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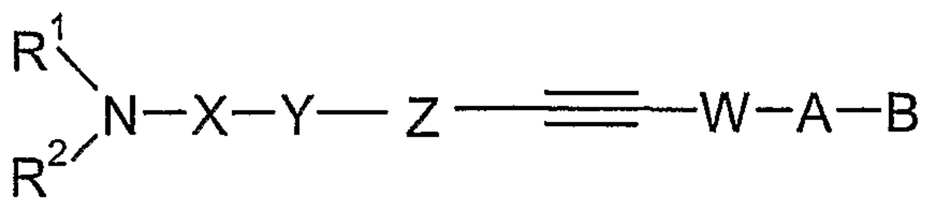
(54) Titre : NOUVEAUX COMPOSES ALKYNE A EFFET ANTAGONISTE DE MCH ET MEDICAMENTS CONTENANT LESDITS COMPOSES

(54) Title: NOVEL ALKYNE COMPOUNDS EXHIBITING AN MCH ANTAGONISTIC EFFECT AND DRUGS CONTAINING SAID COMPOUNDS



(I)

(57) Abrégé/Abstract:
The invention relates to an alkyne compound of general formula (I) in which A, B, W, X, Y, Z, R1 and R2 groups and residuals have the meanings given in claim 1. Drugs containing at least one type of inventive alkyne are also disclosed. The inventive drugs exhibiting an MCH-receptor antagonistic activity are suitable for treating metabolic disturbances and/or eating disorders, in particular adiposity, bulimia, anorexia, hyperphagia and diabetes.

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# ABSTRACT

The invention relates to an alkyne compound of general formula (I) in which A, B, W, X, Y, Z, $R^1$ and $R^2$ groups and residuals have the meanings given in claim 1. Drugs containing at least one type of inventive alkyne are also disclosed. The inventive drugs exhibiting an MCH-receptor antagonistic activity are suitable for treating metabolic disturbances and/or eating disorders, in particular adiposity, bulimia, anorexia, hyperphagia and diabetes.

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# Novel alkyne compounds exhibiting an MCH antagonistic effect and drugs containing said compounds

The present invention relates to new alkyne compounds, the physiologically acceptable salts thereof as well as their use as MCH antagonists and their use in preparing a pharmaceutical preparation which is suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. The invention also relates to the use of a compound according to the invention for influencing eating behaviour and for reducing body weight and/or for preventing any increase in body weight in a mammal. It further relates to compositions and medicaments containing a compound according to the invention and processes for preparing them. Other aspects of this invention relate to processes for preparing the compounds according to the invention.

## Background to the Invention

The intake of food and its conversion in the body is an essential part of life for all living creatures. Therefore, deviations in the intake and conversion of food generally lead to problems and also illness. The changes in the lifestyle and nutrition of humans, particularly in industrialised countries, have promoted morbid overweight (also known as corpulence or obesity) in recent decades. In affected people, obesity leads directly to restricted mobility and a reduction in the quality of life. There is the additional factor that obesity often leads to other diseases such as, for example, diabetes, dyslipidaemia, high blood pressure, arteriosclerosis and coronary heart disease. Moreover, high body weight alone puts an increased strain on the support and mobility apparatus, which can lead to chronic pain and diseases such as arthritis or osteoarthritis. Thus, obesity is a serious health problem for society.

The term obesity means an excess of adipose tissue in the body. In this connection, obesity is fundamentally to be seen as the increased level of fatness which leads to a health risk. There is no sharp distinction between normal individuals and those suffering from obesity, but the health risk accompanying obesity is presumed to rise continuously as the level of fatness increases. For simplicity's sake, in the present invention, individuals with a Body Mass Index (BMI), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, above a value of 25 and more particularly above 30, are preferably regarded as suffering from obesity.

Apart from physical activity and a change in nutrition, there is currently no convincing treatment option for effectively reducing body weight. However, as obesity is a major risk factor in the development of serious and even life-threatening diseases, it is all the more important to have access to pharmaceutical active substances for the prevention and/or treatment of obesity. One approach which has been proposed very recently is the therapeutic use of MCH antagonists (cf. *inter alia* WO 01/21577, WO 01/82925).

Melanin-concentrating hormone (MCH) is a cyclic neuropeptide consisting of 19 amino acids. It is synthesised predominantly in the hypothalamus in mammals and from there travels to other parts of the brain by the projections of hypothalamic neurones. Its biological activity is mediated in humans through two different G-protein-coupled receptors (GPCRs) from the family of rhodopsin-related GPCRs, namely the MCH receptors 1 and 2 (MCH-1R, MCH-2R).

Investigations into the function of MCH in animal models have provided good indications for a role of the peptide in regulating the energy balance, i.e. changing metabolic activity and food intake [1,2]. For example, after intraventricular administration of MCH in rats, food intake was increased compared with control animals. Additionally, transgenic rats which produce more MCH than control animals, when given a high-fat diet, responded by gaining significantly more weight than animals without an experimentally altered MCH level. It was also found that there is a positive correlation between phases of increased desire for food and the quantity of MCH mRNA in the hypothalamus of rats. However, experiments with MCH knock-out mice are particularly important in showing the function of MCH. Loss of the neuropeptide results in lean animals with a reduced fat mass, which take in significantly less food than control animals.

The anorectic effects of MCH are presumably mediated in rodents through the $G_{\forall s}$-coupled MCH-1R [3-6], as, unlike primates, ferrets and dogs, no second MCH receptor subtype has hitherto been found in rodents. After losing the MCH-1R, knock-out mice have a lower fat mass, an increased energy conversion and, when fed on a high fat diet, do not put on weight, compared with control animals. Another indication of the importance of the MCH system in regulating the energy balance results from experiments with a receptor antagonist (SNAP-7941) [3]. In long term trials the animals treated with the antagonist lose significant amounts of weight.

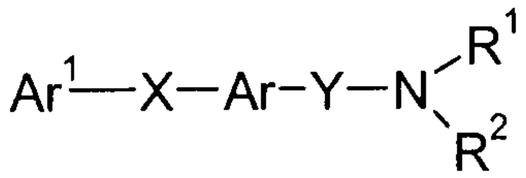
In addition to its anorectic effect, the MCH-1R antagonist SNAP-7941 also achieves additional anxiolytic and antidepressant effects in behavioural experiments on rats [3]. Thus,

there are clear indications that the MCH-MCH-1R system is involved not only in regulating the energy balance but also in affectivity.

Literature:

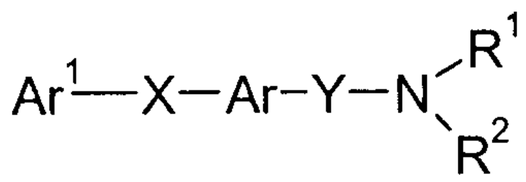
1. Qu, D., et al., *A role for melanin-concentrating hormone in the central regulation of feeding behaviour.* Nature, 1996. **380**(6571): p. 243-7.
2. Shimada, M., et al., *Mice lacking melanin-concentrating hormone are hypophagic and lean.* Nature, 1998. **396**(6712): p. 670-4.
3. Borowsky, B., et al., *Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist.* Nat Med, 2002. **8**(8): p. 825-30.
4. Chen, Y., et al., *Targeted disruption of the melanin-concentrating hormone receptor-1 results in hyperphagia and resistance to diet-induced obesity.* Endocrinology, 2002. **143**(7): p. 2469-77.
5. Marsh, D.J., et al., *Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism.* Proc Natl Acad Sci U S A, 2002. **99**(5): p. 3240-5.
6. Takekawa, S., et al., *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist.* Eur J Pharmacol, 2002. **438**(3): p. 129-35.

In the patent literature certain amine compounds are proposed as MCH antagonists. Thus, WO 01/21577 (Takeda) describes compounds of formula



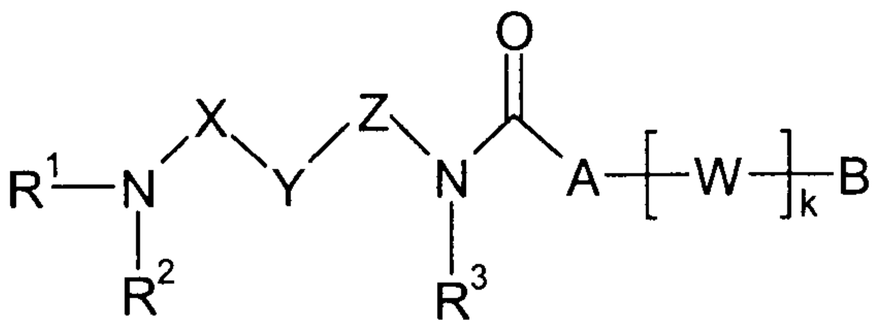
wherein $Ar^1$ denotes a cyclic group, X denotes a spacer, Y denotes a bond or a spacer, Ar denotes an aromatic ring which may be fused with a non-aromatic ring, $R^1$ and $R^2$ independently of one another denote H or a hydrocarbon group, while $R^1$ and $R^2$ together with the adjacent N atom may form an N-containing hetero ring and $R^2$ with Ar may also form a spirocyclic ring, R together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity.

Moreover WO 01/82925 (Takeda) also describes compounds of formula



wherein $Ar^1$ denotes a cyclic group, X and Y represent spacer groups, Ar denotes an optionally substituted fused polycyclic aromatic ring, $R^1$ and $R^2$ independently of one another represent H or a hydrocarbon group, while $R^1$ and $R^2$ together with the adjacent N atom may form an N-containing heterocyclic ring and $R^2$ together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity, *inter alia*.

WO 2004/024702 proposes carboxylic acid amide compounds of formula I



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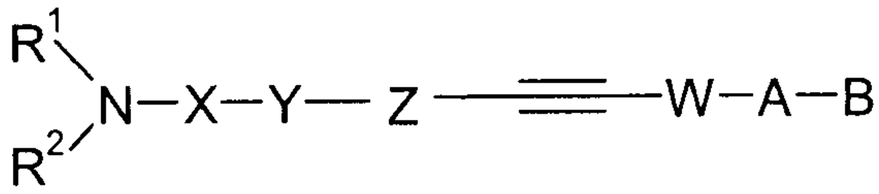
wherein Y, A and B may represent cyclic groups and X, Z and W may denote bridges or bonds, as MCH-antagonists.

