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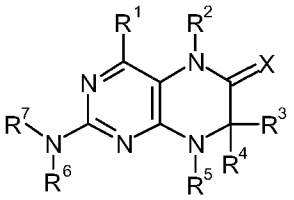
(54) Title: DIHYDROPTERIDINONES IN THE TREATMENT OF RESPIRATORY DISEASES



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(57) Abstract: The present invention relates to the use of dihydropteridinones of formula (1), wherein the groups X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meanings given in the claims and specification, for the preparation of a medicament for the treatment of respiratory diseases.

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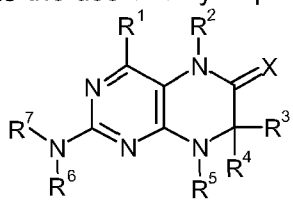
Dihydropteridinones in the treatment of respiratory diseases

The present invention relates to the use of dihydropteridinones of formula **1**



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wherein the groups X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meanings given in the claims and specification, for the preparation of a medicament for the treatment of respiratory diseases.

Background of the invention

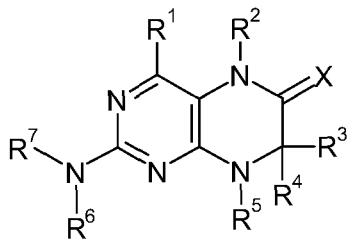
Pteridinone derivatives are known from the prior art as active substances with an antiproliferative activity. WO 01/019825 describes the use of pteridinone derivatives for the treatment of neoplastic and viral diseases. WO 03/020722 discloses new pteridinone derivatives for the treatment of cancer, infections, inflammatory and autoimmune diseases.

The aim of the present invention is the provision of compounds that are suitable in the treatment of respiratory complaints. Another object of the invention is the provision of pharmaceutical compositions for the treatment of respiratory complaints by way of inhalation.

Detailed description of the invention

Surprisingly it has been found that compounds of general formula **1** wherein the groups X and R^1 to R^7 have the meanings given hereinafter are suitable in the treatment of respiratory complaints.

Therefore, the present invention relates to the use of therapeutically effective amounts of a compound of general formula **1**



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wherein

R^1 denotes a group selected from among hydrogen, NH_2, XH, halogen and a C_1-C_3-alkyl group optionally substituted by one or more halogen atoms,

R^2 denotes a group selected from among hydrogen, CHO, XH, -X-C_1-C_2-alkyl and an optionally substituted C_1-C_3-alkyl group,

R^3, R^4 which may be identical or different denote a group selected from among optionally substituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, aryl, heteroaryl, C_3-C_8-cycloalkyl, C_3-C_8-heterocycloalkyl, -X-aryl, -X-heteroaryl, -X-cycloalkyl, -X-heterocycloalkyl, -NR^8-aryl, -NR^8-heteroaryl, -NR^8-cycloalkyl and -NR^8-heterocycloalkyl, or a group selected from among hydrogen, halogen, $COXR^8$, $CON(R^8)_2$, COR^8 and XR^8, or

R^3 and R^4 together denote a 2- to 5-membered alkyl bridge which may contain 1 to 2 heteroatoms,

R^5 denotes hydrogen or a group selected from among optionally substituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, aryl, heteroaryl and -C_3-C_6-cycloalkyl , or

R^3 and R^5 or R^4 and R^5 together denote a saturated or unsaturated C_3-C_4-alkyl bridge which may contain 1 to 2 heteroatoms,

R^6 denotes optionally substituted aryl or heteroaryl,

R^7 denotes hydrogen or -CO-X-C_1-C_4-alkyl, and

X in each case independently of one another denotes O or S,

R^8 in each case independently of one another denotes hydrogen or a group selected from among optionally substituted C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl and phenyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof,
for the preparation of a pharmaceutical composition for the treatment of respiratory complaints.

The compounds of formula **1** mentioned above are known from International Patent Application No. WO 03/020722.

Within the scope of the invention the term respiratory complaints is to be understood as synonymous with the optionally also applied term respiratory diseases.

In a preferred aspect the present invention relates to the use of therapeutically effective amounts of the active substance **1** for preparing a pharmaceutical composition for the treatment of respiratory complaints selected from the group comprising obstructive pulmonary diseases of various origins, pulmonary emphysema of various origins, restrictive pulmonary diseases, interstitial pulmonary diseases, cystic fibrosis, bronchitis of various origins, bronchiectasis, ARDS (adult respiratory distress syndrome) and all forms of pulmonary oedema.

Preferably, therapeutically effective amounts of a compound of formula **1** are used as specified above for preparing a pharmaceutical composition for the treatment of obstructive pulmonary diseases selected from among bronchial asthma, paediatric asthma, severe asthma, acute asthma attacks, chronic bronchitis and COPD (chronic obstructive pulmonary disease), while it is particularly preferable according to the invention to use a compound of formula **1** for preparing a pharmaceutical composition for the treatment of bronchial asthma and COPD.

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of pulmonary emphysema which has its origins in COPD (chronic obstructive pulmonary disease) or α1-proteinase inhibitor deficiency.

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of restrictive pulmonary diseases selected from among allergic alveolitis, restrictive pulmonary diseases triggered by work-related noxious substances, such as asbestosis or silicosis, and restriction caused by lung tumours, such as for example lymphangiosis carcinomatosa, bronchoalveolar carcinoma and lymphomas.

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of interstitial pulmonary diseases selected from among pneumonia caused by infections, such as for example infection by viruses, bacteria, fungi, protozoa, helminths or other pathogens, pneumonitis caused by various factors, such as for example aspiration

and left heart insufficiency, radiation-induced pneumonitis or fibrosis, collagenoses, such as for example lupus erythematodes, systemic sclerodermy or sarcoidosis, granulomatoses, such as for example Boeck's disease, idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis (IPF).

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of cystic fibrosis or mucoviscidosis.

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of bronchitis, such as for example bronchitis caused by bacterial or viral infection, allergic bronchitis and toxic bronchitis.

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of bronchiectasis.

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of ARDS (adult respiratory distress syndrome).

It is also preferable to use therapeutically effective amounts of a compound of formula **1** for preparing a pharmaceutical composition for the treatment of pulmonary oedema, for example toxic pulmonary oedema after aspiration or inhalation of toxic substances and foreign substances.

It is particularly preferable to use the compounds detailed above for preparing a pharmaceutical composition for the treatment of asthma or COPD.

The present invention also relates to a process for treating one of the above-mentioned diseases, which is characterised in that therapeutically effective amounts of active substance of formula **1** are administered.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

In a yet another preferred embodiment the invention relates to the aforementioned use of therapeutically effective amounts of a compound of formula **1**, wherein X and R^6 have the meaning indicated above, and wherein

R^1 denotes hydrogen,

R^2 denotes a group selected from among a CHO, OH, and CH_3 group,

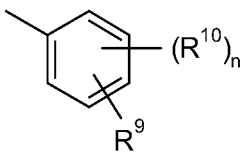
R^3, R^4 which may be identical or different denote a group selected from among optionally substituted C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_7-cycloalkyl, or
R^3 and R^4 together denote a C_2-C_5-alkyl bridge ,

R^5 denotes a group selected from among optionally substituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, C_3-C_6-cycloalkyl and C_3-C_6-cycloalkenyl, or

R^3 and R^5 or R^4 and R^5 together denote a saturated or unsaturated C_3-C_4-alkyl bridge which may contain 1 to 2 heteroatoms, and

R^7 denotes hydrogen,
optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

In a yet another preferred embodiment the invention relates to the aforementioned use of therapeutically effective amounts of a compound of formula **1**, wherein R^1-R^5, R^7, R^8 and X have the meaning indicated above, and wherein
R^6 denotes a group of general formula



wherein
n denotes 1, 2, 3 or 4,

R^9 denotes a group selected from among optionally substituted C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, -CONH-C_1-C_{10}-alkylene, -O-aryl, -O-heteroaryl,

-O-cycloalkyl, -O-heterocycloalkyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl or a group selected from among -O-C_1-C_6-alkyl-Q^1, -$CONR^8$-C_1-C_{10}-alkyl-Q^1, -$CONR^8$-C_2-C_{10}-alkenyl-Q^1, -$CONR^8$-Q^2, halogen, OH, -SO_2R^8, -$SO_2N(R^8)_2$, -COR^8, -$COOR^8$, -$N(R^8)_2$, -$NHCOR^8$, $CONR^8OC_1$-C_{10} alkylQ^1 and $CONR^8OQ^2$,

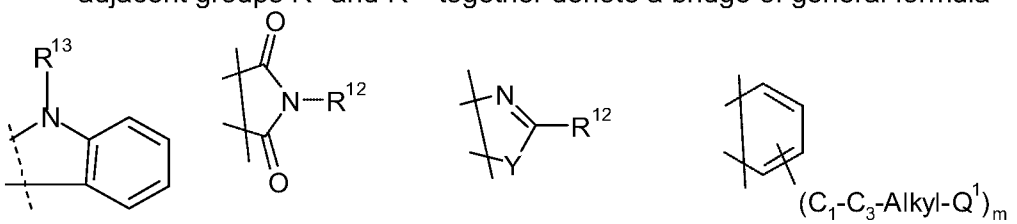
Q^1 denotes hydrogen, -$NHCOR^8$, or a group selected from among an optionally substituted -NH-aryl, -NH-heteroaryl, aryl, heteroaryl, C_3-C_8-cycloalkyl- and heterocycloalkyl group,

Q^2 denotes hydrogen or a group selected from among an optionally substituted aryl, heteroaryl and C_3-C_8-cycloalkyl group,

R^{10} which may be identical or different denotes a group selected from among optionally substituted C_1-C_6-alkyl , C_2-C_6-alkenyl and C_2-C_6-alkynyl, -O-C_1-C_6-alkyl, -O-C_2-C_6-alkenyl, -O-C_2-C_6-alkynyl, C_3-C_6-heterocycloalkyl and C_3-C_6-cycloalkyl, or a group selected from among hydrogen, -$CONH_2$, -$COOR^8$, -$OCON(R^8)_2$, -$N(R^8)_2$, -$NHCOR^8$, -$NHCON(R^8)_2$, -NO_2 and halogen,

or

adjacent groups R^9 and R^{10} together denote a bridge of general formula



Y denotes O, S or NR^{11},

m denotes 0, 1 or 2

R^{11} denotes hydrogen or C_1-C_2-alkyl, and

R^{12} denotes hydrogen or a group selected from among optionally substituted phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, -C_1-C_3-alkyl-phenyl, -C_1-C_3-alkyl-pyridyl, -C_1-C_3-alkyl-pyrazinyl, -C_1-C_3-alkyl-pyrimidinyl and -C_1-C_3-alkyl-pyridazinyl,

R^{13} denotes C_1-C_6-alkyl,

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

In a yet another preferred embodiment the invention relates to the aforementioned use of therapeutically effective amounts of a compound of formula **1**, wherein R^3-R^6, R^8 and X have the meaning indicated above, and wherein

R^1 denotes hydrogen,

R^2 denotes CH_3, and

R^7 denotes hydrogen,

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

The term alkyl groups, including alkyl groups which are a part of other groups, denotes branched and unbranched alkyl groups with 1 to 10 carbon atoms, preferably 1 – 6, most preferably 1-4 carbon atoms, such as, for example: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl. Unless otherwise stated, the abovementioned terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl include all the possible isomeric forms. For example, the term propyl includes the two isomeric groups n-propyl and iso-propyl, the term butyl includes n-butyl, iso-butyl, sec. butyl and tert.-butyl, the term pentyl includes iso-pentyl, neopentyl, etc. In the abovementioned alkyl groups one or more hydrogen atoms may optionally be replaced by other groups. For example these alkyl groups may be substituted by the halogen atoms fluorine, chlorine, bromine or iodine. The substituents fluorine and chlorine are preferred. The substituent chlorine is particularly preferred. All the hydrogen atoms of the alkyl group may optionally also be replaced.
Similarly, in the abovementioned alkyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced for example by an optionally substituted group selected from among CN, $OCOCH_3$, aryl, preferably phenyl, heteroaryl, preferably thienyl, thiazolyl, imidazolyl, pyridyl, pyrimidyl or pyrazinyl, saturated or unsaturated heterocycloalkyl, preferably pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl or tetrahydro-oxazinyl, an amine group, preferably methylamine, benzylamine, phenylamine or heteroarylamine, saturated or unsaturated bicyclic ring systems, preferably benzimidazolyl and cycloalkyl, preferably cyclohexyl or cyclopropyl.

The term alkyl bridge, unless otherwise stated, denotes branched and unbranched alkyl groups with 2 to 5 carbon atoms, for example propylene, isopropylene, n-butylene, iso-butyl, sec. butyl and tert.-butyl etc. bridges. Propylene and butylene

bridges are particularly preferred. In the alkyl bridges mentioned 1 to 2 C-atoms may optionally be replaced by one or more heteroatoms selected from among oxygen, nitrogen or sulphur.

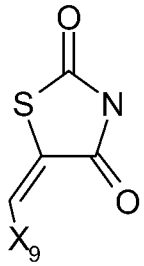
The term alkenyl groups (including those which are a part of other groups) denotes branched and unbranched alkylene groups with 2 to 10 carbon atoms, preferably 2 - 6 carbon atoms, most preferably 2 - 3 carbon atoms, provided that they have at least one double bond. Examples include: ethenyl, propenyl, butenyl, pentenyl etc. Unless otherwise stated, the abovementioned terms propenyl, butenyl, etc also include all the possible isomeric forms. For example, the term butylene includes n-butenyl, 1-methylpropenyl, 2-methylpropenyl, 1.1-dimethylethenyl, 1.2-dimethylethenyl etc. In the abovementioned alkenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other groups. For example, these alkyl groups may be substituted by the halogen atoms fluorine, chlorine, bromine or iodine. The substituents fluorine and chlorine are preferred. The substituent chlorine is particularly preferred. All the hydrogen atoms of the alkenyl group may optionally also be replaced.

The term alkynyl groups (including those which are a part of other groups) denotes branched and unbranched alkynyl groups with 2 to 10 carbon atoms, provided that they have at least one triple bond, for example ethynyl, propargyl, butynyl, pentynyl, hexynyl etc., preferably ethynyl or propynyl.

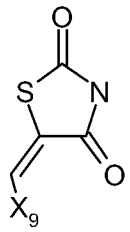
In the abovementioned alkynyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other groups. For example, these alkyl groups may be substituted by the halogen atoms fluorine, chlorine, bromine or iodine. The substituents fluorine and chlorine are preferred. The substituent chlorine is particularly preferred. All the hydrogen atoms of the alkynyl group may optionally also be replaced.

The term aryl denotes an aromatic ring system with 6 to 14 carbon atoms, preferably 6 or 10 carbon atoms, preferably phenyl, which, unless otherwise stated, may carry one or more of the following substituents, for example: OH, NO_2, CN, $-OCHF_2$, $-OCF_3$, $-NH_2$, halogen, for example fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine, C_1-C_{10}-alkyl, preferably C_1-C_5-alkyl, preferably C_1-C_3-alkyl, most preferably methyl or ethyl, -O-C_1-C_3-alkyl, preferably -O-methyl or –O-ethyl, - N-methyl -tetrahydro-oxazinyl, -COOH, -COO-C_1-C_4-alkyl, preferably $-COOCH_2CH_3$, $-COO-C(CH_3)_3$ or $–COOCH_3$, $-CONH_2$,

-CONH-C_1-C_{10}-alkyl, while this alkyl may optionally be further substituted, optionally substituted -CONH-C_3-C_6-cycloalkyl, preferably optionally substituted -CONH-cyclopentyl, optionally substituted -CONH-heterocycloalkyl, preferably piperidinyl, pyrrolidinyl or piperazinyl, optionally substituted -CONH-heteroaryl, preferably optionally substituted -CONH-pyridyl, optionally substituted -CONH-aryl, preferably optionally substituted –CONH-phenyl, -CONMeC_1-C_3-alkyl, while this alkyl may optionally be further substituted, preferably -CONMeCH_2-pyridyl, benzimidazole or a group of formula



Examples of 5-10-membered mono- or bicyclic heteroaryl rings wherein up to three C-atoms may be replaced by one or more heteroatoms selected from among oxygen, nitrogen or sulphur include furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, oxazole, isoxazole, thiazole, thiadiazole and oxadiazole, while each of the abovementioned heterocycles may optionally also be annellated onto a benzene ring, preferably benzimidazole, and unless otherwise stated these heterocycles may for example carry one or more of the following substituents: OH, NO_2, CN, -$OCHF_2$, -OCF_3, -NH_2, halogen, preferably fluorine or chlorine, C_1-C_{10}-alkyl, preferably C_1-C_5-alkyl, preferably C_1-C_3-alkyl, most preferably methyl or ethyl, -O-C_1-C_3-alkyl, preferably -O-methyl or –O-ethyl, -methyl-N-tetrahydro-oxazinyl, -COOH, -COO-C_1-C_4-alkyl, preferably –COO-$C(CH_3)_3$ or –$COOCH_3$, -$CONH_2$, optionally substituted phenyl, optionally substituted heteroaryl, preferably optionally substituted pyridyl or pyrazinyl, -CONH-C_1-C_{10}-alkyl, while this alkyl may itself optionally be substituted, optionally substituted -CONH-C_3-C_6-cycloalkyl, preferably optionally substituted -CONH-cyclopentyl, optionally substituted -CONH-heteroaryl, preferably optionally substituted -CONH-pyridyl, optionally substituted -CONH-aryl, preferably optionally substituted –CONH-phenyl, -CONMeC_1-C_3-alkyl, while this alkyl may itself optionally be substituted, preferably –CONMeCH_2-pyridyl, benzimidazole or a group of formula



The term cycloalkyl groups denotes, for example, saturated or unsaturated cycloalkyl groups with 3 - 8 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl or cyclooctyl, preferably cyclopropyl, cyclopentyl or cyclohexyl, while each of the abovementioned cycloalkyl groups may optionally also carry one or more substituents, preferably =O, or may be annellated to a benzene ring.

