Pyrrolidinyl-Alkyl-Amide Derivatives Their Preparation and Their Therapeutic Application as CCR3 Receptor Ligands

The present invention relates to the CCR3 receptor ligands of the general formula (I) or (IA) -within them favourably to the antagonists-, and to the salts and isomers thereof, to the pharmaceutical compositions containing them, to the use of the compounds of the general formula (I) and (IA), and their salts and isomers and to the preparation of the compounds of the general formula (I) and (IA), and their salts and isomers.

Chemokines are small molecular weight (8 – 12 kDa) secreted polypeptides playing important regulatory role in the immune processes due to their leukocyte attracting (chemotactic) effect. They exert their effects through the chemokine receptors, which belong to the family of the G protein coupled receptors.

The CC chemokine receptors 3 (CCR3 receptors) are expressed by a number of inflammatory cells, like the basofils, mast cells, T lymphocytes, epithelial cells, dendritic cells, but in the greatest amount they can be found on the surface of the eosinofiles.

The CCR3 receptor ligands belong to the family of the C-C kemokines. They have a number of selective and non-selective ligands. The selective ligands are the eotaxin, eotaxin–2 and the lately discovered eotaxin-3. The non-selective ligands are the RANTES, the monocyte chemotactic proteins (MCP-2, MCP-3, MCP-4) and the macrophage inhibitor protein (MIP-1). The best characterized CCR3 ligand known from a long time is the eotaxin.

The eotaxin through the activation of the CCR3 receptors attracts selectively the eosinofils. Prior to an allergen provocation, the measured eotaxin level in the broncho-alveolar lavage fluidum of asthmatic patients was by 67 percent higher. On the effect of provocation a 2.4-fold increase of the epithelial and endothelial cells of the respiratory tract were found.

In the lung the eotaxin is produced in many cells. Following an allergen response, the most important eotaxin sources are the epithelial cells, but a great amount of eotaxin is produced by the fibroblasts of the lung, the smooth muscle cells and the endothelial cells of the respiratory tract, the alveolar macrophages and lymphocytes, and the eosinofils themselves.

Originally the data showed that the CCR3 receptors are to find only in the eosinofil cells (Bertrand CP, Ponath PD., Expert Opin Investig Drugs. 2000 Jan;9(1):43-52.), but on the basis of expression profiles it has been revealed that other inflammatory cells -although in smaller amount- also contain CCR3 receptors (Elsner J, Escher SE, Forssmann U., Allergy. 2004 Dec;59(12):1243-58.). Thus, the CCR3 antagonists possess much wider effect, their activity is not limited to the eosinofils and consequently they can be considered much more valuable and effective targets in the treatment of allergic and inflammatory diseases.

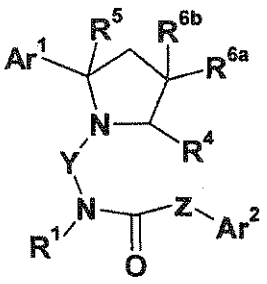
Based on the above observations, CCR3 antagonists may possess important profilactic and therapeutic effects in the treatment of pathologies where in the development of the disease CCR3 receptors play a role. These diseases are characterized by the disorder of the leukocyte functions (activation, chemotaxis), there are numerous chronic inflammatory diseases among them, such as asthma, allergic rhinitis, atopic dermatitis, eczema, inflammatory bowel disease, ulcerative colitis, Crohn disease, allergic conjunctivitis, arthritis, multiple sclerosis, HIV-infection and diseases in conjunction with AIDS.

In the literature numerous CCR3 receptor antagonists have been published to date (e.g.: WO 03/082291, WO 2004/084898, WO 2004/076448, WO 2007/034252, WO 2007/034254). The present invention relates to a new structural type, the pyrrolidinyl-alkyl-amide derivatives. Representatives of these compounds are effective CCR3 receptor antagonists.

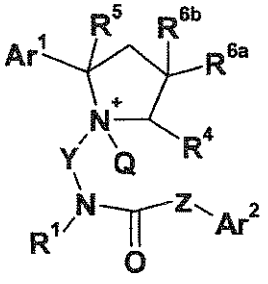
From the aspect of therapeutic use it is essential that the molecules do not bind, or bind only in case of very high concentration to other the CCR receptor subtypes.

Our aim was to prepare compounds of high antagonistic activity, and at the same time selective to the CCR3 receptor, i.e. which inhibit the CCR3 receptor in much smaller concentration as compared to other CCR receptors. Further aim was that the new compounds have stability, bioavailability, therapeutic index and toxicity values which ensure its drugability. Additional aim was that the compounds, through their good enteric absorption can be applied orally.

We have found that the compounds of the general formula (I) or (IA),



(I)



(IA)

where

Ar^1 represents phenyl or naphthyl group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, trifluoromethyl group, cyano group, nitro group, hydroxyl group, C_{1-2} alkylenedioxy group, amino group, amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group;

R^1, represents hydrogen atom, or straight or branched C_{1-4} alkyl group;

R^4, R^5, R^{6a}, R^{6b} represents hydrogen atom, or

R^4 stands for straight or branched C_{1-4} alkyl group and R^5, R^{6a} and R^{6b} represents hydrogen atom, or

R^5 stands for straight or branched C_{1-4} alkyl group and R^4, R^{6a} and R^{6b} represents hydrogen atom, or

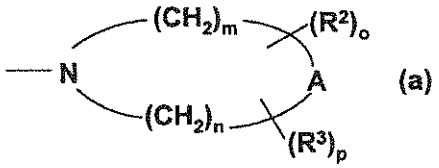
R^{6a} stands for straight or branched C_{1-4} alkyl group and R^{6b} stands for straight or branched C_{1-4} alkyl group or hydrogen atom and R^5, R^4 represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents a phenyl-, thienyl-, or furyl group, –optionally substituted with one or more, identical or non-identical, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, hydroxyl group, cyano group, nitro group, trifluoromethyl group, C_{1-2} alkylenedioxy group, amino group, or amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group; or

5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more, identical or non-identical, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2}

alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where R^7 and R^8 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, or R^7 and R^8 together with the nitrogen atom form a group of general formula (a),



(a)

where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1;

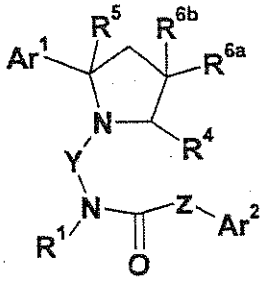
or

the benzologue of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more, identical or non-identical, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, trifluoromethyl group, nitro group, cyano group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above; or

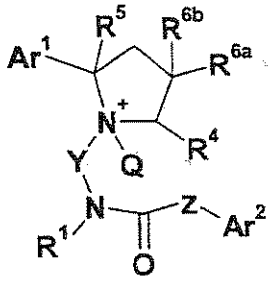
the derivative of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms –optionally substituted with one or more, identical or non-identical, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above;

Q represents $-O^-$ group, $-N^--H$ or $-N^--CO-R^{10}$ group – where R^{10} stands for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl-, benzyl- or $-NH-R^{11}$-group –where R^{11} represents straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl- or benzyl-group-;
and their salts and isomers and the salts thereof, fulfil the above criteria.

In one aspect, there is provided a process for the preparation of the compounds of general formula (I) or (IA) and their salts and isomers and the salt thereof,



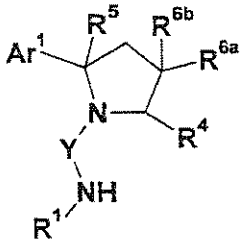
(I)



(IA)

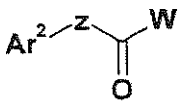
- where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined above
-, characterized in that

a.) to prepare the compounds of general formula (I) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined above- a compound of the general formula (IV),



(IV)

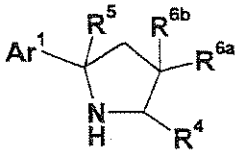
- where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y are as defined above- is reacted with a carboxylic acid derivative of the general formula (V),



(V)

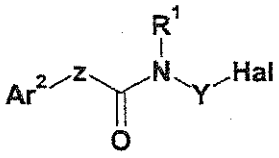
- where the meanings of Ar^2 and Z are as defined above, and W represents halogen atom, hydroxyl group, $-O(C_{1-4}$ alkyl) group or $-OCO-Z-Ar^2$ group, where the meanings of Ar^2 and Z are as defined above- ; or

b.) to prepare the compounds of general formula (I) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined above- an amino compound of the general formula (VI)



(VI)

- where the meanings of Ar^1, R^5, R^4, R^{6a} and R^{6b} are as defined above- is reacted with a halogen compound of the general formula (VII)



(VII)

- where the meanings of Y, R^1, A^2 and Z are as defined above- and Hal represents halogen atom, or

c.) to prepare the compounds of general formula (IA) -where Q represents $-O^-$ group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined above- a compound of the general formula (I) prepared by method a.) or b.) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined above- is oxidized, or

d.) to prepare the compounds of general formula (IA) and their salts -where Q represents $-N^-$-H group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined above.- a compound of the general formula (I) prepared by method a.) or b.) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined above.- is reacted with *O*-tosylhydroxylamine, or

e.) to prepare the compounds of general formula (IA) and their salts -where Q represents $-N^-$-CO-R^{10} group -where R^{10} represents hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl or benzyl group- and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined above.- a

compound of the general formula (IA) prepared by method d.) -where Q represents -N -H group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined above.- is acylated with a group of the general formula HIg-CO-R^{10}- where the meaning of R^{10} is as defined above.- and HIg represents halogen atom, or

f.) to prepare the compounds of general formula (IA) -where Q represents -N -CO-R^{10} group -where R^{10} represents -NH-R^{11} and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and R^{11} are as defined above.- a compound of the general formula (IA) prepared by method d.) -where Q represents -N -H group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined above- is reacted with a compound of the general formula R^{11}NCO –where the meaning of R^{11} is as defined above-,

and -if desired- the substituents of the resulting compound of the general formula (I) or (LA) are transformed into each other by a method known per se, and/or the resulting compound of the general formula (I) or (IA) is transformed into its salt, or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound and if desired the structural isomers are separated.

In one aspect, there is provided a pharmaceutical composition, characterized in that, it comprises one or more of the compounds of the general formula (I) or (IA as defined above and/or its salt or isomer or the salt thereof, and one or more excipients commonly used in the pharmaceutical industry.

In one aspect, there is provided a medicament, characterized in that, it comprises one or more of the compounds of the general formula (I) or (IA) as defined above and/or its salt or isomer or the salt thereof.