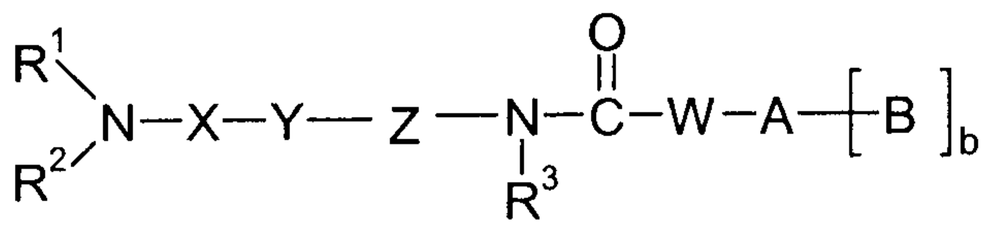
WO 04/039780 A1 describes alkyne compounds of formula I



I

wherein Y, A and B may denote cyclic groups and X, Z and W may denote bridges or bonds, as MCH-antagonists. The following substances are mentioned, *inter alia*:
6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-2-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-quinoline,
6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-methyl-2-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-quinoline,
5-(4-chloro-phenyl)-2-[2-(4-methyl-piperidin-1-ylmethyl)-chroman-6-ylethynyl]-pyridine.

WO 04/039764 A1 describes amide compounds of formula I



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wherein Y, A and B may denote cyclic groups and X denotes an alkylene bridge, Z denotes a bridge or bond and W is selected from the group comprising $-CR^{6a}R^{6b}-O-$ $-CR^{7a}=CR^{7c}$, $-CR^{6a}R^{6b}-NR^8-$, $-CR^{7a}R^{7b}-CR^{7c}R^{7d}-$ and $-NR^8-CR^{6a}R^{6b}-$, as MCH-antagonists.

**Aim of the invention**

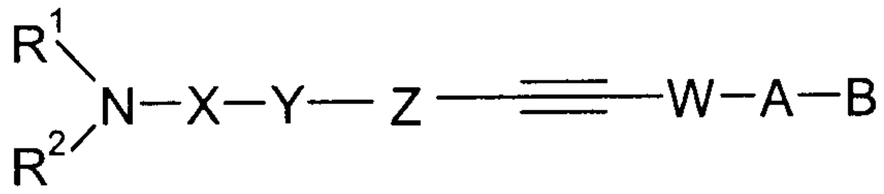
The aim of the present invention is to identify new alkyne compounds, particularly those which are especially effective as MCH antagonists. The invention also sets out to provide new

alkyne compounds which can be used to influence the eating habits of mammals and achieve a reduction in body weight, particularly in mammals, and/or prevent an increase in body weight.

The present invention further sets out to provide new pharmaceutical compositions which are suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or otherwise causally connected to MCH. In particular, the aim of this invention is to provide pharmaceutical compositions for the treatment of metabolic disorders such as obesity and/or diabetes as well as diseases and/or disorders which are associated with obesity and diabetes. Other objectives of the present invention are concerned with demonstrating advantageous uses of the compounds according to the invention. The invention also sets out to provide a process for preparing the amide compounds according to the invention. Other aims of the present invention will be immediately apparent to the skilled man from the foregoing remarks and those that follow.

**Object of the invention**

In a first aspect the present invention relates to alkyne compounds of general formula I



I

wherein

$R^1$, $R^2$ independently of one another denote H, $C_{1-8}$-alkyl, $C_{3-7}$-cycloalkyl or a phenyl or pyridinyl group optionally mono- or polysubstituted by identical or different groups $R^{20}$ and/or monosubstituted by nitro, while the alkyl or cycloalkyl group may be mono- or polysubstituted by identical or different groups $R^{11}$, and a $-CH_2-$ group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by -O-, -S- or $-NR^{13}-$, or

$R^1$ and $R^2$ form a $C_{3-8}$-alkylene bridge, wherein a $-CH_2-$ group not adjacent to the N atom of the $R^1R^2N-$ group may be replaced by -CH=N-, -CH=CH-, -O-, -S-, -SO-, $-(SO_2)-$, -CO-, $-C(=CH_2)-$ or $-NR^{13}-$,

while in the alkylene bridge defined hereinbefore one or more H atoms may be replaced by identical or different groups $R^{14}$, and

the alkylene bridge defined hereinbefore may be substituted by one or two identical or different carbo- or heterocyclic groups Cy such that the bond between the alkylene bridge and the group Cy is made

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system;

X denotes a $C_{1-4}$-alkylene bridge, while in the definition $C_{2-4}$-alkylene one or two C atoms may be monosubstituted by $R^{10}$, or

a $C_{3-4}$-alkylene bridge, wherein a $-CH_2-CH_2-$ group not immediately adjacent to the N atom of the $R^1R^2N-$ group is replaced by -CH=CH- or -C≡C-,

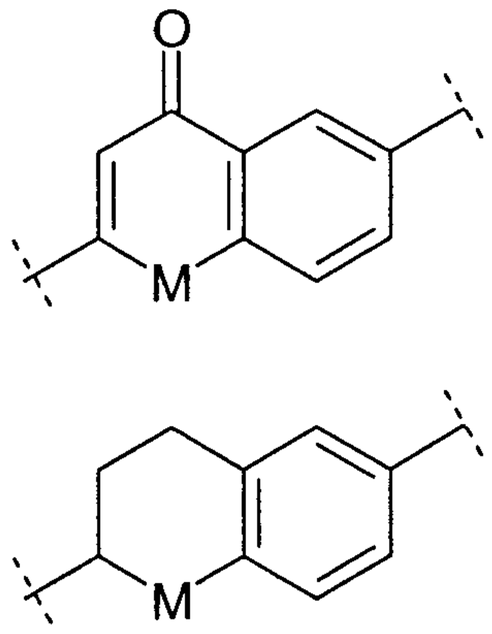
while the meanings given above for X may include a substituent selected from $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-7}$-cycloalkyl and $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl as well as, independently, one, two or three identical or different $C_{1-4}$-alkyl substituents, while two alkyl groups may be joined together forming a 3- to 7-membered cyclic group or an alkyl and an alkenyl group may be joined together forming a 5- to 7-membered cyclic group, and

W, Z independently of one another denote a single bond or a $C_{1-2}$-alkylene bridge,

while two adjacent C atoms may be joined together by an additional $C_{1-4}$-alkylene bridge, and

one or two C atoms independently of one another may be substituted by one or two identical or different $C_{1-3}$-alkyl groups, while two alkyl groups may be joined together, forming a carbocyclic ring, and

Y is selected from the definitions of the partial formulae Y1 and Y2



Y1

Y2

wherein the group M denotes O, S or $NR^M$, where $R^M$ has a meaning selected from among H, $C_{1-6}$-alkyl, $C_{3-6}$-alkenyl, $C_{3-6}$-alkynyl, $C_{3-7}$-cycloalkyl and $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, and

in the partial formulae Y1 and Y2 one or more C atoms may be substituted independently of one another by $R^{20}$, and

A is selected from among the bivalent cyclic groups phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, tetrahydronaphthyl, indolyl, dihydroindolyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, dihydroisoquinolinyl, tetrahydro-isoquinolinyl, benzimidazolyl, benzoxazolyl, thienyl, furanyl, benzothienyl or benzofuranyl, while the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different groups $R^{20}$, and in the case of a phenyl ring may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$,

B has one of the meanings given for A or denotes

$C_{1-6}$-alkyl, $C_{1-6}$-alkenyl, $C_{1-6}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{5-7}$-cycloalkenyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkenyl-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkenyl or $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkynyl, wherein one or more C atoms independently of one another may be mono- or polysubstituted by halogen and/ or monosubstituted by hydroxy or cyano and/ or cyclic groups may be mono- or polysubstituted by identical or different groups $R^{20}$,

Cy denotes a carbo- or heterocyclic group selected from one of the following meanings

- a saturated 3- to 7-membered carbocyclic group,
- an unsaturated 4- to 7-membered carbocyclic group,
- a phenyl group,
- a saturated 4- to 7-membered or unsaturated 5- to 7-membered heterocyclic group with an N, O or S atom as heteroatom,
- a saturated or unsaturated 5- to 7-membered heterocyclic group with two or more N atoms or with one or two N atoms and an O or S atom as heteroatoms,
- an aromatic heterocyclic 5- or 6-membered group with one or more identical or different heteroatoms selected from N, O and/or S,

while the saturated 6- or 7-membered groups mentioned above may also be present as bridged ring systems with an imino, ($C_{1-4}$-alkyl)-imino, methylene, ($C_{1-4}$-alkyl)-methylene or di-($C_{1-4}$-alkyl)-methylene bridge, and

the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different groups $R^{20}$, and in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$,

$R^{10}$ denotes hydroxy, ω-hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy or $C_{1-4}$-alkoxy-$C_{1-3}$-alkyl,

$R^{11}$ denotes halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $R^{15}$-O-, $R^{15}$-O-CO-,$R^{15}$-CO-O- cyano, $R^{16}R^{17}N$, $R^{18}R^{19}N$-CO- or Cy, while in the above-mentioned groups one or more C atoms may be substituted independently of one another by substituents selected from halogen, OH, CN, $CF_3$, $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl;

$R^{13}$ has one of the meanings given for $R^{17}$,

$R^{14}$ denotes halogen, cyano, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $R^{15}$-O- $R^{15}$-O-CO-,$R^{15}$-CO-,$R^{15}$-CO-O- $R^{16}R^{17}N$, $R^{18}R^{19}N$-CO-,$R^{15}$-O-$C_{1-3}$-alkyl, $R^{15}$-O-CO-$C_{1-3}$-alkyl, $R^{15}$-$SO_2$-NH-, $R^{15}$-O-CO-NH-$C_{1-3}$-alkyl, $R^{15}$-$SO_2$-NH-$C_{1-3}$-alkyl, $R^{15}$-CO-$C_{1-3}$-alkyl, $R^{15}$-CO-O-$C_{1-3}$-alkyl, $R^{16}R^{17}N$-$C_{1-3}$-alkyl, $R^{18}R^{19}N$-CO-$C_{1-3}$-alkyl or Cy-

$C_{1-3}$-alkyl,

$R^{15}$ denotes H, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, phenyl, phenyl-$C_{1-3}$-alkyl, pyridinyl or pyridinyl-$C_{1-3}$-alkyl,

$R^{16}$ denotes H, $C_{1-6}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, $C_{4-7}$-cycloalkenyl, $C_{4-7}$-cycloalkenyl-$C_{1-3}$-alkyl, ω-hydroxy-$C_{2-3}$-alkyl, ω-($C_{1-4}$-alkoxy)-$C_{2-3}$-alkyl, amino-$C_{2-6}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{2-6}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{2-6}$-alkyl or cyclo-$C_{3-6}$-alkyleneimino-$C_{2-6}$-alkyl,

$R^{17}$ has one of the meanings given for $R^{16}$ or denotes phenyl, phenyl-$C_{1-3}$-alkyl, pyridinyl, $C_{1-4}$-alkylcarbonyl, hydroxycarbonyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxycarbonyl, $C_{1-4}$-alkoxycarbonyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkylcarbonylamino-$C_{2-3}$-alkyl, N-($C_{1-4}$-alkylcarbonyl)-N-($C_{1-4}$-alkyl)-amino-$C_{2-3}$-alkyl, $C_{1-4}$-alkylsulphonyl, $C_{1-4}$-alkylsulphonylamino-$C_{2-3}$-alkyl or N-($C_{1-4}$-alkylsulphonyl)-N(-$C_{1-4}$-alkyl)-amino-$C_{2-3}$-alkyl;