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

The term heterocycloalkyl groups, unless otherwise described in the definitions, may denote 5-, 6- or 7-membered, saturated or unsaturated heterocycles, which may contain nitrogen, oxygen or sulphur as heteroatoms, for example tetrahydrofuran, tetrahydrofuranon, γ-butyrolactone, α-pyran, γ-pyran, dioxolane, tetrahydropyran, dioxane, dihydrothiophene, thiolan, dithiolan, pyrroline, pyrrolidine, pyrazoline, pyrazolidine, imidazoline, imidazolidine, tetrazole, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, tetrazine, morpholine, thiomorpholine, diazepan, oxazine, tetrahydro-oxazinyl, isothiazole and pyrazolidine, preferably pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl or tetrahydro-oxazinyl, while the heterocycle may optionally be substituted.

Generally, the term halogen denotes fluorine, chlorine, bromine or iodine.

The leaving group L denotes either identical or different leaving groups such as for example chlorine, bromine, iodine, methanesulphonyl, trifluoromethanesulphonyl or p-toluenesulphonyl, preferably chlorine.

The compounds of formula **1** may be present in the form of the individual optical isomers, mixtures of the individual enantiomers, diastereomers or racemates, in the form of the tautomers and also in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids. By acid addition salts of **1** with pharmacologically acceptable acids are meant for example salts selected from the group comprising the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate,

hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. Of the above-mentioned acid addition salts, the salts of hydrochloric acid, methanesulphonic acid, benzoic acid and acetic acid are particularly preferred according to the invention.

The substituent R^1 may denote a group selected from among hydrogen, NH_2, XH, preferably OH, halogen, preferably fluorine or chlorine and a C_1-C_3-alkyl group optionally substituted by one or more, preferably one, two or three halogen atoms, preferably fluorine or chlorine, preferably methyl or ethyl. Most preferably, the substituent R^1 is hydrogen .

The substituent R^2 may denote a group selected from among hydrogen, CHO, XH, preferably OH, -X-C_1-C_2-alkyl, preferably –O-CH_3 or –O-CH_2CH_3, and an optionally substituted C_1-C_3-alkyl group, while the alkyl group preferably consists of 1 to 2 carbon atoms, particularly preferably a carbon atom and may optionally be substituted, preferably by halogen atoms, most preferably by fluorine atoms. In particular, the substituent R^2 denotes methyl.

The substituents R^3 and R^4 may be identical or different and may represent a group selected from among optionally substituted C_1-C_{10}-alkyl, preferably C_1-C_6-alkyl, preferably C_1-C_4-alkyl, most preferably methyl, ethyl or propyl, particularly preferably methyl or ethyl, C_2-C_{10}-alkenyl, preferably ethenyl or propenyl, preferably ethenyl, C_2-C_{10}-alkynyl, preferably ethynyl or propynyl, aryl, preferably optionally substituted phenyl, heteroaryl, C_3-C_8-cycloalkyl, preferably cyclopropyl and cyclobutyl, C_3-C_8-heterocycloalkyl, -X-aryl, -X-heteroaryl, -X-cycloalkyl, -X-heterocycloalkyl, -NR^8-aryl, -NR^8-heteroaryl, -NR^8-cycloalkyl and -NR^8-heterocycloalkyl, or
a group selected from among hydrogen, halogen, $COXR^8$, $CON(R^8)_2$, COR^8 and XR^8, preferably hydrogen, or
the groups R^3 and R^4 may together denote a 2- to 5-membered alkyl bridge, preferably a propylene or butylene bridge which may contain 1 to 2 heteroatoms, preferably oxygen , nitrogen or sulphur . Most preferably, the substituent R^3 denotes hydrogen. The substituent R^4 most preferably denotes methyl. All the groups mentioned in the definition of R^3 and R^4 may optionally be substituted.

The group R^5 may contain hydrogen or a group selected from among optionally substituted C_1-C_{10}-alkyl, for example C_1-C_6-alkyl-aryl or C_1-C_6-alkyl-heteroaryl,

preferably C_1-C_6-alkyl, most preferably C_1-C_5-alkyl, particularly preferably propyl, butyl, pentyl, hexyl, -CH_2-cyclohexyl, $(CH_2)_{1-2}$cyclopropyl or $(CH_2)_4$-$OCOCH_3$, C_2-C_{10}-alkenyl, preferably propenyl, butenyl, pentenyl or hexenyl, preferably propenyl or hexenyl, C_2-C_{10}-alkynyl, preferably propynyl, butynyl or pentynyl, preferably propynyl, aryl, preferably phenyl, heteroaryl, -C_3-C_6-cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and -C_3-C_6-cycloalkenyl, preferably cyclohexenyl or cyclopentenyl, or the substituents
R^3 and R^5 or R^4 and R^5 together denote a saturated or unsaturated C_3-C_4-alkyl bridge which may contain 1 to 2 heteroatoms, preferably oxygen, sulphur or nitrogen.
All the groups mentioned in the definition of R^5 may optionally be substituted.

The substituent R^6 may denote optionally substituted aryl, or heteroaryl, preferably aryl, preferably phenyl.
Most preferably, the substituent R^6 denotes a phenyl group, which may be substituted by one of the groups R^9 and R^{10} described hereinafter, while the phenyl ring may carry one of the groups R^9, preferably in the *para* position, and one, two, three or four, preferably one or two, of the groups R^{10}, preferably in the *ortho* or *meta* position.

The substituent R^7 may denote hydrogen or -CO-X-C_1-C_4-alkyl, preferably hydrogen.

X denotes, in each case independently of one another, O or S, preferably O.

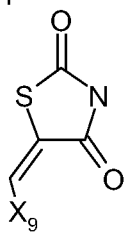
The groups R^8 mentioned in the definitions of the substituents R^3 and R^4 represent, independently of one another in each case, hydrogen or a group selected from among optionally substituted C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl and phenyl, preferably hydrogen or C_1-C_2-alkyl.

The substituent R^9 may represent a group selected from among optionally substituted C_1-C_6-alkyl, preferably C_1-C_4-alkyl, preferably methyl, ethyl or propyl, most preferably methyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, -CONH-C_1-C_{10}-alkylene, preferably -CONH-C_1-C_3-alkylene, preferably -CONH-C_1-C_2-alkylene, -O-aryl, preferably O-C_6-C_{10}-aryl, O-phenyl, -O-heteroaryl, -O-cycloalkyl, preferably O-C_3-C_6-cycloalkyl, O-cyclopropyl, -O-heterocycloalkyl, aryl, preferably C_6-C_{10}-aryl, phenyl, heteroaryl, cycloalkyl, preferably C_3-C_6-cycloalkyl, cyclopropyl, and heterocycloalkyl, or
a group selected from among -O-C_1-C_6-alkyl-Q^1, -$CONR^8$-C_1-C_{10}-alkyl-Q^1, -$CONR^8$-C_1-C_{10}-alkenyl-Q^1, -$CONR^8$-Q^2, halogen, for example fluorine, chlorine, bromine or iodine, OH, -SO_2R^8, -$SO_2N(R^8)_2$, -COR^8, -$COOR^8$, -$N(R^8)_2$, -$NHCOR^8$,

$CONR^8OC_1$-C_{10}-alkylQ^1 and $CONR^8OQ^2$, where Q^1 and Q^2 are as hereinbefore defined.

Preferably, R^9 denotes one of the following groups -CONH-C_1-C_{10}-alkyl, preferably -CONH-C_1-C_3-alkyl, most preferably -CONH-C_1-C_2-alkyl, while this alkyl may itself optionally be substituted, by CN, optionally substituted aryl, preferably optionally substituted phenyl, heteroaryl, preferably thienyl, thiazolyl, imidazolyl, pyridyl, pyrimidyl or pyrazinyl, saturated or unsaturated heterocycloalkyl, preferably pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl or tetrahydro-oxazinyl, an amine group, preferably methylamine, benzylamine, phenylamine or heteroarylamine, saturated or unsaturated bicyclic ring systems, preferably benzimidazolyl and cycloalkyl, preferably cyclohexyl.

Moreover R^9 preferably denotes -CONH-heteroaryl, preferably -CONH-pyridyl, -CONH-C_3-C_{10}-cycloalkyl, preferably -CONH-cyclopentyl, -CONH-C_6-C_{10}-aryl, preferably –CONH-phenyl, COO-C_1-C_3-alkyl, preferably $COOCH_3$, COOH, halogen, preferably F or chlorine, OH or a group of formula

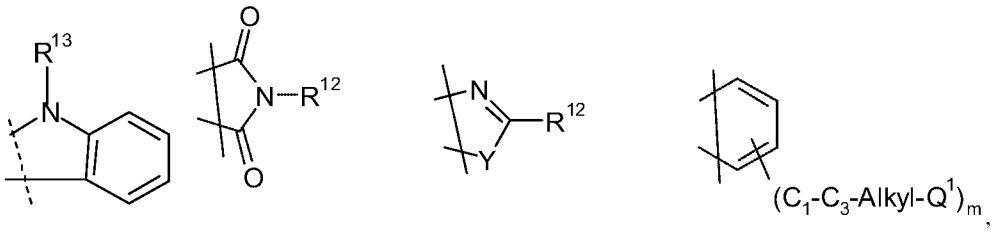


All the groups mentioned in the definition of R^9 may optionally be substituted, preferably by one or more of the groups selected from among OH, OCH_3, Cl, F, CH_3, COOH, $CONHCH_2Ph$ and $CONHCH_2$-pyrazinyl-CH_3.

The substituent R^{10} may be identical or different in each case and may denote a group selected from among optionally substituted C_1-C_6-alkyl , preferably C_1-C_3-alkyl, C_2-C_6-alkenyl, preferably C_2-C_3-alkenyl and C_2-C_6-alkynyl, preferably C_2-C_3-alkynyl, -O-C_1-C_6-alkyl, preferably –O-C_1-C_3-alkyl, -O-C_2-C_6-alkenyl, -O-C_2-C_6-alkynyl, C_3-C_6-heterocycloalkyl and C_3-C_6-cycloalkyl, or a group selected from among hydrogen, $-CONH_2$, $-COOR^8$, $-OCON(R^8)_2$, $-N(R^8)_2$, $-NHCOR^8$, $-NHCON(R^8)_2$, $-NO_2$ and halogen, for example fluorine, chlorine, bromine or iodine.

Preferably, the substituent R^{10} denotes hydrogen, fluorine or chlorine, most preferably hydrogen.

Adjacent groups R^9 and R^{10} may together denote a bridge of general formula



wherein

Y denotes O, S or NR^{11}, preferably NR^{11},

m denotes 0, 1 or 2, preferably 1 ,

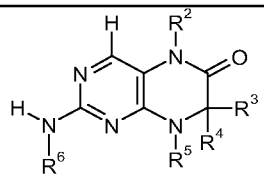
R^{11} denotes hydrogen or C_1-C_2-alkyl, preferably hydrogen or methyl, most preferably hydrogen,

R^{12} denotes hydrogen or a group selected from among optionally substituted phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, -C_1-C_3-alkyl-phenyl, -C_1-C_3-alkyl-pyridyl, -C_1-C_3-alkyl-pyrazinyl, -C_1-C_3-alkyl-pyrimidinyl and -C_1-C_3-alkyl-pyridazinyl, preferably phenyl, pyridyl and pyrazinyl, and

R^{13} denotes C_1-C_6-alkyl, preferably methyl or ethyl.

The compounds according to the invention may be prepared by synthesis methods described in WO 03/020722.

Of particular interest according to the invention is the use of a compound according to formula **1** for the preparation of a medicament for the treatment respiratory diseases, preferably for the treatment of one or several respiratory diseases mentioned herein before, wherein the compound of formula **1** is selected from the group of compounds exemplified in the following table:



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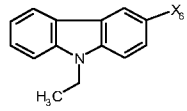
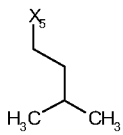
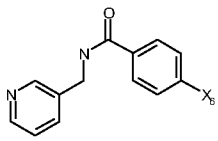
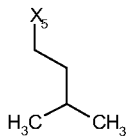
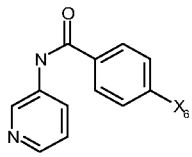
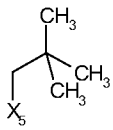
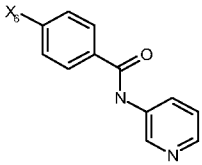
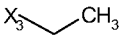
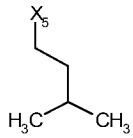
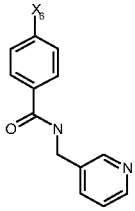
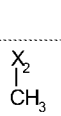
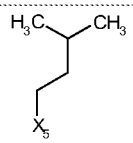
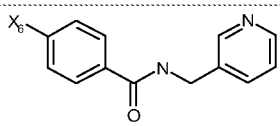
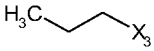
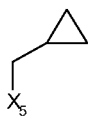
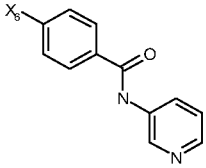
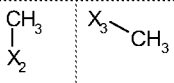
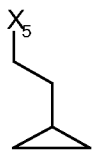
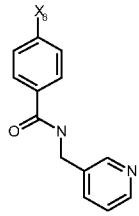
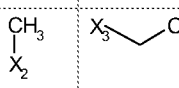
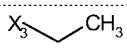
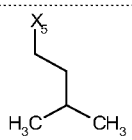
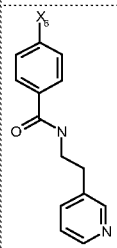
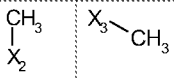
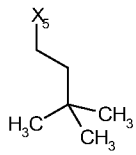
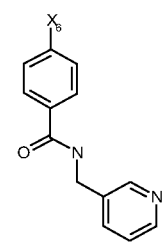
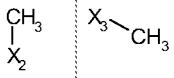
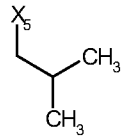
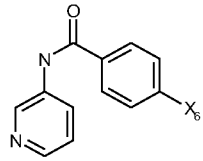
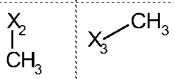
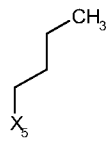
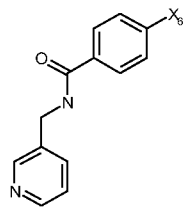
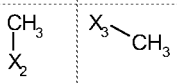
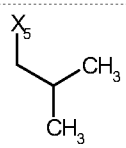
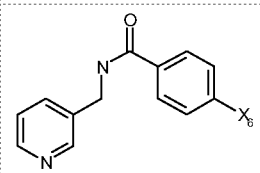
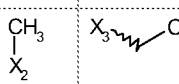
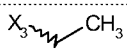
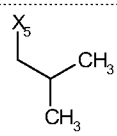
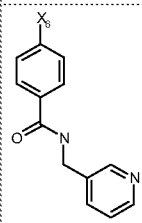
1		H	H	rac.			
2			H	rac.			208
3			H	rac.			241
4			H	rac.			
5			H	rac.			175
6			H	R			190
7			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
8			H	rac.			200
9			H	rac.			168
10			H	rac.			190
11			H	rac.			
12			H	rac.			
13			H	rac.			145
14			H	rac.			