In one aspect, there is provided the use of the compounds of the general formula (I) or (IA) as defined above and their salts and isomers and the salt thereof, for the preparation of a medicament intended for the treatment of pathologies where in the development of the disease CCR3 receptors play a role, selected from asthma, allergic rhinitis, atopic dermatitis, eczema, inflammatory bowel disease, ulcerative colitis, Crohn disease, allergic conjunctivitis, multiple sclerosis or HIV-infection and diseases in conjuction with AIDS.

In one aspect, there is provided compounds of the general formula (I) or (IA) as defined above and their salts and isomers and the salt thereof for the treatment of pathologies where in the development of the disease CCR3 receptors play a role.

The detailed meanings of the above substituents are as follows:

By a C_{1-4} alkyl group we mean a saturated straight- or branched-chain aliphatic group of 1-4 carbon atoms, such as methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, secondary butyl-, tertiary butyl group.

By a C_{1-4} alkylene group we mean a $-(CH_2)_n-$ group where the value of n is 1, 2, 3 or 4, such as a methylene-, ethylene-, propylene-, butylene group.

By a C_{3-6} cycloalkyl group we mean a cyclic alkyl group of 3-6 carbon atoms, such as cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexyl-group.

By a C_{1-4} alkoxy group we mean an —O-(C_{1-4} alkyl group) -where the meaning of alkyl is as defined above-, such as methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, secondary butoxy- or tertiary butoxy group.

By a C_{1-2} alkylenedioxy group we mean an —O-alkylene-O— group, where the meaning of alkylene is as defined above - such as methylenedioxy- or ethylenedioxy-group.

By halogen atom we mean chloro, fluoro, iodo or bromo atom.

A 5- or 6-membered heterocyclic ring containing one, two or three nitrogen atoms may mean an unsaturated, saturated or partially saturated heterocyclic ring, for example pyrrole, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyrimidine, pyridazine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,3-triazine, pyrrolidine, imidazolidine, [1,2,4]-triazolidine, piperidine, piperazine, 2-imidazoline ring.

A 5- or 6-membered heterocyclic ring containing one nitrogen atom and one oxygen or sulphur atom may mean an unsaturated, saturated or partially saturated heterocyclic ring, as for example oxazole, isoxazole, thiazole, isothiazole, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, oxazolidine, thiazolidine, morpholine, thiomorpholine, 2-thiazoline, 2-oxazoline ring.

By benzologue we mean derivetives condensed with benzene ring, for example indole, benzoxazole, benzthiazole, benzimidazole, quinoline, quinazoline, quinoxaline.

The condensed derivatives of a 5- or 6-membered heterocyclic ring -containing one, two or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom- condensed with 6-membered heteroaromatic rings -containing one or two nitrogen atom-, may for example be a thiazolopyridine, triazolopyridine, thiazolopyrimidine, thiazolopyrazine, oxazolopyridine, 9*H*-purine, 3*H*-imidazopyridine.

The group of the general formula (a) preferably represents a pyrrolidino-, piperidino-, morpholino-, piperazino-, 4-methylpiperazino-, 2,6-dimethylmorpholino-group.

By salts of the compounds of general formula (I) or (IA) we mean salts given with inorganic and organic acids and bases. Preferred are the salts formed with pharmaceutically acceptable acids, e.g. hydrochloric acid, sulfuric acid, ethanesulfonic acid, tartaric acid, fumaric acid, citric acid.

By isomers we mean structural and optical isomers. Structural isomers may be tautomeric forms in equilibrium, or isolated desmotrops, which are also subjects of the invention. The compounds of general formula (I) or (IA) may contain one or more asymmetric carbon atom, thus they may be optical isomers, enantiomers or diastereoisomers. These enantiomers and diastereoisomers and the mixtures thereof, including the racemates, are also subjects of the invention.

A narrower group of the compounds of general formula (IA) is formed by those, where

Ar^1 represents phenyl or naphthyl group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, trifluoromethyl group, cyano group, nitro group, hydroxyl group, C_{1-2} alkylenedioxy group, amino group, or amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group;

R^1, represents hydrogen atom, or straight or branched C_{1-4} alkyl group;

R^4, R^5, R^{6a}, R^{6b} represent hydrogen atom, or

R^4 stands for straight or branched C_{1-4} alkyl group and **R^5, R^{6a}** and **R^{6b}** represent hydrogen atom, or

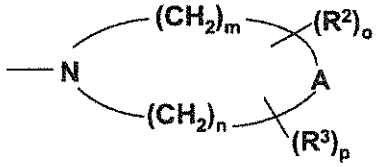
R^5 stands for straight or branched C_{1-4} alkyl group and **R^4, R^{6a}** and **R^{6b}** represent hydrogen atom, or

R^{6a} stands for straight or branched C_{1-4} alkyl group and R^{6b} stands for straight or branched C_{1-4} alkyl group or hydrogen atom and R^5, R^4 represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents a phenyl-, thienyl-, or furyl group, –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, hydroxyl group, cyano group, nitro group, trifluoromethyl group, C_{1-2} alkylenedioxy group, amino group, or amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group; or

5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where R^7 and R^8 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group or R^7 and R^8 together with the nitrogen atom form a group of general formula (a),



(a)

where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1;

or

the benzologue of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen

atom and one sulphur atom –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, trifluoromethyl group, nitro group, cyano group, C_{1-2} alkylenedioxy group, $-NR^7R^8$,$-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above-; or

the derivative of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms, –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above;

Q represents $-\bar{N}-H$ group;

and their salts and isomers and the salts thereof.

Another narrower group of the compounds of general formula (I) or (IA) is formed by those,

where

Ar^1 represents phenyl or naphthyl group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom;

R^1 represents hydrogen atom, or methyl group;

R^4, R^5, R^{6a}, R^{6b} represent hydrogen atom, or

R^4 stands for methyl group and **R^5, R^{6a}** and **R^{6b}** represent hydrogen atom, or

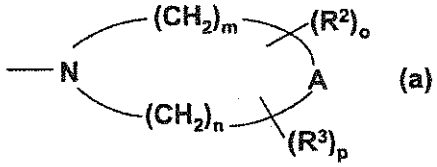
R^5 stands for methyl group and **R^4, R^{6a}** and **R^{6b}** represent hydrogen atom, or

R^{6a} stands for methyl group and **R^{6b}** stands for methyl group or hydrogen atom and **R^5, R^4** represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents the benzologue of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more

identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, trifluoromethyl group, nitro group, cyano group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where R^7 and R^8 independently mean hydrogen atom, straight or branched C_{1-4} alkoxy group, or R^7 and R^8 together with the nitrogen atom form a group of the general formula (a),



(a)

where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1, -

or

the derivative of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above;

Q represents $-O^-$ group, $-N^--H$ or $-N^--CO-R^{10}$ group –where R^{10} stands for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl-, benzyl- or $-NH-R^{11}$ group –where R^{11} represents straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl- or benzyl- group-;

and their salts and isomers and the salts thereof.

A further narrower group of the compounds of general formula (I) or (IA) is formed by those,

where

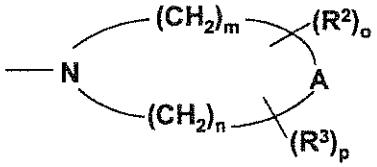
Ar^1 represents phenyl group –optionally substituted with one or more identical or non-identical halogen atom;

R^1 represents hydrogen atom;

R^4, R^5, R^{6a}, R^{6b} represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents the benzologue of a 5- or 6-membered heterocyclic ring containing one nitrogen atom and one sulphur atom –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, or the derivative of a 5- or 6-membered heterocyclic ring containing one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, $-NR^7R^8$ group –where R^7 and R^8 independently mean hydrogen atom, straight or branched C_{1-4} alkyl group or R^7 and R^8 together with the nitrogen atom form a group of the general formula (a);



(a)

where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1;

Q represents $-O^-$ group, $-N^--H$ or $-N^--CO-R^{10}$ group –where R^{10} stands for hydrogen atom, straight or branched C_{1-4} alkyl group, or $-NH-R^{11}$ group –where R^{11} represents straight or branched C_{1-4} alkyl group-;

and their salts and isomers and the salts thereof.

A further narrower group of the compounds of general formula (I) or (IA) is formed by those,

where

Ar^1 represents phenyl group substituted with one or two identical or non-identical halogen atom,

and the meaning of R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q is as defined above,

and their salts-and isomers and the salts thereof.

An even narrower group of the compounds of the general formula (I) or (IA) is formed by the following compounds:

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methoxy[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(methylamino)[1,3]thiazolo [5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methyl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(4-methylpiperazin-1-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-methyl-1,3-benzothiazol-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-piperidin-1-yl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-morpholin-4-yl)[1,3]htiazolo[4,5-*b*]pyrazin-2-yl)propionamide,

N-(3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-morpholin-4-yl [1,3]thiazolo[5,4-*b*]pyridin-2-yl)]propionamide,

N-(3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-piperidin-1-yl [1,3]thiazolo[5,4-*b*]pyridin-2-yl)]propionamide,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-morpholin-4-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-methyl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-[3-({3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl) [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,

1-(Acetylamino)-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-b]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium hydrohloride

and their salts and isomers and the salts thereof.

An even narrower group of the compounds of the general formula (I) or (IA) is formed by the following compounds:

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(methylamino)[1,3]thiazolo [5,4-*b*]pyridin-2-yl)propionamide

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-morpholin-4-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-methyl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-[3-({3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,

and their salts and isomers and the salts thereof.

A further group of the compounds is the compounds of general formula (IA)

where,

Q represents $-\overset{-}{N}$-H group

and the meaning of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 is as defined above

and their salts and isomers and the salts thereof. These compounds possess increased metabolic stability.

The present invention relates furthermore to the pharmaceutical preparations containing the compounds of the general formula (I) or (IA), their isomers or salts which are preferably oral preparations, but inhalable, parenteral and transdermal preparations are also subjects of the present invention. The above pharmaceutical preparations may be solid or liquid formulations, for example tablets, pellets, capsules, patches, solutions, suspensions or emulsions. Preferred are the solid formulations, first of all the tablets and the capsules.

The above pharmaceutical preparations are made by applying the usual excipients and technological operations.