$R^{18}$, $R^{19}$ independently of one another denote H or $C_{1-6}$-alkyl,

$R^{20}$ denotes halogen, hydroxy, cyano, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl, $R^{22}$-$C_{1-3}$-alkyl or has one of the meanings given for $R^{22}$,

$R^{21}$ denotes $C_{1-4}$-alkyl, ω-hydroxy-$C_{2-6}$-alkyl, ω-$C_{1-4}$-alkoxy-$C_{2-6}$-alkyl, ω-$C_{1-4}$-alkyl-amino-$C_{2-6}$-alkyl, ω-di-($C_{1-4}$-alkyl)-amino-$C_{2-6}$-alkyl, ω-cyclo-$C_{3-6}$-alkyleneimino-$C_{2-6}$-alkyl, phenyl, phenyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkyl-carbonyl, $C_{1-4}$-alkoxy-carbonyl, $C_{1-4}$-alkylsulphonyl, aminosulphonyl, $C_{1-4}$-alkylaminosulphonyl, di-$C_{1-4}$-alkylaminosulphonyl or cyclo-$C_{3-6}$-alkylene-imino-sulphonyl,

$R^{22}$ denotes pyridinyl, phenyl, phenyl-$C_{1-3}$-alkoxy, cyclo-$C_{3-6}$-alkyleneimino-$C_{2-4}$-alkoxy, OHC-, HO-N=HC-, $C_{1-4}$-alkoxy-N=HC-, $C_{1-4}$-alkoxy, $C_{1-4}$-alkylthio, carboxy, $C_{1-4}$-alkylcarbonyl, $C_{1-4}$-alkoxycarbonyl, aminocarbonyl, $C_{1-4}$-alkylamino-carbonyl, di-($C_{1-4}$-alkyl)-aminocarbonyl, cyclo-$C_{3-6}$-alkyl-amino-carbonyl, cyclo-$C_{3-6}$-alkyleneimino-carbonyl, phenylaminocarbonyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{2-4}$-alkyl-aminocarbonyl, $C_{1-4}$-alkyl-sulphonyl, $C_{1-4}$-alkyl-sulphinyl, $C_{1-4}$-alkyl-sulphonylamino, amino, $C_{1-4}$-alkylamino, di-($C_{1-4}$-alkyl)-amino, $C_{1-4}$-alkyl-

carbonyl-amino, cyclo-$C_{3-6}$-alkyleneimino, phenyl-$C_{1-3}$-alkylamino, N-($C_{1-4}$-alkyl)-phenyl-$C_{1-3}$-alkylamino, acetylamino, propionylamino, phenylcarbonyl, phenylcarbonylamino, phenylcarbonylmethylamino, hydroxy-$C_{2-3}$-alkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or $C_{1-4}$-alkylaminocarbonylamino,

while in the above-mentioned groups and residues, particularly in W, X, Z, $R^{13}$ to $R^{22}$, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br and/or in each case one or more phenyl rings may independently of one another additionally contain one, two or three substituents selected from among F, Cl, Br, I, cyano, $C_{1-4}$-alkyl, $C_{1-4}$-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, $C_{1-3}$-alkylamino, di-($C_{1-3}$-alkyl)-amino, acetylamino, aminocarbonyl, difluoromethoxy, trifluoromethoxy, amino-$C_{1-3}$-alkyl, $C_{1-3}$-alkylamino-$C_{1-3}$-alkyl- and di-($C_{1-3}$-alkyl)-amino-$C_{1-3}$-alkyl and/or may be monosubstituted by nitro, and

the H atom of any carboxy group present or an H atom bound to an N atom may each be replaced by a group which can be cleaved *in vivo*,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

while the following compounds are not included according to the invention:

6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-2-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-quinoline,

6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-methyl-2-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-quinoline and

5-(4-chloro-phenyl)-2-[2-(4-methyl-piperidin-1-ylmethyl)-chroman-6-ylethynyl]-pyridine.

The compounds according to the present invention, including the physiologically acceptable salts, are especially effective, compared with known, structurally similar compounds, as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit very good affinity in MCH receptor binding studies. In addition, the compounds according to the

invention have a high to very high selectivity with regard to the MCH receptor. Generally the compounds according to the invention have low toxicity, they are well absorbed by oral route and have good intracerebral transitivity, particularly brain accessibility.

The invention also relates to the compounds in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers and in the form of the free bases or corresponding acid addition salts with pharmacologically acceptable acids. The subject of the invention also includes the compounds according to the invention, including their salts, wherein one or more hydrogen atoms are replaced by deuterium.

This invention also includes the physiologically acceptable salts of the alkyne compounds according to the invention as described above and hereinafter.

Also covered by this invention are compositions containing at least one alkyne compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients.

Also covered by this invention are pharmaceutical compositions containing at least one alkyne compound according to the invention and/ or a salt according to the invention optionally together with one or more inert carriers and/or diluents.

This invention also relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for influencing the eating behaviour of a mammal.

The invention further relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for reducing the body weight and/ or for preventing an increase in the body weight of a mammal.

The invention also relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for preparing a pharmaceutical composition with an MCH receptor-antagonistic activity, particularly with an MCH-1 receptor-antagonistic activity.

This invention also relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for preparing a pharmaceutical composition

which is suitable for the prevention and/or treatment of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

A further object of this invention is the use of at least one alkyne compound according to the invention and/or a salt according to the invention for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of metabolic disorders and/or eating disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia.

The invention also relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

In addition the present invention relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, sleep disorders, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

The invention also relates to the use of at least one alkyne compound according to the invention and/or a salt according to the invention for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of urinary problems, such as for example urinary incontinence, overactive bladder, urgency, nycturia and enuresis.

The invention further relates to the use of at least one alkyne compound according to the invention and/ or a salt according to the invention for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of dependencies and/or withdrawal symptoms.

The invention further relates to processes for preparing for preparing a pharmaceutical composition according to the invention, characterised in that at least one alkyne compound

according to the invention and/ or a salt according to the invention is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

The invention also relates to a pharmaceutical composition containing a first active substance which is selected from the alkyne compounds according to the invention and/or the corresponding salts as well as a second active substance which is selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of dyslipidaemia or hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active substances for the treatment of depression, optionally together with one or more inert carriers and/or diluents.

Moreover, in one aspect, the invention relates to a process for preparing alkyne compounds of formula A.5

$R^1R^2N$-X-Y-C≡C-W-A-B (A.5)

while in formulae A.1, A.2, A.3, A.4 and A.5 $R^1$, $R^2$, Y, X, W, A and B have one of the meanings given hereinbefore and hereinafter,

wherein a halogen compound of formula A.1

HO-X-Y-Hal (A.1)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine, is reacted with an alkyne compound of formula A.2

H-C≡C-W-A-B(A.2)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent, and

the compound of formula A.3 obtained

HO-X-Y-C≡C-W-A-B (A.3)

is reacted with methanesulphonic acid chloride (MsCl) to produce the methanesulphonate derivative A.4,

MsO-X-Y-C≡C-W-A-B (A.4)

which is further reacted with an amine of formula H-$NR^1R^2$ to form the end product A.5.

This invention further relates to a process for preparing alkyne compounds of formula B.5

$R^1R^2N$-X-Y-Z-C≡C-A-B (B.5)

while in formulae B.1, B.2, B.3, B.4 and B.5 $R^1$, $R^2$, X, Y, Z, A and B have one of the meanings given hereinbefore and hereinafter,

wherein a halogen compound of formula B.1

Hal-A-B (B.1)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine,
is reacted with an alkyne compound of formula B.2

HO-X-Y-Z-C≡C-H (B.2)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent, and

the resulting compound of formula B.3

HO-X-Y-Z-C≡C-A-B (B.3)

is reacted with methanesulphonic acid chloride (MsCl) to form the methanesulphonate derivative B.4,

MsO-X-Y-Z-C≡C-A-B (B.4)

which is reacted further with an amine of formula H-$NR^1R^2$ to form the end product B.5.

In addition, the invention relates to a process for preparing alkyne compounds of formula C.3

$R^1R^2N$-X-Y-C≡C-W-A-B (C.3)

while in formulae C.1, C.2 and C.3 $R^1$, $R^2$, X, Y, W, A and B have one of the meanings given hereinbefore and hereinafter,

wherein a halogen compound of formula C.1

$R^1R^2N$-X-Y-Hal (C.1)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine,
is further reacted with an alkyne compound of formula C.2

H-C≡C-W-A-B(C.2)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent to yield the end product C.3.

In another aspect the invention relates to a process for preparing alkyne compounds of formula D.3

$R^1R^2N$-X-Y-Z-C≡C-A-B (D.3)

while in formulae D.1, D.2 and D.3 $R^1$, $R^2$, X, Y, Z, A and B have one of the meanings given hereinbefore and hereinafter,

wherein a halogen compound of formula D.2

Hal-A-B (D.2)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine,

is reacted with an alkyne compound of formula D.1

$R^1R^2N$-X-Y-Z-C≡C-H (D.1)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent to form the end product D.3.

The starting materials and intermediate products used in the synthesis according to the invention are also a subject of this invention.

**Detailed description of the invention**

Unless otherwise specified, the groups, residues and substituents, particularly A, B, W, X, Y, Z, cy, $R^1$, $R^1$, $R^2$, $R^{10}$, $R^{11}$, $R^{13}$ to $R^{22}$, $R^M$, have the meanings given hereinbefore.

If groups, residues and/or substituents occur more than once in a compound, they may have the same or different meanings in each case.

If $R^1$ and $R^2$ are not joined together via an alkylene bridge, $R^1$ and $R^2$ independently of one another preferably denote a $C_{1-8}$-alkyl or $C_{3-7}$-cycloalkyl group mono- or polysubstituted by identical or different groups $R^{11}$, while a -$CH_2$- group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by -O-, -S- or -$NR^{13}$-, or a phenyl or pyridinyl group optionally mono- or polysubstituted by identical or different groups $R^{20}$ and/or monosubstituted by nitro, while one or both of the groups $R^1$ and $R^2$ may also represent H.

Preferred meanings of the group $R^{11}$ are F, Cl, Br, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $R^{15}$-O- cyano, $R^{16}R^{17}N$, $C_{3-7}$-cycloalkyl, cyclo-$C_{3-6}$-alkyleneimino, pyrrolidinyl, N-($C_{1-4}$-alkyl)-pyrrolidinyl, piperidinyl, N-($C_{1-4}$-alkyl)-piperidinyl, phenyl and pyridyl, while in the above-mentioned groups and radicals one or more C atoms may be mono- or polysubstituted independently of one another by F, $C_{1-3}$-alkyl or hydroxy-$C_{1-3}$-alkyl, and/or one or two C atoms may be monossubstituted independently of one another by Cl, Br, OH, $CF_3$ or CN, and the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different radicals $R^{20}$, or in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$. If $R^{11}$ has one of the meanings $R^{15}$-O- cyano, $R^{16}R^{17}N$ or cyclo-$C_{3-6}$-alkyleneimino, the C atom of the

alkyl or cycloalkyl group substituted by $R^{11}$ is preferably not directly connected to a heteroatom, such as for example the group -N-X-.

