) imidazole and 4.3 g (28.4 mmol) TBDMSCl are added to a solution of 3.9 g (25.8 mmol) 1,5-Anhydro-2,3-dideoxy-2-fluoro-D-ribo-hexitol (compound A33) in 110 ml anhydrous di-
 5 chloromethane. After subsequent addition of 110 mg DMAP the solution is stirred for 2 h at room temperature. For workup, the mixture is poured into a half saturated aqueous NH_4Cl solution and then extracted three times with CH_2Cl_2 . The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. Subsequent purification by silica gel chromatography [PE/EA (9:1, (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular
 10 peak $\text{M}^+ - 57$ of 207.1 Da.

TLC: [PE/EA (8:2, (v/v))], $R_f=0.5$

EF: $\text{C}_{12}\text{H}_{25}\text{O}_3\text{SiF}$; MW: calc.: 264.46

MS: fnd.: 207.1 ($\text{M}^+ - 57$)

15 **A35. 1,5-Anhydro-6-O-[*tert*-butyl(dimethyl)silyl]-2,3-dideoxy-2-fluoro-4-O-[(4-methylphenyl)sulfonyl]-D-ribo-hexitol**



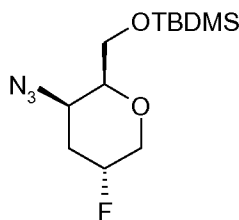
To a solution of 5.92 g (22.4 mmol) 1,5-Anhydro-6-O-[*tert*-butyl(dimethyl)silyl]-2,3-dideoxy-2-fluoro-D-ribo-hexitol (compound A34) in 17 ml pyridine and 150 ml dry dichloromethane 10.7 g (56.1
 20 mmol) p-toluenesulfonyl chloride is added at room temperature under stirring. After the reaction solution is stirred under reflux over night, 150 ml of a half saturated aqueous NaCl solution is slowly poured into the reaction solution and the resulting mixture is extracted three times with CH_2Cl_2 . The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (9:1; (v/v))] affords the title
 25 compound as colourless liquid. The mass spectrum shows the molecular peak $\text{M}^+ - 57$ of 361.2 Da.

TLC: [PE/EA (9:1, (v/v))], $R_f=0.4$

EF: $\text{C}_{19}\text{H}_{31}\text{O}_5\text{SiF}$; MW: calc.: 418.60

MS: fnd.: 361.2 ($\text{M}^+ - 57$)

A36. 1,5-Anhydro-4-azido-6-O-[*tert*-butyl(dimethyl)silyl]-2,3,4-trideoxy-2-fluoro-D-xylo-hexitol

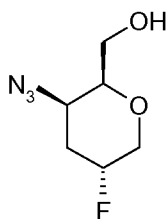


3.9 g (60 mmol) sodium azide is added to a solution of 8.4 g (20.1 mmol) 1,5-Anhydro-6-O-[*tert*-butyl(dimethyl)silyl]-2,3-dideoxy-2-fluoro-4-O-[(4-methylphenyl)sulfonyl]-D-ribo-hexitol (compound A35) in 110 ml dry DMF under stirring. The reaction mixture is stirred at 110°C for 2.5 h. For workup, a half saturated aqueous NaCl solution is poured to the mixture and afterwards it is extracted three times with Et₂O. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo affording the crude title compound as colourless oil. The compound is used for the next step without further purification.

TLC: [PE/EA (9:1; (v/v))], R_f=0.8

EF: C12 H24 N3 O2 Si F; MW: calc.: 289.43

A37. 1,5-Anhydro-4-azido-2,3,4-trideoxy-2-fluoro-D-xylo-hexitol

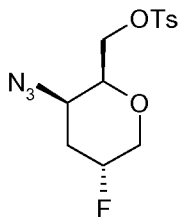


To a solution of 3.5 g (20.1 mmol) crude 1,5-Anhydro-4-azido-6-O-[*tert*-butyl(dimethyl)silyl]-2,3,4-trideoxy-2-fluoro-D-xylo-hexitol (compound A36) in 94 ml absolute THF 18.8 ml (1 M solution in anhydrous THF) TBAF is added at room temperature under stirring. After continuous stirring still at room temperature for 1 h, 100 ml of a half saturated aqueous NaCl solution is poured into the reaction mixture. The resulting solution is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (8:2→7:3, (v/v))] affords the title compound as colourless oil. The mass spectrum shows the molecular peak M⁺ of 175.1 Da.

TLC: [PE/EA (6:4, (v/v))], R_f=0.30

EF: C6 H16 N3 O2 F; MW: calc.: 175.16

MS: fnd.: 175.1 (M⁺)

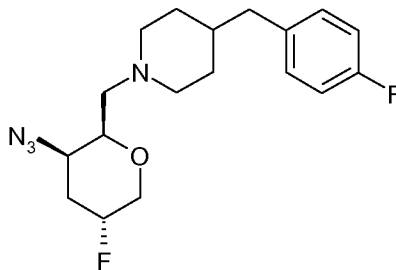
A38. 1,5-Anhydro-4-azido-2,3,4-trideoxy-2-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol

To a solution of 1.77 g (10.1 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-2-fluoro-D-xylo-hexitol (compound A37) in 7.5 ml pyridine and 40 ml dry dichloromethane 4.8 g (25.3 mmol) p-toluenesulfonyl chloride is added at room temperature under stirring. After continuous stirring under reflux for 3 h a half saturated aqueous NaCl solution is poured into the reaction solution and the resulting mixture is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [PE/EA (8:2, (v/v))] affords the title compound as colourless liquid. The mass spectrum shows the molecular peak M⁺ of 346.1 Da.

TLC: [PE/EA (7:3; (v/v))], R_f=0.6

EF: C₁₃ H₁₆ N₃ O₄ S F; MW: calc.: 329.35

MS: fnd.: 346.1 (MNH₄⁺)

A39. 1,5-Anhydro-4-azido-2,3,4,6-tetradexoxy-2-fluoro-6-[(4-(4-fluorobenzyl)piperidin-1-yl)]-D-xylo-hexitol

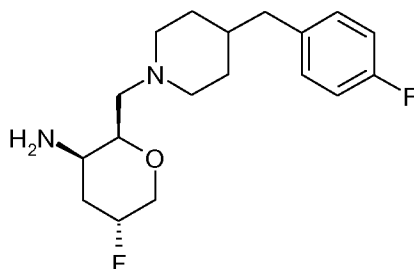
A solution of 3.2 g (9.7 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-2-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (compound A38) and 2.25 g (11.7 mmol) 4-(4-Fluorobenzyl)piperidine (compound A14) in 50 ml absolute DMF is stirred at 110°C for 4 h. After stirring at room temperature over night, 30 ml of a half saturated aqueous NaCl solution is poured into the reaction solution and the resulting mixture is extracted three times with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (9:1, (v/v))] affords the title compound as yellow oil. The mass spectrum shows the molecular peak MH⁺ of 351.1 Da.

TLC: [Tol/Ac (8:2, (v/v))], R_f=0.45

EF: C₁₈ H₂₄ N₄ O F₂; MW: calc.: 350.41

MS: fnd.: 351.1 (MH⁺)

A40. 4-Amino-1,5-anhydro-2,3,4,6-tetra-deoxy-2-fluoro-6-[(4-(4-fluorobenzyl)piperidin-1-yl)]-D-xylo-hexitol



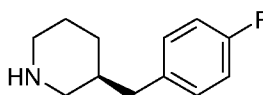
A solution of 1.0 g (2.85 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetra-deoxy-2-fluoro-6-[(4-(4-fluorobenzyl)piperidin-1-yl)]-D-xylo-hexitol (compound A39) in 60 ml methanol is hydrogenated at room temperature over 0.23 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as colourless oil. The mass spectrum shows the molecular peak MH^+ at 325.2 Da. The compound is used for the next step without further purification.

TLC: [$CH_2Cl_2/MeOH$ (95:5, (v/v))], $R_f=0.15$

EF: $C_{18}H_{26}N_2O_2F_2$; MW: calc.: 324.42

MS: fnd.: 325.2 (MH^+)

A41. (3S)-3-(4-Fluorobenzyl)piperidine

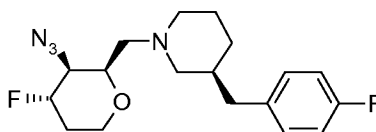


Lit: Yue T. J. et al. *Organic Process Research & Development* **2006**, 10, 262-241

De Lucca G. V. et al. *J. Med. Chem.* **2005**, 48, 2194-2211

Emmett G.C. et al. *Synthesis* **2005**, 1, 92-96

A42. 1,5-Anhydro-4-azido-2,3,4,6-tetra-deoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



A solution of 3.5 g (11.23 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (Compound A8), 3.45 g (18.07 mmol) (3S)-3-(4-Fluorobenzyl)piperidine (Compound A41) and 4 ml triethylamine in 35 ml 1-Methyl-2-pyrrolidone is stirred at 120°C for 3.5 h. After stirring at RT over night further 0.8 g (4.14 mmol) (3S)-3-(4-Fluorobenzyl)piperidine (Compound A41) are added and stirred at 120°C for 2 h once more. Into

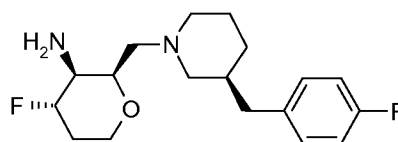
the reaction solution is poured a half saturated aqueous NaCl solution and the resulting mixture is extracted three times with Et₂O. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (95:05; (v/v))] affords the title compound as a yellow viscous fluid.

5 TLC: [Tol/Ac (8:2)], R_f=0.65

EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41

MS: fnd.: 351.1 (MH⁺)

10 **A43. 4-Amino-1,5-anhydro-2,3,4,6-tetradexoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol**



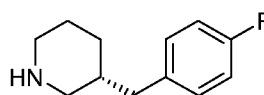
A solution of 2.81 g (8.02 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradexoxy-3-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A42) in 60 ml methanol is hydrogenated at RT over 0.28 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as a grey-yellow wax-like solid. The compound is used for the next step without further purification.

15 TLC: [CH₂Cl₂/MeOH (95:05, (v/v))], R_f=0.15

EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,4124

MS: fnd.: 325.2 (MH⁺)

20 **A44. (3R)-3-(4-Fluorobenzyl)piperidine**

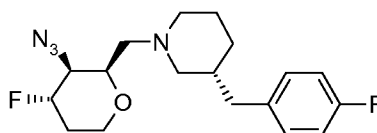


Lit: Yue T. J. et al. Organic Process Research & Development **2006**, 10, 262-241

25 De Lucca G. V. et al. J. Med. Chem. **2005**, 48, 2194-2211

Emmett G.C. et al. Synthesis **2005**, 1, 92-96

A45. 1,5-Anhydro-4-azido-2,3,4,6-tetradexoxy-3-fluoro-6-[(3R)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



30 A solution of 2 g (6.1 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (Compound A8) and 2.05 g (10.6 mmol) (3R)-3-(4-

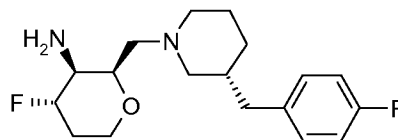
Fluorobenzyl)piperidine (Compound A44) in 20 ml 1-Methyl-2-pyrrolidone is stirred at 120°C for 4 h. Into the reaction solution is poured a half saturated aqueous NaCl solution and the resulting mixture is extracted three times with Et₂O. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (97:03; (v/v))] affords the title compound as a yellow viscous fluid.

TLC: [Tol/Ac (9:1; (v/v))], R_f=0.35

EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41

MS: fnd.: 351.0 (MH⁺)

A46. 4-Amino-1,5-anhydro-2,3,4,6-tetradexo-3-fluoro-6-[(3R)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



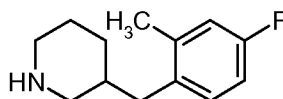
A solution of 1.26 g (3.6 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradexo-3-fluoro-6-[(3R)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A45) in 25 ml methanol is hydrogenated at room temperature over 0.16 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as a slightly yellow viscous fluid. The compound is used for the next step without further purification.

TLC: [CH₂Cl₂/MeOH (95:05; (v/v))], R_f=0.3

EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,41

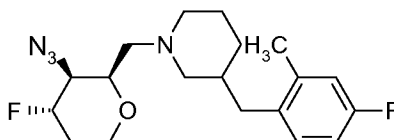
MS: fnd.: 325.2 (MH⁺)

A47. (3RS)-3-(4-Fluoro-2-methylbenzyl)piperidine



The title compound was prepared in analogy to the process described in De Lucca G. V. et al. *J. Med. Chem.* **2005**, 48, 2194-2211.