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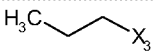
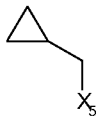
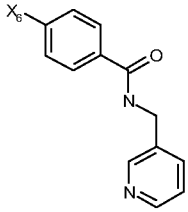
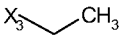
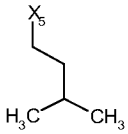
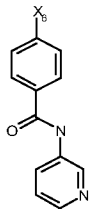
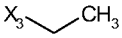
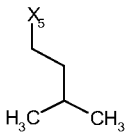
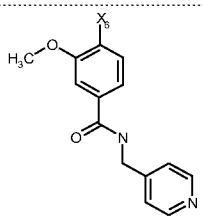
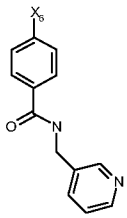
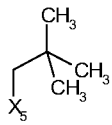
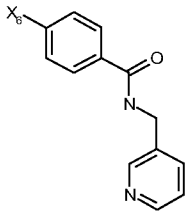
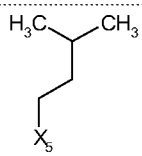
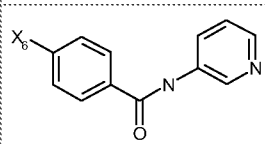
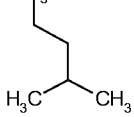
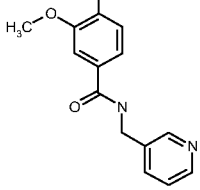
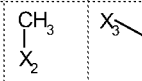
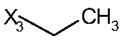
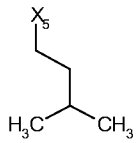
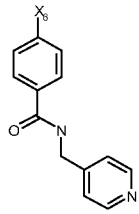
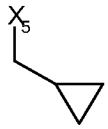
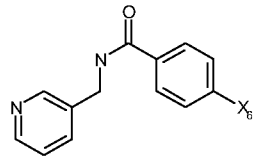
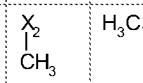
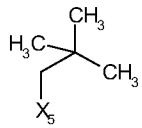
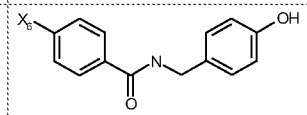
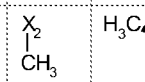
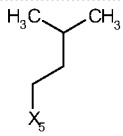
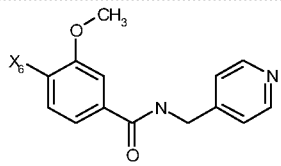
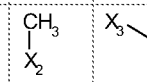
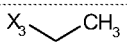
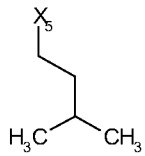
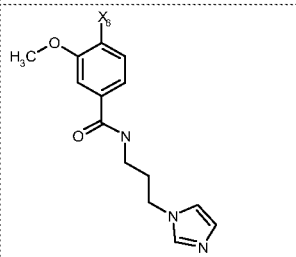
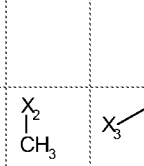
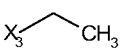
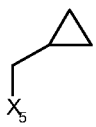
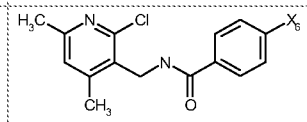
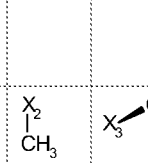
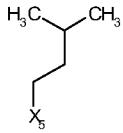
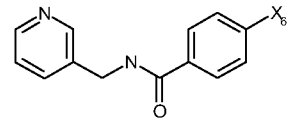
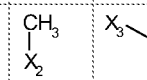
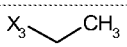
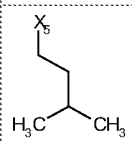
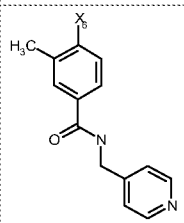
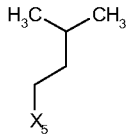
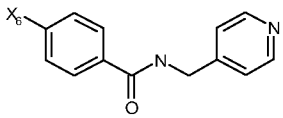
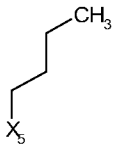
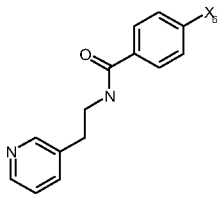
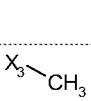
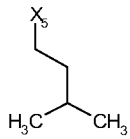
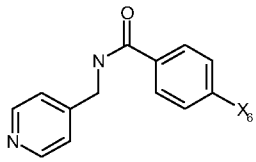
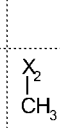
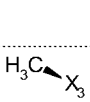
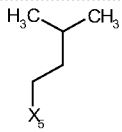
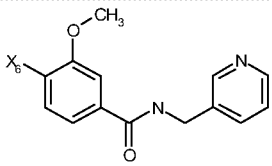
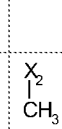
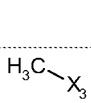
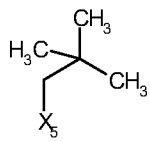
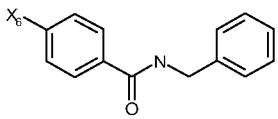
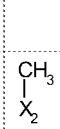
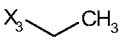
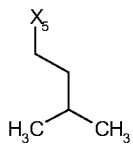
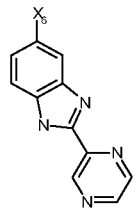
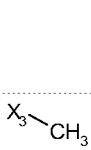
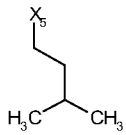
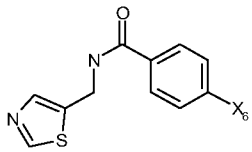
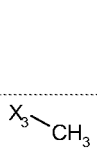
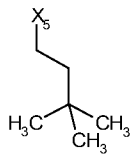
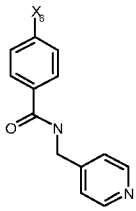
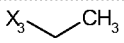
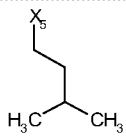
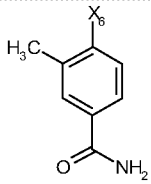
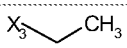
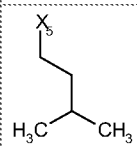
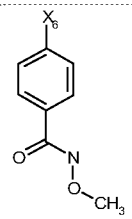
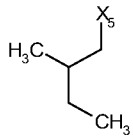
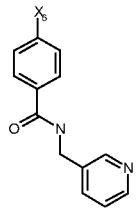
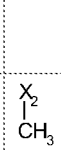
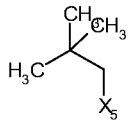
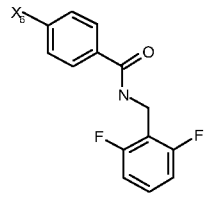
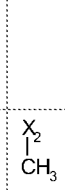
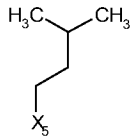
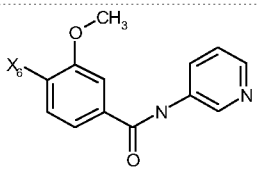
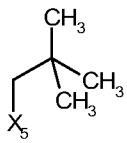
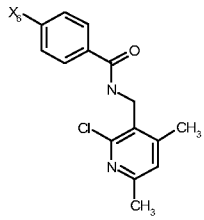
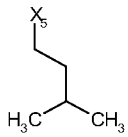
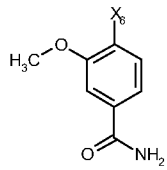
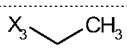
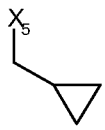
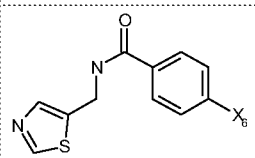
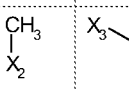
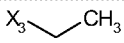
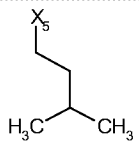
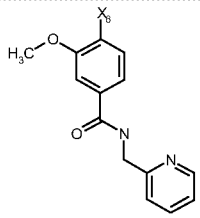
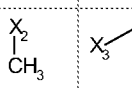
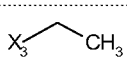
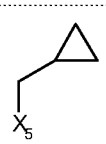
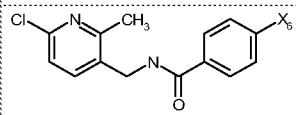
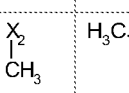
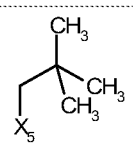
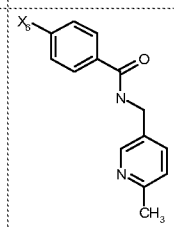
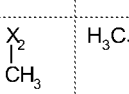
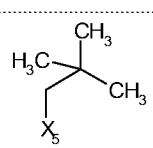
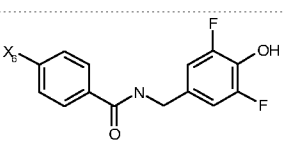
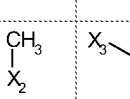
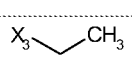
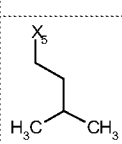
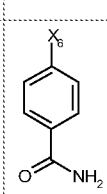
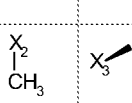
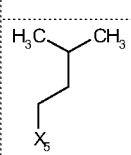
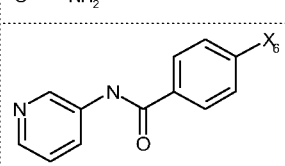
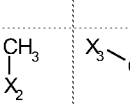
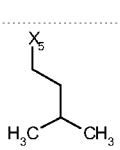
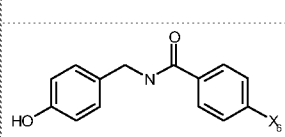
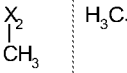
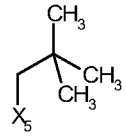
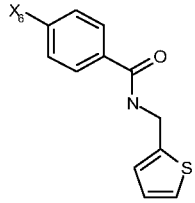
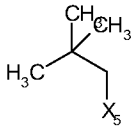
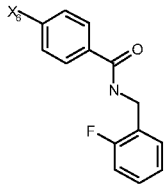
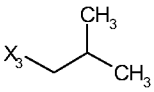
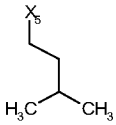
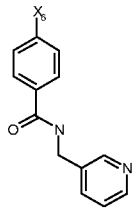
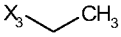
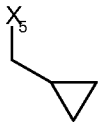
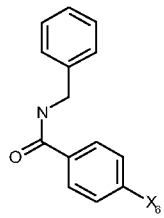
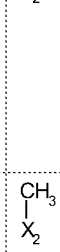
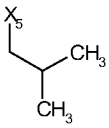
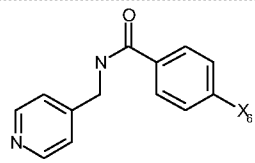
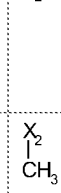
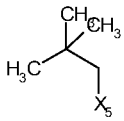
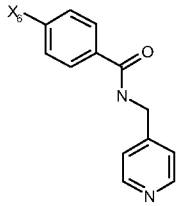
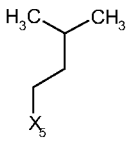
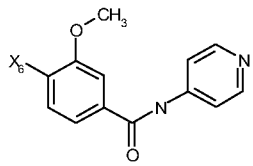
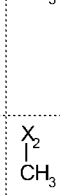
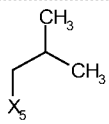
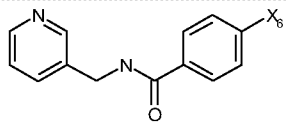
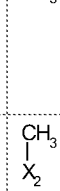
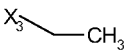
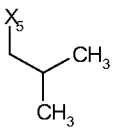
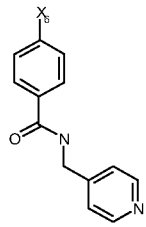
15			H	rac.			55
16			H	rac.			250
17			H	rac.			204
18			H	rac.			
19			H	rac.			
20			H	R			221
21			H	rac.			172

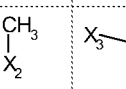
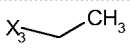
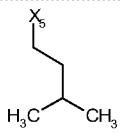
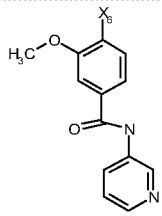
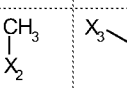
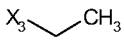
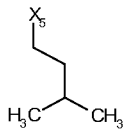
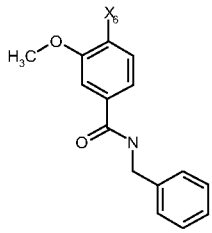
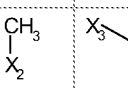
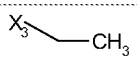
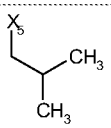
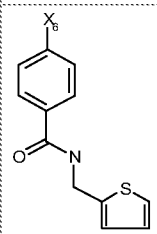
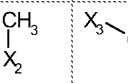
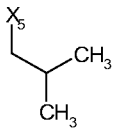
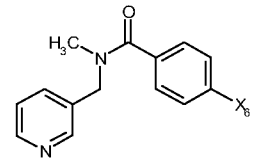
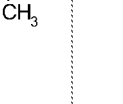
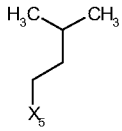
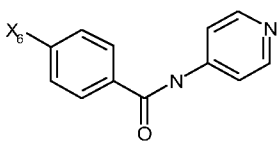
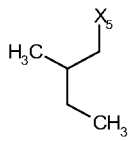
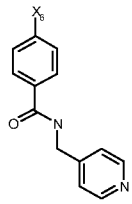
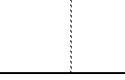
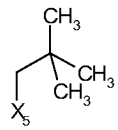
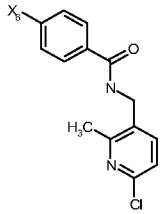
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
22			H	rac.			221
23			H	rac.			
24			H	rac.			210
25			H	R			213
26			H	rac.			188
27			H	rac.			
28			H	S			
29			H	rac.			178

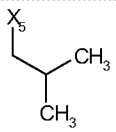
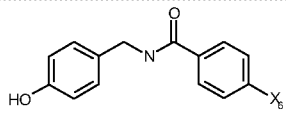
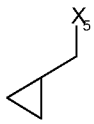
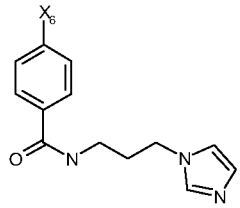
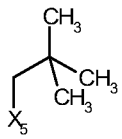
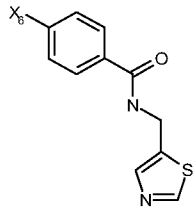
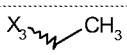
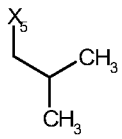
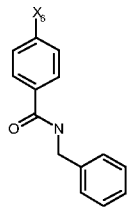
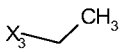
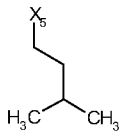
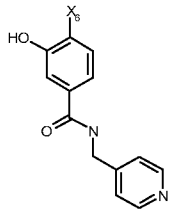
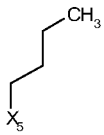
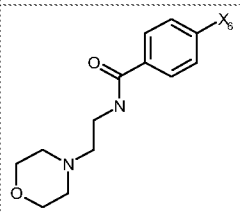
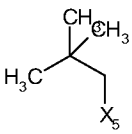
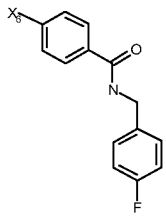
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
30			H	R			175
31			H	rac.			
32			H	rac.			221
33			H	R			124
34			H	rac.			136
35			H	rac.			162
36			H	rac.			169
37			H	rac.			219

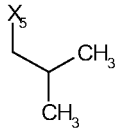
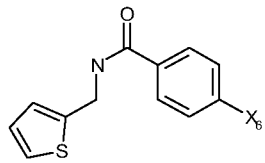
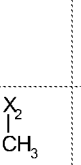
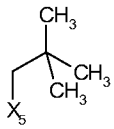
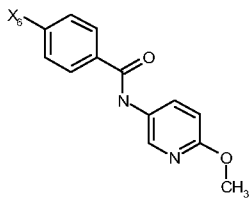
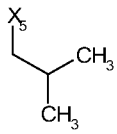
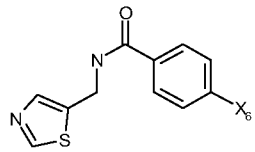
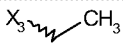
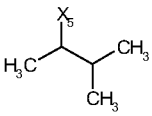
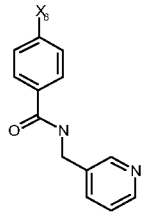
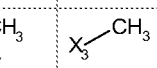
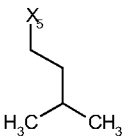
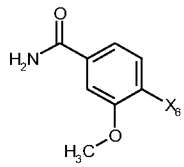
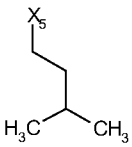
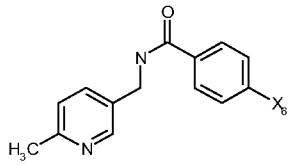
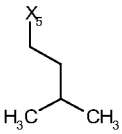
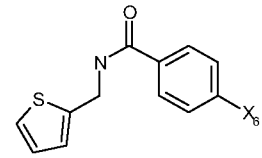
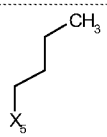
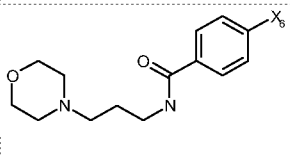
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
38			H	rac.			179
39			H	rac.			211
40			H	rac.			
41			H	rac.			
42			H	R			100
43			H	rac.			175
44			H	rac.			203
45			H	rac.			165

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
46			H	rac.			
47			H	rac.			
48			H	rac.			
49			H	rac.			
50			H	rac.			212
51			H	S			
52			H	rac.			
53			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
54			H	rac.			
55			H	rac.			191
56			H	rac.			158
57			H	rac.			230
58			H	rac.			
59			H	R			125
60		H	H	rac.			250
61			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
62			H	rac.			169
63			H	rac.			178
64			H	rac.			
65			H	rac.			
66			H	R			225
67			H	rac.			
68			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
69			H	rac.			
70			H	rac.			
71			H	rac.			
72			H	rac.			
73			H	rac.			
74			H	rac.			
75			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
76			H	rac.			246
77			H	rac.			
78			H	rac.			172
79			H	rac.			170
80				rac.			222
81			H	rac.			187
82			H	rac.			215
83			H	rac.			