Preferably the groups $R^1$, $R^2$ independently of one another represent H, $C_{1-6}$-alkyl, $C_{3-5}$-alkenyl, $C_{3-5}$-alkynyl, $C_{3-7}$-cycloalkyl, hydroxy-$C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, (hydroxy-$C_{3-7}$-cycloalkyl)-$C_{1-3}$-alkyl, hydroxy-$C_{2-4}$-alkyl, ω-NC-$C_{2-3}$-alkyl, $C_{1-4}$-alkoxy-$C_{2-4}$-alkyl, hydroxy-$C_{1-4}$-alkoxy-$C_{2-4}$-alkyl, $C_{1-4}$-alkoxy-carbonyl-$C_{1-4}$-alkyl, carboxyl-$C_{1-4}$-alkyl, amino-$C_{2-4}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{2-4}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{2-4}$-alkyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{2-4}$-alkyl, pyrrolidin-3-yl, N-($C_{1-4}$-alkyl)-pyrrolidin-3-yl, pyrrolidinyl-$C_{1-3}$-alkyl, N-($C_{1-4}$-alkyl)-pyrrolidinyl-$C_{1-3}$-alkyl, piperidin-3-yl, piperidin-4-yl, N-($C_{1-4}$-alkyl)-piperidin-3-yl, N-($C_{1-4}$-alkyl)-piperidin-4-yl, piperidinyl-$C_{1-3}$-alkyl, N-($C_{1-4}$-alkyl)-piperidinyl-$C_{1-3}$-alkyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, phenyl, phenyl-$C_{1-3}$-alkyl, pyridyl or pyridyl-$C_{1-3}$-alkyl, while in the above-mentioned groups and radicals one or more C atoms independently of one another may be mono- or polysubstituted by F, $C_{1-3}$-alkyl or hydroxy-$C_{1-3}$-alkyl, and/or one or two C atoms independently of one another may be monosubstituted by Cl, Br, OH, $CF_3$ or CN, and the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different radicals $R^{20}$, in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$. Preferred substituents of the above-mentioned phenyl or pyridyl groups are selected from the group F, Cl, Br, I, cyano, $C_{1-4}$-alkyl, $C_{1-4}$-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, $C_{1-3}$-alkylamino, di-($C_{1-3}$-alkyl)-amino, acetylamino, aminocarbonyl, difluoromethoxy, trifluoromethoxy, amino-$C_{1-3}$-alkyl, $C_{1-3}$-alkylamino-$C_{1-3}$-alkyl and di-($C_{1-3}$-alkyl)-amino-$C_{1-3}$-alkyl, while a phenyl group may also be monosubstituted by nitro.

Particularly preferred definitions of the groups $R^1$ and/or $R^2$ are selected from the group consisting of H, $C_{1-4}$-alkyl, hydroxy-$C_{1-4}$-alkyl, $C_{3-5}$-alkenyl, $C_{3-5}$-alkynyl, $C_{3-7}$-cycloalkyl, hydroxy-$C_{3-7}$-cycloalkyl, dihydroxy-$C_{3-6}$-alkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, (hydroxy-$C_{3-7}$-cycloalkyl)-$C_{1-3}$-alkyl, ω-($C_{1-4}$-alkoxy)-$C_{2-3}$-alkyl, pyridyl and benzyl, while an alkyl, cycloalkyl or cycloalkyl-alkyl group may additionally be mono- or disubstituted by hydroxy and/or hydroxy-$C_{1-3}$-alkyl, and/or mono- or polysubstituted by F or $C_{1-3}$-alkyl and/or monosubstituted by $CF_3$, Br, Cl or CN, and one of the groups $R^1$ and $R^2$ may also denote H.

Most particularly preferred groups $R^1$ and/or $R^2$ are selected from the group consisting of H, methyl, ethyl, n-propyl, i-propyl, prop-2-enyl, but-2-enyl, prop-2-ynyl, but-2-ynyl, 2-methoxyethyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl,

hydroxy-$C_{3-7}$-cycloalkyl, (hydroxy-$C_{1-3}$-alkyl)-hydroxy-$C_{3-7}$-cycloalkyl, dihydroxy-$C_{3-5}$-alkyl, 2-hydroxy-1-(hydroxymethyl)-ethyl, 1,1-di(hydroxymethyl)-ethyl, (1-hydroxy-$C_{3-6}$-cycloalkyl)-methyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl and pyridyl, while the above-mentioned groups may be mono- or polysubstituted by F and/or $C_{1-3}$-alkyl, and the phenyl and pyridyl rings may be substituted as specified.

Examples of most particularly preferred groups $R^1$ and/or $R^2$ are therefore H, methyl, ethyl, n-propyl, i-propyl, prop-2-enyl, prop-2-ynyl, 2-methoxyethyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, hydroxy-cyclopentyl, hydroxy-cyclohexyl, (hydroxymethyl)-hydroxy-cyclopentyl, (hydroxymethyl)-hydroxy-cyclohexyl, 2,3-dihydroxypropyl, (1-hydroxy-cyclopropyl)-methyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl and pyridyl.

Particularly preferably, at least one of the groups $R^1$, $R^2$, and most particularly preferably both groups, have a meaning other than H.

If $R^1$ and $R^2$ form an alkylene bridge, this is preferably a $C_{3-7}$-alkylene bridge or a $C_{3-7}$-alkylene bridge, particularly a $C_{4-7}$-alkylene bridge, wherein a -$CH_2$- group not adjacent to the N atom of the $R^1R^2N$- group is replaced by -CH=N-, -CH=CH-, -O-, -S-, -CO- or -$NR^{13}$-,

while in the alkylene bridge defined hereinbefore one or more H atoms may be replaced by identical or different groups $R^{14}$, and

the alkylene bridge defined hereinbefore may be substituted with a carbo- or heterocyclic group cy in such a way that the bond between the alkylene bridge and the group Cy is made

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common adjacent C- and/or N atoms forming a fused bicyclic ring system or
- via three or more C- and/or N atoms forming a bridged ring system.

Preferably also, $R^1$ and $R^2$ form an alkylene bridge such that $R^1R^2N$- denotes a group which is selected from azetidine, pyrrolidine, piperidine, azepan, 2,5-dihydro-1H-pyrrole, 1,2,3,6-tetrahydro-pyridine, 2,3,4,7-tetrahydro-1H-azepine, 2,3,6,7-tetrahydro-1H-azepine, piperazine in which the free imine function is substituted by $R^{13}$, piperidin-4-one, morpholine and thiomorpholine,

is particularly preferably selected from pyrrolidine, piperidine, piperazine in which the free imine function is substituted by $R^{13}$, and morpholine,

while according to the general definition of $R^1$ and $R^2$ one or more H atoms may be replaced by identical or different groups $R^{14}$, and/ or the above-mentioned groups may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in a manner specified according to the general definition of $R^1$ and $R^2$, while the group Cy may be mono- or polysubstituted by $R^{20}$.

Particularly preferred groups Cy are $C_{3-7}$-cycloalkyl, aza-$C_{4-7}$-cycloalkyl, particularly cyclo-$C_{3-6}$-alkyleneimino, as well as 1-$C_{1-4}$-alkyl-aza-$C_{4-7}$-cycloalkyl, while the group Cy may be mono- or polysubstituted by $R^{20}$.

The $C_{3-8}$-alkylene bridge formed by $R^1$ and $R^2$, wherein -$CH_2$- groups may be replaced as specified, may be substituted, as described, by one or two identical or different carbo- or heterocyclic groups Cy, which may be substituted as specified hereinbefore.

In the event that the alkylene bridge is linked to a group Cy through a single bond, Cy is preferably selected from the group consisting of $C_{3-7}$-cycloalkyl, cyclo-$C_{3-6}$-alkyleneimino, 1H-imidazol, thienyl and phenyl.

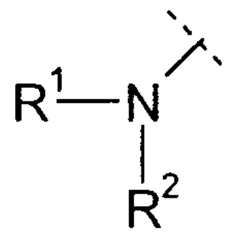
In the event that the alkylene bridge is linked to a group Cy via a common C atom forming a spirocyclic ring system, Cy is preferably selected from the group consisting of $C_{3-7}$-cycloalkyl, aza-$C_{4-8}$-cycloalkyl, oxa-$C_{4-8}$-cycloalkyl, 2,3-dihydro-1H-quinazolin-4-one.

In the event that the alkylene bridge is linked to a group Cy via two common adjacent C and/or N atoms forming a fused bicyclic ring system, Cy is preferably selected from the group consisting of $C_{4-7}$-cycloalkyl, phenyl, thienyl.

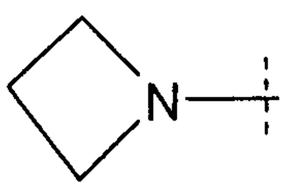
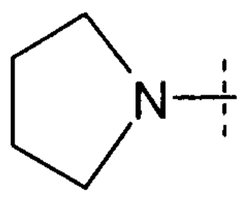
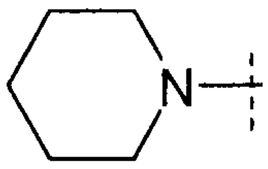
In the event that the alkylene bridge is linked to a group Cy via three or more C and/or N atoms forming a bridged ring system, Cy preferably denotes $C_{4-8}$-cycloalkyl or aza-$C_{4-8}$-cycloalkyl.

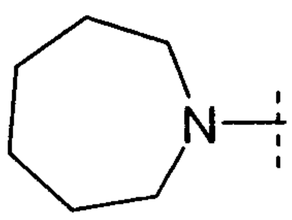
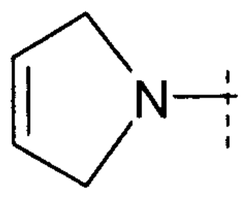
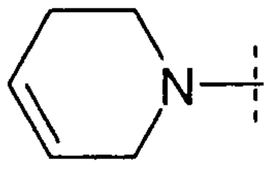
In the event that the heterocyclic group $R^1R^2N$- is substituted by a group Cy, the group Cy is preferably linked to the group $R^1R^2N$- through a single bond, while Cy is preferably selected from the group consisting of $C_{3-7}$-cycloalkyl and cyclo-$C_{3-6}$-alkyleneimino, while these groups

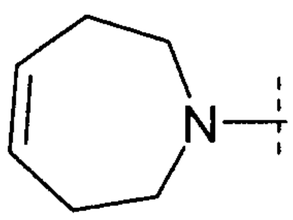
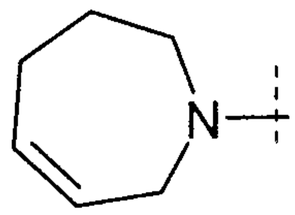
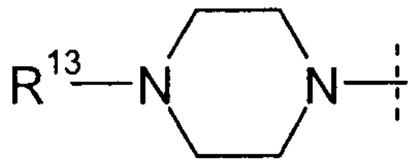
may be substituted as specified, preferably by fluorine, $CF_3$, $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl and hydroxy.