A48. 1,5-Anhydro-4-azido-2,3,4,6-tetradexo-3-fluoro-6-[(3RS)-3-(4-fluoro-2-methylbenzyl)piperidin-1-yl]-D-xylo-hexitol



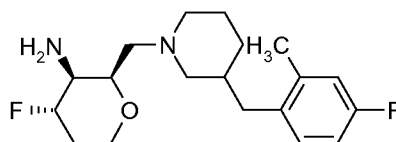
A solution of 1.34 g (4.3 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (Compound A8) and 1.65 g (7.93 mmol) (3RS)-3-(4-Fluoro-2-methylbenzyl)piperidine (Compound A47) in 25 ml 1-Methyl-2-pyrrolidone is stirred at 120°C for 3 h. Into the reaction solution is poured a half saturated aqueous NaCl solution and the resulting mixture is extracted three times with Et₂O. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent double purification of the resulting residue by silica gel chromatography [Tol/Ac (96:04 → 9:1, (v/v))] affords the title compound as a yellow viscous fluid.

TLC: [Tol/Ac (95:05, (v/v))], R_f=0.5

EF: C₁₉ H₂₆ F₂ N₄ O; MW: calc.: 364,44

MS: fnd.: 365.1 (MH⁺)

A49. 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluoro-2-methylbenzyl)piperidin-1-yl]-D-xylo-hexitol



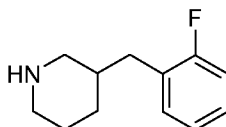
A solution of 0.62 g (1.7 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(4-fluoro-2-methylbenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A48) in 30 ml methanol is hydrogenated at room temperature over 0.118 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as a slightly yellow viscous fluid. The compound is used for the next step without further purification.

TLC: [CH₂Cl₂/MeOH (95:05, (v/v))], R_f=0.3

EF: C₁₉ H₂₈ F₂ N₂ O; MW: calc.: 338,44

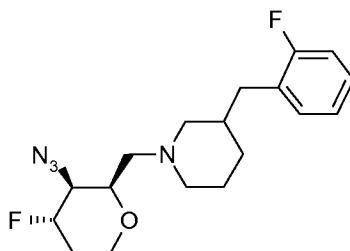
MS: fnd.: 339.2 (MH⁺)

A50. (3RS)-3-(2-Fluor-benzyl)-piperidine



The title compound was prepared as described in De Lucca G. V. et al. *J. Med. Chem.* **2005**, *48*, 2194-2211.

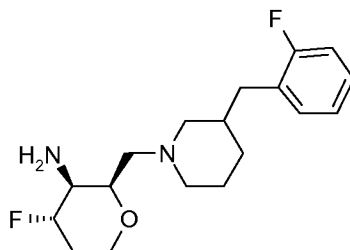
A51. 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(2-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



A solution of 1.8 g (5.5 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-3-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (Compound A8), 2.2 g (11 mmol) (3RS)-3-(2-Fluor-benzyl)-piperidine (Compound A50) and 2 ml triethylamine in 15 ml DMF is stirred at 120°C for 4 h and at RT over night. Into the reaction solution is poured a half saturated aqueous NaCl solution and the resulting mixture is extracted three times with Et₂O. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. The crude compound is used for the next step without further purification.

EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41

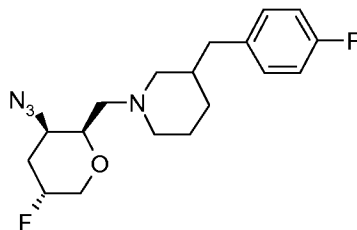
A52. 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(2-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



A solution of 2.6 g crude 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-3-fluoro-6-[(3RS)-3-(2-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A51) in 80 ml methanol is hydrogenated at room temperature over approximately 0.1 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound (1.9 g) as a viscous fluid. The compound is used for the next step without further purification.

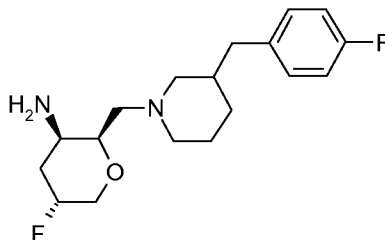
EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,41

A53. 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-2-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



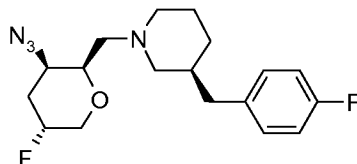
A solution of 2.5 g (75.9 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-2-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (Compound A38) and 2.5 g (129 mmol) (3RS)-3-(4-Fluorobenzyl)-piperidine (Compound A13) in 25 ml 1-Methyl-2-pyrrolidone is stirred at 120°C for 3 h. Into the reaction solution is poured a half saturated aqueous NaCl solution and the resulting mixture is extracted three times with Et₂O. The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (9:1→8:2, (v/v))] affords the title compound as a brownish viscous fluid. TLC: [Tol/Ac (8:2, (v/v))], R_f=0.5
EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41
MS: fnd.: 351.0 (MH⁺)

A54. 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-2-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



A solution of 2.4 g (6.85 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-2-fluoro-6-[(3RS)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A53) in 100 ml methanol is hydrogenated at RT over 0.4 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as a slightly yellow viscous fluid. The compound is used for the next step without further purification. TLC: [CH₂Cl₂/MeOH (95:05, (v/v))], R_f=0.3
EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,41
MS: fnd.: 325.2 (MH⁺)

A55. 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-2-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol



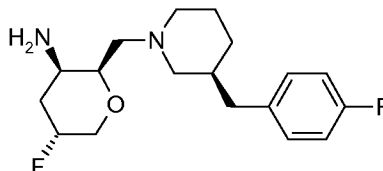
A solution of 0.404 g (1.23 mmol) 1,5-Anhydro-4-azido-2,3,4-trideoxy-2-fluoro-6-O-[(4-methylphenyl)sulfonyl]-D-xylo-hexitol (Compound A38) and 0.411 g (2.12 mmol) (3S)-3-(4-Fluorobenzyl)piperidine (Compound A41) in 4 ml 1-Methyl-2-pyrrolidone is stirred at 120°C for 3 h. Into the reaction solution is poured a half saturated aqueous NaCl solution and the resulting mixture is extracted three times with Et₂O. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (95:05 → 9:1; (v/v))] affords the title compound as a brownish viscous fluid.

TLC: [Tol/Ac (8:2, (v/v))], R_f=0.55

EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41

MS: fnd.: 351.0 (MH⁺)

A56. 4-Amino-1,5-anhydro-2,3,4,6-tetradeoxy-2-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol

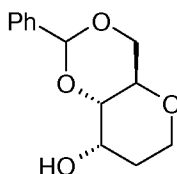


A solution of 0.275 g (0.78 mmol) 1,5-Anhydro-4-azido-2,3,4,6-tetradeoxy-2-fluoro-6-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-xylo-hexitol (Compound A55) in 10 ml methanol is hydrogenated at room temperature over 0.05 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as a slightly yellow viscous fluid. The compound is used for the next step without further purification.

TLC: [CH₂Cl₂/MeOH (95:05, (v/v))], R_f=0.15

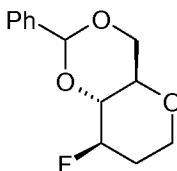
EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,41

MS: fnd.: 325.2 (MH⁺)

A57. 1,5-Anhydro-2-deoxy-4,6-O-(phenylmethyldiene)-D-ribo-hexitol

Lit.: Sasak M. et al. *Angew. Chem.* **1996**, 108(15), 1782-1785

5 Tamaruya Y. et al. *Angew. Chem.* **2004**, 116(21), 2894-2897

A58. 1,5-Anhydro-2,3-dideoxy-3-fluoro-4,6-O-(phenylmethyldiene)-D-arabino-hexitol

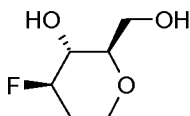
10 To a solution of 56 g (0.23 mol) 1,5-Anhydro-2-deoxy-4,6-O-(phenylmethyldiene)-D-ribo-hexitol (compound A57) in 550 ml anhydrous dichloromethane, 188 ml (2.3 mol) Pyridin is added. After cooling to -20°C a solution of 79 ml (0.46 mol) triflic anhydride in 650 ml anhydrous dichloromethane is slowly added (within 1 h). The stirring is continued for 1 h at 0°C. For working-up the reaction mixture is diluted with 250 ml aqueous HCl (1 M), the organic phase is separated and ex-
15 tracted with a saturated aqueous solution of NaHCO₃. The combined organic phases are dried over Na₂SO₄ and filtered. To the filtrate 1140 ml (1.15 mol, 1 M solution in anhydrous THF) TBAF is added at 0°C. After stirring over night at room temperature the reaction solution is diluted with 1000 ml water and extracted with 1000 ml dichloromethane (2 x). The combined organic phases are dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product is subsequently purified
20 by silica gel chromatography [Heptane/EA (4:1 (v/v))] affording the title compound as colourless crystals of m.p. 69-70°C.

TLC: [Heptane/EA (2:1 (v/v))], R_f=0.40

EF: C₁₃ H₁₅ O₃ F; MW: calc.: 238.26

MS: fnd.: 239.2 (MH⁺), 261.2 (MNa⁺)

25

A59. 1,5-Anhydro-2,3-dideoxy-3-fluoro-D-arabino-hexitol

A solution of 10.5 g (44 mmol) 1,5-Anhydro-2,3-dideoxy-3-fluoro-4,6-O-(phenylmethyldiene)-D-arabino-hexitol (compound A58) in 100 ml acetic acid is hydrogenated at 55°C over 1.0 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo and co evaporated with toluene (2 x). Further purification of
30

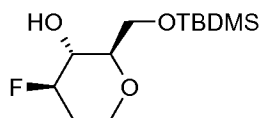
the resulting residue by silica gel chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5, (v/v))] affords the title compound (5.1 g) as a colourless solid.

TLC: [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5, (v/v))] $R_f=0.25$

EF: $\text{C}_6 \text{H}_{11} \text{F O}_3$; MW: calc.: 150,15

5 MS: fnd.: 132.1 (M^+-18), 119.0 (M^+-31)

A60. 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-D-arabino-hexitol



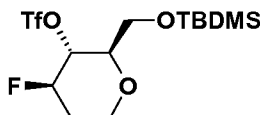
To a solution of 1.09 g (7.3 mmol) 1,5-Anhydro-2,3-dideoxy-3-fluoro-D-arabino-hexitol (compound A59) in 30 ml anhydrous dichloromethane are added 1.23 g (18.1 mmol) imidazole, 1.24 g (7.9 mol) TBDMSCl and 0.032 g DMAP. The solution is stirred for 2 h at room temperature. For workup, the mixture is poured into a half saturated NaCl solution and then extracted with CH_2Cl_2 . The combined organic phases are dried over Na_2SO_4 , filtered and concentrated in vacuo. Further purification of the resulting residue by silica gel chromatography [PE/EA (9:1, (v/v))] affords the title compound as a colorless viscous oil.

15 TLC: [PE/EA (8:2, (v/v))] $R_f=0.6$

EF: $\text{C}_{12} \text{H}_{25} \text{F O}_3 \text{ Si}$; MW: calc.: 264,41

MS: fnd.: 265.0 (MH^+)

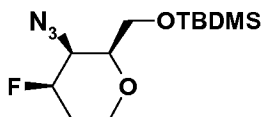
20 **A61. 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-4-O-[(trifluoromethyl)sulfonyl]-D-arabino-hexitol**



0.74 ml (8.3 mmol) trifluoromethanesulfonic acid anhydride is added drop wise to a solution of 1.7 g (6.42 mmol) 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-D-arabino-hexitol (compound A60) in 35 ml dry dichloromethane and 5 ml pyridine at -40°C . The reaction mixture is stirred for 1 h till the temperature is warmed-up to about $+15^\circ\text{C}$. For workup half concentrated NaCl solution is added to the reaction mixture and then it is extracted three times with CH_2Cl_2 . The combined organic phases are dried over MgSO_4 , filtered and concentrated in vacuo. The resulting residue is used for the next step without further purification.

30

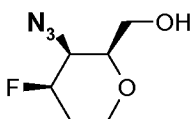
35

A62. 2,6-Anhydro-3-azido-1-O-[tert-butyl(dimethyl)silyl]-3,4,5-trideoxy-4-fluoro-D-arabino-hexitol

To a solution of the crude 1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2,3-dideoxy-3-fluoro-4-O-
 5 [(trifluoromethyl)sulfonyl]-D-arabino-hexitol (compound A61) (approx. 6.42 mol) in dry DMF is
 added 1.3 g (20 mol) sodium azide. The mixture is stirred over night. For workup, a half saturated
 aqueous NaCl solution is poured to the mixture and afterwards it is extracted with diethyl ether. The
 combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo (300 mbar,
 50°C) affording the title compound containing residual solvent, which is used for the next step with-
 10 out further purification.