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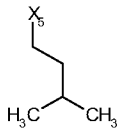
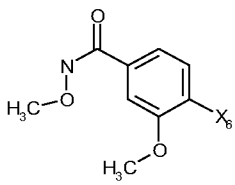
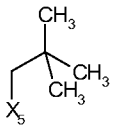
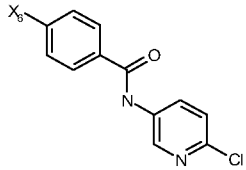
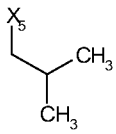
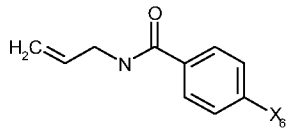
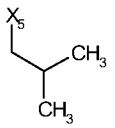
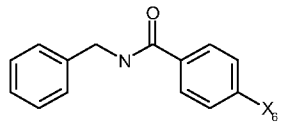
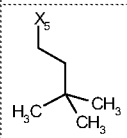
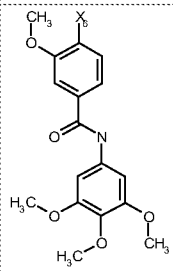
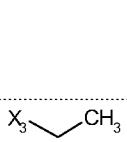
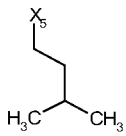
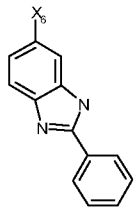
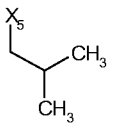
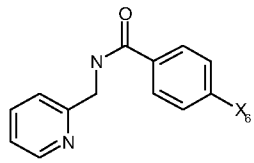
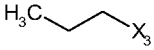
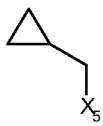
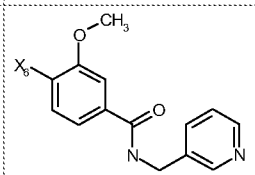
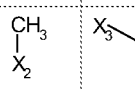
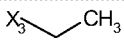
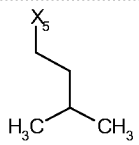
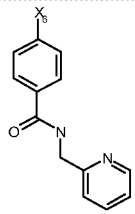
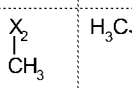
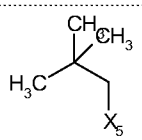
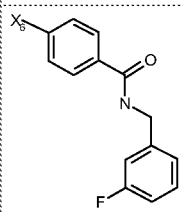
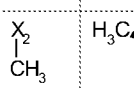
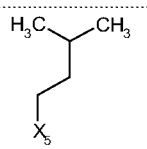
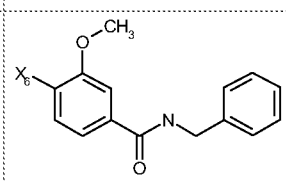
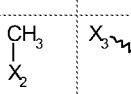
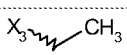
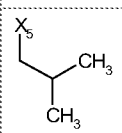
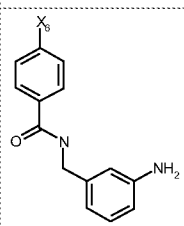
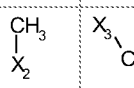
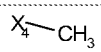
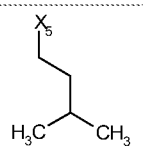
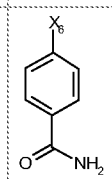
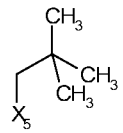
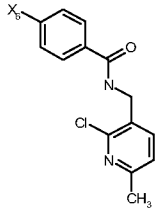
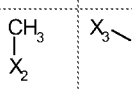
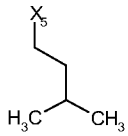
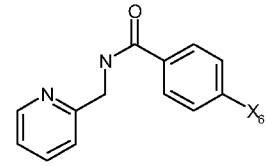
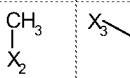
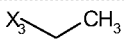
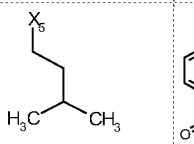
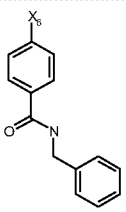
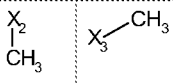
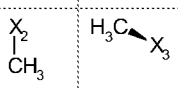
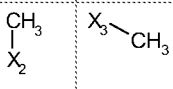
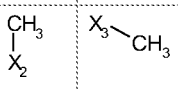
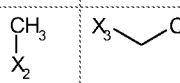
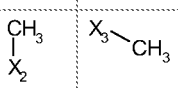
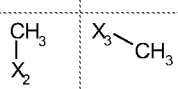
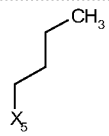
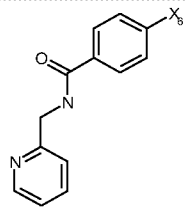
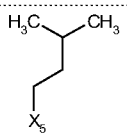
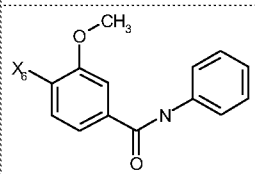
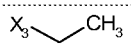
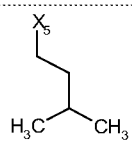
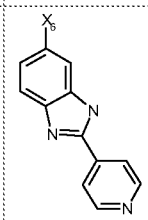
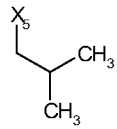
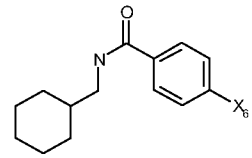
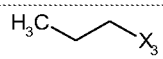
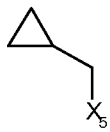
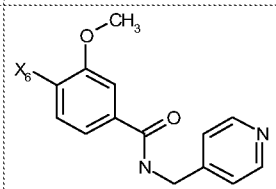
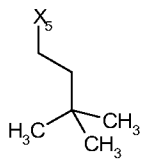
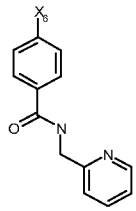
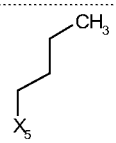
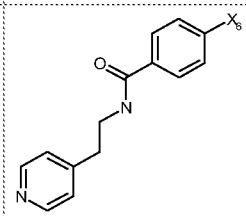
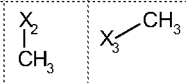
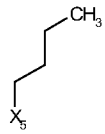
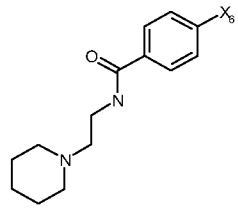
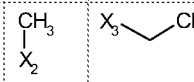
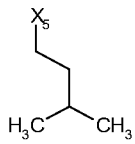
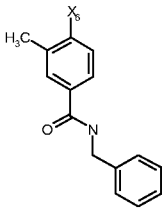
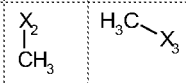
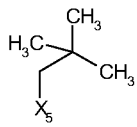
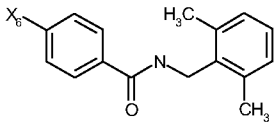
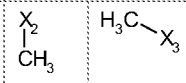
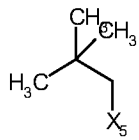
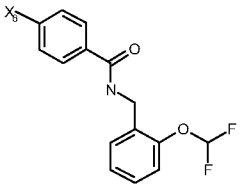
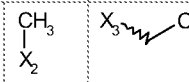
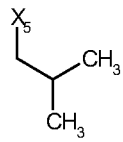
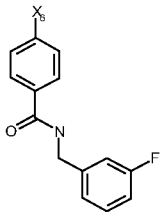
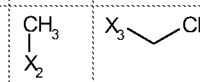
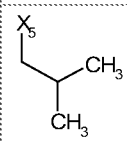
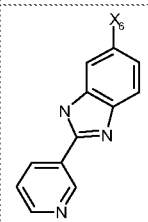
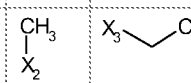
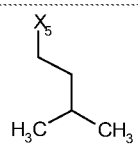
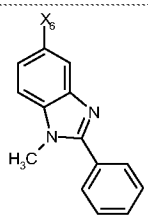
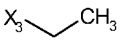
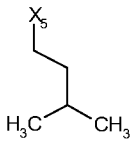
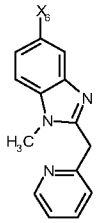
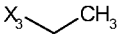
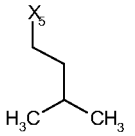
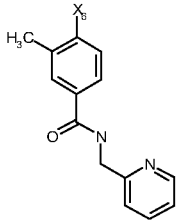
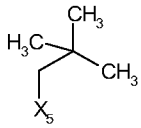
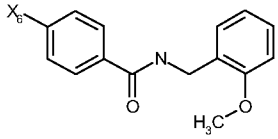
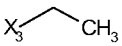
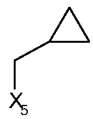
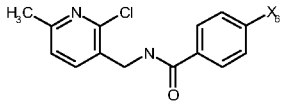
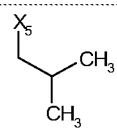
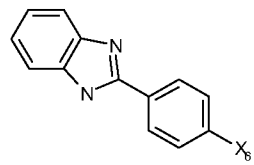
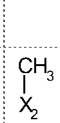
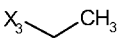
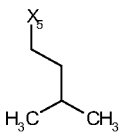
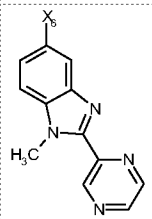
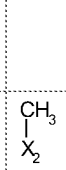
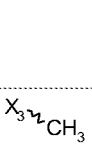
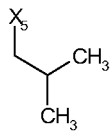
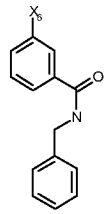
84				rac.			127
85			H	rac.			
86			H	rac.			169
87			H	rac.			250
88			H	rac.			233
89			H	rac.			160
90			H	rac.			154
91			H	rac.			

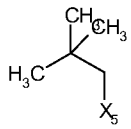
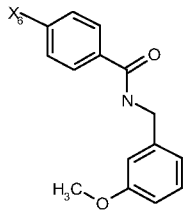
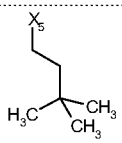
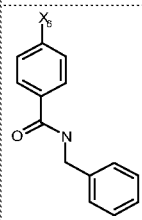
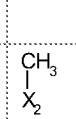
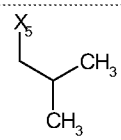
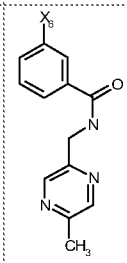
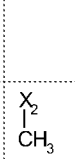
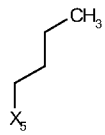
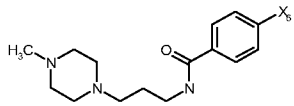
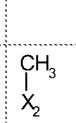
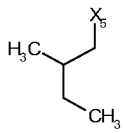
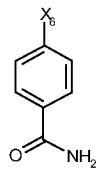
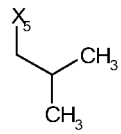
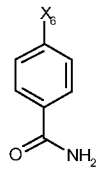
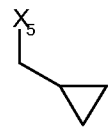
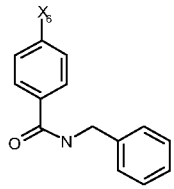
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
92			H	rac.			
93			H	rac.			
94			H	R			
95			H	rac.			150
96				rac.			300
97			H	rac.			243
98			H	rac.			209
99			H	rac.			182

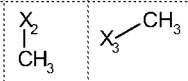
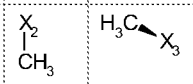
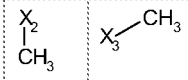
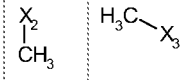
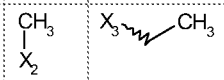
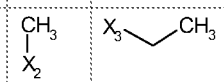
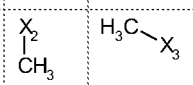
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
100			H	rac.			
101			H	R			232
102			H	rac.			
103			H	rac.			
104			H	rac.			146
105			H	rac.			209
106			H	rac.			286

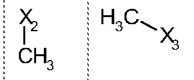
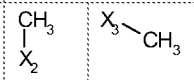
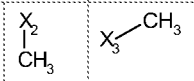
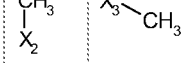
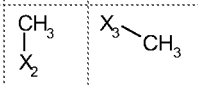
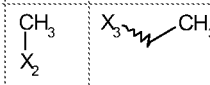
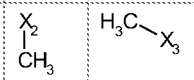
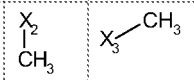
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
107			H	rac.			
108			H	R			202
109			H	rac.			180
110			H	rac.			
111			H	rac.			250
112			H	rac.			
113			H	rac.			

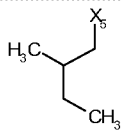
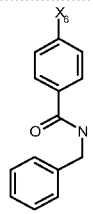
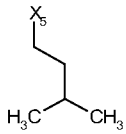
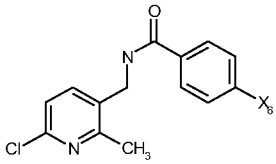
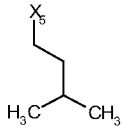
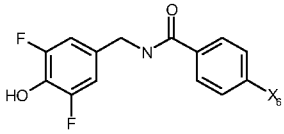
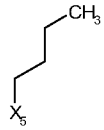
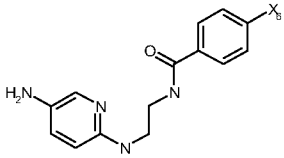
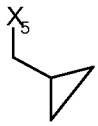
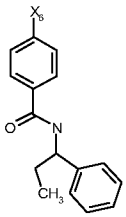
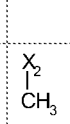
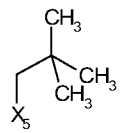
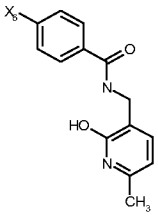
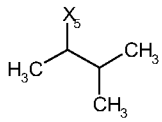
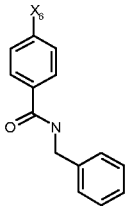
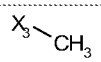
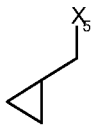
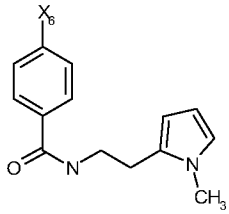
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
114			H	rac.			
115			H	rac.			135
116			H	rac.			
117			H	rac.			
118			H	rac.			
119			H	rac.			213
120			H	rac.			198

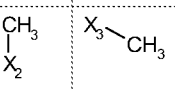
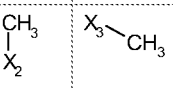
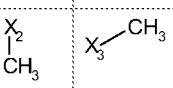
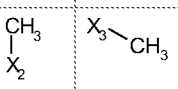
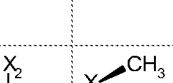
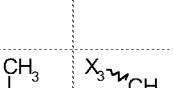
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
121			H	rac.			
122			H	rac.			
123			H	rac.			
124			H	rac.			
125			H	rac.			287
126			H	rac.			195
127			H	rac.			

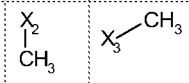
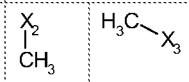
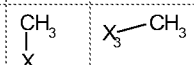
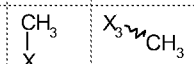
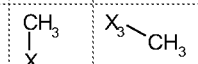
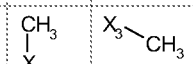
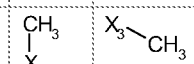
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
128			H	rac.			
129			H	rac.			247
130			H	rac.			
131			H	rac.			
132			H	rac.			
133			H	rac.			
134			H	rac.			208

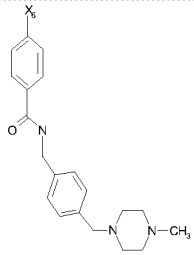
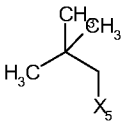
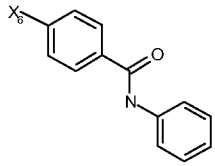
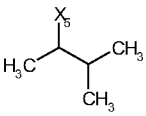
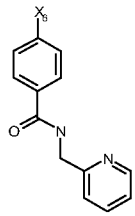
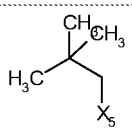
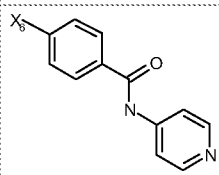
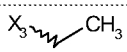
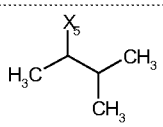
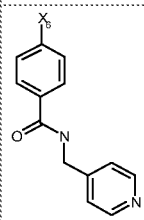
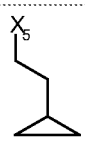
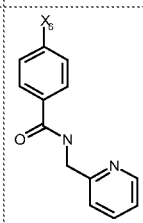
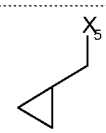
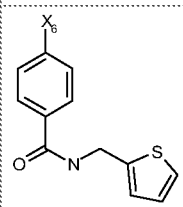
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
135			H	rac.			
136			H	R			192
137			H	rac.			212
138			H	rac.			
139			H	rac.			
140			H	rac.			148
141			H	rac.			

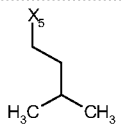
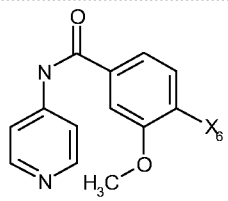
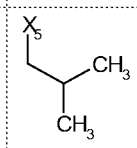
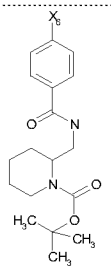
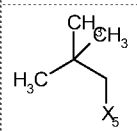
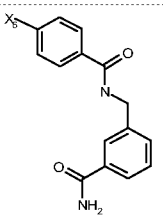
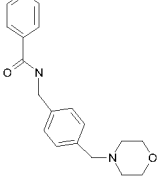
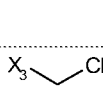
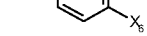
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
142			H	rac.			
143			H	rac.			186
144			H	rac.			
145			H	rac.			214
146			H	rac.			155
147			H	rac.			
148			H	rac.			
149			H	rac.			245

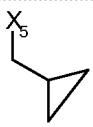
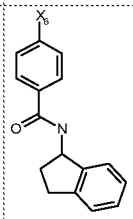
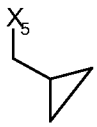
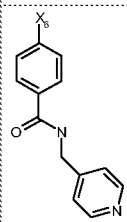
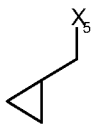
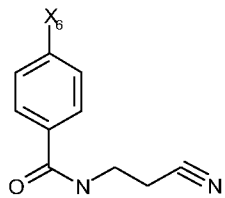
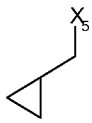
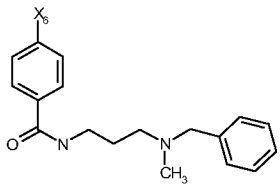
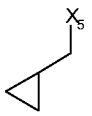
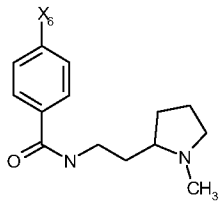
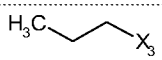
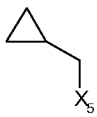
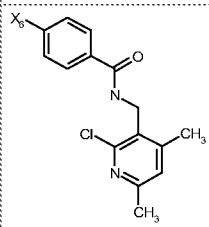
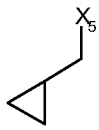
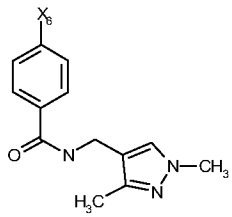
Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
150			H	rac.			
151			H	rac.			
152			H	rac.			
153			H	rac.			
154			H	rac.			
155			H	rac.			
156			H	rac.			265
157			H	rac.			192

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
158			H	rac.			222
159			H	rac.			221
160			H	rac.			187
161			H	rac.			181
162			H	S			
163			H	rac.			
164			H	rac.			227
165			H	rac.			258

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
166			H	rac.			
167			H	rac.			
168				rac.			159
169			H	rac.			
170			H	rac.			213
171			H	rac.			228
172			H	rac.			181

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
173			H	rac.			182
174			H	rac.			
175			H	rac.			197
176			H	rac.			
177			H	rac.			216
178			H	rac.			200
179			H	rac.			197

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
180				rac.			143
181			H	rac.			
182			H	rac.			
183			H	rac.			169
184			H	rac.			
185			H	rac.			198
186			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
187			H	rac.			200
188			H	rac.			
189			H	rac.			198
190			H	rac.			
191			H	rac.			184
192			H	rac.			
193			H	rac.			201