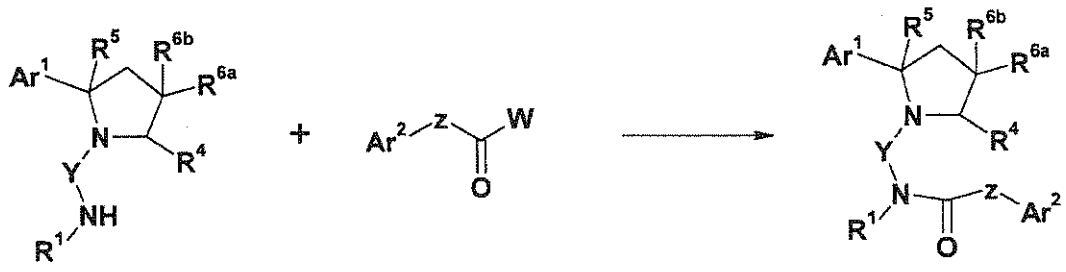
The compounds of the general formula (I) or (IA) according to the invention and their salts and isomers, and the salt thereof, can be used for the treatment of pathologies where CCR3 receptors play a role in the development of the disease.

The compounds according to the present invention can favourably used in the treatment of diseases like asthma, allergic rhinitis, atopic dermatitis, eczema, inflammatory bowel disease, ulcerative colitis, Crohn disease, allergic conjunctivitis, multiple sclerosis, HIV-infection and diseases in conjunction with AIDS.

A further subject of the invention is the use of the compounds of the general formula (I) or (IA) according to the invention and their salts and isomers, and the salt thereof, for the treatment of the above pathologies. The suggested daily dose is **1-100 mg / person**, of the active ingredient, depending on the nature and severity of the disease and the sex and weight of the patient.

A further subject of the invention is the preparation of the compounds of general formula (I) and (IA), -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined above- and their salts and isomers, and the salt thereof.

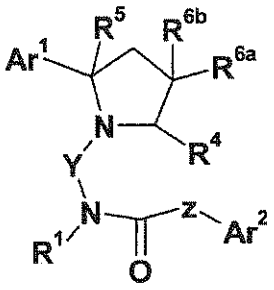
Figure 1. presents one of the possible methods for the preparation of the compounds of general formula (I) (process version a.)



(IV) (V) (I)

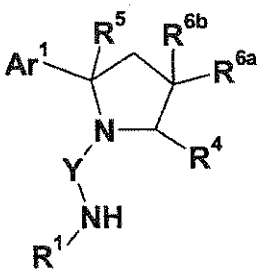
Figure 1.

According to version a.) of the process for the preparation of the compounds of general formula (I) and their salts and isomers, and the salt thereof



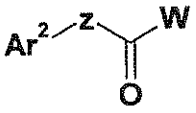
(I)

- wherein the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined above - a compound of general formula (IV),



(IV)

-wherein the meanings of Ar^1, R^1, R^4 , R^5, R^{6a}, R^{6b} and Y, are as defined above-, is reacted with a carboxylic acid derivative of general formula (V),



(V)

where the meanings of Ar^2 and Z are as defined above and W represents halogen atom, hydroxyl group, C_{1-4} straight or branched alkoxy group or a $-O-CO-Z-Ar^2$ group -where the meanings of Z and Ar^2 are as defined above- and if desired, the substituents of the resulting compound of general formula (I) are transformed into each-other by a method known *per se*, and/or the resulting compound of general formula (I) is transformed into its salt, or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound and if desired the structural isomers are separated.

A preferred method to carry out process version a) according to the invention is to treat the acid of the general formula (V), where W represents hydroxyl group, with a reagent suitable to form acid halides, preferably thionyl chloride, to prepare the acid

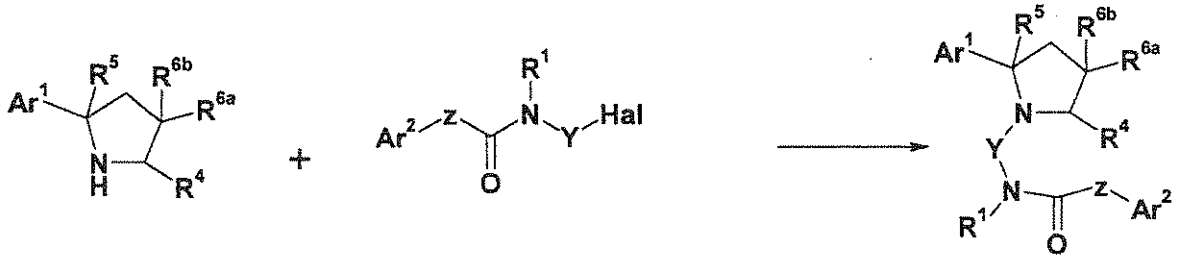
chloride which is then reacted with an amine of the general formula (IV) in an inert solvent (*e.g.* in a chlorinated hydrocarbone, such as dichloromethane, chloroform, or in ethyl acetate) in the presence of a base (*e.g.* triethyl amine) or in pyridine, at room temperature or at the boiling point of the solvent.

Another preferred method is when the acid of the general formula (V) is reacted with an amine of the general formula (IV) in the presence of an activating agent. Activation of the carboxylic acids may be achieved by preparation of carboxylic acid mixed anhydrides as intermediates, by use of *e.g.* pivalyl chloride (M.T. Leplawy: Tetrahedron 1960, **11**, 39), ethyl chloroformate (T. Wieland: J. Liebigs Ann. Chem. 1951, **572**, 190), isobutyl chloroformate (J. R. Vaughan: JACS. 1951, **73**, 3547) or dicyclohexyl carbodiimide (DCC) (R. Arshady: J. Chem. Soc. Perkin Trans. 1, 1981, 529 or D. Hudson: J. Org. Chem. 1988, **53**, 617), in an inert solvent (*e.g.* dichloromethane, chloroform, tetrahydrofuran, acetonitrile), in the presence of an acid- binding agent, *e.g.* a tertiary amine (triethylamine, *N*-methylmorpholine), at a temperature between -10 and 25 °C.

The activation may also be achieved by use of carbonyl-diimidazole (H. A. Staab: Lieb. Ann. Chem: 1957, 609, 75), in inert solvents, preferably in dichloromethane, chloroform, tetrahydrofuran or in the mixture thereof. Activation can also be performed with benzotriazol-1-yl-oxy-tripyrrolidinophosphonium-hexafluoro-phosphate (PyBOP), in inert solvents (J. Corte: Tetrahedron Lett. 31, 1990, 205).

If the compound of the general formula (I) is a carboxylic acid ester, where in the formula W represents a C_{1-4} straight or branched alkoxy group, then the reaction can be carried out favourably by the known method, at 150°C without solvent, in melt.

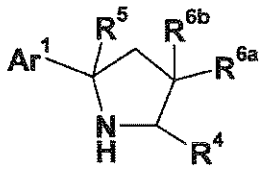
The compounds of the general formula (I) according to the invention can also be prepared by the method demonstrated in Figure 2. (process version b.).



(VI) (VII) (I)

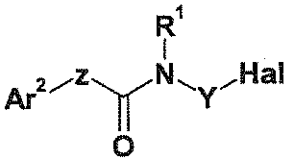
Figure 2.

In process version b.) according to the invention the compounds of the general formula (I) –where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined above– and their salts, isomers and the salts thereof, are prepared by reacting an amino compound of the general formula (VI),



(VI)

where the meanings of Ar^1, R^5, R^4, R^{6a} and R^{6b} are as defined above, with a halogen compound of the general formula (VII),

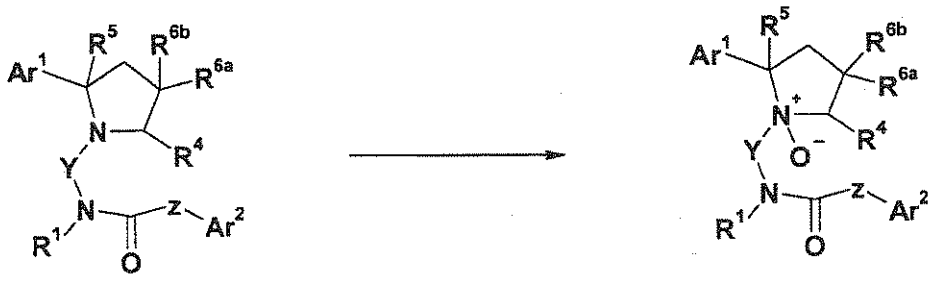


(VII)

-where the meanings of Y, R^1, Ar^2 and Z are as defined above and Hal represents halogen atom-, and if desired the substituents of the resulting compound of general formula (I) are transformed into each-other by a method known *per se*, and/or the resulting compound of general formula (I) is transformed into its salt or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound and if desired the structural isomers are separated.

A preferred embodiment of process version b.) is when the reaction of the amine of the general formula (VI) and the halogen compound of the general formula (VII) is carried in an inert solvent, perferably in dichloromethane, in the presence of organic bases as acid binders.

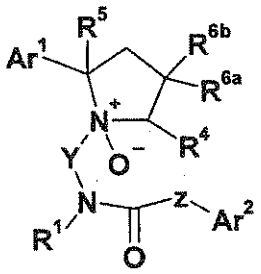
The compounds of the general formula (IA) according to the invention -where Q represents $-O^-$ group and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 have the meanings as defined above- can be prepared by the method demonstrated in Figure 3. (process version c.).



(I) (IA)

Figure 3.

In version c.) of the process according to the invention, the compounds of the general formula (IA) and their salts and isomers and the salts thereof -where Q represents -O^- group



(IA)

and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined above- are prepared so that a compound of the general formula (IA) prepared by method a.) or b), -where Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 have the meanings as defined above- is oxidized and -if desired- the substituents of the compound of the general formula (IA) are transformed into each other by a method known *per se*, and/or the resulting compound of the general formula (IA) is transformed into its salt or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound and if desired the structural isomers are separated.

In version c) of the process according to the invention, the reaction is preferably carried out in an inert solvent at a temperature of 0-30 °C using known oxidants, such as hydrogen peroxide, potassium permanganate, favourably meta-chloro-perbenzoic acid. As for inert solvent halogenated solvents, such as dichloromethane, chloroform, acetonitrile, preferably dichloromethane can be used.

The compounds of the general formula (IA) according to the invention -where Q represents $-\bar{N}$-H group and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and X have the meanings as defined above- can be prepared by the method demonstrated in Figure 4. (process version d.).

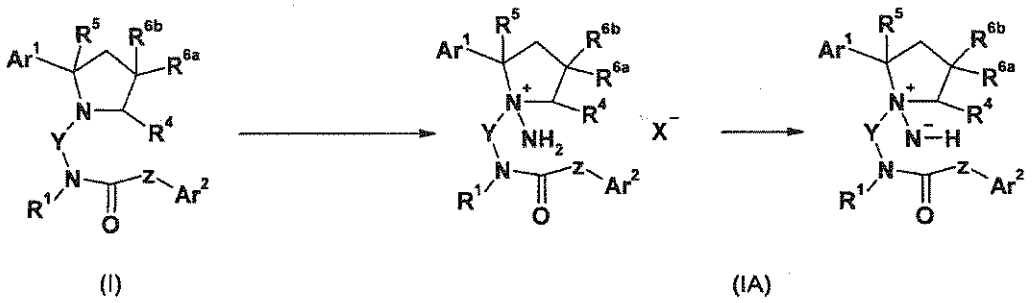


Figure 4.