EF: C₁₂H₂₄FN₃O₂Si; MW: calc.: 289.43

MS: fnd.: 289 (M⁺), 274.2 (M⁺-15), 232.4 (M⁺-57)

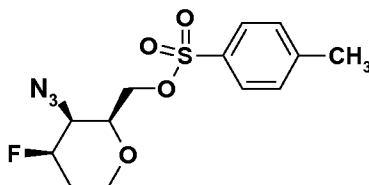
A63. 2,6-Anhydro-3-azido-3,4,5-trideoxy-4-fluoro-D-arabino-hexitol

To a solution of wet 2,6-Anhydro-3-azido-1-O-[tert-butyl(dimethyl)silyl]-3,4,5-trideoxy-4-fluoro-D-
 arabino-hexitol (compound A62) (approx. 6.42 mmol) in 13 ml absolute THF 4.8 ml TBAF (4.8 ml, 1
 M solution in anhydrous THF) is added at room temperature. The mixture is stirred for 1 h. For
 workup, a half saturated aqueous NaCl solution is poured to the mixture and afterwards it is ex-
 20 tracted with CH₂Cl₂. The combined organic phases are dried over MgSO₄, filtered and concentrated
 in vacuo. Further purification of the resulting residue by silica gel chromatography [PE/EA (7:3 →
 6:4, (v/v))] affords the title compound as a colorless viscous fluid.

TLC: [PE/EA (7:3, (v/v))] R_f=0.21

EF: C₆ H₁₀ F N₃ O₂ F; MW: calc.: 175,16

25 MS: fnd.: 175.1 (M⁺)

A64. 2,6-Anhydro-3-azido-3,4,5-trideoxy-4-fluoro-1-O-[(4-methylphenyl)sulfonyl]-D-arabino-hexitol

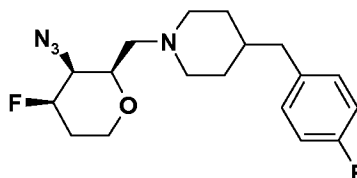
30 To a solution of 2.46 g (14.0 mmol) 2,6-Anhydro-3-azido-3,4,5-trideoxy-4-fluoro-D-arabino-hexitol
 (compound A63) in 11.5 ml Pyridine and 60 ml dry dichloromethane 8.3 g (43.5 mmol) p-

toluenesulfonylchloride is added at room temperature with stirring. After continuous stirring at room temperature over night, half saturated aqueous NaCl solution is poured into the reaction solution and the resulting mixture is extracted with CH₂Cl₂. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography for three times (2x) [PE/EA (7:3, (v/v))] and [PE/EA (9:1 → 8:2, (v/v))] affords the title compound as a colorless viscous fluid.

EF: C₁₃ H₁₆ F N₃ O₄ S; MW: calc.: 329,35

MS: fnd.: 347.0 (MNH₄⁺)

A65. 2,6-Anhydro-3-azido-1,3,4,5-tetradeoxy-4-fluoro-1-[4-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol

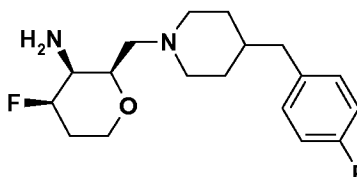


A solution of 1.0 g (3.0 mmol) 2,6-Anhydro-3-azido-3,4,5-trideoxy-4-fluoro-1-O-[(4-methylphenyl)sulfonyl]-D-arabino-hexitol (compound A64) and 1.17 g (6.06 mmol) 4-(4-Fluorobenzyl)piperidine (compound A14) in 10 ml 1-Methyl-2-pyrrolidone and 1 ml triethylamine is stirred at 120°C for 4 h. For workup, a half saturated NaCl solution is poured into the mixture and then extracted with Et₂O. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (95:5, (v/v))] affords the title compound as a yellowish viscous fluid.

EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41

MS: fnd.: 351.1 (MH⁺)

A66. 3-Amino-2,6-anhydro-1,3,4,5-tetradeoxy-4-fluoro-1-[4-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol



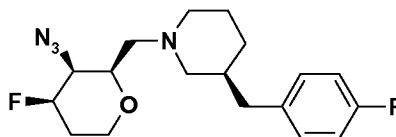
A solution of 0.68 g (1.95 mmol) 2,6-Anhydro-3-azido-1,3,4,5-tetradeoxy-4-fluoro-1-[4-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol (Compound A65) in 23 ml methanol is hydrogenated at room temperature over 0.089 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as a colorless viscous fluid. The compound is used for the next step without further purification.

TLC: [CH₂Cl₂/MeOH (95:5, (v/v))] R_f=0.26

EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,41

MS: fnd.: 325.3 (MH⁺)

A67. 2,6-Anhydro-3-azido-1,3,4,5-tetradexoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol



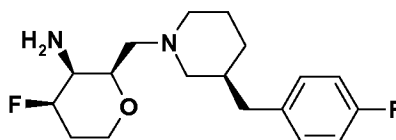
A solution of 1.2 g (3.6 mmol) 2,6-Anhydro-3-azido-3,4,5-trideoxy-4-fluoro-1-O-[(4-methylphenyl)sulfonyl]-D-arabino-hexitol (compound A64) and 1.23 g (6.37 mmol) (3S)-3-(4-Fluorobenzyl)piperidine (compound A41) in 12 ml 1-Methyl-2-pyrrolidone and 1 ml triethylamine is stirred at 120°C for 4 h. For workup, a half saturated NaCl solution is poured into the mixture and then extracted with Et₂O. The combined organic phases are dried over MgSO₄, filtered and concentrated in vacuo. Subsequent purification of the resulting residue by silica gel chromatography [Tol/Ac (95:5, (v/v))] affords the title compound as a yellowish viscous oil.

TLC: [Tol/Ac (9:1, (v/v))] R_f=0.81

EF: C₁₈ H₂₄ F₂ N₄ O; MW: calc.: 350,41

MS: fnd.: 351.2 (MH⁺)

A68. 3-Amino-2,6-anhydro-1,3,4,5-tetradexoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol



A solution of 0.44 g (1.26 mmol) 2,6-Anhydro-3-azido-1,3,4,5-tetradexoxy-4-fluoro-1-[(3S)-3-(4-fluorobenzyl)piperidin-1-yl]-D-arabino-hexitol (Compound A67) in 15 ml methanol is hydrogenated at room temperature over 0.057 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated in vacuo to give the title compound as colorless viscous fluid. The compound is used for the next step without further purification.

TLC: [CH₂Cl₂/MeOH (95:5, (v/v))] R_f=0.26

EF: C₁₈ H₂₆ F₂ N₂ O; MW: calc.: 324,41

MS: fnd.: 325.3 (MH⁺)

Commercial utility

The compounds of formula (1), the stereoisomers thereof, the salts of the compounds of formula (1) and the salts of the stereoisomers of the compounds of formula (1) are hereinafter referred to as compounds of the invention. In particular, the compounds of the invention are pharmaceutically acceptable.

The compounds of the invention have valuable pharmaceutical properties, which make them commercially utilizable. In particular, as CC chemokine receptor 3 (CCR3) modulators, they are able to influence the physiological and pathophysiological function of various cells. Those modulators are able to influence angiogenesis in vivo in animal eyes, particularly angiogenesis in mammals, e.g. mice or humans. A certain form of angiogenesis comprises the invasion of the retina by choroidal neovascularisation (CNV).

In this specification the following definitions are used:

A "ligand" is a molecule that binds to a receptor.

A "modulator" is a ligand that interacts with the receptor with the consequence to modulate the receptor activity or responsiveness to a ligand.

"Modulators" as used herein is intended to encompass antagonists, agonists, partial antagonists, partial agonists, inverse agonists and/or co-agonists.

An "allosteric ligand" is a ligand that interacts with the receptor at a site distinct from the site recognized by an endogenous ligand, e. g. transmitter or hormone. On binding, the allosteric ligand can alter the constitutive activity of the receptor and can qualitatively or quantitatively influence the activity of orthosteric ligands in a non-competitive manner.

An "orthosteric ligand" is a ligand that interacts with the receptor at a site that corresponds to or overlaps with the site recognized by the endogenous ligand. Orthosteric ligands can compete with endogenous ligand for the receptor and can behave as agonists, inverse agonists or antagonists.

"Agonists" are ligands with selective affinity for the active conformation of the receptor. Through stabilization of this active conformation, the agonists can promote induction of related intracellular responses.

"Full agonists" as herein understood means agonists that are able to elicit a maximal response following receptor occupation and activation.

“Partial agonists” are agonists that can activate receptors but are unable to elicit the maximal response of the receptor system.

- 5 In particular, agonists or agonistic effects can be determined according to the “Eosinophil shape-change assay” disclosed in part “Biological Investigations” of this specification.

“Antagonists” interact with the receptor, and can thereby prevent binding of ligands, e. g. agonists. The conformation of the receptor seems to be uninfluenced by the interaction. In general,
10 antagonists exhibit affinity for the receptor but do not have intrinsic activity at the receptor and are neutral to any cellular action.

Antagonists that bind to the receptor in a manner that blocks essentially binding of agonists to the receptor are referred to as “competitive antagonists”. A key point about competitive antagonists is
15 that like agonists, they bind in a reversible manner.

Several receptors independently can activate distinct functional responses. The “functional selectivity” of a ligand refers to its property to influence these responses differentially. At the extreme, functionally selective ligands may be both agonists and antagonists at different functions
20 mediated by the same receptor. A consequence of a functional selective agonism may be, for example, that a functional selective receptor internalizing agonist may result in functional inhibition of the receptor.

The compounds of the invention modulate CCR3 activity on cells that express the CCR3 receptor
25 including eosinophils, basophils or endothelial cells, in particular choroidal endothelial cells (CECs), and sub-types of Th2 cells. While competitive antagonists inhibit the ligand-induced action of CCR3, including calcium-flux, receptor internalization, extracellular regulated kinase (ERK) activation and promotion of chemotaxis, CCR3 agonists activate one or more of these actions. Partial antagonists inhibit the activity of an agonist while having intermediate to low intrinsic activity
30 for one or more of these actions. Inverse agonists downmodulate the constitutive and induced activity of CCR3 in unstimulated and stimulated cells. Co-agonists provide an additive or synergistic effect to the effect of an agonist, e.g. by increasing the potency and/or the maximal efficacy of an agonist. Co-agonists itself can have partial or full agonistic activity. Under pathological conditions chemokines that act agonistic for CCR3 are induced at sites of a primary
35 inflammatory response and build up a chemokine gradient that is used by CCR3 expressing cells to migrate towards the site of inflammation. Prevention of the recruitment of CCR3 expressing cells by CCR3 modulators represents an important therapeutic target. However, in the case of choroidal neovascularisation (CNV) it was demonstrated that the pathological conditions are uncoupled from inflammation.

Compounds of the invention that contain a 4-piperidinyl substitution show on eosinophils at least partial agonistic effects when measured in functional eosinophil shape change assay, in the chemotaxis assay using transwell cell culture plates or in the CCR3 internalization assay.

5 A person skilled in the art is familiar with such assays, in particular it is known to a person skilled in the art how to establish, conduct and evaluate such assays. For example, the eosinophil shape change assay is disclosed in part "Biological investigations" of this specification.

Compounds of the invention that contain a 3-piperidinyl substitution show competitive antagonistic properties when measured in eosinophil shape change assay.

10 It is in the scope of the invention that compounds of the invention containing a 4-piperidinyl substitution and additionally a fluor substitution in 3-piperidinyl position are regarded as 4-piperidinyl substituted compounds, in particular these compounds can display an at least partial agonistic effect.

15 The compounds of the invention are distinguished by one or more valuable and desirable properties, such as, for example, high efficacy, high selectivity, low toxicity, superior bioavailability in general (e.g. good enteral absorption), superior therapeutic window, superior pharmacokinetics (e.g. half-life), absence of significant side effects, and further beneficial effects related with their therapeutic and pharmaceutical suitability.

20

Accordingly, the invention further relates to the compounds of the invention for use in the treatment or prophylaxis of diseases, especially diseases alleviated by modulation of the CC chemokine receptor 3 (CCR3) activity. In particular, the invention relates to the compounds of the invention for use in the treatment or prophylaxis of the following diseases:

25

- Respiratory diseases associated with inflammatory or allergic disorders, including bronchial asthma, chronic asthmatic disorders with reduced lung function and airway hyperreactivity, bronchial acute exacerbations, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disorder (COPD) and idiopathic pulmonary fibrosis;
- 30 • Inflammatory or allergic diseases, including allergic rhinitis and nasal polyposis;
- Skin diseases associated with inflammatory or allergic disorders, including pruritis, atopic dermatitis, eczema, psoriasis, dermatitis, erythema multiforma, scleroderma, hypersensitivity vasculitis, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus and pemphigus, pemphigus vulgaris and Hyper IgE syndrome;
- 35 • Eye diseases associated with inflammatory or allergic disorders, including conjunctivitis;
- Eye diseases associated with non-inflammatory disorders, including angiogenetic disorders, which are comprising the invasion of the retina by choroidal neovascularisation (CNV), which are influenced by choroidal endothelial cells (CECs), e.g. age-related macular degeneration (AMD), in particular the so called wet form of AMD;

- Intestinal diseases associated with inflammatory or allergic disorders, including inflammatory bowel disease, Crohn's disease, eosinophil-related disorders including eosinophilic esophagitis, eosinophilic gastroenteritis and eosinophilic pancreatitis;
- Systemic eosinophilic diseases including hypereosinophilia and Churg-Strauss-Syndrome;
- 5 • Infections including HIV infection and influenza infection;
- Cancer/leukemias including Hodgkin's disease, leukemia, lymphoproliferative disorder, renal cell carcinoma, colorectal cancer and cellular leiomyoma;
- Autoimmune disease such as type I diabetes, thyroiditis, multiple sclerosis, vasculitic glomerulonephritis, rheumatic disease, osteoarthritis and atherosclerosis;
- 10 • Transplant rejection including rejection of cardiac allograft, skin allograft, lung transplants, liver transplant, corneal allograft, renal allograft and post-coronary artery bypass grafts;
- Miscellaneous diseases including Kimura's disease, septic shock, parasitic disease, dementia, Alzheimer's disease, genital ulcer disease, encephalopathy, idiopathic inflammatory myopathies and drug-induced liver disease.