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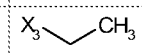
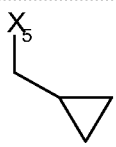
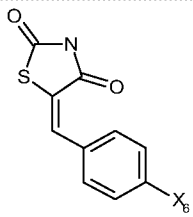
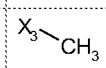
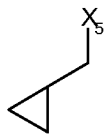
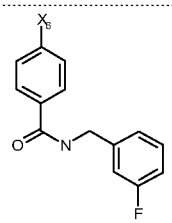
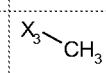
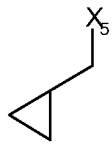
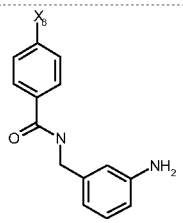
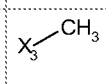
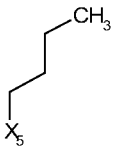
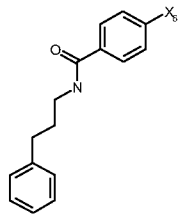
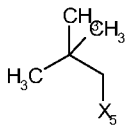
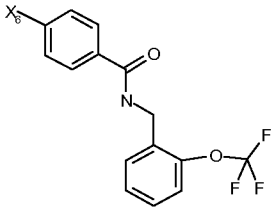
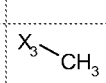
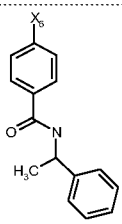
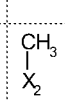
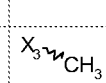
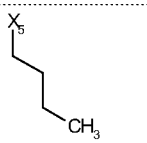
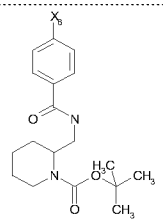
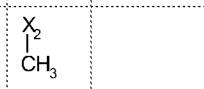
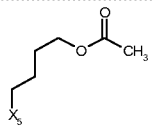
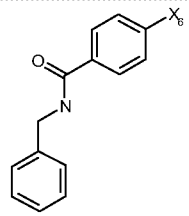
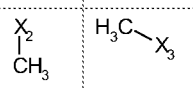
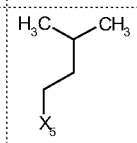
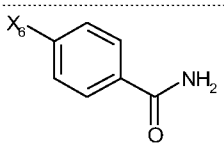
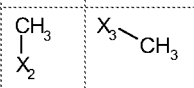
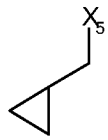
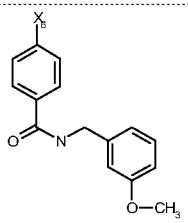
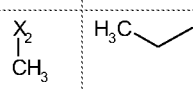
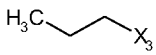
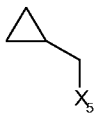
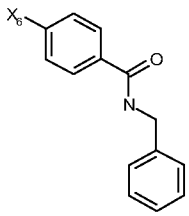
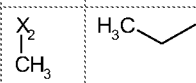
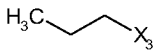
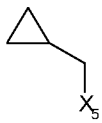
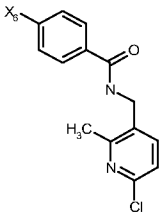
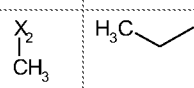
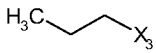
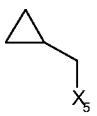
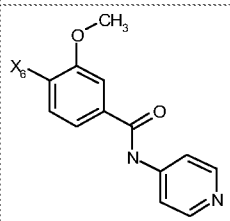
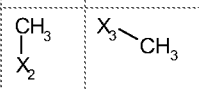
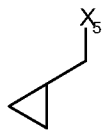
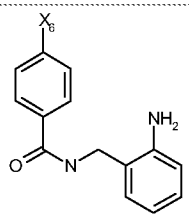
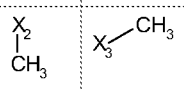
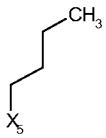
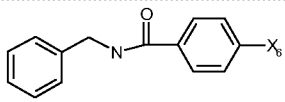
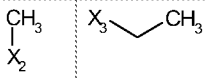
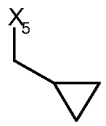
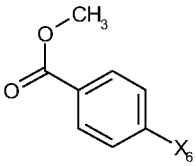
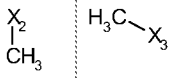
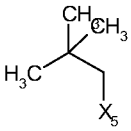
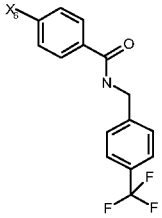
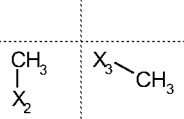
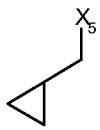
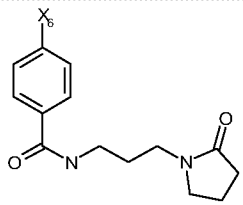
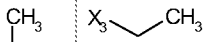
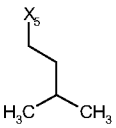
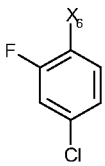
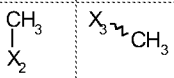
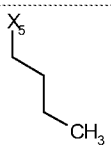
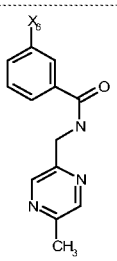
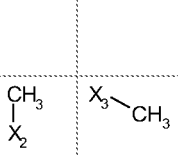
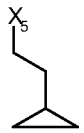
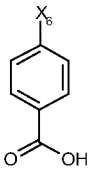
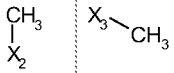
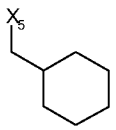
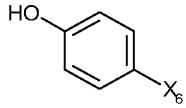
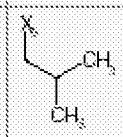
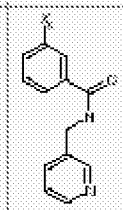
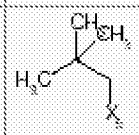
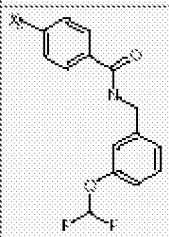
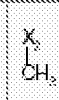
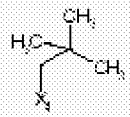
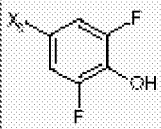
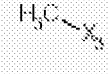
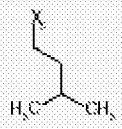
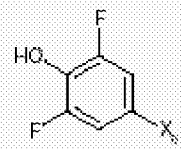
194			H	rac.			250
195			H	rac.			198
196			H	rac.			245
197			H	rac.			
198			H	rac.			
199			H	rac.			
200			H	rac.			

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
201		H	H	rac.			
202			H	rac.			
203			H	rac.			198
204			H	rac.			
205			H	rac.			
206			H	rac.			
207			H	rac.			184

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C
208			H	rac.			253
209			H	rac.			240
210			H	rac.			
211			H	rac.			150
212			H	rac.			
213			H	rac.			
214			H	rac.			
215			H	rac.			232

Ex.	R^2	R^3	R^4	Config. R^3 or R^4	R^5	R^6	mp.[°C]
216			H	rac.			
217			H	rac.			
218			H	rac.			>250
219			H	rac.			260 (desco mp.)
In the preceding Table the abbreviations X^1 to X^6 in the groups specified denote the bond which links the group in question to the corresponding group R1 to R6.							

The compounds of general formula **1** may be used on their own or combined with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances.

In another preferred embodiment the invention relates to medicament combinations which contain in addition to one or more, preferably one compound of formula **1** a second active ingredient **2** which is selected from the group consisting of betamimetics (**2a**), anticholinergics (**2b**), PDEIV-inhibitors (**2c**), steroids (**2d**), LTD4 antagonists (**2e**), EGFR-inhibitors (**2f**), 5-lipoxygenase inhibitors (**2g**), and anti-IgE monoclonal antibodies (**2h**) optionally together with a pharmaceutically acceptable excipient.

Within the instant application the term betamimetic is optionally also replaced by the term beta$_2$- agonist. According to the instant invention preferred beta$_2$ agonists **2a** in the combinations according to the invention are selected from the group consisting of albuterol (**2a.1**), bambuterol (**2a.2**), bitolterol (**2a.3**), broxaterol (**2a.4**), carbuterol

(2a.5), clenbuterol (2a.6), fenoterol (2a.7), formoterol (2a.8), hexoprenaline (2a.9), ibuterol (2a.10), isoetharine (2a.11), isoprenaline (2a.12), levosalbutamol (2a.13), mabuterol (2a.14), meluadrine (2a.15), metaproterenol (2a.16), orciprenaline (2a.17), pirbuterol (2a.18), procaterol (2a.19), reproterol (2a.20), TD 3327 (2a.21), ritodrine (2a.22), salmeterol (2a.23), salmefamol (2a.24), soterenot (2a.25), sulphonterol (2a.26), tiaramide (2a.27), terbutaline (2a.28), tolubuterol (2a.29), CHF-4226 (= TA 2005 or carmoterol; 2a.30), HOKU-81 (2a.31), KUL-1248 (2a.32), 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide (2a.33) , 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one (2a.34) , 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone (2a.35), 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol (2a.36), 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol (2a.37), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol (2a.38), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol (2a.39), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol (2a.40), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol (2a.41), 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one (2a.42), 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert.-butylamino)ethanol (2a.43), 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol (2a.44), and N-[2-Hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide (2a.45), optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

According to the instant invention more preferred beta$_2$ agonists 2a in the combinations according to the invention are selected from the group consisting of bambuterol (2a.2), bitolterol (2a.3), carbuterol (2a.5), clenbuterol (2a.6), fenoterol (2a.7), formoterol (2a.8), hexoprenaline (2a.9), ibuterol (2a.10), pirbuterol (2a.18), procaterol (2a.19), reproterol (2a.20), TD 3327 (2a.21), salmeterol (2a.23), sulphonterol (2a.26), terbutaline (2a.28), tolubuterol (2a.29), CHF-4226 (= TA 2005 or carmoterol; 2a.30), 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide (2a.33), 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one (2a.34), 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone (2a.35), 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-

butylamino]ethanol (**2a.36**), 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol (**2a.37**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol (**2a.38**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol (**2a.39**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol (**2a.40**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol (**2a.41**), 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one (**2a.42**), 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert.-butylamino)ethanol (**2a.43**), 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol (**2a.44**), and N-[2-Hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide (**2a.45**), optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

More preferably, the betamimetics **2a** used as within the compositions according to the invention are selected from the group consisting of fenoterol (**2a.7**), formoterol (**2a.8**), salmeterol (**2a.23**), CHF-4226 (= TA 2005 or carmoterol; **2a.30**), 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide (**2a.33**), 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one (**2a.34**), 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol (**2a.37**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol (**2a.38**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol (**2a.39**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol (**2a.40**), 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol (**2a.41**), and N-[2-Hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide (**2a.45**), optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof. Of the betamimetics mentioned above the compounds formoterol (**2a.8**), salmeterol (**2a.23**), CHF-4226 (= TA 2005 or carmoterol; **2a.30**), 3-(4-{6-[2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulfoneamide (**2a.33**), 5-[2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one are (**2a.34**), and N-[2-Hydroxy-5-(1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide (**2a.45**), particularly preferred, optionally in the form of the racemates, the enantiomers, the

diastereomers and optionally the pharmacologically acceptable acid addition salts thereof, and the hydrates thereof.

Examples of pharmacologically acceptable acid addition salts of the betamimetics **2a** according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid, 5-(2.4-difluorophenyl)salicylic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts **2a**.

According to the invention, the salts of the betamimetics **2a** selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate, 4-phenylcinnamate, 5-(2.4-difluorophenyl)salicylate, maleate and xinafoate are preferred. Particularly preferred are the salts of **2a** in the case of salmeterol selected from among the hydrochloride, sulphate, 4-phenylcinnamate, 5-(2.4-difluorophenyl)salicylate and xinafoate, of which the 4-phenylcinnamate, 5-(2.4-difluorophenyl)salicylate and especially xinafoate are particularly important. Particularly preferred are the salts of **2a** in the case of formoterol selected from the hydrochloride, sulphate, hemifumarate and fumarate, of which the hydrochloride, hemifumarate and fumarate are particularly preferred. Of exceptional importance according to the invention is formoterol fumarate dihydrate or formoterol hemifumarate hydrate.

Any reference to the term betamimetics **2a** also includes a reference to the relevant enantiomers or mixtures thereof.

In the pharmaceutical compositions according to the invention, the compounds **2a** may be present in the form of their racemates, enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.) If the compounds **2a** are used in the form of their enantiomers, it is particularly preferable to use the enantiomers in the R configuration at the C-OH group. If the compounds **2a** possess 2 chiral carbon atoms they are preferably used in the form of their pure diastereomers, particularly in the form of those diasteromers that possess R configuration at the C-OH group. An example may be R,R-formoterol.

In the medicament combinations according to the invention the anticholinergic **2b** is preferably selected from among the tiotropium salts (**2b.1**), oxitropium salts (**2b.2**),

flutropium salts (2b.3), ipratropium salts (2b.4), glycopyrronium salts (2b.5), trospium salts (2b.6) and the compounds of formulae 2b.7 to 2b.13.

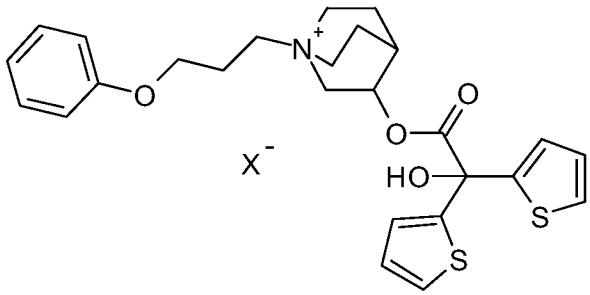
In the above-mentioned salts 2b.1 to 2b.6 the cations tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium and trospium are the pharmacologically active constituents. Explicit references to the above-mentioned cations are indicated by the numerals 2b.1' to 2b.6'. Each reference to the above-mentioned salts 2b.1 to 2b.6 naturally includes a reference to the corresponding cations tiotropium (2b.1'), oxitropium (2b.2'), flutropium (2b.3'), ipratropium (2b.4'), glycopyrronium (2b.5') and trospium (2b.6').

By the salts 2b.1 to 2b.6 are meant according to the invention those compounds which contain in addition to the cations tiotropium (2b.1'), oxitropium (2b.2'), flutropium (2b.3'), ipratropium (2b.4'), glycopyrronium (2b.5') and trospium (2b.6') as counter-ion (anion) chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate contain, while the chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts the chloride, bromide, iodide and methanesulphonate are particularly preferred.
In the case of the trospium salts (2b.6) the chloride is particularly preferred. Of the other salts 2b.1 to 2b.5 the methanesulphonates and bromides are of particular importance.
Of particular importance are medicament combinations which contain tiotropium salts (2b.1), oxitropium salts (2b.2) or ipratropium salts (2b.4), while the respective bromides are particularly important according to the invention. Of particular importance is the tiotropium bromide (2b.1). The above-mentioned salts may optionally be present in the medicament combinations according to the invention in the form of their solvates or hydrates, preferably in the form of their hydrates. In the case of tiotropium bromide the medicament combinations according to the invention preferably contain this in the form of the crystalline tiotropium bromide monohydrate, which is known from WO 02/30928. If the tiotropium bromide is used in anhydrous form in the medicament combinations according to the invention, it is preferable to use the anhydrous crystalline tiotropium bromide which is known from WO 03/000265.

The above-mentioned anticholinergics optionally have chiral carbon centres. In this case the medicament combinations according to the invention may contain the anticholinergics in the form of their enantiomers, mixtures of enantiomers or

racemates, while enantiomerically pure anticholinergics as for instance R,R-glycopyrrolate (**2b.5**) are preferably used .

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the salts of formula **2b.7**



2b.7

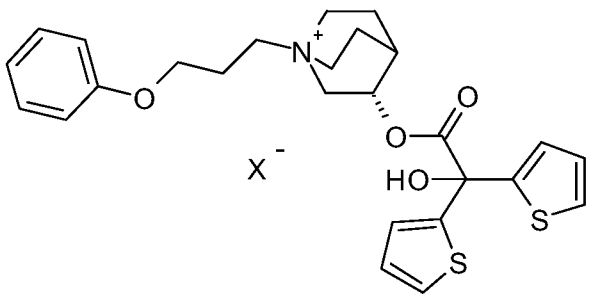
wherein

X^- denotes an anion with a single negative charge, preferably an anion selected from among the fluoride, chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate,

optionally in the form of the racemates, enantiomers or hydrates thereof.

Particularly preferred medicament combinations contain the compound of formula **2b.7** in the form of the bromide.

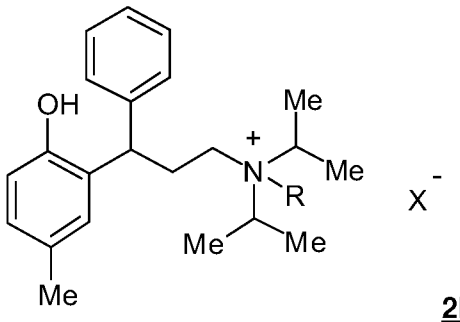
Of particular importance are those medicament combinations which contain the enantiomers of formula **2b.7-en**



2b.7-en

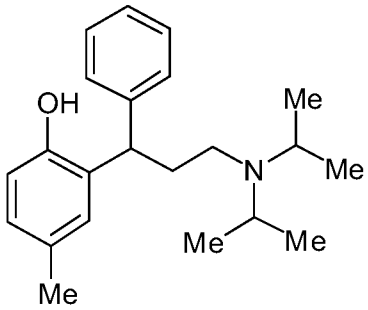
wherein X^- may have the above-mentioned meanings.

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the salts of formula **2b.8**



2b.8

wherein R denotes either methyl (**2b.8.1**) or ethyl (**2b.8.2**) and wherein X^- may have the above-mentioned meanings. In an alternative embodiment the compound of formula **2b.8** is present in the form of the free base **2b.8-base**



2b.8-base

The medicament combinations according to the invention may contain the anticholinergic of formula **2b.8** (or **2b.8-base**) in the form of the enantiomers, mixtures of enantiomers or racemates thereof . Preferably the anticholinergics of formula **2b.8** (or **2b.8-base**) are present in the form of their R-enantiomers.

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the group consisting of

- tropenol 2,2-diphenylpropionate methobromide (**2b.9.1**),
- scopine 2,2-diphenylpropionate methobromide (**2b.9.2**),
- scopine 2-fluoro-2,2-diphenylacetate methobromide (**2b.9.3**),
- tropenol 2-fluoro-2,2-diphenylacetate methobromide (**2b.9.4**);

These compounds may optionally be present in the form of the enantiomers, mixtures of enantiomers or racemates thereof, as well as optionally in the form of the hydrates and/or solvates thereof.
The aforementioned compounds are known in the art (WO 02/32899).