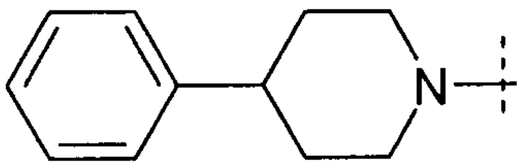
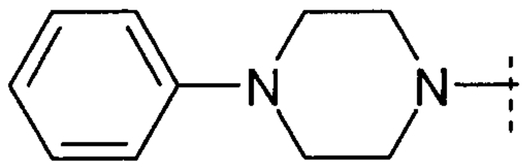
Particularly preferably the group 

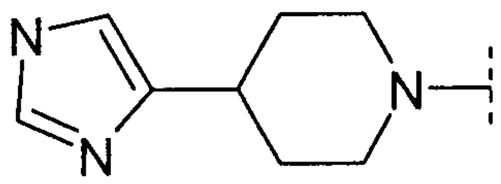
is defined according to one of the following partial formulae

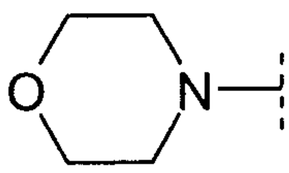
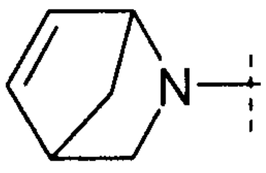
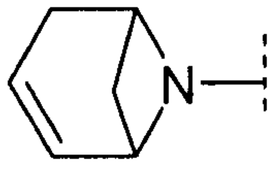
 ,  ,  ,

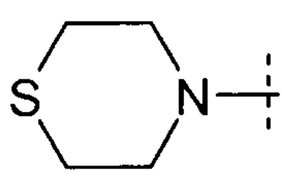
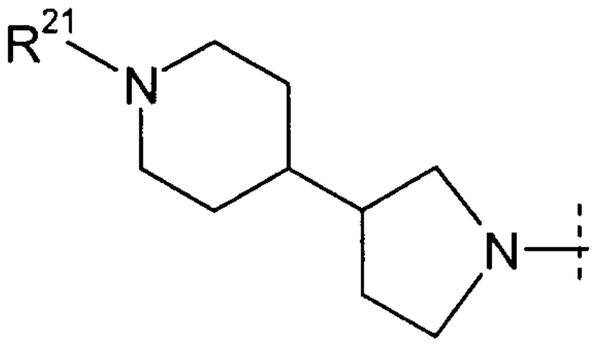
 ,  ,  ,

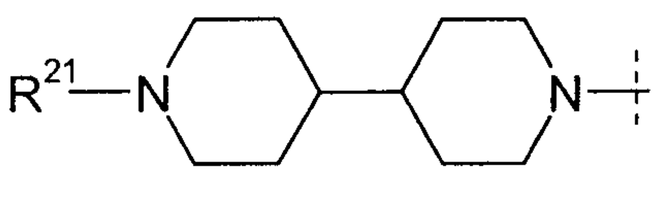
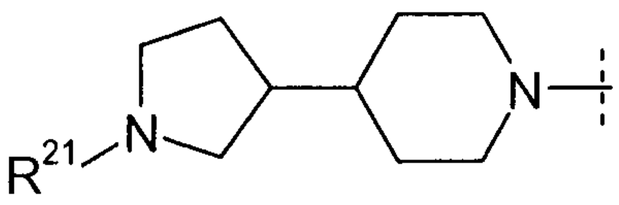
 ,  ,  ,

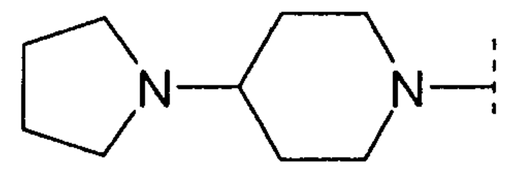
 ,  ,

 ,

 ,  ,  ,

 ,  ,

 ,  ,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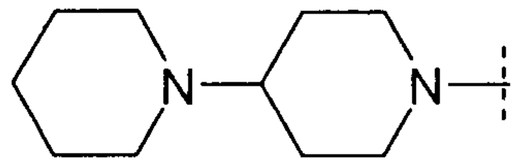
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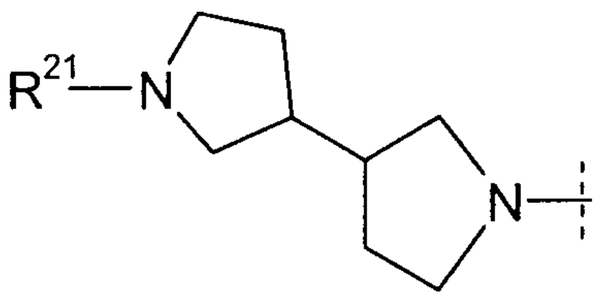
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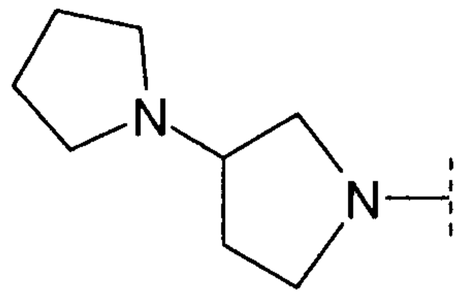
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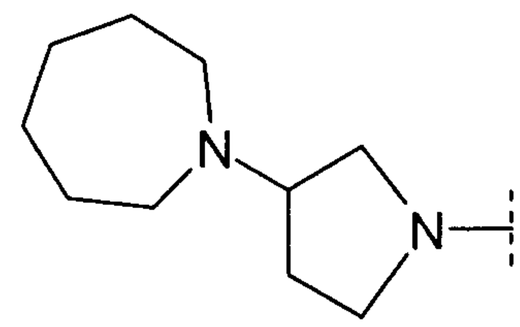
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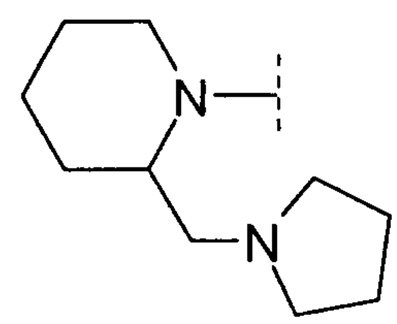
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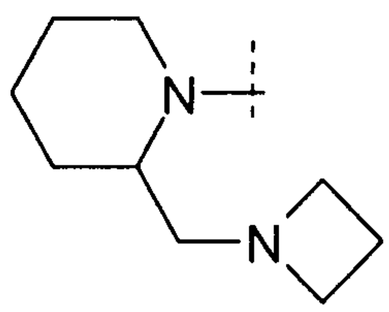
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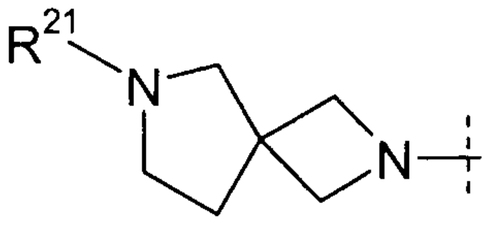
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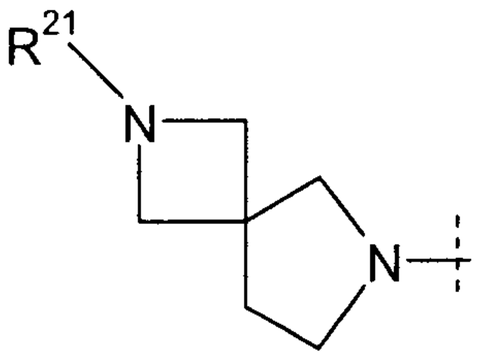
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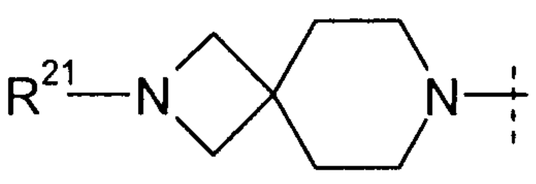
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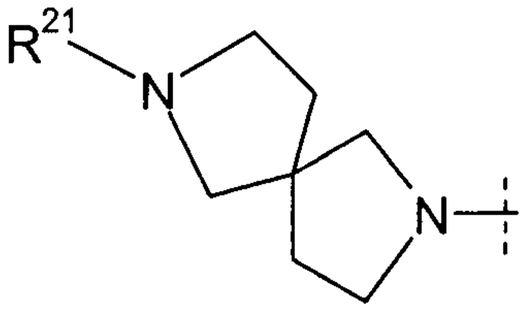
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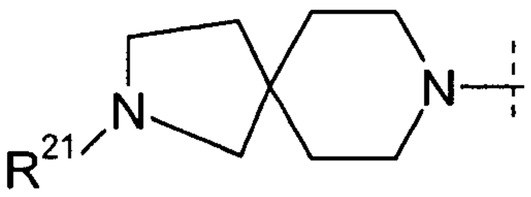
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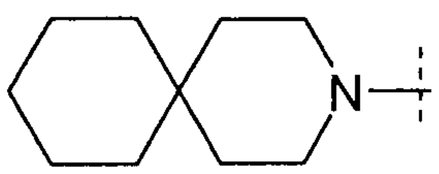
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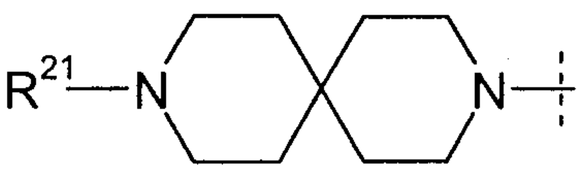
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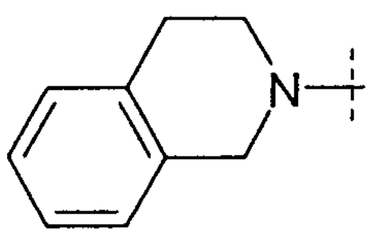
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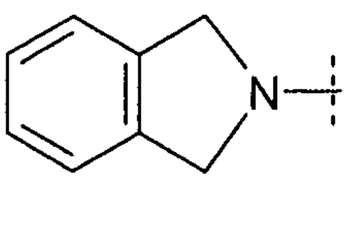
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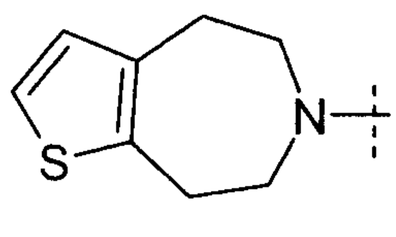
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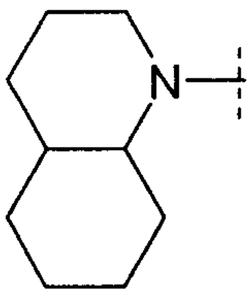
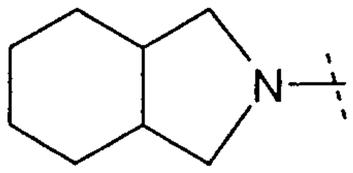
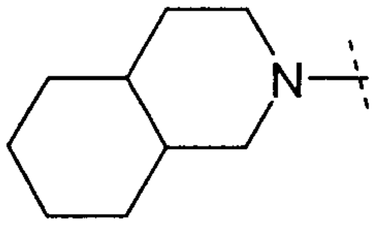
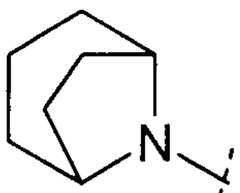





wherein one or more H atoms of the heterocycle formed by the group $R^1R^2N$- may be replaced by identical or different groups $R^{14}$, and