15

Preferably, the invention further relates to the compounds of the invention for use in the treatment or prophylaxis of one or more of the following diseases: bronchial asthma, chronic asthmatic disorders with reduced lung function and airway hyperreactivity, bronchial acute exacerbations, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disorder (COPD) and idiopathic pulmonary fibrosis.

20

In addition, the invention relates to the compounds of the invention for use in the treatment or prophylaxis of allergic rhinitis.

25

Furthermore, the invention relates to the compounds of the invention for use in the treatment or prophylaxis of skin diseases, such as, but not limited to atopic dermatitis, eczema, psoriasis and pruritis.

30

As well, the invention relates to the compounds of the invention for use in the treatment and prophylaxis of intestinal diseases, such as, but not limited to inflammatory bowel disease, crohn's disease, eosinophilic esophagitis and eosinophilic gastroenteritis.

35

In a preferred embodiment of the invention the compound of the invention for use in the treatment or prophylaxis of the abovementioned diseases is one of the examples or a pharmaceutically acceptable salt thereof.

The invention relates furthermore to the compounds for use in the treatment and prophylaxis of systemic eosinophilic diseases, such as, but not limited to hypereosinophilia and Churg-Strauss-Syndrome.

Additionally, the invention relates to the compounds of the invention for use in the treatment or prophylaxis of eye diseases, which are influenced by choroidal endothelial cells (CECs), e.g. wet age-related macular degeneration (AMD).

5

Preferably the compounds of the invention are selected from one of the compounds that contain a 4-piperidiny1 substitution. Compounds that contain a 4-piperidiny1 substitution and additionally a fluor substitution in 3-piperidiny1 position are regarded as 4-piperidiny1 substituted compounds in the herein presented invention, in particular these compounds can display an at least partial agonistic effect.

10

In particular the 4-piperidiny1 substituted compounds can comprise at least a partial agonistic effect on CC chemokine receptor 3. Preferably these compounds comprise at least a partial CC chemokine receptor 3 internalizing effect.

15

It also can be preferred that the compounds are selected from one of the compounds that contain a 3-piperidiny1 substitution.

In a further embodiment it is preferred that the 3-piperidiny1 substituted compounds comprise an antagonistic effect on CC chemokine receptor 3.

20

The invention also relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition modulating CC chemokine receptor 3 activity, in particular a pharmaceutical composition for the treatment or prophylaxis of diseases alleviated by modulation of the CC chemokine receptor 3 activity, preferably, a pharmaceutical composition for the treatment or prophylaxis of the diseases exemplified above.

25

In particular, the invention relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of one or more of the following diseases: bronchial asthma, chronic asthmatic disorders with reduced lung function and airway hyperreactivity, bronchial acute exacerbations, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disorder (COPD) and idiopathic pulmonary fibrosis.

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The invention relates also to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of allergic rhinitis.

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Furthermore, the invention relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of dermatological diseases, such as, but not limited to atopic dermatitis, eczema, psoriasis and pruritis.

Additionally, the invention relates to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of intestinal diseases, such as, but not limited to inflammatory bowel disease, crohn's disease, eosinophilic esophagitis and eosinophilic gastroenteritis.

The invention relates furthermore to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of a systemic eosinophilic disease, such as, but not limited to hypereosinophilia and Churg-Strauss-Syndrome.

The invention relates furthermore to the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of eye disorders, which are comprising the invasion of the retina by choroidal neovascularisation (CNV), which are influenced by choroidal endothelial cells (CECs), e.g. wet age-related macular degeneration (AMD).

In a particularly preferred embodiment of the invention, the use of a compound of the invention in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of the abovementioned diseases is carried out with one of the examples or a pharmaceutically acceptable salt thereof according to the present invention.

The invention further relates to a method of treating or preventing a disease comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

In particular, the invention relates to a method of treating or preventing one of the above mentioned diseases comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

Especially, the invention relates to a method of treating or preventing a disease, which is alleviated by modulation of the CC chemokine receptor 3 activity comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

Preferably, the invention relates to a method of treating or preventing one or more of the following diseases: bronchial asthma, chronic asthmatic disorders with reduced lung function and airway hyperreactivity, bronchial acute exacerbations, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disorder (COPD) and idiopathic pulmonary fibrosis, comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

The invention also relates to a method of treating or preventing allergic rhinitis comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.

- 5 Furthermore, the invention preferably relates to a method of treating or preventing skin diseases, such as, but not limited to, atopic dermatitis, eczema, psoriasis and pruritis, comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.
- 10 Additionally, the invention preferably relates to a method of treating or preventing intestinal diseases, such as, but not limited to inflammatory bowel disease, crohn's disease, eosinophilic esophagitis and eosinophilic gastroenteritis, comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.
- 15 The invention furthermore relates to a method of treating or preventing a systemic eosinophilic disease, such as, but not limited to, hypereosinophilia and Churg-Strauss-Syndrome, comprising administering to a patient in need thereof a therapeutically effective amount of at least one of the compounds of the invention.
- 20 The invention furthermore relates to a method of treating or preventing eye disorders, which are comprising the invasion of the retina by choroidal neovascularisation (CNV), which are influenced by choroidal endothelial cells (CECs), e.g. wet age-related macular degeneration (AMD).

In the above methods, the patient is preferably a mammal, more preferably a human. Furthermore,
25 in the above methods, at least one of the compounds of the invention can be used. Preferably, one or two of the compounds of the invention are used, more preferably, one of the compounds of the invention is used.

In a particularly preferred embodiment of the invention, the above methods of treating or preventing
30 one of the above mentioned diseases comprise administering to a patient in need thereof a therapeutically effective amount of one of the examples or a pharmaceutically acceptable salt thereof according to the present invention.

The invention furthermore relates to a pharmaceutical composition which comprises at least one of
35 the compounds of the invention together with at least one pharmaceutically acceptable auxiliary.

Preferably, the pharmaceutical composition comprises one or two of the compounds of the invention. More preferably, the pharmaceutical composition comprises one of the compounds of the invention.

In a particularly preferred embodiment of the invention, the pharmaceutical composition comprises one of the examples or a pharmaceutically acceptable salt thereof according to the present invention together with at least one pharmaceutically acceptable auxiliary.

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The invention furthermore relates to pharmaceutical compositions according to the invention, as defined above, modulating the CC chemokine receptor 3 activity, especially for the treatment or prophylaxis of diseases alleviated by modulation of the CC chemokine receptor 3 activity, in particular for the treatment or prophylaxis of the diseases exemplified above.

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The invention also encompasses pharmaceutical compositions according to the invention, as defined above, for the treatment or prophylaxis of one or more of the following diseases: bronchial asthma, chronic asthmatic disorders with reduced lung function and airway hyperreactivity, bronchial acute exacerbations, chronic bronchitis, acute respiratory distress syndrome, chronic obstructive pulmonary disorder (COPD) and idiopathic pulmonary fibrosis.

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The invention also relates to pharmaceutical compositions according to the invention, as defined above, for the treatment or prophylaxis of allergic rhinitis.

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Furthermore, the invention relates to pharmaceutical compositions according to the invention, as defined above, for the treatment or prophylaxis of skin diseases, such as, but not limited to, atopic dermatitis, eczema, psoriasis and pruritis.

As well, the invention relates to pharmaceutical compositions according to the invention, as defined above, for the treatment and prophylaxis of intestinal diseases, such as, but not limited to inflammatory bowel disease, crohn's disease, eosinophilic esophagitis and eosinophilic gastroenteritis.

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The invention furthermore relates to pharmaceutical compositions according to the invention, as defined above, for the treatment and prophylaxis of a systemic eosinophilic disease, such as, but not limited to, hypereosinophilia and Churg-Strauss-Syndrome.

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The invention furthermore relates to pharmaceutical compositions according to the invention, as defined above, for the treatment and prophylaxis of eye disorders, which are comprising the invasion of the retina by choroidal neovascularisation (CNV), which are influenced by choroidal endothelial cells (CECs), e.g. wet age-related macular degeneration (AMD).

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Depending on the particular disease to be treated or prevented, additionally therapeutic agents, which are normally administered to treat or prevent that disease, may optionally be co-administered with the compounds of the invention.

In a preferred embodiment, at least one of the compounds of the invention is co-administered with at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics and angiogenesis inhibitors.

In this respect, the "therapeutic agent" includes the corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics and angiogenesis inhibitors in form of the free compounds, the pharmaceutically acceptable salts thereof, the pharmaceutically acceptable derivatives thereof (e.g., but not limited to, ester derivatives, N-oxides etc.), the solvates (hydrates) thereof and the stereoisomers of the compounds, salts, derivatives and solvates.

Co-administration of at least one of the compounds of the invention with at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics and angiogenesis inhibitors can take place in form of a fixed combination, a non-fixed combination or a kit of parts.

A "fixed combination" is defined as a combination wherein the compound of the invention and the therapeutic agent intended for co-administration are present in one dosing unit or in a single entity. One example of a fixed combination is a pharmaceutical composition wherein the compound of the invention and the therapeutic agent are present in admixture for simultaneous administration. Another example of a fixed combination is a pharmaceutical composition wherein the compound of the invention and the therapeutic compound are present in one dosing unit without being in direct admixture (for example, in form of pellets, which are filled in a capsule, whereby a part of the pellets contains the compound of the invention and another part of the pellets contains the therapeutic agent).

A "non-fixed combination" or "kit of parts" is defined as a combination wherein the compound of the invention and the therapeutic agent are present in more than one dosing unit. In a non-fixed combination or a kit of parts the compound of the invention and the therapeutic compound are provided as separate formulations. They might be packaged and presented together as separate

components of a combination pack for simultaneous, sequential or separate use in combination therapy. Simultaneous or sequential administration of the compound of the invention and the therapeutic agent are preferred. In case of sequential or separate administration of the compound of the invention and the therapeutic agent, the compound of the invention can be administered
5 before or after administration of the therapeutic agent.

Sequential administration encompasses a short time period between the administration of the compound of the invention and the therapeutic agent or vice versa (for example, the time that is needed to swallow one tablet after the other).

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Separate administration encompasses longer time periods between the administration of the compound of the invention and the therapeutic agent. In a preferred embodiment of the invention, the compound of the invention is administered while the therapeutic agent (or vice versa) still has an therapeutic effect on the patient being treated.

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In a particularly preferred embodiment of the invention the co-administration of at least one of the compounds of the invention with at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4
20 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics and angiogenesis inhibitors leads to a therapeutic effect that is greater than the sum of the therapeutic effects that will be achieved in case the compound of the invention respectively the additional therapeutic agent are given alone.

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The type of formulation of the compound of the invention and the therapeutic agent of a non-fixed combination or a kit of parts can be identical, similar, i.e. both, the compound of the invention and the therapeutic agent are formulated in separate tablets or capsules, or can be different, i.e. suited for different administration forms, such as e.g. the compound of the invention is formulated as
30 tablet or capsule and the therapeutic agent is formulated as powder, solution or suspension.

Accordingly, the invention additionally relates to a fixed combination, a non-fixed combination or kit of parts comprising at least one of the compounds of the invention, at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin
35 antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics and angiogenesis inhibitors, and at least one pharmaceutically acceptable auxiliary.

Several of the abovementioned combinations of a compound of the invention and a therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immune modulators, cytokine inhibitors, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics and angiogenesis inhibitors are particularly useful for the treatment or prophylaxis of inflammatory and allergic airway disorders, such as, but not limited to bronchial asthma, COPD and allergic rhinitis. Others are particularly useful for the treatment or prophylaxis of dermatological diseases, such as, but not limited to, psoriasis and atopic dermatitis.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a corticosteroid and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and budesonide,
- a compound of the invention and fluticasone,
- a compound of the invention and beclometasone,
- a compound of the invention and mometasone,
- a compound of the invention and fluocinolone, preferably fluocinolone acetonide,
- a compound of the invention and triamcinolone acetonide, or
- a compound of the invention and ciclesonide,

and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment, the pharmaceutically acceptable derivative of fluticasone is fluticasone-17-propionate. In another preferred embodiment, the pharmaceutically acceptable derivative of beclometasone is beclometasone 17, 21-dipropionate ester. In a preferred embodiment, the pharmaceutically acceptable derivative of mometasone is mometasone furoate.