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the group consisting of

- tropenol 3,3',4,4'-tetrafluorobenzilate methobromide (**2b.10.1**),
- scopine 3,3',4,4'-tetrafluorobenzilate methobromide (**2b.10.2**),
- tropenol 4,4'-difluorobenzilate methobromide (**2b.10.3**),
- scopine 4,4'-difluorobenzilate methobromide (**2b.10.4**),
- tropenol 3,3'-difluorobenzilate methobromide (**2b.10.5**),
- scopine 3,3'-difluorobenzilate methobromide (**2b.10.6**).

These compounds may optionally be present in the form of the enantiomers, mixtures of enantiomers or racemates thereof, as well as optionally in the form of the hydrates and/or solvates thereof. The aforementioned compounds are known in the art (WO 02/32898).

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the group consisting of

- tropenol 9-hydroxy-fluorene-9-carboxylate methobromide (**2b.12a.1**);
- tropenol 9-fluoro-fluorene-9-carboxylate methobromide (**2b.12a.2**) ;
- scopine 9-hydroxy-fluorene-9-carboxylate methobromide (**2b.12a.3**) ;
- scopine 9-fluoro-fluorene-9-carboxylate methobromide (**2b.12a.4**) ;
- tropenol 9-methyl-fluorene-9-carboxylate methobromide (**2b.12a.5**) ;
- scopine 9-methyl-fluorene-9-carboxylate methobromide (**2b.12a.6**) ;

These compounds may optionally be present in the form of the enantiomers, mixtures of enantiomers or racemates thereof, as well as optionally in the form of the hydrates and/or solvates thereof. The aforementioned compounds are known in the art (WO 03/064419).

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the group consisting of

- cyclopropyltropine benzilate methobromide (**2b.12b.1**);
- cyclopropyltropine 2,2-diphenylpropionate methobromide (**2b.12b.2**);
- cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide (**2b.12b.3**);
- cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide (**2b.12b.4**);
- cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide (**2b.12b.5**);
- cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide (**2b.12b.6**);
- cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide (**2b.12b.7**).

In another preferred embodiment of the present invention the anticholinergics **2b** contained in the medicament combinations according to the invention are selected from the group consisting of

- tropenol 9-hydroxy-xanthene-9-carboxylate methobromide (**2b.12c.1**);
- scopine 9-hydroxy-xanthene-9-carboxylate methobromide (**2b.12c.2**);
- tropenol 9-methyl-xanthene-9-carboxylate methobromide (**2b.12c.3**);
- scopine 9-methyl-xanthene-9-carboxylate methobromide (**2b.12c.4**);
- tropenol 9-ethyl-xanthene-9-carboxylate methobromide (**2b.12c.5**);
- tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide (**2b.12c.6**);
- scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide (**2b.12c.7**).

These compounds may optionally be present in the form of the enantiomers, mixtures of enantiomers or racemates thereof, as well as optionally in the form of the hydrates and/or solvates thereof. The aforementioned compounds are known in the art (WO 03/064418).

The compounds of formula **2b.13** may optionally be present in the form of the enantiomers, mixtures of enantiomers or racemates thereof, as well as optionally in the form of the hydrates and/or solvates thereof.

Within the scope of the present invention any reference to anticholinergics **2b'** is to be taken as a reference to the pharmacologically active cations of the various salts. These cations are for instance tiotropium (**2b.1'**), oxitropium (**2b.2'**), flutropium (**2b.3'**), ipratropium (**2b.4'**), glycopyrronium (**2b.5'**), trospium (**2b.6'**).

In the medicament combinations according to the invention the PDE IV-inhibitor **2c** is preferably selected from among enprofyllin (**2c.1**), theophyllin (**2c.2**), roflumilast (**2c.3**), ariflo (Cilomilast, **2c.4**)), CP-325,366 (**2c.5**), BY343 (**2c.6**), D-4396 (Sch-351591, **2c.7**)), AWD-12-281 (GW-842470, **2c.8**)), N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide (**2c.9**), NCS-613 (**2c.10**), pumafentine (**2c.11**), (-)p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide (**2c.12**), (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone (**2c.13**), 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone (**2c.14**), cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] (**2c.15**), 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one (**2c.16**), cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol] (**2c.17**), (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate

(**2c.18**), (S)-(-)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate(**2c.19**), 4-(3-cyclopentyloxy-4-methoxy-phenyl)-3-(1-hydroxy-ethyl)-3-methyl-pyrrolidine-1-carboxylic acid methyl ester (=IC 485, **2c.20**), CDP840 (**2c.21**), Bay-198004 (**2c.22**), D-4418 (**2c.23**), PD-168787 (**2c.24**), T-440 (**2c.25**), T-2585 (**2c.26**), arofyllin (**2c.27**), atizoram (**2c.28**), V-11294A (**2c.29**), Cl-1018 (**2c.30**), CDC-801 (**2c.31**), CDC-3052 (**2c.32**), D-22888 (**2c.33**), YM-58997 (**2c.34**), Z-15370 (**2c.35**), 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine (**2c.36**), 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(*tert*-butyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine (**2c.37**), and tetomilast (**2c.38**), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

In particularly preferred medicament combinations the PDE IV-inhibitor **2c** is selected from the group comprising enprofyllin (**2c.1**), roflumilast (**2c.3**) optionally also in form of the roflumilast N-oxide, ariflo (cilomilast) (**2c.4**), AWD-12-281 (GW-842470) (**2c.8**), N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxy benzamide (**2c.9**), T-440 (**2c.25**), T-2585 (**2c.26**), cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid] (**2c.15**), 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one (**2c.16**), cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol] (**2c.17**), 4-(3-cyclopentyloxy-4-methoxy-phenyl)-3-(1-hydroxy-ethyl)-3-methyl-pyrrolidine-1-carboxylic acid methyl ester (=IC 485, **2c.20**), PD-168787 (**2c.24**), arofyllin (**2c.27**), atizoram (**2c.28**), V-11294A (**2c.29**), Cl-1018 (**2c.30**), CDC-801 (**2c.31**), D-22888 (**2c.33**), YM-58997 (**2c.34**), Z-15370 (**2c.35**), 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine (**2c.36**), 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(*tert*-butyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine (**2c.37**), and tetomilast (**2c.38**), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

In particularly preferred medicament combinations the PDE IV-inhibitor **2c** is selected from the group comprising roflumilast (**2c.3**), ariflo (cilomilast) (**2c.4**), AWD-12-281 (GW-842470) (**2c.8**), 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one (**2c.16**), cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol] (**2c.17**), 4-(3-cyclopentyloxy-4-methoxy-phenyl)-3-(1-hydroxy-ethyl)-3-methyl-pyrrolidine-1-carboxylic acid methyl ester (=IC 485, **2c.20**), arofyllin (**2c.27**), atizoram (**2c.28**), Z-15370 (**2c.35**), 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-

a]pyridine (**2c.36**), 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(*tert*-butyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine (**2c.37**), and tetomilast (**2c.38**), while roflumilast (**2c.3**), Z-15370 (**2c.35**) and AWD-12-281 (**2c.8**) are of particular significance, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

By the acid addition salts with pharmacologically acceptable acids which the compounds **2c** may possibly be capable of forming are meant for example salts selected from the group comprising the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Other preferred medicament combinations according to the invention contain as an additional active substance, in addition to one or more, preferably one compound **1** , one or more, preferably one steroid **2d**, optionally in combination with pharmaceutically acceptable excipients.

In such medicament combinations the steroid **2d** is preferably selected from among prednisolone (**2d.1**), prednisone (**2d.2**), butixocortpropionate (**2d.3**), RPR-106541 (**2d.4**), flunisolide (**2d.5**), beclomethasone (**2d.6**), triamcinolone (**2d.7**), budesonide (**2d.8**), fluticasone (**2d.9**), mometasone (**2d.10**), ciclesonide (**2d.11**), rofleponide (**2d.12**), ST-126 (**2d.13**), dexamethasone (**2d.14**), (S)-fluoromethyl 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothionate (**2d.15**), (S)-(2-oxo-tetrahydro-furan-3S-yl)6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothionate (**2d.16**) and etiprednol-dichloroacetate (BNP-166, **2d.17**), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

In particularly preferred medicament combinations the steroid **2d** is selected from the group comprising flunisolide (**2d.5**), beclomethasone (**2d.6**), triamcinolone (**2d.7**), budesonide (**2d.8**), fluticasone (**2d.9**), mometasone (**2d.10**), ciclesonide (**2d.11**), rofleponide (**2d.12**), ST-126 (**2d.13**), dexamethasone (**2d.14**), (S)-fluoromethyl 6α,9α-difluoro-17? -[(2-furanylcarbonyl)oxy]-11β-hydroxy-16? -methyl-3-oxo-androsta-1,4-diene-17β-carbothionate (**2d.15**), (S)-(2-oxo-tetrahydro-furan-3S-

yl)6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothionate (**2d.16**) and etiprednol-dichloroacetate (**2d.17**), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

In particularly preferred medicament combinations the steroid **2d** is selected from the group comprising budesonide (**2d.8**), fluticasone (**2d.9**), mometasone (**2d.10**), ciclesonide (**2d.11**), (S)-fluoromethyl 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothionate (**2d.15**) and etiprednol-dichloroacetate (**2d.17**), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

Any reference to steroids **2d** includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids **2d** may be: alkali metal salts, such as for example sodium or potassium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

Other preferred medicament combinations according to the invention contain, as an additional active substance, in addition to one or more, preferably one compound **1** , one or more, preferably one, LTD4 antagonist **2e**, optionally in combination with pharmaceutically acceptable excipients.

In such medicament combinations the LTD4 antagonist **2e** is preferably selected from among montelukast (**2e.1**), 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl) phenyl)-3-(2-(2- hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid (**2e.2**), 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropanacetic acid (**2e.3**), pranlukast (**2e.4**), zafirlukast (**2e.5**), [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]-oxymethyl]-phenyl]acetic acid (**2e.6**), MCC-847 (ZD-3523) (**2e.7**), MN-001 (**2e.8**), MEN-91507 (LM-1507) (**2e.9**), VUF-5078 (**2e.10**), VUF-K-8707 (**2e.11**) and L-733321 (**2e.12**), optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof as well as optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

In preferred medicament combinations the LTD4 antagonist **2e** is selected from the group comprising montelukast (**2e.1**), pranlukast (**2e.4**), zafirlukast (**2e.5**), MCC-847

(ZD-3523) (**2e.7**), MN-001 (**2e.8**), MEN-91507 (LM-1507) (**2e.9**), VUF-5078 (**2e.10**), VUF-K-8707 (**2e.11**) and L-733321 (**2e.12**), optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof as well as optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

In particularly preferred medicament combinations the LTD4 antagonist **2e** is selected from the group comprising montelukast (**2e.1**), pranlukast (**2e.4**), zafirlukast (**2e.5**), MCC-847 (ZD-3523) (**2e.7**), MN-001 (**2e.8**) and MEN-91507 (LM-1507) (**2e.9**), while montelukast (**2e.1**), pranlukast (**2e.4**) and zafirlukast (**2e.5**) are particularly preferred, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof as well as optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

By the acid addition salts with pharmacologically acceptable acids which the compounds **2e** may possibly be capable of forming are meant for example salts selected from the group comprising the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.
Examples of possible salts and derivatives which the compounds **2e** may possibly be capable of forming include for example: alkali metal salts, such as for example sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

Other preferred medicament combinations according to the invention contain, as an additional active substance, in addition to one or more, preferably one compound **1** , one or more, preferably one, EGFR-inhibitor **2f**, optionally in combination with pharmaceutically acceptable excipients.

In such medicament combinations the EGFR-inhibitor **2f** is selected for example from the group comprising 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-

dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(*R*)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(*S*)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((*S*)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(*R*)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(*R*)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*R*)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((*S*)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(*R*)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(*S*)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(*R*)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-

[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy- quinazoline, 4-[(3-chloro-4-fluoro-

phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-

methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, cetuximab, trastuzumab, ABX-EGF and Mab ICR-62, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

In such medicament combinations the EGFR-inhibitor **2f** is preferably selected from among the 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-

phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-

fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-

methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and cetuximab, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Particularly preferably, the EGFR-inhibitors **2f** used within the scope of the medicament combinations according to the invention are selected from the group comprising 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-

methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Particularly preferred medicament combinations according to the invention contain as EGFR-inhibitors **2f** those compounds which are selected from the group comprising

- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-cyclopropylmethoxy-quinazoline (**2f.1**),

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline (**2f.2**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline (**2f.3**),
- 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline (**2f.4**),
- 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline (**2f.5**),
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline (**2f.6**),
- 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline (**2f.7**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline (**2f.8**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline (**2f.9**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline (**2f.10**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline (**2f.11**),
- 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline (**2f.12**),
- 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline (**2f.13**),
- 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline (**2f.14**),
- 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline (**2f.15**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline (**2f.16**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline (**2f.17**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline (**2f.18**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline (**2f.19**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline (**2f.20**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline (**2f.21**),

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline (**2f.22**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline (**2f.23**),
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline (**2f.24**) and
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline (**2f.25**),

optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

By the acid addition salts with pharmacologically acceptable acids which the compounds **2f** may possibly be capable of forming are meant for example salts selected from the group comprising the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Other preferred medicament combinations according to the invention contain, as an additional active substance, in addition to one or more, preferably one compound **1** , one or more, preferably one, 5-lipoxygenase inhibitor **2g**, optionally in combination with pharmaceutically acceptable excipients. A preferred 5-lipoxygenase inhibitor **2g** is zileuton, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Other preferred medicament combinations according to the invention contain, as an additional active substance, in addition to one or more, preferably one compound **1** , one or more, preferably one, anti-IgE monoclonal antibody **2h**, optionally in combination with pharmaceutically acceptable excipients. A preferred anti-IgE monoclonal antibody **2h** is omalizumab.

In a yet another preferred embodiment the invention relates to medicament combinations comprising beside a compound of formula **1** two other active ingredients selected from the classes of compounds mentioned hereinbefore.

Particularly preferred combinations which contain two other active substances in addition to a compound of formula **1** are selected from the active substance combinations listed below . These are medicament combinations which may contain, for example :

1) compound **1**, a betamimetic **2a**, an anticholinergic **2b**;
2) compound **1**, a betamimetic **2a**, a PDEIV inhibitor **2c**;
3) compound **1**, a betamimetic **2a**, a steroid **2d**;
4) compound **1**, a betamimetic **2a**, a LTD4 antagonist **2e**;
5) compound **1**, a betamimetic **2a**, an EGFR inhibitor **2f**;
6) compound **1**, a betamimetic **2a**, a 5-lipoxygenase inhibitor **2g**;
7) compound **1**, a betamimetic **2a**, an anti-IgE monoclonal antibody **2h**;
8) compound **1**, an anticholinergic **2b**, a PDEIV inhibitor **2c**;
9) compound **1**, an anticholinergic **2b**, a steroid **2d**;
10) compound **1**, an anticholinergic **2b**, a LTD4 antagonist **2e**;
11) compound **1**, an anticholinergic **2b**, an EGFR inhibitor **2f**;
12) compound **1**, an anticholinergic **2b**, a 5-lipoxygenase inhibitor **2g**;
13) compound **1**, an anticholinergic **2b**, an anti-IgE monoclonal antibody **2h**;
14) compound **1**, a PDEIV inhibitor **2c**, a steroid **2d**;
15) compound **1**, a PDEIV inhibitor **2c**, a LTD4 antagonist **2e**;
16) compound **1**, a PDEIV inhibitor **2c**, an EGFR inhibitor **2f**;
17) compound **1**, a PDEIV inhibitor **2c**, a 5-lipoxygenase inhibitor **2g**;
18) compound **1**, a PDEIV inhibitor **2c**, an anti-IgE monoclonal antibody **2h**;
19) compound **1**, a steroid **2d**, a LTD4 antagonist **2e**;
20) compound **1**, a steroid **2d**, an EGFR inhibitor **2f**;
21) compound **1**, a steroid **2d**, a 5-lipoxygenase inhibitor **2g**;
22) compound **1**, a steroid **2d**, an anti-IgE monoclonal antibody **2h**;
23) compound **1**, a LTD4 antagonist **2e**, an EGFR inhibitor **2f**;
24) compound **1**, a LTD4 antagonist **2e**, a 5-lipoxygenase inhibitor **2g**;
25) compound **1**, a LTD4 antagonist **2e**, an anti-IgE monoclonal antibody **2h**;
26) compound **1**, an EGFR inhibitor **2f**, a 5-lipoxygenase inhibitor **2g**;
27) compound **1**, an EGFR inhibitor **2f**, an anti-IgE monoclonal antibody **2h**;
28) compound **1**, a 5-lipoxygenase inhibitor **2g**, an anti-IgE monoclonal antibody **2h**.

In a preferred embodiment the medicament combinations according to the invention contain as the betamimetic **2a** one or more, preferably one compound selected from the group consisting of **2a.8**, **2a.23**, **2a.30**, **2a.33**, **2a.34**, and **2a.45** more preferably selected from among **2a.30**, **2a.33**, and **2a.34**.

In a yet another preferred embodiment the medicament combinations according to the invention contain as the anticholinergic **2b** one or more, preferably one compound selected from the group consisting of **2b.1**, **2b.4**, **2b.5**, **2b.7**, **2b.9.1**, **2b.9.2**, **2b.12b.1** and **2b.12b.2**, more preferably selected from among **2b.1**, **2b.5**, **2b.7**, **2b.9.1** and **2b.9.2**.

In a yet another preferred embodiment the medicament combinations according to the invention contain as the PDE IV inhibitor **2c** one or more, preferably one compound selected from among **2c.3**, **2c.8,** and **2c.35**.

In a yet another preferred embodiment the medicament combinations according to the invention contain as steroid **2d** one of the compounds **2d.5**, **2d.6**, **2d.7**, **2d.8**, **2d.9**, **2d.10**, **2d.11**, **2d.12**, **2d.13**, **2d.14**, **2d.15**, **2d.16** or **2d.17** , while those combinations which contain one of the compounds **2d.8**, **2d.9**, **2d.10**, **2d.11**, **2d.15** or **2d.17** are particularly important according to the invention.