In version d.) of the process according to the invention, the compounds of the general formula (IA) and their salts and isomers and the salts thereof -where Q represents $-\bar{N}$-H group and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and X have the meanings as defined above- can be prepared so that a compound of the general formula (IA) prepared by method a.) or b.) -where Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 have the meanings as defined above- is reacted with O-tosylhydroxylamine to obtain the tosylate salt, which after alkaline treatment results the zwitter-ionic structure, and -if desired- the substituents of the resulting compound of the general formula (IA) are transformed into each other by a method known *per se*, and/or the resulting compound of the general formula (IA) is transformed into its salt or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound and if desired the structural isomers are separated.

The reaction is preferably carried out in an inert solvent at a temperature of 0-50 °C using O-tosylhydroxylamine. As for inert solvent, halogenated solvents, such as dichloromethane, chloroform, tetrahydrofuran, acetonitrile, preferably dichloromethane can be used.

The compounds of the general formula (IA) according to the invention -where Q represents $-\bar{N}$-CO-R^{10} group and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, R^{10} and Ar^2 have the meanings as defined above- can be prepared by the method demonstrated in Figure 5. (process version e.).

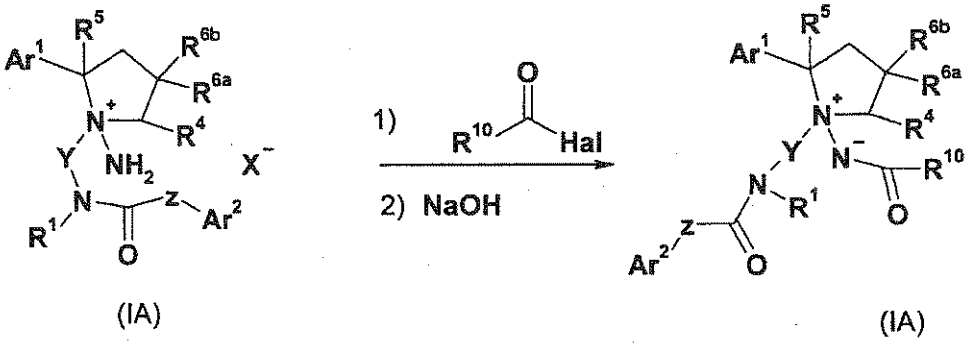


Figure 5.

In version e.) of the process according to the invention, the compounds of the general formula (IA) and their salts and isomers and the salts thereof -where Q represents -N^--CO- group, wherein R^{10} stands for hydrogen atom, C_{1-4} straight or branched alkyl group, C_{3-6} cycloalkyl, phenyl or benzyl group, and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 have the meanings as defined above- can be prepared so that a compound of the general formula (IA) prepared by method d.) -where Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 have the meanings as defined above- is acylated with a compound of the general formula Hal-CO-R^{10} -where R^{10} has the meaning as defined above and Hal represents halogen atom, and -if desired- the substituents of the resulting compound of the general formula (IA) are transformed into each other by a method known *per se*, and/or the resulting compound of the general formula (IA) is transformed into its salt or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound, and -if desired- the structural isomers are separated. The acylation is preferably performed with alkyl or aralkyl acid halides, in inert solvents, preferably in dichloromethane, using organic or inorganic acid binders, preferably potassium carbonate.

In version f.) of the process according to the invention, the compounds of the general formula (IA) and their salts and isomers and the salts thereof -where Q represents –N^--CO-R^{10} group, wherein R^{10} stands for –NH-R^{11} group and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and R^{11} have the meanings as defined above- can be prepared so that a compound of the general formula (IA) prepared by method d.) -where Q represents –N^--H group and Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 have the meanings as defined above- is reacted with a compound of the general formula R^{11}NCO where R^{11} has the meaning as defined above, and -if desired- the substituents of the resulting compound of the general formula (IA) are transformed into each other by a method known *per se*, and/or the resulting compound of the general formula (IA) is transformed into its salt or liberated from its salt and/or

separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound, and -if desired- the structural isomers are separated. The urea is preferably formed by use of alkyl or aralkyl isocyanates in inert solvents, preferably in dichloromethane or dioxane, favourably in the presence of potassium carbonate.

Separation of the enantiomers of the racemic compounds of general formula (I) or (IA) can be performed by chiral preparative column chromatography or by any other method known for the resolution of compounds of basic character.

The compounds of the general formula (IV) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b} and Y, are as defined above- can be most generally prepared by alkylating the amine derivatives of the general formula (VI) with the commercially available halogeno-alkylamines of the general formula (XVII), preferably with bromo-alkylamines, or with the salts thereof (figure 6.), in alkoholic media, preferably in boiling *i*-propanol, often in the presence of an acid binding base, such as triethylamine or DBU.

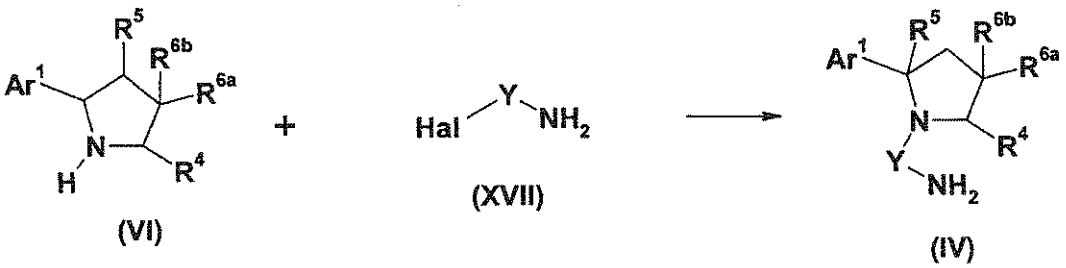


Figure 6.

For the preparation of a diamine of the general formula (IV) from the compound of the general formula (VI), an additional route is also avavilable. If Y stands for straight C_{3-4} alkylene group, optionally substituted by one or more, identical or non-identical C_{1-4} straight or branched alkyl group, the alkylation reaction can be carried out using halogeno-alkyl-cyanides of the general formula (XVIII), – some of which can be purchased, others can be prepared by methods known in the literature –, preferably in dimethylformamide, in the presence of an acid binding base, preferably triethylamine, at a temperature between 20°C and reflux temperature. In the nitrile of the general formula (XIV), R^{13} and R^{14} independently represent hydrogen atom or C_{1-4} straight or branched alkyl group and the value of r equals 0 or 1. The diamines of the general formula (IV) can be obtained from compounds (XIV) by catalytic hydrogenation by analogy of methods known in the literature, in alkoholic or hexane solution, in the presence of ammonia, using Raney nickel or rhodium catalyst, in a given case under pressure (Shapiro et al.: JACS 1959, 81, 3084 and Roufos: J. Med. Chem. 1996, 39, 7, 1514). (Figure 7.).

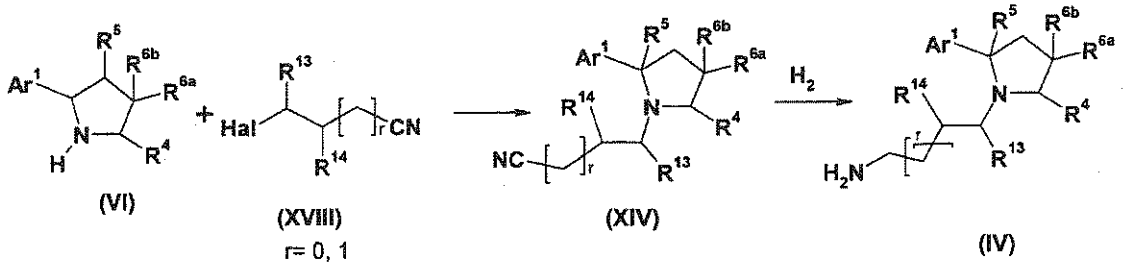


Figure 7.

If Y stands for 1,3-propylene, 1-methyl-1,3-propylene, 2-methyl-1,3-propylene or 1,4-butylene (R^{15} and R^{16} independently represent hydrogen atom or methyl group, r equals 0 or 1), and the meanings of the other substituents are as defined above, the cyanides of the general formula (XIV) can be prepared from the amines of the general formula (VI) with the alkene-cyanides of the general formula (XIII) by literature analogy (Figure 8.) (King et al.: JACS. 1946, 68, 1468). The alkene-cyanides of the general formula (XIII) are commercially available. The diamines of the general formula (IV) can be obtained from the compounds of the general formula (XIV) by catalytic hydrogenation as described above.

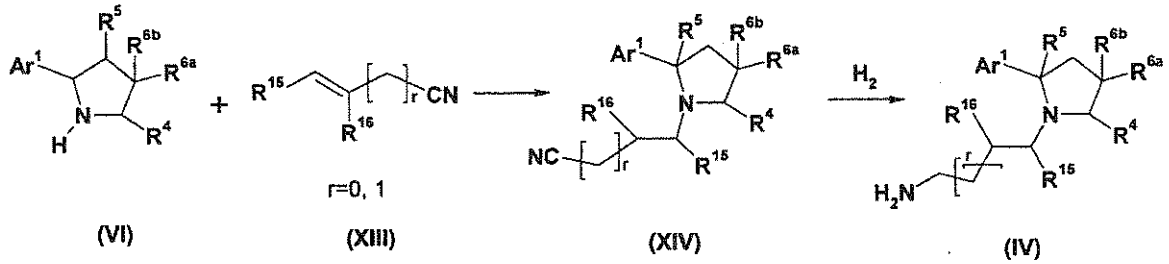


Figure 8.

The diamines of the general formula (IV) where Y stands for 3-methylpropylene, and the meanings of the other substituents are as defined above, can also be prepared by the method demonstrated in Figure 9. Mannich reaction performed from the amines of the general formula (VI) with paraformaldehyde and acetone results the compound of the general formula (XV). The reaction, after literature analogy, can be carried out in *i*-propanol at reflux temperature (JACS. **1959**, 81, 2214-18). The oximes of the general formula (XVI) can be prepared from the compound of the general formula (XV) with hydroxylamine, in aqueous *i*-propanol solution, after analogous examples taken from the literature (JACS. **1959**, 81, 2214-18). The amine of the general formula (IV) can be obtained from the oxime of the general formula (XVI) by literature analogy, by catalytic hydrogenation in the presence of Raney-nickel catalyst, in ethanol-ammonia.