The combination comprising a compound of the invention and a corticosteroid preferably is for the treatment and prophylaxis of bronchial asthma, COPD, allergic rhinitis, eosinophilic esophagitis, wet AMD or a dermatological disease, such as for example atopic dermatitis. Preferably the corticosteroid is used for intranasal, inhaled or (in case of a dermatological disease) transdermal administration; in severe cases, the corticosteroid may also be used orally.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), an anticholinergic and

at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

a compound of the invention and glycopyrronium bromide,

a compound of the invention and acridinium bromide,

5 a compound of the invention and tiotropium bromide, or

a compound of the invention and ipratropium bromide,

and at least one pharmaceutically acceptable auxiliary.

10 In a preferred embodiment, the stereoisomer of glycopyrronium bromide is (R,R)-glycopyrronium bromide. In a preferred embodiment, tiotropium bromide is used in form of its monohydrate.

Preferably, the anticholinergic is for inhaled administration. The combination comprising a compound of the invention and an anticholinergic is preferably for the treatment or prophylaxis of COPD.

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In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a β_2 -adrenoreceptor agonist and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

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a compound of the invention and salbutamol,

a compound of the invention and milveterol,

a compound of the invention and indacaterol,

a compound of the invention and carmoterol,

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a compound of the invention and salmeterol,

a compound of the invention and formoterol,

and at least one pharmaceutically acceptable auxiliary.

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In a preferred embodiment, the pharmaceutically acceptable salt of salbutamol is salbutamol sulfate. In a preferred embodiment, the pharmaceutically acceptable salt of milveterol is milveterol

hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of carmoterol is

carmoterol hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of sal-

salmeterol is salmeterol xinafoate. In another preferred embodiment, the pharmaceutically acceptable

salt of formoterol is formoterol hemifumarate monohydrate. In another preferred embodiment, the

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stereoisomer of formoterol is R,R-formoterol. In another preferred embodiment, the pharmaceuti-

cally acceptable salt of R,R-formoterol is R,R-formoterol L-tartrate.

Preferably the β 2-adrenoreceptor agonist is a long-acting β 2-adrenoreceptor agonist; particularly preferred in this respect are those β 2-adrenoreceptor agonists having a therapeutic effect over a 12-24 hours period.

- 5 Preferably, the combination comprising a compound of the invention and a β 2-adrenoreceptor agonist is for the treatment or prophylaxis of bronchial asthma and COPD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of
10 the examples of the invention), a H1 receptor antagonist and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and azelastine,
a compound of the invention and olopatadine,
15 a compound of the invention and loratadine,
a compound of the invention and desloratadine, or
a compound of the invention and cetirizine,
and at least one pharmaceutically acceptable auxiliary.

- 20 In a preferred embodiment, the pharmaceutically acceptable salt of azelastine is azelastine hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of olapatadine is olapatadine hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of cetirizine is cetirizine dihydrochloride. In a preferred embodiment, the stereoisomer of cetirizine is levo-cetirizine. In another preferred embodiment, the pharmaceutically acceptable salt of levocetirizine
25 is levocetirizine dihydrochloride.

The combination comprising a compound of the invention and a H1 receptor agonist or antagonist is preferably for the treatment or prophylaxis of allergic rhinitis or bronchial asthma.

- 30 In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention), a leukotriene receptor antagonist and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:
35 a compound of the invention and montelukast,
a compound of the invention and pranlukast, or
a compound of the invention and zafirlukast,
and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment, the pharmaceutically acceptable salt of montelukast is montelukast sodium. In another preferred embodiment, pranlukast is used in form of its monohydrate.

5 The combination comprising a compound of the invention and a leukotriene receptor antagonist is preferably for the treatment or prophylaxis of bronchial asthma or allergic rhinitis.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a 5-lipoxygenase
10 inhibitor and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise: a compound of the invention and zileuton, and at least one pharmaceutically acceptable auxiliary.

15 The combination comprising a compound of the invention and a 5-lipoxygenase inhibitor is preferably for the treatment or prophylaxis of bronchial asthma.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of
20 the examples of the invention or a pharmaceutically acceptable salt thereof), an endothelin antagonist and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise: a compound of the invention and bosentan, a compound of the invention and ambrisentan,
25 a compound of the invention and atrasentan, a compound of the invention and darusentan, a compound of the invention and clazosentan, or a compound of the invention and avosentan, and at least one pharmaceutically acceptable auxiliary.

30 In another preferred embodiment, bosentan is used in form of its monohydrate. In another preferred embodiment the pharmaceutically acceptable salt of clazosentan is the disodium salt of clazosentan. In another preferred embodiment the pharmaceutically acceptable salts of atrasentan are atrasentan hydrochloride or the sodium salt of atrasentan. In another preferred embodiment the
35 R-enantiomer of atrasentan is used. In another preferred embodiment the S-enantiomer of darusentan is used.

The combination comprising a compound of the invention and an endothelin antagonist is preferably for the treatment or prophylaxis of bronchial asthma.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a type 4 phosphodiesterase inhibitor and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and roflumilast,
- a compound of the invention and roflumilast-N-oxide,
- 10 a compound of the invention and oglemilast,
- a compound of the invention and tielupokast,
- and at least one pharmaceutically acceptable auxiliary.

The combination comprising a compound of the invention and a type 4 phosphodiesterase inhibitor is preferably for the treatment or prophylaxis of bronchial asthma, COPD and wet AMD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), theophylline and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and theophylline,
- and at least one pharmaceutically acceptable auxiliary.

25 The combination comprising a compound of the invention and theophylline is preferably for the treatment or prophylaxis of bronchial asthma and COPD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), an immune modulator and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and omalizumab, or
- a compound of the invention and lumiliximab,
- 35 and at least one pharmaceutically acceptable auxiliary.

The combination comprising a compound of the invention and one of the abovementioned immune modulators is preferably for the treatment or prophylaxis of bronchial asthma or eosinophilic esophagitis.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a cytokine inhibitor
5 and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and suplatast,
- a compound of the invention and mepolizumab,
- a compound of the invention and etanercept, or
- 10 a compound of the invention and maraviroc,
- and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment suplatast is used in form of its tosylate salt.

- 15 The combination comprising a compound of the invention and one of the abovementioned cytokine inhibitors may be preferably used for the treatment or prophylaxis of bronchial asthma, allergic rhinitis, eosinophilic esophagitis or wet AMD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of
20 parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a HMG-CoA reductase inhibitor and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- 25 a compound of the invention and lovastatin,
- a compound of the invention and pravastatin,
- a compound of the invention and simvastatin,
- a compound of the invention and atorvastatin,
- a compound of the invention and fluvastatin,
- 30 a compound of the invention and rosuvastatin,
- a compound of the invention and pitavastatin,
- a compound of the invention and bervastatin,
- a compound of the invention and dalvastatin, or
- a compound of the invention and glenvastatin,
- 35 and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment the pharmaceutically acceptable salts of pravastatin are the potassium, lithium, sodium and hemi-calcium salt of pravastatin. A particularly preferred pharmaceutically acceptable salt of pravastatin is the sodium salt of pravastatin. In a preferred embodiment the phar-

maceutically acceptable salt of simvastatin is the sodium salt of simvastatin. In a preferred embodiment the pharmaceutically acceptable salts of atorvastatin are the potassium, sodium and the hemi-calcium salt of atorvastatin. A particularly preferred pharmaceutically acceptable salt of atorvastatin is the hemi-calcium salt of atorvastatin. As an example for a hydrate of atorvastatin may be mentioned the trihydrate and the sesqui-hydrate of the hemi-calcium salt of atorvastatin. In a preferred embodiment of the pharmaceutically acceptable salt of fluvastatin is the sodium salt of fluvastatin. In a preferred embodiment the pharmaceutically acceptable salts of rosuvastatin are the potassium, lithium, sodium, hemi-magnesium and the hemi-calcium salt of rosuvastatin. A particularly preferred pharmaceutically acceptable salt of rosuvastatin is the hemi-calcium salt of rosuvastatin. Another particularly preferred pharmaceutically acceptable salt of rosuvastatin is the sodium salt of rosuvastatin. In a preferred embodiment the pharmaceutically acceptable salts of pitavastatin are the potassium, sodium and the hemi-calcium salt of pitavastatin. A particularly preferred pharmaceutically acceptable salt of pitavastatin is the hemi-calcium salt of pitavastatin.

The combination comprising a compound of the invention and a HMG-CoA reductase inhibitor is preferably for the treatment or prophylaxis of COPD or wet AMD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention), a lung surfactant and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

a compound of the invention and lusupultide,
a compound of the invention and poracant alfa,
a compound of the invention and sinapultide,
a compound of the invention and beracant,
a compound of the invention and bovacant,
a compound of the invention and colfosceril palmitate,
a compound of the invention and surfactant-TA, or
a compound of the invention and calfacant,
and at least one pharmaceutically acceptable auxiliary.

The combination comprising a compound of the invention and a lung surfactant is preferably for the treatment or prophylaxis of bronchial asthma or COPD.

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In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), an antibiotic and at

least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

a compound of the invention and amoxicillin,

a compound of the invention and ampicillin,

5 a compound of the invention and levofloxacin,

a compound of the invention and clarithromycin,

a compound of the invention and ciprofloxacin,

a compound of the invention and telithromycin, or

a compound of the invention and azithromycin,

10 and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment, amoxicillin is used in form of its trihydrate. In another preferred embodiment, ampicillin is used in form of its trihydrate. In another preferred embodiment, the pharmaceutically acceptable salt of ampicillin is ampicillin natrium. In another preferred embodiment

15 levofloxacin is used in form of its hemi hydrate. In another preferred embodiment, the pharmaceutically acceptable salt of ciprofloxacin is ciprofloxacin hydrochloride monohydrate. In another preferred embodiment, azithromycin is used in form of its monohydrate.

The combination comprising a compound of the invention and an antibiotic is preferably for the

20 treatment or prophylaxis of exacerbations associated with bronchial asthma, COPD or wet AMD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), an angiogenesis inhibitor and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

a compound of the invention and Pegaptanib, preferably Pegaptanib octasodium,

a compound of the invention and Anecortave, preferably Anecortave acetate

a compound of the invention and Ranibizumab,

30 a compound of the invention and Aflibercept,

a compound of the invention and Bevacizumab,

a compound of the invention and Everolimus,

a compound of the invention and Pazopanib, preferably Pazopanib hydrochloride,

a compound of the invention and Vatalanib, preferably Vatalanib succinate,

35 a compound of the invention and Sonepcizumab, or

a compound of the invention and AGN 211745,

and at least one pharmaceutically acceptable auxiliary.

The combination comprising a compound of the invention and an angiogenesis inhibitor is preferably for the treatment or prophylaxis of wet AMD.

In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), an the following compounds and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and AL-8309B,
- a compound of the invention and Zinc compounds, preferably Zinc-monocysteine,
- a compound of the invention and Mecamylamine, preferably Mecamylamine hydrochloride,
- a compound of the invention and Brimonidine, preferably Brimonidine tartrate, or
- a compound of the invention and Sirolimus,
- and at least one pharmaceutically acceptable auxiliary.

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The combination comprising a compound of the invention and AL-8309B, Zinc compounds, preferably Zinc-monocysteine, Mecamylamine, preferably Mecamylamine hydrochloride, Brimonidine, preferably Brimonidine tartrate, or Sirolimus is preferably for the treatment or prophylaxis of wet AMD.

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In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a corticosteroid, a β_2 -adrenoceptor agonist and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention, budesonide and salbutamol,
- a compound of the invention, budesonide and milveterol,
- a compound of the invention, budesonide and indacaterol,
- a compound of the invention, budesonide and carmoterol,
- a compound of the invention, budesonide and salmeterol,
- a compound of the invention, budesonide and formoterol,
- a compound of the invention, fluticasone and salbutamol,
- a compound of the invention, fluticasone and milveterol,
- a compound of the invention, fluticasone and indacaterol,
- a compound of the invention, fluticasone and carmoterol,
- a compound of the invention, fluticasone and salmeterol,
- a compound of the invention, fluticasone and formoterol,
- a compound of the invention, beclometasone and salbutamol,

a compound of the invention, beclometasone and milveterol,
a compound of the invention, beclometasone and indacaterol,
a compound of the invention, beclometasone and carmoterol,
a compound of the invention, beclometasone and salmeterol,
5 a compound of the invention, beclometasone and formoterol,
a compound of the invention, mometasone and salbutamol,
a compound of the invention, mometasone and milveterol,
a compound of the invention, mometasone and indacaterol,
a compound of the invention, mometasone and carmoterol,
10 a compound of the invention, mometasone and salmeterol,
a compound of the invention, mometasone and formoterol,
a compound of the invention, triamcinolone acetonide and salbutamol,
a compound of the invention, triamcinolone acetonide and milveterol,
a compound of the invention, triamcinolone acetonide and indacaterol,
15 a compound of the invention, triamcinolone acetonide and carmoterol,
a compound of the invention, triamcinolone acetonide and salmeterol,
a compound of the invention, triamcinolone acetonide and formoterol,
a compound of the invention, ciclesonide and salbutamol,
a compound of the invention, ciclesonide and milveterol,
20 a compound of the invention, ciclesonide and indacaterol,
a compound of the invention, ciclesonide and carmoterol,
a compound of the invention, ciclesonide and salmeterol, or
a compound of the invention, ciclesonide and formoterol,
and at least one pharmaceutically acceptable auxiliary.