In a yet another preferred embodiment the medicament combinations according to the invention contain as compound **2e** one of the compounds **2e.1**, **2e.4**, **2e.5**, **2e.7**, **2e.8**, **2e.9**, **2e.10**, **2e.11** or **2e.12**, while those combinations which contain one of the compounds **2e.1**, **2e.4**, **2e.5**, **2e.7**, **2e.8** or **2e.9** are particularly important according to the invention, and those combinations which contain one of the compounds **2e.1**, **2e.4** or **2e.5** are of exceptional importance.

In a yet another preferred embodiment the medicament combinations according to the invention contain as compound **2f** one of the compounds **2f.1**, **2f.2**, **2f.3**, **2f.4**, **2f.10**, **2f.11**, **2f.14**, **2f.16**, **2f.17**, **2f.18**, **2f.19**, **2f.20**, **2f.21**, **2f.22**, **2f.23**, **2f.24** or **2f.25** , while those combinations which contain one of the compounds **2f.2**, **2f.3** or **2f.4** are particularly important according to the invention.

Within the scope of the present invention by a pharmaceutical combination of components **1** and **2** is meant the joint administration of the active substances in a single preparation or formulation or the separate administration of the active substances in separate formulations. If the active substances are administered in separate formulations, this separate administration may be done simultaneously or at different times, i.e. successively.

In one aspect the present invention relates to the above-mentioned medicament combinations which contain in addition to therapeutically effective amounts of **1**, optionally also **2** and a pharmaceutically acceptable carrier. In one aspect the

present invention relates to the above-mentioned pharmaceutical compositions which do not contain a pharmaceutically acceptable carrier in addition to therapeutically effective amounts of **1** and **2**.

The present invention also relates to the use of therapeutically effective amounts of the active substances **1** for preparing a pharmaceutical composition also containing one or more, preferably one active substance **2** for the treatment of inflammatory and obstructive respiratory complaints, for inhibiting premature labour in midwifery (tocolysis), for restoring sinus rhythm in the heart in atrioventricular block, for correcting bradycardic heart rhythm disorders (antiarrhythmic), for treating circulatory shock (vasodilatation and increasing the heart volume) as well as for the treatment of skin irritations and inflammation .

In a preferred aspect the present invention relates to the use of therapeutically effective amounts of the active substance **1** for preparing a pharmaceutical composition also containing one or more, preferably one, active substance **2** for the treatment of respiratory complaints selected from the group comprising obstructive pulmonary diseases of various origins, pulmonary emphysema of various origins, restrictive pulmonary diseases, interstitial pulmonary diseases, cystic fibrosis, bronchitis of various origins, bronchiectasis, ARDS (adult respiratory distress syndrome) and all forms of pulmonary oedema.

Preferably the medicament combinations according to the invention are used as specified above for preparing a pharmaceutical composition for the treatment of obstructive pulmonary diseases selected from among bronchial asthma, paediatric asthma, severe asthma, acute asthma attacks, chronic bronchitis and COPD (chronic obstructive pulmonary disease), while it is particularly preferable according to the invention to use them for preparing a pharmaceutical composition for the treatment of bronchial asthma and COPD.

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of pulmonary emphysema which has its origins in COPD (chronic obstructive pulmonary disease) or α1-proteinase inhibitor deficiency.

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of restrictive pulmonary diseases selected from among allergic alveolitis, restrictive pulmonary diseases triggered by work-related noxious substances, such as asbestosis or silicosis, and

restriction caused by lung tumours, such as for example lymphangiosis carcinomatosa, bronchoalveolar carcinoma and lymphomas.

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of interstitial pulmonary diseases selected from among pneumonia caused by infections, such as for example infection by viruses, bacteria, fungi, protozoa, helminths or other pathogens, pneumonitis caused by various factors, such as for example aspiration and left heart insufficiency, radiation-induced pneumonitis or fibrosis, collagenoses, such as for example lupus erythematodes, systemic sclerodermy or sarcoidosis, granulomatoses, such as for example Boeck's disease, idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis (IPF).

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of cystic fibrosis or mucoviscidosis.

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of bronchitis, such as for example bronchitis caused by bacterial or viral infection, allergic bronchitis and toxic bronchitis.

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of bronchiectasis.

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of ARDS (adult respiratory distress syndrome).

It is also preferable to use the medicament combinations according to the invention for preparing a pharmaceutical composition for the treatment of pulmonary oedema, for example toxic pulmonary oedema after aspiration or inhalation of toxic substances and foreign substances.

It is particularly preferable to use the compounds detailed above for preparing a pharmaceutical composition for the treatment of asthma or COPD. Also of particular importance is the above-mentioned use of medicament combinations according to the invention for preparing a pharmaceutical composition for once-a-day treatment of

inflammatory and obstructive respiratory complaints, particularly for the once-a-day treatment of asthma or COPD.

The present invention also relates to the use of therapeutically effective amounts of an active substance **1** in combination with therapeutically effective amounts of active substance **2** for preparing a pharmaceutical composition for the treatment of one of the above-mentioned diseases.

The present invention also relates to a process for treating one of the above-mentioned diseases, which is characterised in that therapeutically effective amounts of active substance **1** are administered in combination with therapeutically effective amounts of active substance **2**.

Within the scope of the instant invention for example, 1 - 10000 µg **1** are administered per single dose. Preferably, amounts of **1** are administered such that each single dose contains 10 - 5000µg, preferably 50 - 2500 µg, particularly preferably 100-1000 µg of **1**. For example and without restricting the present invention thereto, 100µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg, 200µg, 205µg, 210µg, 215µg, 220µg, 225µg, 230µg, 235µg, 240µg, 245µg, 250µg, 255µg, 260µg, 265µg, 270µg, 275µg, 280µg, 285µg, 290µg, 295µg, 300µg, 305µg, 310µg, 315µg, 320µg, 325µg, 330µg, 335µg, 340µg, 345µg, 350µg, 355µg, 360µg, 365µg, 370µg, 375µg, 380µg, 385µg, 390µg, 395µg, 400µg, 405µg, 410µg, 415µg, 420µg, 425µg, 430µg, 435µg, 440µg, 445µg, 450µg, 455µg, 460µg, 465µg, 470µg, 475µg, 480µg, 485µg, 490µg, 495µg, 500µg, 505µg, 510µg, 515µg, 520µg, 525µg, 530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg, 585µg, 590µg, 595µg, 600µg, 605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg, 705µg, 710µg, 715µg, 720µg, 725µg, 730µg, 735µg, 740µg, 745µg, 750µg, 755µg, 760µg, 765µg, 770µg, 775µg, 780µg, 785µg, 790µg, 795µg, 800µg, 805µg, 810µg, 815µg, 820µg, 825µg, 830µg, 835µg, 840µg, 845µg, 850µg, 855µg, 860µg, 865µg, 870µg, 875µg, 880µg, 885µg, 890µg, 895µg, 900µg, 905µg, 910µg, 915µg, 920µg, 925µg, 930µg, 935µg, 940µg, 945µg, 950µg, 955µg, 960µg, 965µg, 970µg, 975µg, 980µg, 985µg, 990µg, 995µg or 1000µg of **1** may be administered per single dose. In the event that acid addition salts of **1** are used, the corresponding amount of salt used can easily be calculated by the skilled man from the values given hereinbefore, depending on the choice of acid.

Without restricting the invention thereto, in the case of **2a.8** a dosage range of from 1 - 50µg, preferably from 2- 25 µg is preferred according to the invention. Particularly preferably, the pharmaceutical compositions according to the invention containing **2a.8** are administered in such an amount that 2 - 10 µg, in case of the fumarate dihydrate particularly preferably 4 - 10µg, in case of the hemifumarate monohydrate preferably 2.5 - 5 µg of the compound **2a.8** are administered per single dose . Without restricting the invention thereto, in the case of **2a.23** a dosage range of from 5 - 100µg, preferably from 10 - 75 µg is preferred according to the invention. Particularly preferably, the pharmaceutical compositions according to the invention containing **2a.23** are administered in such an amount that 30 - 60 µg of the compound **2a.8** , preferably in form of the xinafoate thereof are administered per single dose .

Without restricting the invention thereto, in the case of **2a.30** a dosage range of from 1 - 50µg, preferably from 2- 25 µg is preferred according to the invention. Particularly preferably, the pharmaceutical compositions according to the invention containing **2a.8** are administered in such an amount that 2 - 10 µg are administered per single dose .

Without restricting the invention thereto, in the case of **2a.34** a dosage range of from 50 - 800µg, preferably from 75 - 700 µg is preferred according to the invention. Particularly preferably, the pharmaceutical compositions according to the invention containing **2a.34** are administered in such an amount that 100 - 600 µg are administered per single dose .

Particularly preferably, the compounds of formula **1** are administered in the above-mentioned dosage ranges in the form of the enantiomerically pure compounds, particularly preferably in the form of the R-enantiomers thereof.

If the compounds of formula **1** are administered in conjunction with an anticholinergic **2**, the amount of anticholinergic used will fluctuate considerably depending on the choice of active substance.

Without restricting the invention thereto, in the case of tiotropium **2b.1'** amounts of anticholinergic **2b** may be administered such that each single dose contains 0.1 - 80µg, preferably 0.5 - 60 µg, particularly preferably about 1 - 50µg of **2b.1'** . For example and without restricting the present invention thereto, 2.5µg, 5µg, 10µg, 18µg, 20µg, 36µg or 40µg **2b.1'** may be administered per single dose. The corresponding amount of salt **2b.1** or of any hydrate or solvate used in each case

can easily be calculated by the skilled man, depending on the choice of anion. If for example tiotropium bromide is used as the preferred tiotropium salt **2b.1** according to the invention, the amounts of the active substance **2b.1'** administered per single dose as specified by way of example hereinbefore correspond to the following amounts of **2b.1** administered per single dose: 3µg, 6µg, 12µg, 21.7µg, 24.1µg, 43.3µg and 48.1µg **2b.1**. In the case of tiotropium **2b.1'** the dosages specified above are preferably administered once or twice a day, while administration once a day is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cation **2b.2'** amounts of anticholinergic **2b** may be administered such that each single dose contains 1 - 500µg, preferably 5 - 300 µg, particularly preferably 15-200 µg **2b.2'** . For example and without restricting the present invention thereto, 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg or 200µg of **2b.2'** may be administered per single dose. The corresponding amount of salt **2b.2** used in each case or of any hydrate or solvate used can easily be calculated by the skilled man, depending on the choice of anion. In the case of oxitropium **2b.2'** the dosages specified above are preferably administered one to four times a day, while administration two to three times a day is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cation **2b.3'** amounts of anticholinergic **2b** may be administered such that each single dose contains 1 - 500µg, preferably 5 - 300 µg, particularly preferably 15-200 µg **2b.3'** . For example and without restricting the present invention thereto, 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg or 200µgof **2b.3'** may be administered per single dose. The corresponding amount of salt **2b.3** used in each case or of any hydrate or solvate used can easily be calculated by the skilled man, depending on the choice of anion. In the case of flutropium **2b.3'** the dosages specified above are preferably administered one to four times a day, while administration two to three times a day is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cation **2b.4'** amounts of anticholinergic **2b** may be administered such that each single dose contains 1 -

500µg, preferably 5 - 300 µg, particularly preferably 20-200 µg **2b.4'** . For example and without restricting the present invention thereto, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg or 200µg of **2b.4'** may be administered per single dose . The corresponding amount of salt **2b.4** used in each case or of any hydrate or solvate used can easily be calculated by the skilled man, depending on the choice of anion. In the case of ipratropium **2b.4'** the dosages specified above are preferably administered one to four times a day, while administration two to three times a day, more preferably three times a day, is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cation **2b.5'** amounts of anticholinergic **2b** may be administered such that each single dose contains 1 - 500µg, preferably 5 - 300 µg, particularly preferably 15-200 µg . For example and without restricting the present invention thereto, 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg or 200µg of **2b.5'** may be administered per single dose . The corresponding amount of salt **2b.5** used in each case or of any hydrate or solvate used can easily be calculated by the skilled man, depending on the choice of anion. In the case of glycopyrronium **2b.5'** the dosages specified above are preferably administered one to four times a day, while administration two to three times a day is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cation **2b.6'** amounts of anticholinergic **2b** may be administered such that each single dose contains 1000 - 6500µg, preferably 2000 - 6000µg, particularly preferably 3000 - 5500µg, particularly preferably 4000 - 5000µg **2b.6'** . For example and without restricting the present invention thereto, 3500µg, 3750µg, 4000µg, 4250µg, 4500µg, 4750µg, or 5000µg of **2b.6'** may be administered per single dose. The corresponding amount of salt **2b.6** used in each case or of any hydrate or solvate used can easily be calculated by the skilled man, depending on the choice of anion. In the case of trospium **2b.6'** the dosages specified above are preferably administered one to four times a day, while administration two to three times a day is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cation **2b.7'** amounts of anticholinergic **2b** may be administered such that each single dose contains 50 - 1000µg, preferably 100 - 800µg, particularly preferably 200 - 700µg, particularly preferably 300 - 600µg **2b.7'** . For example and without restricting the present invention thereto, 300µg, 350µg, 400µg, 450µg, 500µg, 550µg, or 600µg of **2b.7'** may be administered per single dose. The corresponding amount of salt **2b.7** used in each case or of any hydrate or solvate used can easily be calculated by the skilled man, depending on the choice of anion. In the case of the cation **2b.7'** the dosages specified above are preferably administered one to three times a day, while administration once or twice a day, more preferably once a day, is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cations in the compounds **2b.9** and **2b.10** , amounts of anticholinergic **2b** may be administered such that each single dose contains 1 - 500µg, preferably 5 - 300 µg, particularly preferably 15-200 µg cation. For example and without restricting the present invention thereto, 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg or 200µg of compounds **2b.9** or **2b.10** (based on amount of cation) may be administered per single dose. The corresponding amount of salt **2b.9** or **2b.10** or of any hydrate or solvate used in each case can easily be calculated by the skilled man, depending on the choice of anion. In the case of the cations in compounds **2b.9** or **2b.10** the dosages specified above are preferably administered one to three times a day, while administration once or twice a day, more preferably once a day, is particularly preferred according to the invention.

Without restricting the invention thereto, in the case of the cations in the compounds **2b.11** to **2b.13** , amounts of anticholinergic **2b** may be administered such that each single dose contains 1 - 500µg, preferably 5 - 300 µg, particularly preferably 10-200 µg cation. For example and without restricting the present invention thereto, 10µg, 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg or 200µg of compounds **2b.11**, **2b.12** or **2b.13** (based on amount of cation) may be administered per single dose . The corresponding amount of salt **2b.11**, **2b.12** or **2b.13** or of any hydrate or solvate used in each case can easily be calculated by the skilled man, depending on the choice of anion. In the case of the cations in compounds **2b.11**, **2b.12** or **2b.13** the dosages specified above are

preferably administered one to three times a day, while administration once or twice a day, more preferably once a day, is particularly preferred according to the invention.

In the combinations according to the invention the PDE IV-inhibitor **2c** is preferably administered in such an amount that about 1 - 10000 µg **2c** are administered per single dose. Preferably, amounts of **2c** are administered such that each single dose contains 10 - 5000µg, preferably 50 - 2500 µg, particularly preferably 100-1000 µg of **2c** . For example and without restricting the present invention thereto, 100µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg, 200µg, 205µg, 210µg, 215µg, 220µg, 225µg, 230µg, 235µg, 240µg, 245µg, 250µg, 255µg, 260µg, 265µg, 270µg, 275µg, 280µg, 285µg, 290µg, 295µg, 300µg, 305µg, 310µg, 315µg, 320µg, 325µg, 330µg, 335µg, 340µg, 345µg, 350µg, 355µg, 360µg, 365µg, 370µg, 375µg, 380µg, 385µg, 390µg, 395µg, 400µg, 405µg, 410µg, 415µg, 420µg, 425µg, 430µg, 435µg, 440µg, 445µg, 450µg, 455µg, 460µg, 465µg, 470µg, 475µg, 480µg, 485µg, 490µg, 495µg, 500µg, 505µg, 510µg, 515µg, 520µg, 525µg, 530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg, 585µg, 590µg, 595µg, 600µg, 605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg, 705µg, 710µg, 715µg, 720µg, 725µg, 730µg, 735µg, 740µg, 745µg, 750µg, 755µg, 760µg, 765µg, 770µg, 775µg, 780µg, 785µg, 790µg, 795µg, 800µg, 805µg, 810µg, 815µg, 820µg, 825µg, 830µg, 835µg, 840µg, 845µg, 850µg, 855µg, 860µg, 865µg, 870µg, 875µg, 880µg, 885µg, 890µg, 895µg, 900µg, 905µg, 910µg, 915µg, 920µg, 925µg, 930µg, 935µg, 940µg, 945µg, 950µg, 955µg, 960µg, 965µg, 970µg, 975µg, 980µg, 985µg, 990µg, 995µg or 1000µg of **2c** may be administered per single dose. In the event that acid addition salts of **2c** are used, the corresponding amount of salt used can easily be calculated by the skilled man from the values given hereinbefore, depending on the choice of acid.

If the compounds of formula **1** are administered in combination with a steroid **2d** , preferably about 1 - 10000 µg of **2d** are administered per single dose . Preferably, amounts of **2d** are administered such that each single dose contains 5 - 5000µg, preferably 5 - 2500 µg, particularly preferably 10-1000 µg of **2d** . For example and without restricting the present invention thereto, 10µg, 15µg, 20µg, 25µg, 30µg, 35µg, 40µg, 45µg, 50µg, 55µg, 60µg, 65µg, 70µg, 75µg, 80µg, 85µg, 90µg, 95µg, 100µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg, 200µg, 205µg, 210µg, 215µg, 220µg, 225µg, 230µg, 235µg, 240µg, 245µg, 250µg, 255µg, 260µg, 265µg, 270µg,

275µg, 280µg, 285µg, 290µg, 295µg, 300µg, 305µg, 310µg, 315µg, 320µg, 325µg, 330µg, 335µg, 340µg, 345µg, 350µg, 355µg, 360µg, 365µg, 370µg, 375µg, 380µg, 385µg, 390µg, 395µg, 400µg, 405µg, 410µg, 415µg, 420µg, 425µg, 430µg, 435µg, 440µg, 445µg, 450µg, 455µg, 460µg, 465µg, 470µg, 475µg, 480µg, 485µg, 490µg, 495µg, 500µg, 505µg, 510µg, 515µg, 520µg, 525µg, 530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg, 585µg, 590µg, 595µg, 600µg, 605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg, 705µg, 710µg, 715µg, 720µg, 725µg, 730µg, 735µg, 740µg, 745µg, 750µg, 755µg, 760µg, 765µg, 770µg, 775µg, 780µg, 785µg, 790µg, 795µg, 800µg, 805µg, 810µg, 815µg, 820µg, 825µg, 830µg, 835µg, 840µg, 845µg, 850µg, 855µg, 860µg, 865µg, 870µg, 875µg, 880µg, 885µg, 890µg, 895µg, 900µg, 905µg, 910µg, 915µg, 920µg, 925µg, 930µg, 935µg, 940µg, 945µg, 950µg, 955µg, 960µg, 965µg, 970µg, 975µg, 980µg, 985µg, 990µg, 995µg or 1000µg of **2d** may be administered per single dose. In the event that salts or derivatives of **2d** are used, the corresponding amount of salt/derivative used can easily be calculated by the skilled man from the values given hereinbefore, depending on the choice of salt/derivative.