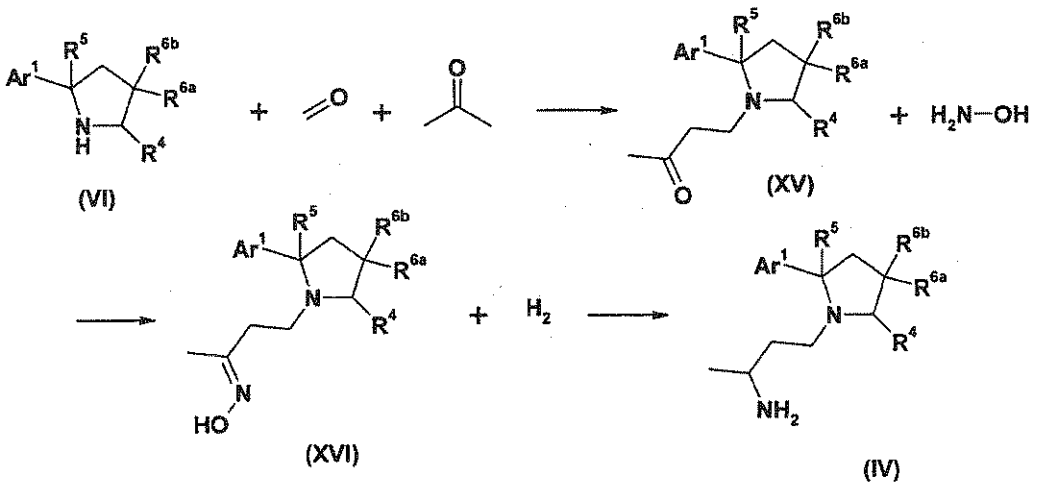


Figure 9.

The pyrrolidine derivatives where in the formula R^5, R^4, R^{6a}, R^{6b} represent hydrogen atom, can be prepared by the method known in the literature (J. Org. Chem. 23, 1958, 1281 and J. Med. Chem. 1972, 15, 827), demonstrated in Figure 10. Reacting substituted bromobenzenes with 4-chlorobutyronitrile in Grignard reaction in the presence of magnesium, the derivative (IX) can be obtained which is hydrogenated using Pt-C catalyst.

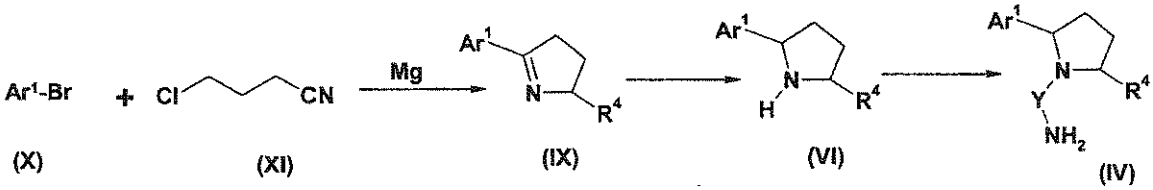


Figure 10.

In another route, from the substituted 4-oxo-4-phenylbutyronitrile (XII) the 5-phenyl-3,4-dihydro-2H-pyrrol (IX) is obtained which after hydrogenation in the presence of Raney-nickel results the derivative (VI) (J. Org. Chem. 23, 1958, 1281), Figure 11.

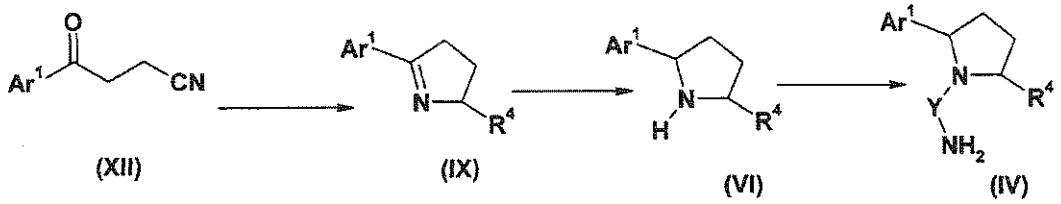


Figure 11.

If R^5=C_{1-4} straight or branched alkyl group, R^4=R^{6a}=R^{6b}=H, the preparation of compound (VI) can be carried out by analogy of literature reference (Tetrahedron Lett. 34, 39, 1993, 6205).

If R^{6a}=R^{6b}=R^5=H and R^4=C_{1-4} straight or branched alkyl group, the preparation of compound (VI) can be carried out by literature analogy (Monatsh. Chem., 83, 1952, 523).

If R^{6a} or R^{6b} represent C_{1-4} straight or branched alkyl group and the other substituents are hydrogen atoms, the compound can be prepared by literature analogy (Chem. Ber. 125, 10, 1992, 2243-48).

If R^{6a}=R^{6b} represent C_{1-4} straight or branched alkyl group and the other substituents are hydrogen atoms, the compound can be prepared by literature analogy (J. Org. Chem. 32, 1967, 3241).

The compounds of the general formulae (X), (XI) and (XII) are described in the literature.

The compounds of the general formulae (V) and (VII) -wherein Ar^2, Z, R^1, Y, W, Z and Hal have the meanings as defined above- can be prepared as described in patent application of publication number WO 2007/034252, or in analogous manner.

Examples:

Example 1.

***N*-{3-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methoxy[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide**

In the general formula (I) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents 1,3-propylene group, Z represents 1,2-ethylene group, Ar^2 stands for 5-methoxy[1,3]thiazolo[5,4-*b*]pyridin-2-yl group.

a.) **5-(3,4-Dichlorophenyl)-3,4-dihydro-2*H*-pyrrole**

Related literature for the preparation of the compound: J. Med. Chem. 15, 1972, 827

b.) **2-(3,4-Dichlorophenyl)pyrrolidine**

Related literature for the preparation of the compound: J. Med. Chem. 15, 1972, 827

c.) **3-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]-propan-1-nitrile**

To the solution of 2.4 g (11.2 mmol) 2-(3,4-dichlorophenyl)pyrrolidine in 13 ml abs. methanol dropwise under stirring at room temperature 2.21 ml (33.6 mmol) acrylnitrile is added. The reaction mixture is stirred for 3 days at room temperature, then evaporated. The residue is purified by column chromatography using at first chloroform, then chloroform:methanol 100:1 ratio mixture as eluent, to obtain 2.1 g title compound in the form of an oil. LC-MS[MH^+]=269 ($C_{13}H_{14}Cl_2N_2$ 269.14).

d.) **3-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]propane-1-amine**

1.9 g (7.1 mmol) nitrile is dissolved in 143 ml methanol-ammonium hydroxide 4:1 mixture and hydrogenated in a H-CUBE THALES apparatus under 30 bar pressure at 45°C. The reaction mixture is evaporated to obtain 3.1 g title compound in the form of an oil.

LC-MS[MH^+]=273 ($C_{13}H_{18}Cl_2N_2$ 273.205)

e.) ***N*-{3-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methoxy[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide**

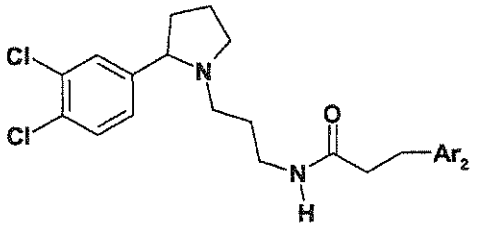
To the solution of 0.33 g (1.4 mmol) 6-methoxy-[1,3]thiazolo[5,4-*b*]pyridin-2-yl-propionic acid in 9 ml abs. dimethylformamide 0.34 g (2.8 mmol) carbonyl-diimidazole is added. The mixture is stirred at room temperature for 0.5 h. then the solution of 0.38 g (1.4 mmol) 3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propane-1-amine in 8.5 ml abs. dimethylformamide, as obtained in point d.) but also containing 0.48 ml (0.35 g, 3.5 mmol) triethylamine, is added to it. The reaction mixture is stirred at room tempertaure overnight and evaporated in vacuum. The residue is mixed with crushed ice, extracted with 3x15 ml ether, dried over sodium sulfate and evaporeted in vacuum. After purification by column chromatography using chloroform-methanol 100:1 mixture as eluent, 0.3 g title compound is obtained in the form of an oil.

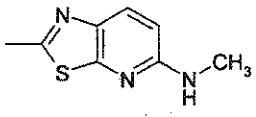
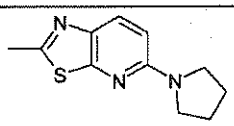
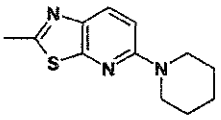
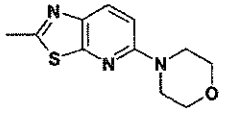
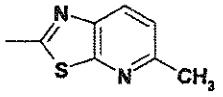
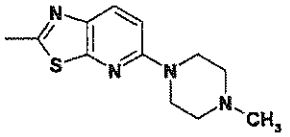
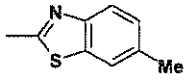
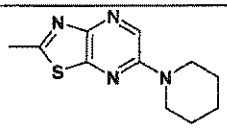
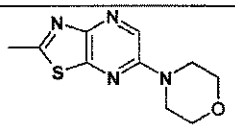
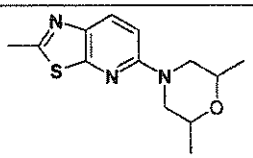
LC-MS[MH^+]=493 ($C_{23}H_{26}Cl_2N_2O_2S$ 493.456)

^{1}H NMR: 7.51, d, 1.9 Hz (1H), 6.95, d, 8.1 Hz (1H), 7.28, dd, 8.1 & 1.9 Hz (1H), 3.19, m (1H), 1.45, m (1H), 2.10, m (1H), 1.65-1.85 (2H), 2.09, m (1H) 3.19, m (1H), 2.00, m (1H), 2.37, m (1H), 1.40-1.55, m (2H), 2.90-3.10, m (2H), 7.84, t, 5.3 Hz (N-H), 2.56, t, 7.2 Hz (2H), 3.24, t, 7.2 Hz (2H), 8.17, d, 8.4 Hz (1H), 6.95, d, 8.4 Hz (1H), 3.92, s (3H)

According to the process described in **Example 1.** the following compounds of **Table 1.** are prepared:

Table 1.