25

In a preferred embodiment, the pharmaceutically acceptable salt of salbutamol is salbutamol sulfate. In a preferred embodiment, the pharmaceutically acceptable salt of milveterol is milveterol hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of carmoterol is carmoterol hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of salmeterol is salmeterol xinafoate. In another preferred embodiment, the pharmaceutically acceptable salt of formoterol is formoterol hemifumarate monohydrate. In another preferred embodiment, the stereoisomer of formoterol is R,R-formoterol. In another preferred embodiment, the pharmaceutically acceptable salt of R,R-formoterol is R,R-formoterol L-tartrate. In a preferred embodiment, the pharmaceutically acceptable salt of fluticasone is fluticasone-17-propionate. In another preferred embodiment, the pharmaceutically acceptable salt of beclometasone is beclometasone dipropionate. In a preferred embodiment, the pharmaceutically acceptable salt of mometasone is mometasone furoate.

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In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a β_2 -adrenoceptor agonist, an anticholinergic and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention, salbutamol and glycopyrronium bromide,
 - a compound of the invention, salbutamol and aclidinium bromide,
 - a compound of the invention, salbutamol and tiotropium bromide,
 - 10 a compound of the invention, salbutamol and ipratropium bromide,
 - a compound of the invention, milveterol and glycopyrronium bromide,
 - a compound of the invention, milveterol and aclidinium bromide,
 - a compound of the invention, milveterol and tiotropium bromide,
 - a compound of the invention, milveterol and ipratropium bromide,
 - 15 a compound of the invention, salmeterol and glycopyrronium bromide,
 - a compound of the invention, salmeterol and aclidinium bromide,
 - a compound of the invention, salmeterol and tiotropium bromide,
 - a compound of the invention, salmeterol and ipratropium bromide,
 - a compound of the invention, formoterol and glycopyrronium bromide,
 - 20 a compound of the invention, formoterol and aclidinium bromide,
 - a compound of the invention, formoterol and tiotropium bromide,
 - a compound of the invention, formoterol and ipratropium bromide,
 - a compound of the invention, indacaterol and glycopyrronium bromide,
 - a compound of the invention, indacaterol and aclidinium bromide,
 - 25 a compound of the invention, indacaterol and tiotropium bromide,
 - a compound of the invention, indacaterol and ipratropium bromide,
 - a compound of the invention, carmoterol and glycopyrronium bromide,
 - a compound of the invention, carmoterol and aclidinium bromide,
 - a compound of the invention, carmoterol and tiotropium bromide, or
 - 30 a compound of the invention, carmoterol and ipratropium bromide,
- and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment, the pharmaceutically acceptable salt of salbutamol is salbutamol sulfate. In a preferred embodiment, the pharmaceutically acceptable salt of milveterol is milveterol hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of carmoterol is carmoterol hydrochloride. In a preferred embodiment, the pharmaceutically acceptable salt of salmeterol is salmeterol xinafoate. In another preferred embodiment, the pharmaceutically acceptable salt of formoterol is formoterol hemifumarate monohydrate. In another preferred embodiment, the stereoisomer of formoterol is R,R-formoterol. In another preferred embodiment, the pharmaceuti-

cally acceptable salt of R,R-formoterol is R,R-formoterol L-tartrate. In a preferred embodiment, the stereoisomer of glycopyrronium bromide is (R,R)-glycopyrronium bromide. In a preferred embodiment, tiotropium bromide is used in form of its monohydrate.

5 In a preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a corticosteroid, an anticholinergic and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts com-
10 prise:

a compound of the invention, budesonide and glycopyrronium bromide,
a compound of the invention, budesonide and aclidinium bromide,
a compound of the invention, budesonide and tiotropium bromide,
a compound of the invention, budesonide and ipratropium bromide,
15 a compound of the invention, fluticasone and glycopyrronium bromide,
a compound of the invention, fluticasone and aclidinium bromide,
a compound of the invention, fluticasone and tiotropium bromide,
a compound of the invention, fluticasone and ipratropium bromide,
a compound of the invention, beclometasone and glycopyrronium bromide,
20 a compound of the invention, beclometasone and aclidinium bromide,
a compound of the invention, beclometasone and tiotropium bromide,
a compound of the invention, beclometasone and ipratropium bromide,
a compound of the invention, mometasone and glycopyrronium bromide,
a compound of the invention, mometasone and aclidinium bromide,
25 a compound of the invention, mometasone and tiotropium bromide,
a compound of the invention, mometasone and ipratropium bromide,
a compound of the invention, triamcinolone acetonide and glycopyrronium bromide,
a compound of the invention, triamcinolone acetonide and aclidinium bromide,
a compound of the invention, triamcinolone acetonide and tiotropium bromide,
30 a compound of the invention, triamcinolone acetonide and ipratropium bromide,
a compound of the invention, ciclesonide and glycopyrronium bromide,
a compound of the invention, ciclesonide and aclidinium bromide,
a compound of the invention, ciclesonide and tiotropium bromide, or
a compound of the invention, ciclesonide and ipratropium bromide,
35 and at least one pharmaceutically acceptable auxiliary.

In a preferred embodiment, the pharmaceutically acceptable salt of fluticasone is fluticasone-17-propionate. In another preferred embodiment, the pharmaceutically acceptable salt of beclometasone is beclometasone dipropionate. In a preferred embodiment, the pharmaceutically

acceptable salt of mometasone is mometasone furoate. In a preferred embodiment, the stereoisomer of glycopyrronium bromide is (R,R)-glycopyrronium bromide. In a preferred embodiment, tiotropium bromide is used in form of its monohydrate.

- 5 The abovementioned triple combinations may preferably be used in the treatment or prophylaxis of bronchial asthma or COPD.

Exemplary combinations, in particular for transdermal administration (for example versus atopic dermatitis or psoriasis), may include a compound of the invention and an immunosuppressant, for
10 example a calcineurin inhibitor, such as pimecrolimus or tacrolimus.

Therefore, in another preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), an
15 immunosuppressant and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the above mentioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and pimecrolimus,
a compound of the invention and tacrolimus,
20 a compound of the invention and methotrexate,
a compound of the invention and ascomycin, or
a compound of the invention and cyclosporin A,
and at least one pharmaceutically acceptable auxiliary.

- 25 The externally topically (transdermal) administrable immunosuppressant can be administered or administrable in an external-topical composition separately from the compound of the invention (non-fixed combination or kit of parts) or it can be contained with the compound of the invention in a combined externally-topically administrable composition (fixed combination). In a preferred embodiment the externally topically administrable composition is a cream containing pimecrolimus at
30 ca. 1% w/w concentration. In another preferred embodiment the externally topically administrable composition is an ointment containing tacrolimus at from about 0.03% to about 0.1% w/w concentration).

Other combinations for external topical administration, in particular for the treatment or prophylaxis
35 of atopic dermatitis and psoriasis, may include a compound of the invention and a corticosteroid. Beside the corticosteroid combinations mentioned above also the following corticosteroid combinations may be useful.

In another preferred embodiment, the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a corticosteroid and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the
5 above mentioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and prednisolone,
- a compound of the invention and dexamethasone,
- a compound of the invention and clobetasol,
- a compound of the invention and betamethasone, or
- 10 a compound of the invention and hydrocortisone,
- and at least one pharmaceutically acceptable auxiliary.

In another preferred embodiment, the abovementioned corticosteroids are used in form of an ester, such as, for example, prednisolone valerate acetate, hydrocortisone butyrate, hydrocortisone ace-
15 tate, dexamethasone valerate, dexamethasone propionate, dexamethasone dipropionate, be-
tamethasone butyrate propionate or prednisolone valerate acetate. In another preferred embodi-
ment the pharmaceutically acceptable derivative of clobetasol is clobetasol propionate.

Further combinations for external topical (transdermal) administration, in particular for the treatment
20 of psoriasis, may include a compound of the invention and a vitamin D analogue.

Therefore, in another preferred embodiment the abovementioned fixed combination, non-fixed combination or kit of parts comprise a compound of the invention (in particular the compound of the invention is one of the examples of the invention or a pharmaceutically acceptable salt thereof), a
25 vitamin D analogue and at least one pharmaceutically acceptable auxiliary. In a particularly preferred embodiment, the above mentioned fixed combination, non-fixed combination or kit of parts comprise:

- a compound of the invention and calcitriol,
- a compound of the invention and calcipotriol, or
- 30 a compound of the invention and tacalcitol,
- and at least one pharmaceutically acceptable auxiliary.

The pharmaceutical compositions according to the invention – if not indicated otherwise explicitly - preferably contain the compound or compounds of the invention in a total amount of from 0.1 to
35 99.9 wt%, more preferably 5 to 95 wt%, in particular 20 to 80 wt%. In case at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung

surfactants, antibiotics, angiogenesis inhibitors, AL-8309B, Zinc compounds, preferably Zinc-monocysteine, Mecamylamine, preferably Mecamylamine hydrochloride, Brimonidine, preferably Brimonidine tartrate, or Sirolimus is present in the pharmaceutical compositions of the invention, the total amount of said therapeutic agent or therapeutic agents in the pharmaceutical
5 compositions is – if not indicated otherwise explicitly - preferably in the range of from 0.1 to 99.9 wt%, more preferably 5 to 95 wt%, in particular 20 to 80 wt%, under the provision that the total amount of the compound or compounds of the invention and the therapeutic agent or therapeutic agents is less than 100 wt%.

10 As pharmaceutically acceptable auxiliaries, any auxiliaries known to be suitable for preparing pharmaceutical compositions/formulations can be used. Examples thereof include, but are not limited to, solvents, excipients, dispersants, emulsifiers, solubilizers, gel formers, ointment bases, antioxidants, preservatives, stabilizers, carriers, fillers, binders, thickeners, complexing agents, disintegrating agents, buffers, permeation promoters, polymers, lubricants, coating agents,
15 propellants, tonicity adjusting agents, surfactants, colorants, flavorings, sweeteners and dyes. In particular, auxiliaries of a type appropriate to the desired formulation and the desired mode of administration are used.

The pharmaceutical compositions/formulations can be formulated, for example, into tablets, coated
20 tablets (dragees), pills, cachets, capsules (caplets), granules, powders, suppositories, solutions (e.g., but not limited to, sterile solutions, for example eye drops), emulsions, suspensions, ointments, creams, lotions, pastes, oils, gels, sprays and patches (e.g., but not limited to, transdermal therapeutic systems). Additionally, the pharmaceutical compositions can be prepared as e.g. liposome delivery systems, systems in which the compound of the invention is coupled to
25 monoclonal antibodies and systems in which the compound of the invention is coupled to polymers (e.g., but not limited to, soluble or biodegradable polymers).

The pharmaceutical compositions/formulations can be manufactured in a manner known to a person skilled in the art, e.g. by dissolving, mixing, granulating, dragee-making, levigating,
30 emulsifying, encapsulating, entrapping or lyophilizing processes.

The selected formulation depends inter alia on the route of administering the pharmaceutical composition. The pharmaceutical compositions/formulations of the invention can be administered by any suitable route, for example, by the oral, sublingual, buccal, intravenous, intraarterial,
35 intramuscular, subcutaneous, intracutaneous, topical, transdermal, intranasal, intraocular, intravitreal, intraperitoneal, intrasternal, intracoronary, transurethral, rectal or vaginal route, by inhalation or by insufflation. Oral administration of the compounds of the invention is preferred.

In case of non-fixed combinations or kit of parts comprising at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics, angiogenesis inhibitors, AL-8309B, Zinc compounds, preferably Zinc-monocysteine, Mecamylamine, preferably Mecamylamine hydrochloride, Brimonidine, preferably Brimonidine tartrate, or Sirolimus, the compound of the invention and the therapeutic agent may be administered by the same route, e.g., without limitation, orally, or by different routes, e.g., without limitation, the compound of the invention can be administered orally and the therapeutic agent can be administered for example, subcutaneous or by inhalation, or intravitreal.

In case of pharmaceutical compositions comprising at least one of the compounds of the invention and at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics, angiogenesis inhibitors, AL-8309B, Zinc compounds, preferably Zinc-monocysteine, Mecamylamine, preferably Mecamylamine hydrochloride, Brimonidine, preferably Brimonidine tartrate, or Sirolimus, the compound of the invention and the therapeutic agent may be formulated together into the same dosage form (e.g., but not limited to, tablets), separately into the same dosage form (e.g., but not limited to, tablets), or into different dosage forms (without limitation e.g. the compound of the invention may be formulated as tablet and the therapeutic agent may be formulated as powder, solution or suspension).

Tablets, coated tablets (dragees), pills, cachets, capsules (caplets), granules, solutions, emulsions and suspensions are e.g. suitable for oral administration. In particular, said formulations can be adapted so as to represent, for example, an enteric form, an immediate release form, a delayed release form, a repeated dose release form, a prolonged release form or a sustained release form. Said forms can be obtained, for example, by coating tablets, by dividing tablets into several compartments separated by layers disintegrating under different conditions (e.g. pH conditions) or by coupling the compound of the invention to a biodegradable polymer.