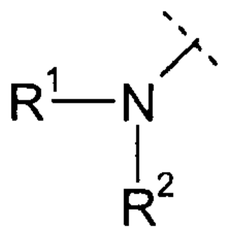
the heterocycle formed by the group $R^1R^2N$- may be substituted by one or two, preferably one $C_{3-7}$-cycloalkyl group, while the cycloalkyl group may be mono- or polysubstituted by $R^{20}$, and

the ring linked to the heterocycle formed by the group $R^1R^2N$- may be mono- or polysubstituted at one or more C atoms by $R^{20}$, and in the case of a phenyl ring may also additionally be monosubstituted by nitro and

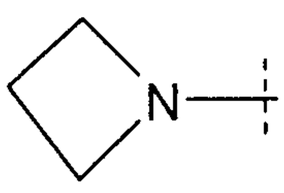
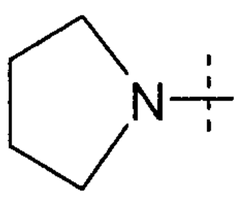
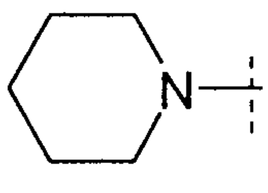
wherein $R^{13}$, $R^{14}$, $R^{20}$, $R^{21}$ have the meanings given above and hereinafter.

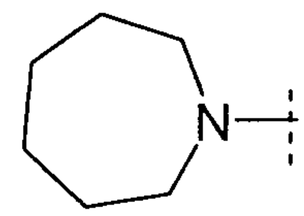
If the heterocycle formed by the group $R^1R^2N$- is substituted as specified by one or two cycloalkyl groups mono- or polysubstituted by $R^{20}$, the substituents $R^{20}$ independently of one another preferably denote $C_{1-4}$-alkyl, $C_{1-4}$-alkoxy-$C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl, hydroxy, fluorine, chlorine, bromine or $CF_3$, particularly hydroxy.

Most particularly preferably the group



is defined according to one of the following partial formulae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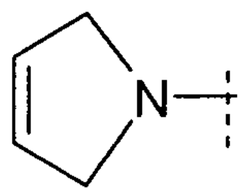
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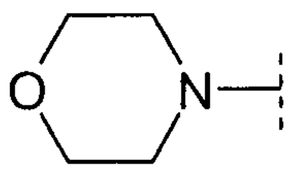
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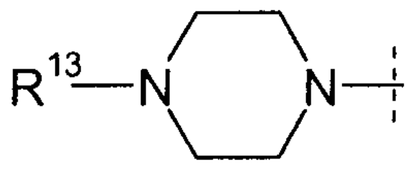
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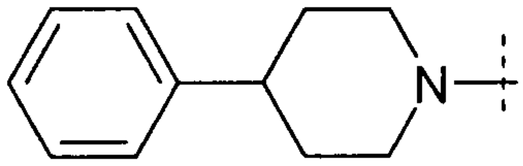
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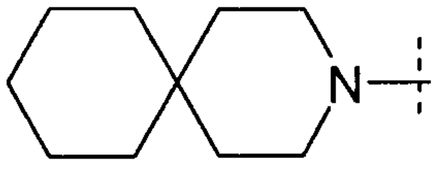
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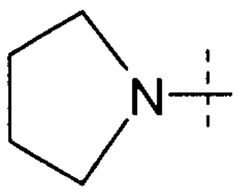
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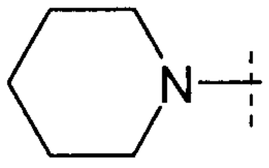
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where $R^{13}$ has the meanings given above and hereinafter, and

the heterocycle formed by the group $R^1R^2N$- may be substituted by $C_{3-6}$-cycloalkyl, hydroxy-$C_{3-6}$-cycloalkyl or (hydroxy-$C_{3-6}$-cycloalkyl)-$C_{1-3}$-alkyl, and

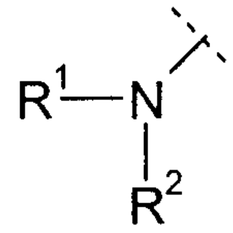
the heterocycle formed by the group $R^1R^2N$- may be mono-, di or trisubstituted by identical or different radicals $R^{14}$. The substituents $R^{14}$ preferably denote independently of one another F, Cl, Br, OH, $C_{1-4}$-alkyl, $C_{1-4}$-alkoxy, $C_{1-4}$-alkoxy-$C_{1-3}$-alkyl, hydroxy-$C_{1-4}$-alkyl or $CF_3$, particularly hydroxy, $C_{1-3}$-alkyl, $CF_3$ or hydroxy-$C_{1-3}$-alkyl.

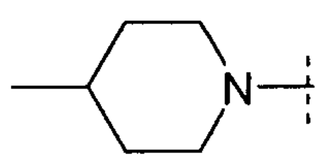
If the partial formulae shown above are substituted as specified, the following definitions of the group $R^1R^2N$- are particularly preferred: hydroxypyrrolidinyl, hydroxypiperidinyl, 3,4-dihydroxypyrrolidinyl, 3,4-dihydroxypiperidinyl, 3,5-dihydroxypiperidinyl, (hydroxymethyl)-pyrrolidinyl, (hydroxymethyl)-piperidinyl, (hydroxymethyl)-hydroxy-pyrrolidinyl, (hydroxymethyl)-hydroxy-piperidinyl,

while in the groups specified a hydroxymethyl group at the C atom may be mono- or disubstituted by methyl, while two methyl substituents may be joined together, forming a cyclopropyl group, and

while in one or two hydroxy groups the H atom may be replaced by a methyl group, and

the groups specified do not have any other substituents or have one or two substituents selected independently of one another from fluorine, hydroxy, $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl, $CF_3$.