Example	Ar^2	$[MH^+]$	Rt (min)	Mp (°C)
2.		492	4.74	119-121
3.		532	6.37	137-138
4.		546	7.41	93-95
5.		548	5.76	111-112
6.		477	5.32	125-130
7.		561	4.74	
8.		476	6.82	76-79
9.		547	6.74	105
10.		549	5.34	165
11.		576	6.60	

Chemical name of the compounds mentioned in Table 1:

2. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(methylamino)[1,3] thiazolo [5,4-*b*]pyridin-2-yl)propionamide

3. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide

4. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide

5. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

6. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methyl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

7. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(4-methylpiperazin-1-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

8. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-methyl-1,3-benzothiazol-2-yl)propionamide,

9. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-piperidin-1-yl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)propionamide,

10. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-morpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)propionamide,

11. *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide.

Example 12.

_N_-(3-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)]propionamide

In the general formula (I) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents $-CH_2-CH_2-CH(CH_3)-$ group, Z represents 1,2-ethylene group, Ar^2 stands for 5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl group.

a.) **4-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]butan-2-one**

To the solution of 4 g (18.5 mmol) 2-(3,4-dichlorophenyl)-pyrrolidine in 10 ml acetone, during ice-water cooling, the mixture of 10 ml acetone and 1.6 ml cc. hydrochloric acid is added. The mixture is stirred for 15 minutes under cooling for 10 minutes at room temperature, then the solution of 0.83 g (9.3 mmol) paraformaldehyde in 9.2 ml *iso*-propanol is added and the reaction mixture is heated at reflux temperature for 4 hours. After cooling, 15 ml of water is added and the mixture is extracted with 3x20 ml

dichloromethane, dried over sodium sulphate and evaporated in vacuum. The residue is crystallized in hexane to obtain 2.11 g title compound. Mp: 160-162°C.

b.) **(2*E*)-4-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]butan-2-one oxime**

2.11 g (7.4 mmol) of 4-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]butan-2-one as obtained in point a.) is suspended in 11.7 ml iso-propanol and the solution of 0.54 g (7.7 mmol) hydroxylamine hydrochloride in 5 ml of water is added to it. The mixture is stirred for 2 hours. The alcohol is distilled off, the aqueous residue is made alkaline with 5N sodium hydroxide solution, from the resulting sticky precipitate the water is decanted, the residue treated with ether, filtered off and washed with ether. 1.13 g title compound is obtained. Mp: 145-147°C.

c.) **4-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]butan-2-amine**

0.9 g (2.99 mmol) 4-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]butan-2-one oxime as obtained in section b.) is hydrogenated in 100 ml methanol in the presence of Raney-nickel catalyst. After evaporation of the solvent 0.68 g title compound is obtained in the form of an oil. LC-MS[MH^+]= 287 ($C_{14}H_{20}Cl_2N_2$ 287.23).

d.) ***N*-(3-[2-(3,4-Dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)]propionamide**

0.2 g (0.68 mmol) 5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridine is dissolved in 5 ml abs. dimethylformamide and 0.106 g (0.65 mmol) carbonyl-diimidazole is added. The mixture is stirred at room temperature for 1 hour, then the solution of 0.15 g (0.55 mmol) 4-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]butan-2-amine in 4 ml abs. dimethylformamide, as obtained in section d.) but also containing 0.19 ml (1.36 mmol) triethylamine, is added to it. The reaction mixture is stirred at room temperature overnight then poured onto ice-water, extracted with 4x10 ml ether, dried over sodium sulfate, evaporated and purified by column chromatography using chloroform-methanol 9:1 mixture as eluent. The resulting oil is treated with hexane to obtain 85 mg title compound. Mp: 128-132°C, LC-MS[MH^+]= 562, Rt=6.04 min.

Example 13.

***N*-(3-[2-(3,4- Dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-piperidin-1-yl [1,3]thiazolo[5,4-*b*]pyiridin-2-yl)]propionamide**

In the general formula (I) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents $-CH_2-CH_2-CH(CH_3)-$ group, Z represents 1,2-ethylene group, Ar^2 stands for 5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl group.

As described in Example 12. but starting from 0.287 g (1 mmol) of 4-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]butan-2-amine and 0.29 g (1.02 mmol) 5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridine, 0.21 g crystalline title compound is obtained. Mp: 134-140°C, LC-MS[MH^+]= 560, Rt=7.71 min.

Example 14.

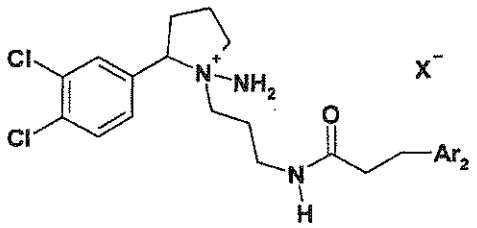
1-Amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate

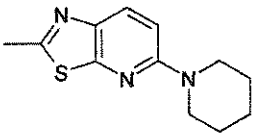
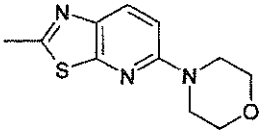
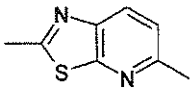
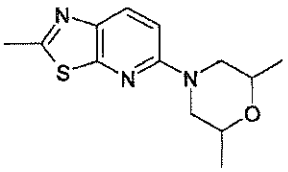
In the general formula (IA) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents 1,3-propylene group, Z represents 1,2-ethylene group, Ar^2 stands for 5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl group, Q stands for $-\bar{N}-H$ group.

To the solution of 0.34 g (0.64 mmol) *N*-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide in 10 ml dichloromethane and 6 ml dimethylformamide, 0.26 g (1.92 mmol) potassium carbonate and then dropwise, under ice-water cooling, the solution of 0.18g (0.96 mmol) *O*-tosylhydroxylamine in 10 ml dichloromethane are added. The reaction mixture is stirred under ice-water cooling for 2 hours, then 20 ml of water is added, the phases are separated, the organic phase is washed with 20 ml of water, dried over sodium sulfate and evaporated. The residual oil is crystallized with ether to obtain 0.34 g title compound. Mp: 115-118°C, LC-MS[M^+]= 547, Rt=4.37 min.

According to the process described in **Example 14**. the following compounds of **Table 2**. are prepared:

Table 2.



Example	Ar^2	Mp (°C)	Rt (min)	$[M^+]$
15.		119-122	4.97	561
16.		215-218	3.89	563
17.		103-106	3.51/3.58	492
18.		102-106	4.08	591

Chemical name of the compounds mentioned in Table 2:

15. 1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

16. 1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-morpholin-4-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

17. 1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-methyl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

18. 1-amino-2-(3,4-dichlorophenyl)-1-[3-({3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate.

Example 19.

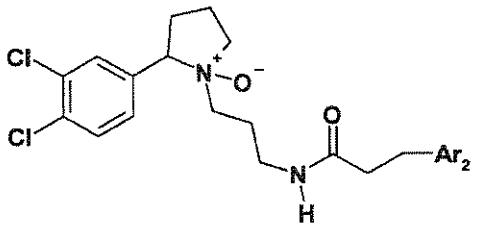
***N*-{3-[2-(3,4-Dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}[3-(5-methyl-1,3-benzothiazol-2-yl)propionamide**

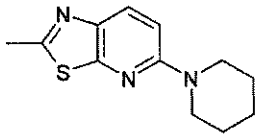
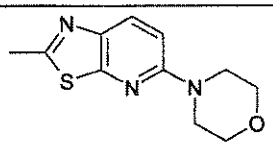
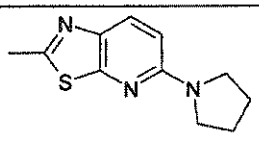
In the general formula (IA) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents 1,3-propylene group, Z represents 1,2-ethylene group, Ar^2 stands for 5-methyl-benzthiazol-2-yl group and Q represents $-O^-$ group.

The solution of 0.146 g (0.31 mmol) N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methyl-1,3-benzthiazol-2-yl)propionamide in 5 ml dichloromethane is cooled to 0°C, 53 mg (0.31 mmol) *m*-chloroperbenzoic acid is added to it under stirring and the mixture is stirred for 1 hour. The acid is neutralized with solid potassium carbonate, the precipitated salts are filtered off, the dichloromethane solution is evaporated. The residue is purified by column chromatography using chloroform-methanol 9:1 mixture as eluent to obtain 88 mg title compound in the form of white crystals. Mp. 145-148°C, **[MH^+]=492, Rt=4.31 min**.

According to the process described in **Example 19**. the following compounds of **Table 3**. are prepared:

Table 3.



Example	Ar^2	Mp (°C)	[MH^+]	Rt (min)
20.		185-187	562	2.91
21.		172-175	564	3.72
22.		185-188	548	4.19

Chemical name of the compounds mentioned in Table 3:

20. *N*-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl) [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,

21. *N*-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,

22. *N*-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide.

Example 23.

1-(Acetylamino)-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-b]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium hydrochloride

In the general formula (IA) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents 1,3-propylene group, Z represents 1,2-ethylene group, Ar^2 stands for 5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl group, Q represents $-N^-$-CO-CH_3 group.

To the solution made of 0.11 g (0.15 mmol) 1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2yl)propanoyl]amino}propyl) pyrrolidinium tosylate and 25 ml dichloromethane, 0.083 g (0.6 mmol) potassium carbonate and 0.013 ml (0.18 mmol) acetyl chloride are added and the mixture is refluxed for 6 hours. Then, additional 0.166 g (1.2 mmol) potassium carbonate and 0.026 ml (0.36 mmol) acetyl chloride are added and the mixture is refluxed for 16 hours. The addition of potassium carbonate and acetyl chloride is repeated twice and the mixture is refluxed for further 50 hours. The reaction mixture is filtered, the precipitated inorganic salts are washed with dichloromethane, the organic phase is evaporated and purified by flash chromatography using dichloromethane-methanol 95:5 mixture. The united fractions are dissolved in 10 ml water, made alkaline with 1N sodium hydroxide, extracted with 3x5 ml dichloromethane, dried over sodium sulphate and evaporated. From the oily residue the salt is formed with hydrogen chloride in ether solution to obtain 0.8 g title compound in the form of crystals. Mp: 77-80°C, **$[M^+]$=603, Rt=4.62/4.71/5.13 min**.

Example 24.

1-(3-Ethyl-ureido)-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-(2,6-dimethyl-morpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium hydrochloride

In the general formula (IA) Ar^1 represents 3,4-dichlorophenyl group, R^4, R^5, R^{6a}, R^{6b}, R^1 represent hydrogen atom, Y represents 1,3-propylene group, Z represents 1,2-ethylene group, Ar^2 stands for 2,6-dimethyl-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl group, Q represents $-\bar{N}$-CO-NH-C_2H_5 group-

To the solution made of 0.13 g (0.17 mmol) 1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(2,6-dimethylmorfolin-4-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate and 15 ml dichloroethane, 0.1 g (0.51 mmol) potassium carbonate and 0.05 ml (0.63 mmol) ethyl isocyanate are added and the mixture is refluxed for 10 hours. After cooling, the organic part is evaporated. The residue is taken up in 10 ml water and extracted with 3x10 ml dichloroethane. The united organic phase is dried, filtered, evaporated in vacuum and purified by flash chromatography using dichloromethane-methanol 98:5 mixture. From the oily residue the salt is formed in dichloromethane with hydrogen chloride in ether solution to obtain 0.1 g title compound in the form of crystals. Mp: 115-118°C, **$[M^+]$=662, Rt=5.52 min**.