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Administration by inhalation or instillation is preferably made by using an aerosol. The aerosol is a liquid-gaseous dispersion, a solid-gaseous dispersion or a mixed liquid/solid-gaseous dispersion.

The aerosol may be generated by means of aerosol-producing devices such as dry powder inhalers (DPIs), pressurized metered dose inhalers (PMDIs) and nebulizers. Depending on the kind of the compound of the invention to be administered, the aerosol-producing device can contain the compound in form of a powder, a solution or a dispersion. The powder may contain, for example, one or more of the following auxiliaries: carriers, stabilizers and fillers. The solution may contain in addition to the solvent, for example, one or more of the following auxiliaries: propellants, solubilizers (co-solvents), surfactants, stabilizers, buffers, tonicity adjusting agents, preservatives and flavorings. The dispersion may contain in addition to the dispersant, for example, one or more of the following auxiliaries: propellants, surfactants, stabilizers, buffers, preservatives and flavorings. Examples of carriers include, but are not limited to, saccharides, e.g. lactose and glucose. Examples of propellants include, but are not limited to, fluorohydrocarbons, e.g. 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane.

The particle size of the aerosol particles (solid, liquid or solid/liquid particles) is preferably less than 100 μm , more preferably it is in the range of from 0.5 to 10 μm , in particular in the range of from 2 to 6 μm (D50 value, measured by laser diffraction).

Specific aerosol-producing devices which may be used for inhaled administration include, but are not limited to, Cyclohaler®, Diskhaler®, Rotadisk®, Turbohaler®, Autohaler®, Novolizer®, Easyhaler®, Aerolizer®, Jethaler®, Diskus®, Ultrahaler® and Mystic® inhalers. The aerosol-producing devices may be combined with spacers or expanders, e.g. Aerochamber®, Nebulator®, Volumatic® and Rondo®, for improving inhalation efficiency.

In case of topical administration, suitable pharmaceutical formulations are, for example, ointments, creams, lotions, pastes, gels, powders, solutions, emulsions, suspensions, oils, sprays and patches (e.g., but not limited to, transdermal therapeutic systems).

For parenteral modes of administration such as, for example, intravenous, intraarterial, intramuscular, subcutaneous, intracutaneous, intraperitoneal and intrasternal administration, preferably solutions (e.g., but not limited to, sterile solutions, isotonic solutions) are used. They are preferably administered by injection or infusion techniques.

In case of intranasal administration, for example, sprays and solutions to be applied in drop form are preferred formulations.

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For intraocular administration, solutions to be applied in drop form, gels and ointments are exemplified formulations.

In case of co-administration of at least one compound of the invention with at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics, angiogenesis inhibitors, AL-8309B, Zinc compounds, preferably Zinc-monocysteine, Mecamylamine, preferably Mecamylamine hydrochloride, Brimonidine, preferably Brimonidine tartrate, or Sirolimus, in form of a fixed combination, non-fixed combination or kit of parts the dose of the compound of the invention as well as the dose of the therapeutic agent will be in a range customary for the mono-therapy, it more likely being possible, on account of the individual action, which are mutually positively influencing and reinforcing, to reduce the respective doses in case of co-administration of the compound(s) of the invention and the therapeutic agent.

Generally, the pharmaceutical compositions according to the invention can be administered such that the dose of the compound of the invention is in the range customary for CC chemokine receptor 3 modulators. In particular, a dose in the range of from 0.05 to 500 mg, preferably 0.1 to 200 mg of the compound of the invention per day is preferred for an average adult patient having a body weight of 70 kg. In this respect, it is to be noted that the dose is dependent, for example, on the specific compound used, the species treated, age, body weight, general health, sex and diet of the subject treated, mode and time of administration, rate of excretion, severity of the disease to be treated and drug combination.

The pharmaceutical composition can be administered in a single dose per day or in multiple subdoses, for example, 2 to 4 doses per day. A single dose unit of the pharmaceutical composition can contain e.g. from 0.05 mg to 500 mg, preferably 0.1 mg to 200 mg, more preferably 0.1 to 100 mg, most preferably 0.1 to 10 mg, of the compound of the invention.

In case of co-administration of at least one compound of the invention and at least one therapeutic compound selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants, antibiotics, angiogenesis inhibitors, AL-8309B, Zinc compounds, preferably Zinc-monocysteine, Mecamylamine, preferably Mecamylamine hydrochloride, Brimonidine, preferably Brimonidine tartrate, or Sirolimus, in form of a fixed combination, a non-fixed combination or a kit of parts a single dose unit of the respective pharmaceutical composition/formulation can contain e.g. from 0.05 mg to 500 mg, preferably 0.1 mg to 200 mg, more preferably 0.1 to 100 mg of the compound of the invention and/or e.g. from 0.01 mg to 4000 mg, preferably 0.1 mg to 2000 mg, more preferably 0.5 mg to 1000 mg, most preferably 1 mg

to 500 mg, of the therapeutic agent, depending on the therapeutic agent being used, the disease to be treated and the administration route selected. Preferably, the at least one compound of the invention and the at least one therapeutic agent are present in the pharmaceutical compositions/formulations in a weight ratio of from 1000:1 to 1:1000, more preferably in a weight ratio of
5 from 100:1 to 1:100, even more preferably in a weight ratio of from 25:1 to 1:25.

Furthermore, the pharmaceutical composition may be adapted to weekly, monthly or even more infrequent administration, for example by using an implant, e.g. a subcutaneous or intramuscular implant, by using the compound of the invention in form of a sparingly soluble salt or by using the
10 compound of the invention coupled to a polymer.

Biological Investigations

1) In vitro Experiments

a) Receptor Ligand Binding Assay:

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Isolated human peripheral blood polymorphnuclear granulocytes were resuspended in assay buffer [PBS (Dulbecco); 10 mM HEPES, 10 mM Glucose, 0.1% BSA (pH7.4)] to a concentration of 1x10⁶ cells/ml. In a 96-well plate 1 µl test compound in 10 different concentrations was mixed with 100 µl assay buffer. 10 µl of the diluted compound was added to 50 µl 18nM eotaxin coupled to AlexaFluor647 (Dictagene, Swiss, now available by ALMAC Biosciences, UK; Cat. No. CAF-3; diluted in assay buffer), subsequently 40 µl cell suspension was added (final concentration in the assay 400.000 cells/assay in 100 µl). The 96-well plate was sealed and incubated at 37°C for 90 min.. Subsequently, the cells were washed once with 1 ml assay buffer and centrifuged at 300 g for 10 min. at room temperature. The supernatant was aspirated and the cell pellet resuspended in 130 µl 1x BD CellFixTM (BD Biosciences, Cat. No. 340181). Binding of eotaxin to eosinophils was determined by flow cytometry using FACS Arrays Instruments from BD Biosciences. Autofluorescence of eosinophils was used to distinguish between eosinophils and neutrophils. Gated eosinophils were analysed for their fluorescence in the RedA filter that detects the fluorescence induced by AlexaFluor647. The fluorescence is a direct measure of eotaxin bound by eosinophils. To determine total binding, wells received all additions but instead of the compound an equal volume of DMSO as solvent was added. To determine non-specific binding, wells received the IC99 concentration of a CCR3 antagonist. Percent control binding was assessed by subtracting the unspecific binding from each well and then expressing the number of fluorescent units associated with the compound treated sample as a percent of the control binding in the absence of compound addition. IC50 values have been calculated by GraphPad Prism 4.0 Software. The assay was performed 4 times with cells of 4 different donors each in duplicates.

Results:

Examples 1 to 32 showed, when tested in the above-described assay system, an inhibition of the eotaxin binding on eosinophils [measured as $-\log IC_{50}$ (mol/l)] in the range from 6.6 to 8.9. Examples 4, 6, 17 and 18 were in the range from 7.3 to 7.8.

b) Eosinophil shape-change assay

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The assay was published in:

Bryan, S. A., Jose, P. J., Topping, J. R., Wilhelm, R., Soderberg, C., Kertesz, D., Barnes, P. J., Williams, T. J., Hansel, T. T., and Sabroe, I. 2002. Responses of leukocytes to chemokines in whole blood and their antagonism by novel CC-chemokine receptor 3 antagonists (Am. J. Respir.

CritCare Med. 165:1602-1609). Another term for this assay is "gated-autofluorescence/forward-scatter assay".

The protocol used for the eosinophil shape change assay followed in general the publication of Bryan et al.. Apart from this protocol, the assay was adapted in regard to the timespan it was conducted with. The assay was used for the determination and quantification of the relative eotaxin-induced shape change on eosinophils that peaks after 10 min. at 37°C ("Eosinophil shape-change assay"). It is well known by the person skilled in the art how to evaluate the cellular shape change and estimate or calculate the percentage of the shape change.

Citrate blood of healthy volunteer donors was used to purify polymorphonuclear cells (PMNs) that were washed in assay buffer in the absence of calcium and magnesium ions according to the publication of Bryan et al.. Aliquots of 4×10^5 PMNs were incubated with increasing concentrations of test compound or eotaxin as natural agonist and buffer as negative control in 37°C water bath for 10 min after which they were transferred to an ice-water bath. Immediately afterwards, ice-cold fixative (Cellfix™) was added to terminate the reaction and maintain the cell shape change until analysis. The samples were analysed on a FACS Array (BD Biosciences) by absorption of laser light in the forward scatter of at least 1000 gated autofluorescent eosinophiles from which the median value was used.

An increase of cell shape change of at least about 20 %, induced by a certain compound compared to the maximal cell shape change induced by eotaxin, was considered as "agonistic activity". A maximal increase below the threshold of about 20 % cell shape change was considered as "no agonistic activity".

In order to determine antagonistic (inhibitory) activity aliquots of 4×10^5 PMNs were preincubated with increasing concentrations of test compound for 15 minutes at room temperature and then mixed with 0.2 nM eotaxin (corresponding to tenfold EC₅₀ value of eotaxin in this assay) or buffer in 37°C water bath for 10 min after which they were transferred to an ice-water bath. Immediately afterwards, ice-cold fixative (Cellfix™) was added to terminate the reaction and maintain the cell shape change until analysis. The samples were analysed on a FACS Array (BD Biosciences) by absorption of laser light in the forward scatter of at least 1000 gated autofluorescent eosinophiles from which the median value was used. The control sample that contains DMSO without eotaxin was set to 100% inhibition and the sample containing DMSO with eotaxin as 0% inhibition.

Examples 4, 6, 17 and 18 were in the range of 40 % to 100 %. Examples 4, 17 and 18 were used in a maximal concentration of 10 nM, example 6 in a maximal concentration of 100 nM, respectively, which means that those compounds displayed agonistic activity.

5 **2) In vivo Experiments**

a) Eotaxin-induced peritoneal eosinophilia

Eosinophilia is established by intraperitoneal stimulation with recombinant mouse Eotaxin (in saline for injection + 0.25% HSA + 1% Carboxymethylcellulose (CMC, low viscosity, BDH, VWR International Ltd., Poole, England), [10ml/kg]) in transgenic mice harbouring the coding sequence of human CCR3 instead of the murine CCR3 coding sequence. 1.5 mg/kg body weight eotaxin solution is injected into the peritoneal cavity in a volume of 10ml/kg. Test substances are administered per os 1 h before eotaxin stimulation. 6 h after eotaxin stimulation animals are euthanized by cervical dislocation. Peritoneal lavage is performed by injection of 4 ml PBS (containing 2mM EDTA) and retrieval of the lavage fluid with 14 G plastic cannulae. The lavages are analysed by cellular differentiation of eosinophils and determination of total eosinophil number using an automated hematology analyzer (Sysmex XT-2000iV).

Selected Compounds from the list of the Examples 1 to 32 inhibited the eotaxin induced eosinophilia in this model with half-maximal effective doses in the range of 0.1 to 50 mg/kg. Examples 4, 6, 17 and 18 were in the range of 0.3 to 6.0 mg/kg.

b) Ovalbumin-induced broncho-alveolar eosinophilia in sensitised animals

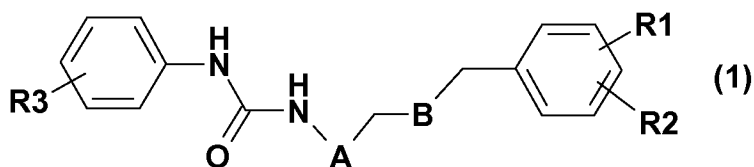
Ovalbumin (OVA) sensitisation and challenge with aerolised Ovalbumin results in eosinophilia in bronchoalveolar lavage. Ovalbumin induced eosinophilia is established in transgenic mice harbouring the coding sequence of human CCR3 instead of the murine CCR3 coding sequence by sensitisation with 10µg OVA/Imject Alum (i.p. at day 1, 14, 21) and a challenge with aerolised OVA at day 26 and 27 for 1 hour. Test substances are administered 1 h before and 5 h after each challenge at day 26 and 27. At day 28 animals are euthanized by i.v. Narcoren/Heparin [60/17 mg/kg] injection. In order to insert the plastic cannulae a midline skin incision over the sternum and a small incision between two trachea rings is performed. A 20G plastic cannulae reduced to a length of 1 cm is introduced into the trachea. The broncho-alveolar lavage is performed by two injections of 0.8 ml 0.9% NaCl into the trachea and retrieval of the lavage fluid. The lavages are analysed by cellular differentiation of eosinophils and determination of total eosinophil number using an automated hematology analyzer (Sysmex XT-2000iV).