The following partial formulae are most particularly preferred definitions of the above-mentioned heterocyclic group  :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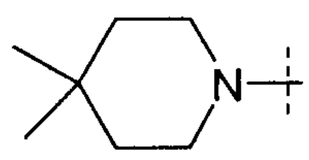
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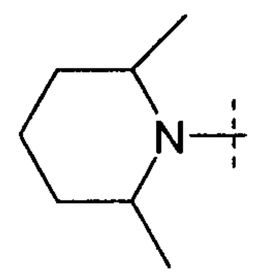
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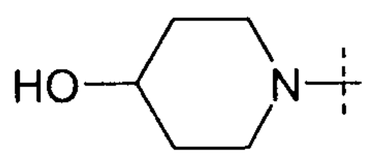
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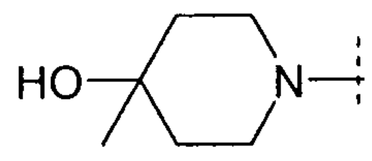
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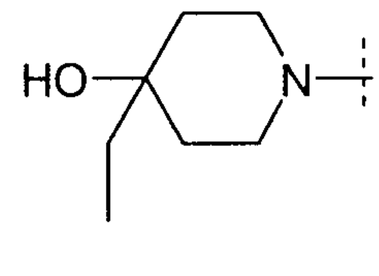
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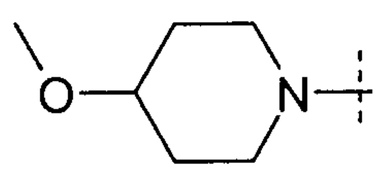
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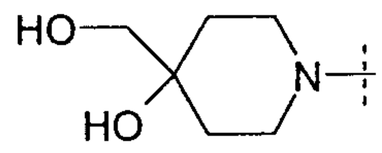
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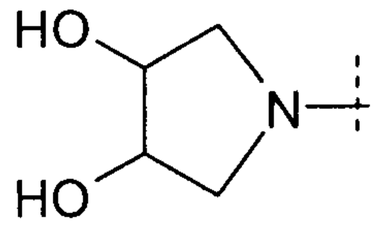
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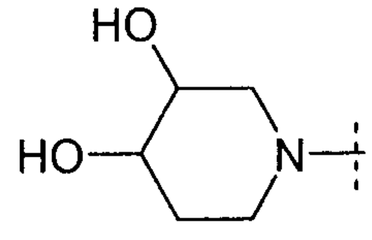
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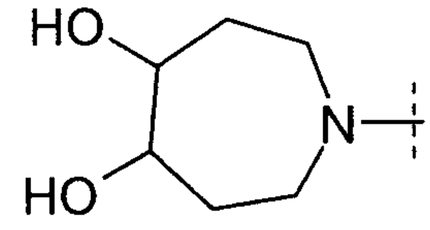
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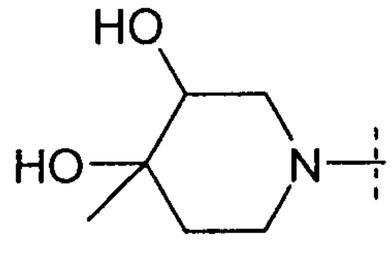
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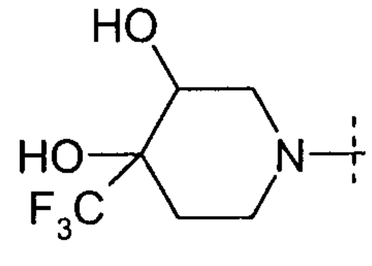
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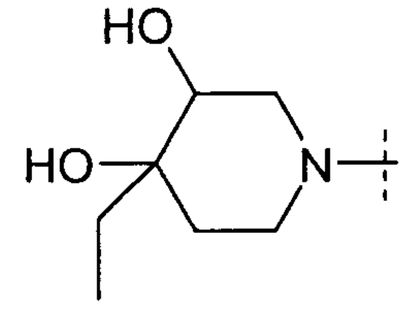
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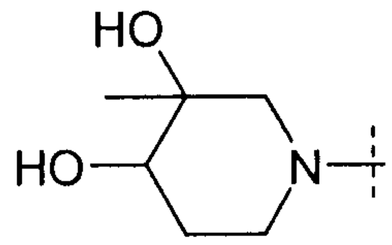
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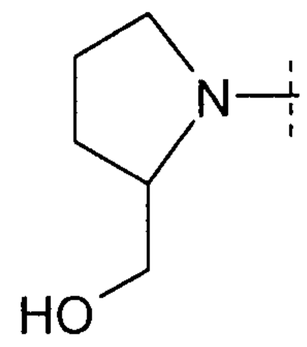
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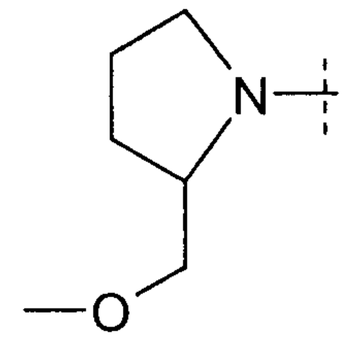
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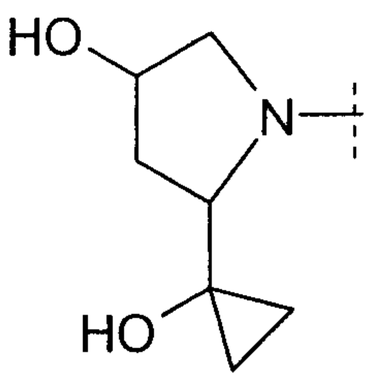
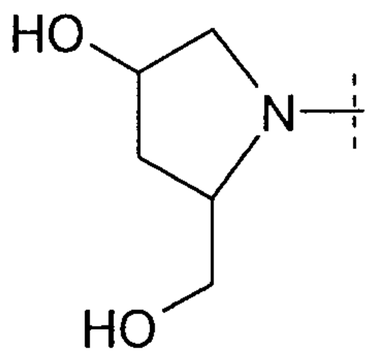
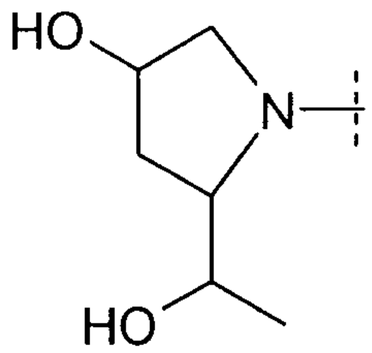
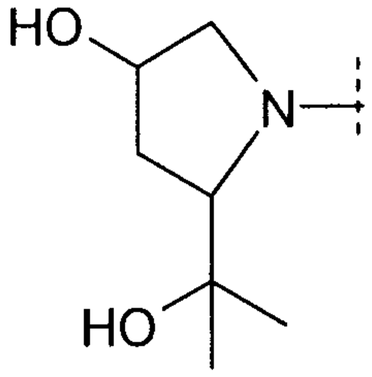
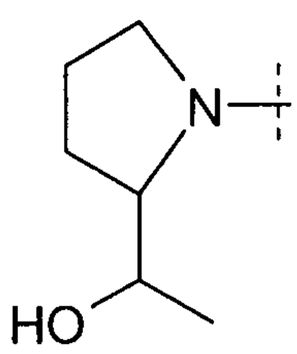
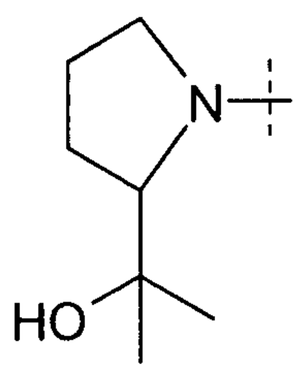
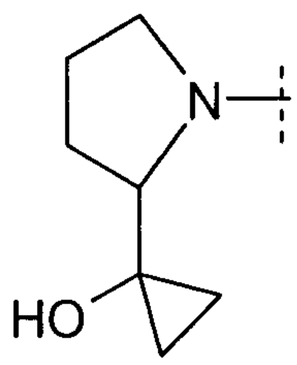
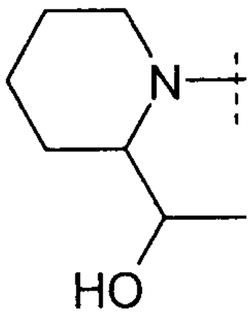
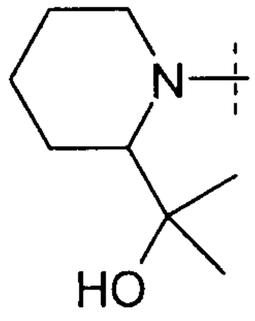
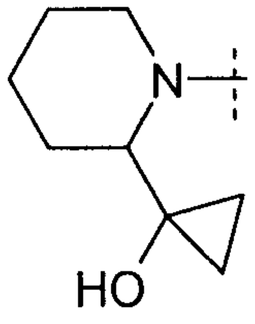











wherein the groups specified are not further substituted, or

wherein methyl or ethyl groups may be mono-, di or trisubstituted by fluorine, and wherein one or more H atoms of the heterocycle formed by the group $R^1R^2N$- which are bound to carbon may be substituted independently of one another by fluorine, chlorine, CN, $CF_3$, $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl, particularly $C_{1-3}$-alkyl or $CF_3$, preferably methyl, ethyl, $CF_3$.

Among the preferred and particularly preferred meanings of $R^1R^2N$- listed above, the following definitions of the substituent $R^{14}$ are preferred: F, Cl, Br, cyano, $C_{1-4}$-alkyl, $C_{2-4}$-alkenyl, $C_{2-4}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, hydroxy, hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy, ω-($C_{1-4}$-alkoxy)-$C_{1-3}$-alkyl, $C_{1-4}$-alkyl-carbonyl, carboxy, $C_{1-4}$-alkoxycarbonyl, hydroxy--carbonyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxycarbonyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy-carbonylamino, $C_{1-4}$-alkoxy-carbonylamino-$C_{1-3}$-alkyl, amino, $C_{1-4}$-alkyl-amino, $C_{3-7}$-cycloalkyl-amino, N-($C_{3-7}$-cycloalkyl)-N-($C_{1-4}$-alkyl)-amino, di-($C_{1-4}$-alkyl)-amino, cyclo-$C_{3-6}$-alkyleneimino, amino-$C_{1-3}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkyl-amino-$C_{1-3}$-alkyl, N-($C_{3-7}$-cycloalkyl)-N-($C_{1-4}$-alkyl)-amino-

$C_{1-3}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{1-3}$-alkyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{1-3}$-alkyl, aminocarbonyl, $C_{1-4}$-alkyl-amino-carbonyl, $C_{3-7}$-cycloalkyl-amino-carbonyl, N-($C_{3-7}$-cycloalkyl)-N-($C_{1-4}$-alkyl)-amino-carbonyl, di-($C_{1-4}$-alkyl)-amino-carbonyl, pyridinyl-oxy, pyridinyl-amino, pyridinyl-$C_{1-3}$-alkyl-amino.

Particularly preferred meanings of the substituent $R^{14}$ are F, Cl, Br, $C_{1-4}$-alkyl, hydroxy, hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy, ω-($C_{1-4}$-alkoxy)-$C_{1-3}$-alkyl, amino-$C_{1-3}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkyl-amino-$C_{1-3}$-alkyl, N-($C_{3-7}$-cycloalkyl)-N-($C_{1-4}$-alkyl)-amino-$C_{1-3}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{1-3}$-alkyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{1-3}$-alkyl, aminocarbonyl and pyridylamino.

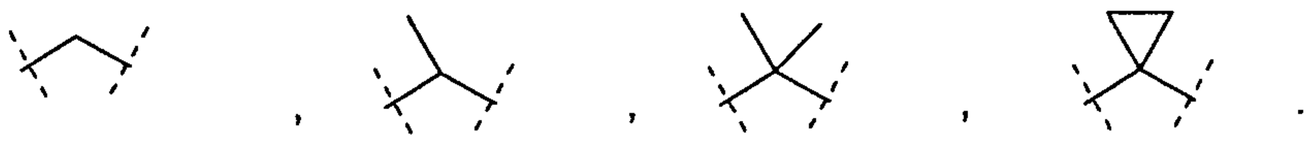
In the above-mentioned preferred meanings of $R^{14}$ in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms may independently of one another additionally be monosubstituted by Cl or Br. Thus, preferred meanings of $R^{14}$ also include for example -$CF_3$, -$OCF_3$, $CF_3$-CO- and $CF_3$-CHOH-.

Most particularly preferred meanings of the substituent $R^{14}$ are $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl, methoxymethyl, hydroxy, $CF_3$, $CF_3$-CHOH, particularly hydroxy, methyl, ethyl, $CF_3$ and hydroxymethyl.

According to a preferred first embodiment the group X is a methylene, ethylene or propylene bridge, particularly preferably a methylene or ethylene bridge, which is unsubstituted or substituted by one or two identical or different $C_{1-3}$-alkyl substituents and/or a substituent selected from $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-6}$-cycloalkyl or $C_{3-6}$-cycloalkyl-$C_{1-3}$-alkyl, while two alkyl substituents may be joined together to form a 3- to 6-membered cycloalkyl group or an alkyl and an alkenyl substituent may be joined together to form a 5- or 6-membered cycloalkenyl group. According to this embodiment, X representing methylene or ethylene is preferably unsubstituted or mono- or disubstituted by methyl, ethyl or i-propyl, while two alkyl substituents may be linked together forming a $C_{3-6}$-cycloalkyl group.

Particularly preferably according to this embodiment X is a -$CH_2$- bridge, which is unsubstituted or mono- or disubstituted by methyl, while two methyl groups may be joined together forming a cyclopropyl group. Most particularly preferably X is an unsubstituted -$CH_2$- bridge.