If the compounds of formula **1** are administered in combination with an LTD4-antagonist **2e** , preferably about 0,01 - 500 mg **2e** are administered per single dose . Preferably, amounts of **2e** are administered such that each single dose contains 0.1 - 250mg, preferably 0.5 - 100 mg, particularly preferably 1-50 mg of **2e** . For example and without restricting the present invention thereto, 1mg, 2.5mg, 5mg, 5.5mg, 7 mg, 7, 5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg, 27.5mg, 30mg, 32.5mg, 35mg, 37.5mg, 40mg, 42.5mg, 45mg, 47.5mg or 50mg of **2e** may be administered per single dose. In the event that acid addition salts, salts or derivatives of **2e** are used, the corresponding amount of salt/derivative used can easily be calculated by the skilled man from the values given hereinbefore, depending on the choice of salt/derivative.

If the compounds of formula **1** are administered in combination with an EGFR-inhibitor **2f**, preferably about 100 - 15000 µg of **2f** are administered per single dose. Preferably, amounts of **2f** are administered such that each single dose contains 500 - 10000µg, preferably 750 - 8000 µg, particularly preferably 1000-7000 µg of **2f** . For example and without restricting the present invention thereto, 1000µg, 1150µg, 1200µg, 1250µg, 1300µg, 1350µg, 1400µg, 1450µg, 1500µg, 1550µg, 1600µg, 1650µg, 1700µg, 1750µg, 1800µg, 1850µg, 1900µg, 1950µg, 2000µg, 2050µg, 2100µg, 2150µg, 2200µg, 2250µg, 2300µg, 2350µg, 2400µg, 2450µg, 2500µg, 2550µg, 2600µg, 2650µg, 2700µg, 2750µg, 2800µg, 2850µg, 2900µg, 2950µg,

3000µg, 3050µg, 3100µg, 3150µg, 3200µg, 3250µg, 3300µg, 3350µg, 3400µg, 3450µg, 3500µg, 3550µg, 3600µg, 3650µg, 3700µg, 3750µg, 3800µg, 3850µg, 3900µg, 3950µg, 4000µg, 4050µg, 4100µg, 4150µg, 4200µg, 4250µg, 4300µg, 4350µg, 4400µg, 4450µg, 4500µg, 4550µg, 4600µg, 4650µg, 4700µg, 4750µg, 4800µg, 4850µg, 4900µg, 4950µg, 5000µg, 5050µg, 5100µg, 5150µg, 5200µg, 5250µg, 5300µg, 5350µg, 5400µg, 5450µg, 5500µg, 5550µg, 5600µg, 5650µg, 5700µg, 5750µg, 5800µg, 5850µg, 5900µg, 5950µg, 6000µg, 6050µg, 6100µg, 6150µg, 6200µg, 6250µg, 6300µg, 6350µg, 6400µg, 6450µg, 6500µg, 6550µg, 6600µg, 6650µg, 6700µg, 6750µg, 6800µg, 6850µg, 6900µg, 6950µg, or 7000µg of **2f** may be administered per single dose. In the event that acid addition salts of **2f** are used, the corresponding amount of the salt used can easily be calculated by the skilled man from the values given hereinbefore, depending on the choice of acid.

The active substance components **1** may be administered in each case by inhalation or by oral, parenteral or some other route, in known manner, in substantially conventional formulations such as for example plain or coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions, powders and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents.

In combinations of **1** and **2** the active substance components **1** and **2** may be administered - together or separately - in each case by inhalation or by oral, parenteral or some other route, in known manner, in substantially conventional formulations such as for example plain or coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions, powders and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents.

Suitable preparations for administering the compounds **1** (optionally combined with **2**) include tablets, capsules, suppositories, solutions, powders, etc. The proportion of pharmaceutically active compound or compounds should be in the range from 0.05 to 90 % by weight, preferably 0.1 to 50 % by weight of the total composition. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example

collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations of active substances according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules. Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof. Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral administration the tablets may, of course, contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting

process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

In case of combinations the components **1** and **2** may also be administered separately. In case **2** is selected from **2a** and **2b**, these components **2a** and **2b** are preferably always administered by inhalation even if **1** and/or other components **2** are administered by another route of administration. For instance component **2c** may also be administered for example by oral or parenteral route using formulations conventional in the art such as plain or coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions, powders and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents.

In one preferred embodiment, however, the medicament combinations according to the invention are administered by inhalation by means of a single preparation containing the active substances **1** and **2** or by means of separate preparations each containing only one of the active substances **1** and **2** suitable for administration by inhalation.

Inhalable preparations comprising **1** alone or optionally combinations thereof with **2** include inhalable powders, propellant-containing metered dose aerosols or propellant-free inhalable solutions. Inhalable powders according to the invention containing the the active substance(s) **1** and optionally **2** may consist of the active substance on their own or of a mixture of the active substances with physiologically acceptable excipients. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The preparations according to the invention may contain the active substance(s) **1** and optionally **2** either together in one formulation or in two separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

A) Inhalable powder:

The inhalable powders according to the invention may contain **1** and optionally **2** either on their own or in admixture with suitable physiologically acceptable excipients. If the active substances are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextrans), polyalcohols (e.g. sorbitol, mannitol,

xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose, trehalose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates.

Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to 250µm, preferably between 10 and 150µm, most preferably between 15 and 80µm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 to 9µm to the excipients mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance preferably with an average particle size of 0.5 to 10µm, more preferably from 1 to 6µm, is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and finally mixing the ingredients together are known from the prior art. The inhalable powders according to the invention may be administered using inhalers known from the prior art. Inhalable powders according to the invention which contain a physiologically acceptable excipient in addition to **1** and optionally **2** may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630A, or by other means as described in DE 36 25 685 A. The inhalable powders according to the invention which contain **1** and optionally **2** optionally in conjunction with a physiologically acceptable excipient may be administered, for example, using the inhaler known by the name Turbuhaler® or using inhalers as disclosed for example in EP 237507 A. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to **1** and optionally **2** are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

A particularly preferred inhaler for using the pharmaceutical combination according to the invention in capsules is shown in Figure 1.

This inhaler (Handihaler®) for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured by a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, and a mouthpiece 12 which is connected to the housing 1, the deck 3 and a cover

11 via a spindle 10 to enable it to be flipped open or shut, and air through-holes 13 for adjusting the flow resistance.

If the inhalable powders according to the invention are to be packaged in capsules, in accordance with the preferred method of administration described above, the capsules should preferably contain from 1 to 30 mg each. According to the invention they contain
either together or separately the dosages per single dose specified for **1** and **2** hereinbefore.

B) Propellant gas-driven inhalation aerosols:
Inhalation aerosols containing propellant gas according to the invention may contain substances **1** and optionally **2** dissolved in the propellant gas or in dispersed form. **1** and optionally **2** may be present in separate formulations or in a single preparation, in which **1** and optionally **2** are either both dissolved, both dispersed or only one component is dissolved and the other is dispersed. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as preferably chlorinated and fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are halogenated alkane derivatives selected from TG11, TG12, TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof, the propellant gases TG134a, TG227 and mixtures thereof being preferred.

The propellant-driven inhalation aerosols according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

The inhalation aerosols containing propellant gas according to the invention may contain up to 5 wt.-% of active substance **1** and optionally **2**. Aerosols according to the invention contain, for example, 0.002 to 5 wt.-%, 0.01 to 3 wt.-%, 0.015 to 2 wt.-%, 0.1 to 2 wt.-%, 0.5 to 2 wt.-% or 0.5 to 1 wt.-% of active substance **1** and optionally **2**.

If the active substances **1** and optionally **2** are present in dispersed form, the particles of active substance preferably have an average particle size of up to 10 μm, preferably from 0.1 to 6 μm, more preferably from 1 to 5 μm.

The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers). Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of propellant-driven aerosols as hereinbefore described combined with one or more inhalers suitable for administering these aerosols. In addition, the present invention relates to inhalers which are characterised in that they contain the propellant gas-containing aerosols described above according to the invention.

The present invention also relates to cartridges which are fitted with a suitable valve and can be used in a suitable inhaler and which contain one of the above-mentioned propellant gas-containing inhalation aerosols according to the invention. Suitable cartridges and methods of filling these cartridges with the inhalable aerosols containing propellant gas according to the invention are known from the prior art.

C) Propellant-free inhalable solutions or suspensions:

Propellant-free inhalable solutions according to the invention contain for example aqueous or alcoholic, preferably ethanolic solvents, possibly ethanolic solvents in admixture with aqueous solvents. In the case of aqueous/ethanolic solvent mixtures the relative proportion of ethanol to water is not restricted, but the maximum limit is up to 70 percent by volume, more particularly up to 60 percent by volume of ethanol. The remainder of the volume is made up of water. The solutions or suspensions containing **1** and optionally **2**, separately or together, are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid, etc. Preferred inorganic acids are hydrochloric acid and sulphuric acid. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may also be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

According to the invention, the addition of edetic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabiliser or complexing agent is unnecessary in the present formulation. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium edetate is less than 100mg/100ml, preferably less than 50mg/100 ml, more preferably less than 20mg/ 100 ml. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10mg/100ml are preferred.

Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins and provitamins occurring in the human body.

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50mg/100ml, more preferably between 5 and 20mg/100ml.

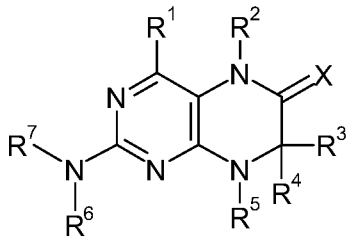
Preferred formulations contain, in addition to the solvent water and the active substances **1** and optionally **2** only benzalkonium chloride and sodium edetate. In another preferred embodiment, no sodium edetate is present.

The propellant-free inhalable solutions according to the invention are administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Within the scope of the present invention, preferred inhalers are those in which a quantity of less than 100µL, preferably less than 50µL, more preferably between 10 and 30µL of active substance solution can be nebulised in preferably one spray action to form an aerosol with an average particle size of less than 20µm, preferably less than 10µm, such that the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

An apparatus of this kind for propellant-free delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687 (cf. in particular Figures 6a and 6b). The nebulisers (devices) described therein are known by the name Respimat®.

Patent Claims

1) Use of therapeutically effective amounts of a compound of general formula **1**



1

wherein

R^1 denotes a group selected from among hydrogen, NH_2, XH, halogen and a C_1-C_3-alkyl group optionally substituted by one or more halogen atoms,

R^2 denotes a group selected from among hydrogen, CHO, XH, -X-C_1-C_2-alkyl and an optionally substituted C_1-C_3-alkyl group,

R^3, R^4 which may be identical or different denote a group selected from among optionally substituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, aryl, heteroaryl, C_3-C_8-cycloalkyl, C_3-C_8-heterocycloalkyl, -X-aryl, -X-heteroaryl, -X-cycloalkyl, -X-heterocycloalkyl, -NR^8-aryl, -NR^8-heteroaryl, -NR^8-cycloalkyl and -NR^8-heterocycloalkyl, or a group selected from among hydrogen, halogen, $COXR^8$, $CON(R^8)_2$, COR^8 and XR^8, or

R^3 and R^4 together denote a 2- to 5-membered alkyl bridge which may contain 1 to 2 heteroatoms,

R^5 denotes hydrogen or a group selected from among optionally substituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, aryl, heteroaryl and -C_3-C_6-cycloalkyl , or

R^3 and R^5 or R^4 and R^5 together denote a saturated or unsaturated C_3-C_4-alkyl bridge which may contain 1 to 2 heteroatoms,

R^6 denotes optionally substituted aryl or heteroaryl,

R^7 denotes hydrogen or -CO-X-C_1-C_4-alkyl, and

X in each case independently of one another denotes O or S,

R^8 in each case independently of one another denotes hydrogen or a group selected from among optionally substituted C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl and phenyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof,
for the preparation of a pharmaceutical composition for the treatment of respiratory complaints.

2) Use according to claim 1, wherein the respiratory complaints are selected from the group comprising obstructive pulmonary diseases of various origins, pulmonary emphysema of various origins, restrictive pulmonary diseases, interstitial pulmonary diseases, cystic fibrosis, bronchitis of various origins, bronchiectasis, ARDS (adult respiratory distress syndrome) and all forms of pulmonary oedema.

3) Use according to claim 2, wherein the obstructive pulmonary diseases are selected from among bronchial asthma, paediatric asthma, severe asthma, acute asthma attacks, chronic bronchitis and COPD (chronic obstructive pulmonary disease), while it is particularly preferable according to the invention to use them for preparing a pharmaceutical composition for the treatment of bronchial asthma and COPD.

4) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of pulmonary emphysema which has its origins in COPD or α1-proteinase inhibitor deficiency.

5) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of restrictive pulmonary diseases selected from among allergic alveolitis, restrictive pulmonary diseases triggered by work-related noxious substances, such as asbestosis or silicosis, and restriction caused by lung tumours, such as for example lymphangiosis carcinomatosa, bronchoalveolar carcinoma and lymphomas.

6) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of interstitial pulmonary diseases selected from among pneumonia caused by infections, such as for example infection by viruses, bacteria, fungi, protozoa, helminths or other pathogens, pneumonitis caused by various factors, such as for example aspiration and left heart insufficiency, radiation-induced pneumonitis or fibrosis, collagenoses, such as for example lupus erythematodes, systemic sclerodermy or sarcoidosis, granulomatoses, such as for example Boeck's disease, idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis (IPF).

7) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of cystic fibrosis or mucoviscidosis.

8) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of bronchitis, such as bronchitis caused by bacterial or viral infection, allergic bronchitis and toxic bronchitis.

9) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of bronchiectasis.

10) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of ARDS (adult respiratory distress syndrome).

11) Use according to claim 2, for preparing a pharmaceutical composition for the treatment of pulmonary oedema.

12) Medicament combinations which contain in addition to one or more, preferably one compound of formula **1** as defined in claim 1, a second active ingredient **2** which is selected from the group consisting of betamimetics (**2a**), anticholinergics (**2b**), PDEIV-inhibitors (**2c**), steroids (**2d**), LTD4 antagonists (**2e**), EGFR-inhibitors (**2f**), 5-lipoxygenase inhibitors (**2g**), and anti-IgE monoclonal antibodies (**2h**) optionally together with a pharmaceutically acceptable excipient.

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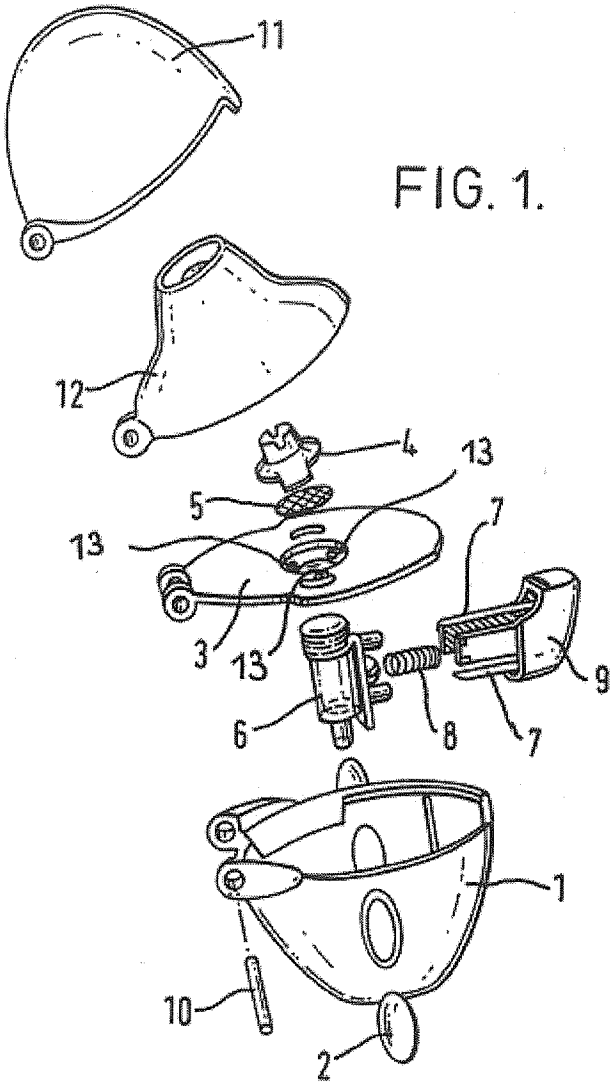

FIG. 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/064305

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/519 A61P11/08

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)
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, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, 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.
Y	WO 2005/067935 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 28 July 2005 (2005-07-28) claims 1-11	1-12
Y	WO 03/020722 A (BOEHRINGER INGELHEIM PHARMA KG; HOFFMANN, MATTHIAS; GRAUERT, MATTHIAS;) 13 March 2003 (2003-03-13) cited in the application page 1, line 24 - page 3, line 21; page 88, line 12-30	1-12

[ ] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
5 October 2006	16/10/2006

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Borst, Markus

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/064305

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 2005067935	A	28-07-2005	AR	047386	A1	18-01-2006
			CA	2552540	A1	28-07-2005
WO 03020722	A	13-03-2003	AT	332898	T	15-08-2006
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			HR	20040213	A2	28-02-2005
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