Selected Compounds from the list of the Examples 1 to 32 inhibited the eosinophilia in this asthma model with half-maximal effective doses in the range of 0.1 to 50 mg/kg.

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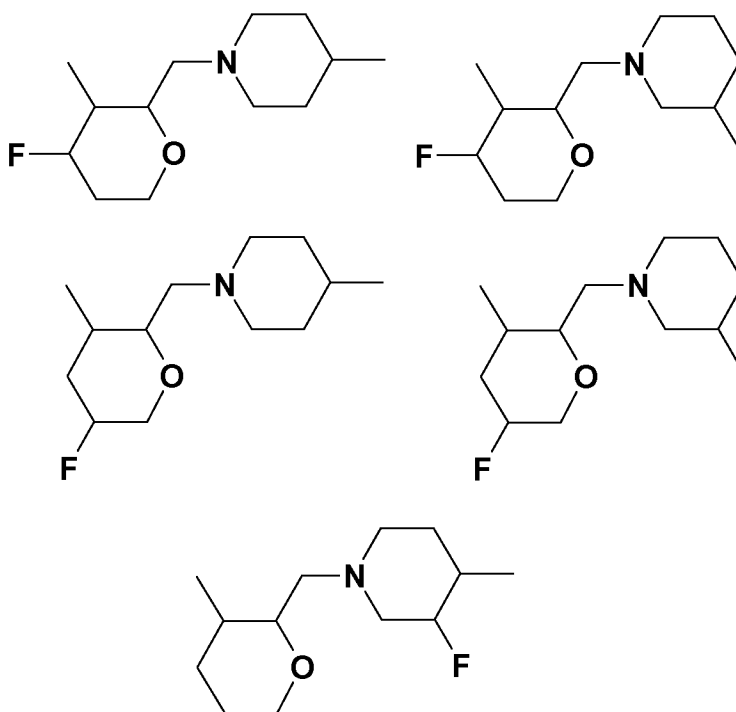
Claims

1. A compound of formula (1)



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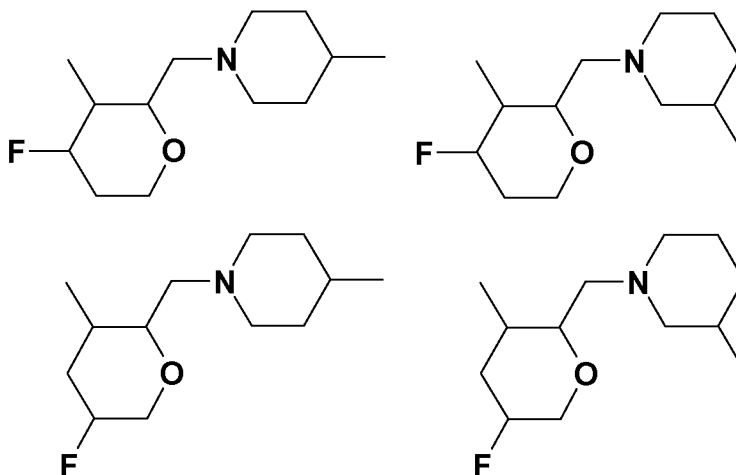
wherein the group $-A-CH_2-B-$ is selected from



- R1 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
- 10 R2 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine, and
- R3 is hydrogen, halogen, cyano, hydroxycarbonyl, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl, 1-4C-alkoxy-carbonyl, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylamino-
- 15 carbonyl,
- or a salt, a stereoisomer or a salt of a stereoisomer thereof.

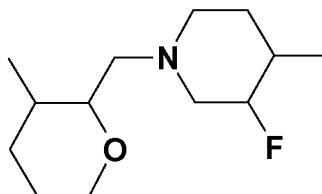
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2. A compound of formula (1) according to claim 1, wherein the group -A-CH₂-B- is selected from



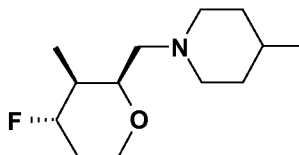
- 5 R1 is fluorine, chlorine, methoxy or difluoromethoxy,
 R2 is hydrogen, fluorine, chlorine, methyl or difluoromethoxy, and
 R3 is cyano, fluorine, methyl, methoxy, ethoxy, difluoromethoxy or acetyl,
 or a salt, a stereoisomer or a salt of a stereoisomer thereof.

- 10 3. A compound of formula (1) according to claim 1, wherein the group -A-CH₂-B- is selected from



- R1 is fluorine, chlorine, methoxy or difluoromethoxy,
 R2 is hydrogen, fluorine, chlorine, methyl or difluoromethoxy, and
 15 R3 is cyano, fluorine, methyl, methoxy, ethoxy, difluoromethoxy or acetyl,
 or a salt, a stereoisomer or a salt of a stereoisomer thereof.

4. A compound of formula (1) according to any of claim 1 or 2, wherein the group -A-CH₂-B- stands for

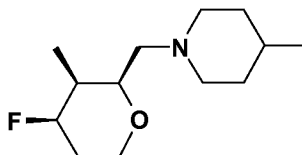


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or a salt of this compound.

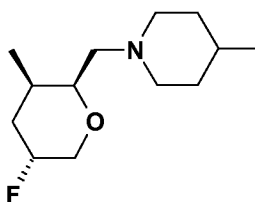
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5. A compound of formula (1) according to any of claims 1 or 2, wherein the group $-A-CH_2-B-$ stands for



- 5 or a salt of this compound.

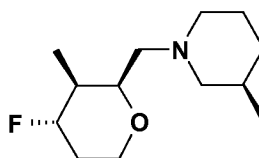
6. A compound of formula (1) according to any of claims 1 or 2, wherein the group $-A-CH_2-B-$ stands for



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- or a salt of this compound.

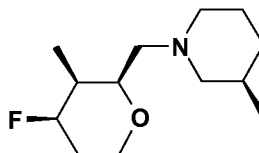
7. A compound of formula (1) according to any of claims 1 or 2, wherein the group $-A-CH_2-B-$ stands for



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- or a salt of this compound.

8. A compound of formula (1) according to any of claims 1 or 2, wherein the group $-A-CH_2-B-$ stands for

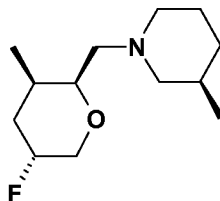


- or a salt of this compound.

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9. A compound of formula (1) according to any of claims 1 or 2, wherein the group –A-CH₂-B- stands for



5 or a salt of this compound.

10. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to any of claims 1 to 9 for use in the treatment or prophylaxis of diseases.
- 10 11. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to claim 10, wherein the compound is selected from one of the compounds of any of claims 3 to 6.
- 15 12. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to claim 10 or 11, wherein the compound is selected from one of the compounds of any of claims 4 to 6.
- 20 13. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to claim 10 to 12, wherein the compound comprises at least a partial agonistic effect on CC chemokine receptor 3.
- 25 14. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to any of claims 10 to 13, wherein the compound comprises at least a partial CC chemokine receptor 3 internalizing effect.
- 30 15. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to claim 10, wherein the compound is selected from one of the compounds of any of claims 7 to 9.
16. Compound, stereoisomer or pharmaceutically acceptable salt of the compound or stereoisomer according to claim 10 or 15, wherein the compound comprises an antagonistic effect on CC chemokine receptor 3.

17. Pharmaceutical composition comprising at least one of the compounds, stereoisomers or pharmaceutically acceptable salts of the compounds or stereoisomers according to any of claims 1 to 9 together with at least one pharmaceutically acceptable auxiliary.
- 5 18. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to any of claims 1 to 9 in the manufacture of a pharmaceutical composition modulating CC chemokine receptor 3 activity.
- 10 19. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 18, wherein the compound is selected from one of the compounds of any of claims 3 to 6.
- 15 20. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 18 or 19, wherein the compound is selected from one of the compounds of any of claims 4 to 6.
- 20 21. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 18 to 20, wherein the compound comprises at least a partial agonistic effect on CC chemokine receptor 3.
22. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to any of claims 18 to 21, wherein the compound comprises at least a partial CC chemokine receptor 3 internalizing effect.
- 25 23. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 18, wherein the compound is selected from one of the compounds of any of claims 7 to 9.
- 30 24. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 18 or 23, wherein the compound comprises an antagonistic effect on CC chemokine receptor 3.
- 35 25. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to any of claims 1 to 9 in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of bronchial asthma, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis or wet age-related macular degeneration (AMD).

26. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 25, wherein the compound is selected from one of the compounds of any of claims 3 to 6.
- 5 27. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 25 or 26, wherein the compound is selected from one of the compounds of any of claims 4 to 6.
- 10 28. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 25 to 27, wherein the compound comprises at least a partial agonistic effect on CC chemokine receptor 3.
- 15 29. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to any of claims 25 to 28, wherein the compound comprises at least a partial CC chemokine receptor 3 internalizing effect.
- 20 30. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 25, wherein the compound is selected from one of the compounds of any of claims 7 to 9.
31. Use of a compound, stereoisomer or pharmaceutically acceptable salt of a compound or stereoisomer according to claim 25 or 30, wherein the compound comprises an antagonistic effect on CC chemokine receptor 3.
- 25 32. Method of treating or preventing a disease, which is alleviated by modulation of the CC chemokine receptor 3 activity comprising administering to a patient in need thereof a therapeutically effective amount of at least one of compound, stereoisomer or pharmaceutical acceptable salt of a compound or stereoisomer according to any of claims 1 to 9.
- 30 33. Method according to claim 32, wherein the disease is selected from bronchial asthma, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis and wet age-related macular degeneration (AMD).
- 35 34. Pharmaceutical composition according to claim 17 for the treatment or prophylaxis of bronchial asthma, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis or wet age-related macular degeneration (AMD).
35. A fixed combination, a non-fixed combination or kit of parts comprising at least one of the compounds, stereoisomers or pharmaceutically acceptable salts of the compounds or

stereoisomers according to any of claims 1 to 9, at least one therapeutic agent selected from the group consisting of corticosteroids, anticholinergics, β_2 -adrenoreceptor agonists, H1 receptor antagonists, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, endothelin antagonists, type 4 phosphodiesterase inhibitors, theophylline, immunosuppressants, immune modulators, cytokine inhibitors, vitamin D analogues, HMG-CoA reductase-inhibitors, lung surfactants and antibiotics, and at least one pharmaceutically acceptable auxiliary.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/067247

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D309/14 A61P11/06 A61K31/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/02525 A (DU PONT PHARM CO [US] BRISTOL MYERS SQUIBB PHARMA CO [US]) 10 January 2002 (2002-01-10) cited in the application page 191 - page 192; example 44J -----	
A	NAYA A ET AL: "Chemokine CCR3 antagonists" EXPERT OPINION ON THERAPEUTIC PATENTS 200401 GB, vol. 14, no. 1, January 2004 (2004-01), pages 7-16, XP002523959 ISSN: 1354-3776 ----- -/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 February 2010

Date of mailing of the international search report

08/03/2010

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/067247

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GEORGE V DE LUCCA: "RECENT DEVELOPMENTS IN CCR3 ANTAGONISTS" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT, CURRENT DRUGS, LONDON, GB, vol. 9, no. 4, 1 January 2006 (2006-01-01), pages 516-524, XP008078469 ISSN: 1367-6733	
A	----- PRUITT JAMES R ET AL: "CC chemokine receptor-3 (CCR3) antagonists: improving the selectivity of DPC168 by reducing central ring lipophilicity." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 JUN 2007, vol. 17, no. 11, 1 June 2007 (2007-06-01), pages 2992-2997, XP002523960 ISSN: 0960-894X cited in the application the whole document	
A	----- DHAR T G MURALI ET AL: "Urea based CCR3 antagonists employing a tetrahydro-1,3-oxazin-2-one spacer." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 JAN 2009, vol. 19, no. 1, 6 November 2008 (2008-11-06), pages 96-99, XP002524028 ISSN: 1464-3405	
A	----- SMART B E: "Fluorine substituent effects (on bioactivity)" JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER, NL, vol. 109, no. 1, 1 June 2001 (2001-06-01), pages 3-11, XP004246489 ISSN: 0022-1139 page 4 - page 5 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/067247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0202525	A	10-01-2002	
		AU 7312901 A	14-01-2002
		BR 0111878 A	24-05-2005
		CA 2413245 A1	10-01-2002
		CN 1440402 A	03-09-2003
		EP 1296978 A2	02-04-2003
		JP 2004517805 T	17-06-2004
		MX PA02012712 A	25-04-2003