Example 25.

By known methods tablets of the following composition are prepared:

Active ingredient:	40 mg
Lactose:	35 mg
Avicel:	21 mg
Crospovidone:	3 mg
Magnesium stearate:	1 mg

Example 26.

A.) Human recombinant CCR3 receptor (hr-CCR3) binding assay

The CCR3 receptor antagonist effect of the compounds of general formula (I) was examined on eotaxin binding test on hCCR3 receptor expressing recombinant K562 and

RBL2H3 cells. To the tests Eotaxin labelled with radioactive iodine ^{125}I- (2200 Ci/mmol) was used.

In the assay 200.000 cells are incubated in the presence of 0.11 nM ^{125}I-Eotaxin, incubation: 60 minutes at 37 °C. Composition of the assay buffer: RPMI-1640 medium, pH=7.6 (GIBCO), [containing 80 mg CHAPS, 500 BSA (protease free), 100 mg Gelatine, 3 ml 25 mM HEPES in 100 ml RPMI]. The test compounds are dissolved in DMSO, the stock solution is diluted with the assay buffer. The final DMSO concentration is not more than 1 %. The cells are incubated with the test compounds for 15 minutes, then the labelled eotaxin is added. The non-specific binding is determined in the presence of 200 nM non-labelled eotaxin. After 1 hour of incubation, 500 µl ice-cold assay buffer containing 0.5 M NaCl solution is added. Since the experiments were performed in deep-well plates, the reaction is terminated by centrifugation in plate centrifuge (JUAN) at 3600 g for 6 minutes. The supernatants are poured off by turning the plates in upside-down position. The remaining droplets were blotted with tissue paper.

For solubilization 200 µl 0.5 M NaOH solution is added to the pellets. After 1 hour of solubilization at room temperature the radioactivity is counted in gamma counter (1470 Wizard, Wallac).

The radioactivity of the solution is in direct ratio with the number of the receptors of the cells, with the amount of the bound ^{125}I-Eotaxin and with the activity of the tested antagonist.

The specific binding is calculated as the difference between the total and the non-specific bindings. The activity of the compounds is calculated from the specific binding and from the binding measured in the presence of the antagonist molecule.

The activity of the compounds is characterized with the IC_{50} value.

<u>B.) Investigation of Ca^{2+} mobilization in hCCR3-RBL and hCCR3 K562 cells</u>

HCCR3-K562 and hCCE3-RBL2H3 cells in 40,000 cells/well density (number of cells in one well of the microplate) are cultured for 24 hours. The cells are washed and loaded with calcium indicator dye (Calcium Plus assay Kit, Molecular Devices). The cells are incubated in the presence of the dye for 60 minutes while loading takes place. The dye is a fluorescent calcium indicator, which sensitively indicates the intracellular calcium concentration. The intracellular calcium concentration is in direct ratio with the fluorescent

signal of the sample. The experiments are performed in a BMG NOVOSTAR apparatus, at excitation and emission wavelengths.

The selective agonists used in the experiments are:

Eotaxin

Eotaxin-2

Eotaxin-3

RANTES

Following the addition of the selective agonist, the intracellular calcium concentration in the cells significantly increases which can be monitored with the help of the fluorescent signal. In the experiments an agonist concentration is used which causes a 75% calcium signal compared to the maximum attainable signal.

Antagonists are added 15 minutes before the agonist treatment.

The change of the fluorescent signal is monitored for 30 seconds, during that period the process takes place.

The intensity of the maximum calcium signal following the addition of the agonist is compared with the calcium signal obtained after the addition of the same agonist, but in the presence of the inhibitor.

The activity of the compounds is characterized with the IC_{50} values.

On the basis of tests A and B the compounds of general formula (I) and (IA) were found biologically active.

The compounds of general formula (I) and (IA) according to Claim 5 which form a narrower group of the compounds of general formula (I) and (IA) of Claim 1 were found the most potent. The IC_{50} values of these compounds were below 200 nM. Most of the compounds had IC_{50} values were below 50 nM. A number of compounds exhibited IC_{50} values below 5 nM.

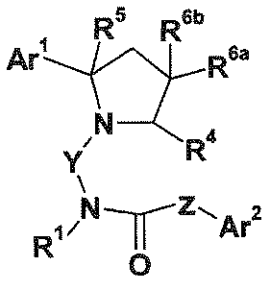
For example, of the compounds of general formula (I) or (IA), those described in certain Examples exhibited the following IC_{50} values, as determined in test B:

Example:	**IC_{50} [nM]**
9.	3.9
17.	1.9
20.	13
23.	13
2.	18

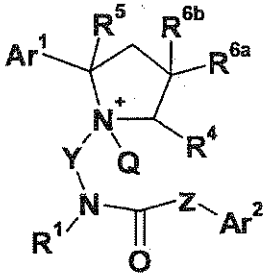
3.	5
4.	3.4
5.	0.9
11.	1.6
14.	1
15.	0.9
16.	0.3
18.	0.95
21.	82.5

Claims

1. Compounds of the general formula (I) or (IA),



(I)



(IA)

where

Ar^1 represents phenyl or naphthyl group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, trifluoromethyl group, cyano group, nitro group, hydroxyl group, C_{1-2} alkylenedioxy group, amino group, or amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group;

R^1, represents hydrogen atom, or straight or branched C_{1-4} alkyl group;

R^4, R^5, R^{6a}, R^{6b} represents hydrogen atom, or

R^4 stands for straight or branched C_{1-4} alkyl group and R^5, R^{6a} and R^{6b} represent hydrogen atom, or

R^5 stands for straight or branched C_{1-4} alkyl group and R^4, R^{6a} and R^{6b} represent hydrogen atom, or

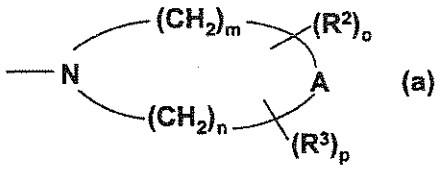
R^{6a} stands for straight or branched C_{1-4} alkyl group and R^{6b} stands for straight or branched C_{1-4} alkyl group or hydrogen atom and R^5, R^4 represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents a phenyl-, thienyl-, or furyl group, –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, hydroxyl group, cyano group, nitro group, trifluoromethyl group, C_{1-2} alkylenedioxy group, amino group, amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group; or

5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur

atom –optionally substituted with one or more, identical or non-identical, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where R^7 and R^8 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, or R^7 and R^8 together with the nitrogen atom form a group of general formula (a),



where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group–,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1;

or

the benzologue of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, trifluoromethyl group, nitro group, cyano group, C_{1-2} alkylenedioxy group, $-NR^7R^8$,$-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above; or

the derivative of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms, –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group,

$-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above;

Q represents $-O^-$ group, $-N^--H$ or $-N^--CO-R^{10}$ group –where R^{10} stands for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl-, benzyl- or $-NH-R^{11}$ group –where R^{11} represents straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl- or benzyl-group-;

and their salts and isomers and the salts thereof.

2. The compounds of the general formula (IA) according to Claim 1,

where

Ar^1 represents phenyl or naphthyl group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, trifluoromethyl group, cyano group, nitro group, hydroxyl group, C_{1-2} alkylenedioxy group, amino group, or amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group;

R^1, represents hydrogen atom, or straight or branched C_{1-4} alkyl group;

R^4, R^5, R^{6a}, R^{6b} represent hydrogen atom, or

R^4 stands for straight or branched C_{1-4} alkyl group and **R^5**, **R^{6a}** and **R^{6b}** represent hydrogen atom, or

R^5 stands for straight or branched C_{1-4} alkyl group and **R^4**, **R^{6a}** and **R^{6b}** represent hydrogen atom, or

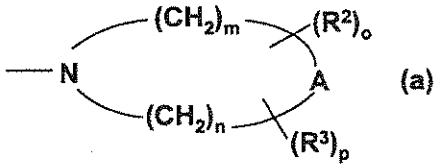
R^{6a} stands for straight or branched C_{1-4} alkyl group and **R^{6b}** stands for straight or branched C_{1-4} alkyl group or hydrogen atom and **R^5**, **R^4** represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents a phenyl-, thienyl-, or furyl group, –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom, hydroxyl group, cyano group, nitro group, trifluoromethyl group, C_{1-2} alkylenedioxy group, amino group, or amino group substituted with one or two identical or non-identical straight or branched C_{1-4} alkyl group; or

5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more identical or non-identical straight or

branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where R^7 and R^8 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group or R^7 and R^8 together with the nitrogen atom form a group of general formula (a),



(a)

where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group–,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1,

or

the benzologue of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more, identical or non-identical, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, trifluoromethyl group, nitro group, cyano group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meaning of R^7 and R^8 are as defined above-; or

the derivative of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms, –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group,

$-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above;

Q represents $-\bar{N}-H$ group;

and their salts and isomers and the salts thereof.

3. The compounds of general formula (I) or (IA) according to Claim 1,

where

$\mathbf{Ar^1}$ represents phenyl or naphthyl group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, halogen atom;

$\mathbf{R^1}$ represents hydrogen atom, or methyl group;

$\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^{6a}}$, $\mathbf{R^{6b}}$ represents hydrogen atom, or

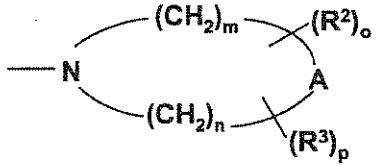
$\mathbf{R^4}$ stands for methyl group and $\mathbf{R^5}$, $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ represent hydrogen atom, or

$\mathbf{R^5}$ stands for methyl group and $\mathbf{R^4}$, $\mathbf{R^{6a}}$ and $\mathbf{R^{6b}}$ represent hydrogen atom, or

$\mathbf{R^{6a}}$ stands for methyl group and $\mathbf{R^{6b}}$ stands for methyl group or hydrogen atom and $\mathbf{R^5}$, $\mathbf{R^4}$ represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

$\mathbf{Ar^2}$ represents the benzologue of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, trifluoromethyl group, nitro group, cyano group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where R^7 and R^8 independently mean hydrogen atom, straight or branched C_{1-4} alkoxy group, or R^7 and R^8 together with the nitrogen atom form a group of the general formula (a),



(a)

where,

$\mathbf{R^2}$, $\mathbf{R^3}$ represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents $-CHR^{12}$ group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1, - or

the derivative of a 5- or 6-membered heterocyclic ring containing one, two, or three nitrogen atoms, or one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxyl group, halogen atom, nitro group, cyano group, trifluoromethyl group, C_{1-2} alkylenedioxy group, $-NR^7R^8$, $-CONR^7R^8$ or $-SO_2NR^7R^8$ group –where the meanings of R^7 and R^8 are as defined above;

Q represents $-O^-$ group, $-N^-$-H or $-N^-$-CO-R^{10} group –where R^{10} stands for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl-, benzyl- or $-NH-R^{11}$ group –where R^{11} represents straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl- or benzyl-group-;

and their salts-and isomers and the salts thereof.

4. The compounds of general formula (I) or (IA) according to Claims 1 or 3,

where

Ar^1 represents phenyl group –optionally substituted with one or more identical or non-identical halogen atom;

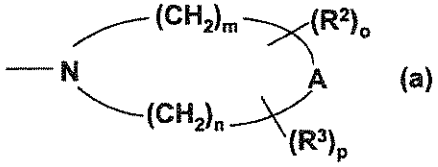
R^1 represents hydrogen atom;

R^4, R^5, R^{6a}, R^{6b} represent hydrogen atom;

Y, Z independently represent straight C_{1-4} alkylene group –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group;

Ar^2 represents the benzologue of a 5- or 6-membered heterocyclic ring containing one nitrogen atom and one sulphur atom –optionally substituted with one or more, identical or non-identical straight or branched C_{1-4} alkyl group, or

the derivative of a 5- or 6-membered heterocyclic ring containing one nitrogen atom and one sulphur atom, condensed with heteroaromatic 6-membered rings containing one or two nitrogen atoms –optionally substituted with one or more identical or non-identical straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, $-NR^7R^8$ group, –where R^7 and R^8 independently mean hydrogen atom, straight or branched C_{1-4} alkyl group or R^7 and R^8 together with the nitrogen atom form a group of the general formula (a);



(a)

where,

R^2, R^3 represent straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group,

A represents -CHR^{12} group, oxygen atom, sulphur atom or $-NR^9$ group –where R^{12} and R^9 stand for hydrogen atom, straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-,

m has the value of 1, 2 or 3,

n has the value of 1 or 2,

o has the value of 0 or 1,

p has the value of 0 or 1;

Q represents $-O^-$ group, $-N^-$-H or $-N^-$-CO-R^{10} group –where R^{10} stands for hydrogen atom, straight or branched C_{1-4} alkyl group, or –NH-R^{11} group –where R^{11} represents straight or branched C_{1-4} alkyl group;

and their salts and isomers and the salts thereof.

5. The compounds of general formula (I) or (IA) according to any of Claims 1-4, where

Ar^1 represents phenyl group substituted with one or two identical or non-identical halogen atom,

and their salts-and isomers and the salts thereof.

6. The following compounds according to any of Claim 1 or Claims 3-5:

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methoxy[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(methylamino)[1,3]thiazolo [5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-methyl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(4-methylpiperazin-1-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-methyl-1,3-benzothiazol-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-piperidin-1-yl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)propionamide,

N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(6-morpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyrazin-2-yl)propionamide,

N-(3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-morpholin-4-yl [1,3]thiazolo[5,4-*b*]pyridin-2-yl)]propionamide,

N-(3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]-1-methylpropyl)-3-(5-piperidin-1-yl [1,3]thiazolo[5,4-*b*]pyridin-2-yl)]propionamide,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-morpholin-4-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-methyl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

1-amino-2-(3,4-dichlorophenyl)-1-[3-({3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,

N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl) [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,
N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,
N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,
1-(Acetylamino)-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-b]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium hydrohloride
and their salts and isomers and the salts thereof.

7. The following compounds according to any of Claim 1 or Claims 3-6:
N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(methylamino)[1,3]thiazolo [5,4-*b*]pyridin-2-yl)propionamide,
N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-pyrrolidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,
N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-piperidin-1-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,
N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,
N-{3-[2-(3,4-dichlorophenyl)pyrrolidin-1-yl]propyl}-3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[5,4-*b*]pyridin-2-yl)propionamide,
1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-pyrrolidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,
1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-piperidin-1-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,
1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-morpholin-4-yl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,
1-amino-2-(3,4-dichlorophenyl)-1-(3-{[3-(5-methyl[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,
1-amino-2-(3,4-dichlorophenyl)-1-[3-({3-(5-(2,6-dimethylmorpholin-4-yl)[1,3]thiazolo[4,5-*b*]pyridin-2-yl)propanoyl]amino}propyl)pyrrolidinium tosylate,
N-{3-[2-(3,4-dichlorophenyl)-1-oxidopyrrolidin-1-yl]propyl}-3-(5-morpholin-4-yl [1,3]thiazolo[4,5-*b*]pyridin-2-yl)propionamide,
and their salts and isomers and the salts thereof.

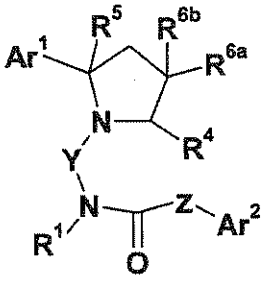
8. The compounds of general formula (IA) according to any of Claims 3-7,

where,

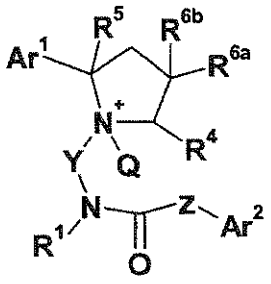
Q represents $-\bar{N}$-H group

and their salts-and isomers and the salts thereof.

9. Process for the preparation of the compounds of general formula (I) or (IA) and their salts and isomers and the salt thereof,



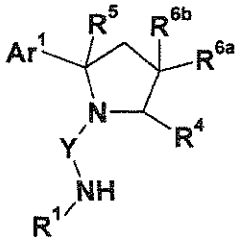
(I)



(IA)

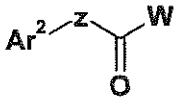
- where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined in Claim 1 -, characterized in that

a.) to prepare the compounds of general formula (I) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined in Claim 1- a compound of the general formula (IV),



(IV)

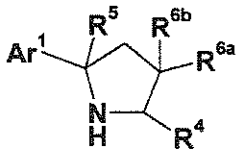
-where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y are as defined in Claim 1- is reacted with a carboxylic acid derivative of the general formula (V),



(V)

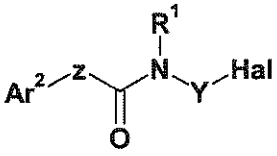
-where the meanings of Ar^2 and Z are as defined in Claim 1, and W represents halogen atom, hydroxyl group, –O(C_{1-4} alkyl) group or –OCO-Z-Ar^2 group, where the meanings of Z and Ar^2 are as defined in Claim 1- ; or

b.) to prepare the compounds of general formula (I) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and Q are as defined in Claim 1- an amino compound of the general formula (VI)



(VI)

-where the meanings of Ar^1, R^5, R^4, R^{6a} and R^{6b} are as defined in Claim 1- is reacted with a halogen compound of the general formula (VII)



(VII)

-where the meanings of Y, R^1, Ar^2 and Z are as defined in Claim 1- and Hal represents halogen atom, or

c.) to prepare the compounds of general formula (IA) -where Q represents $-O^-$ group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined in Claim 1- a compound of the general formula (I) prepared by method a.) or b.) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined in Claim 1- is oxidized, or

d.) to prepare the compounds of general formula (IA) and their salts -where Q represents $-N^-$-H group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined in Claim 1.- a compound of the general formula (I) prepared by method a.) or b.) -where the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 are as defined in Claim 1.- is reacted with *O*-tosylhydroxylamine, or

e.) to prepare the compounds of general formula (IA) and their salts -where Q represents $-N^-$-CO-R^{10} group -where R^{10} represents hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, phenyl or benzyl group- and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined in Claim 1.- a

compound of the general formula (IA) prepared by method d.) -where Q represents -N -H group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined in Claim 1.- is acylated with a group of the general formula HIg-CO-R^{10} - where the meaning of R^{10} is as defined in Claim 1.- and HIg represents halogen atom, or

f.) to prepare the compounds of general formula (IA) -where Q represents -N -CO-R^{10} group -where R^{10} represents -NH-R^{11} and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z, Ar^2 and R^{11} are as defined in Claim 1.- a compound of the general formula (IA) prepared by method d.) -where Q represents -N -H group and the meanings of Ar^1, R^1, R^4, R^5, R^{6a}, R^{6b}, Y, Z and Ar^2 are as defined in Claim L- is reacted with a compound of the general formula R^{11}NCO -where the meaning of R^{11} is as defined in Claim-,

and -if desired- the substituents of the resulting compound of the general formula (I) or (LA) are transformed into each other by a method known per se, and/or the resulting compound of the general formula (I) or (IA) is transformed into its salt, or liberated from its salt and/or separated into its optically active isomers, or the optically active isomer is transformed into the racemic compound and if desired the structural isomers are separated.

10. Pharmaceutical composition, characterized in that, it comprises one or more of the compounds of the general formula (I) or (IA according to any of claims 1 to 8 and/or its salt or isomer or the salt thereof, and one or more excipients commonly used in the pharmaceutical industry.

11. Medicament, characterized in that, it comprises one or more of the compounds of the general formula (I) or (IA) according to any of claims 1 to 8 and/or its salt or isomer or the salt thereof.

12. Use of the compounds of the general formula (I) or (IA) according to any of claims 1 to 8 and their salts and isomers and the salt thereof, for the preparation of a medicament intended for the treatment of pathologies where in the development of the disease CCR3 receptors play a role, selected from asthma, allergic rhinitis, atopic dermatitis, eczema, inflammatory bowel disease, ulcerative colitis, Crohn disease, allergic conjunctivitis, multiple sclerosis or HIV-infection and diseases in conjuction with AIDS.

13. Compounds of of the general formula (I) or (IA) according to any of claims 1 to 8 and their salts and isomers and the salt thereof for the treatment of pathologies where in the development of the disease CCR3 receptors play a role.

14. Compounds according to Claim 13 and their salts and isomers and the salt thereof for the treatment of asthma, allergic rhinitis, atopic dermatitis, eczema, inflammatory bowel disease, ulcerative colitis, Crohn disease, allergic conjunctivitis, multiple sclerosis or HIV-infection and diseases in conjunction with AIDS.