Examples of particularly preferred meanings of X are therefore

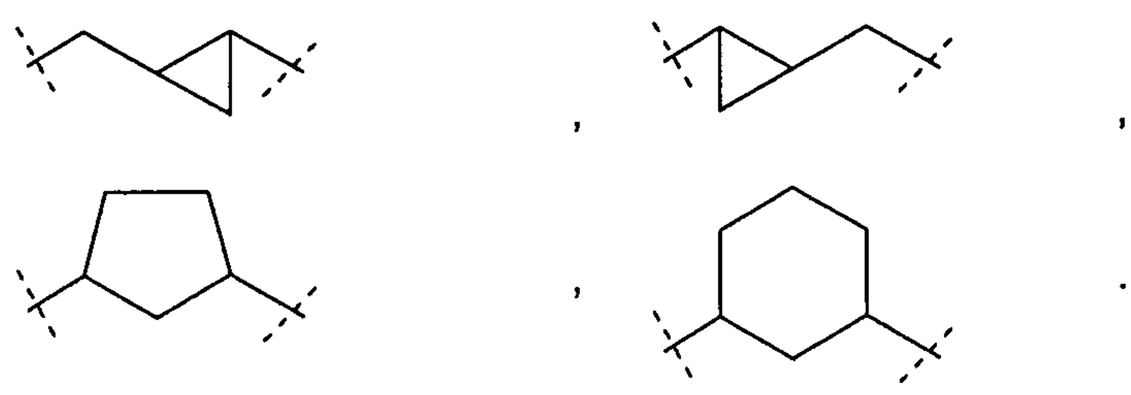


According to another embodiment the group X is preferably an unbranched propylene or butylene bridge, while one or two C atoms may be monosubstituted by hydroxy, hydroxy-$C_{1-3}$-alkyl or $C_{1-3}$-alkoxy, particularly hydroxy, and one or two C atoms may each be substituted by one or two identical or different $C_{1-3}$-alkyl substituents and/or a substituent selected from $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-6}$-cycloalkyl or $C_{3-6}$-cycloalkyl-$C_{1-3}$-alkyl, while two alkyl substituents may be joined together forming a 3- to 6-membered cycloalkyl group or an alkyl and an alkenyl substituent may be joined together forming a 5- or 6-membered cycloalkenyl group. In the group X one or more C atoms may be mono- or polysubstituted by F and/or Cl, preferably F.

According to another embodiment the group X is preferably an unbranched propylene or butylene bridge, wherein a $-CH_2-CH_2-$ group not directly adjacent to the N atom of the $R^1R^2N$-group is replaced by -CH=CH- or -C≡C-, particularly a $-CH_2-CH=CH-$ or $-CH_2-C\equiv C-$ bridge, while the meanings specified for X are unsubstituted or comprise one or two identical or different substituents selected independently of one another from fluorine and $C_{1-3}$-alkyl and/or a cyclopropyl substituent, while two alkyl groups may be joined together to form a $C_{3-6}$-cycloalkyl group.

Another preferred definition of X is also $C_{3-4}$-alkylene, particularly propylene, which has one or two identical or different substituents selected independently of one another from fluorine, chlorine, hydroxy and $C_{1-3}$-alkyl and/or a cyclopropyl substituent, while two alkyl substituents may be joined together, forming a $C_{3-6}$-cycloalkyl group.

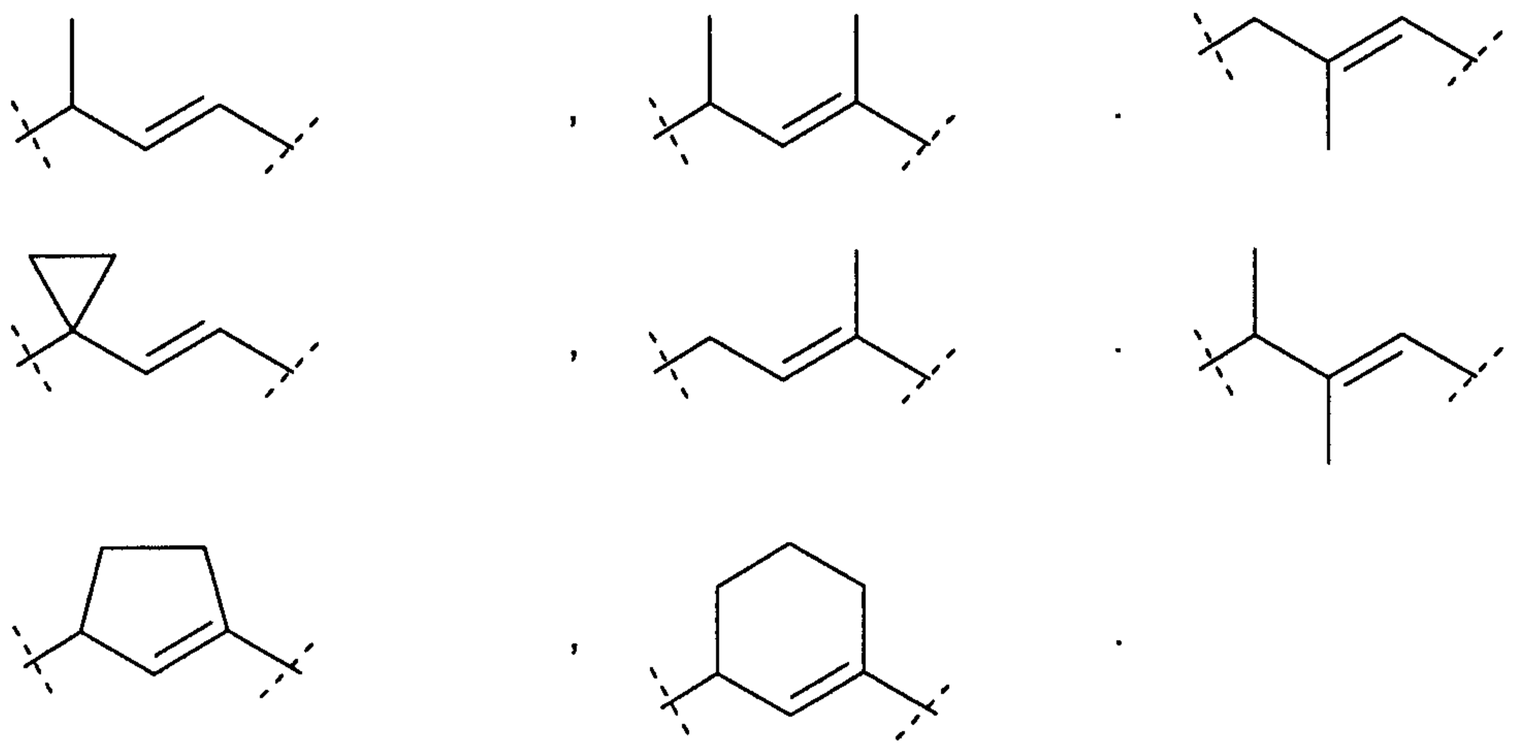
Preferred meanings under the definition of substituted propylene are for example



Other preferred meanings of X are $-CH_2-CH=CH-$ or $-CH_2-C\equiv C-$, while the meanings specified for X are unsubstituted or have one or two identical or different substituents selected

independently of one another from fluorine and $C_{1-3}$-alkyl and/or a cyclopropyl substituent, while two alkyl groups may be joined together forming a $C_{3-6}$-cycloalkyl group. Particularly preferably, the meaning given above for X are mono- or disubstituted by identical or different radicals selected from methyl, ethyl and i-propyl, while two alkyl groups may be joined together as specified, to form a cyclic group.

Other preferred meanings of X are $-CH_2-CH=CH-$ and substituted $-CH_2-CH=CH-$ selected from the group consisting of



For X representing substituted alkenylene, only one of the two possible E/Z configurations is given above. Obviously, the other of the two E/Z configurations is also included according to the invention.

Preferred meanings of the group $R^{10}$ are -OH, methoxy and hydroxymethyl, particularly -OH.

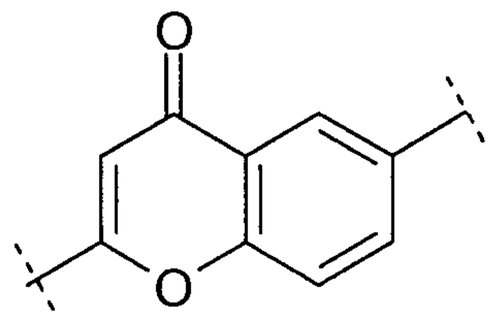
The bridge W preferably denotes a single bond or ethylene, particularly preferably a single bond.

The bridge Z preferably denotes a single bond or ethylene, which may have one or two methyl substituents which may be joined together, forming a cyclopropyl group. Particularly preferably, Z denotes a single bond.

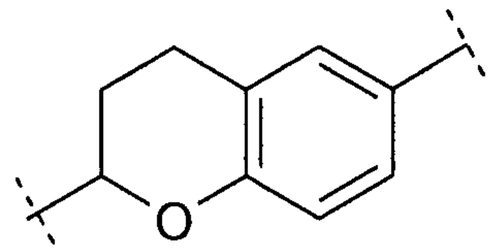
Preferred meanings of the group $R^M$ in the group Y, in the event that M denotes $NR^M$, are selected from H, $C_{1-3}$-alkyl, prop-2-enyl, prop-2-ynyl, $C_{3-6}$-cycloalkyl, $C_{3-6}$-cycloalkylmethyl. Most particularly preferably $R^M$ denotes H or $C_{1-3}$-alkyl, particularly H or methyl.

The preferred alkyne compounds are those wherein M preferably denotes O or S.

Preferred definitions of the group Y are selected from the partial formulae



Y1.1



Y2.1

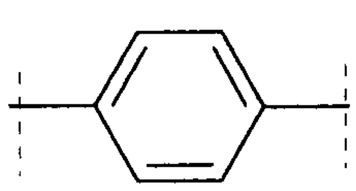
while both partial formulae are unsubstituted or in the two partial formulae one or more, preferably one or two C atoms are substituted independently of one another by $R^{20}$.

Particularly preferred substituents $R^{20}$ of the group Y are selected from the group consisting of fluorine, chlorine, bromine, cyano, nitro, $C_{1-4}$-alkyl, $C_{2-6}$-alkenyl, hydroxy, ω-hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy, trifluoromethyl, trifluoromethoxy, $C_{2-4}$-alkynyl, $C_{1-4}$-alkoxy-carbonyl, ω-($C_{1-4}$-alkoxy)-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy-carbonylamino, amino, $C_{1-4}$-alkyl-amino, di-($C_{1-4}$-alkyl)-amino, aminocarbonyl, $C_{1-4}$-alkyl-amino-carbonyl- and di-($C_{1-4}$-alkyl)-amino-carbonyl.

Most particularly preferred substituents $R^{20}$ of the group Y are selected from the group consisting of fluorine, chlorine, bromine, cyano, $C_{1-3}$-alkyl, $C_{2-3}$-alkenyl, $C_{2-3}$-alkynyl, $C_{1-3}$-alkoxy, $C_{1-4}$-alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, and in the case of a phenyl ring nitro as well. Examples of particularly preferred meanings of the substituent $R^{20}$ are F, Cl, Br, methyl, ethyl, acetyl or methoxy.

Preferably the group A is selected from among the bivalent cyclic groups phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, which may be mono- or polysubstituted at one or more C atoms by identical or different radicals $R^{20}$, and in the case of a phenyl ring may also additionally be monosubstituted by nitro.

Most particularly preferably, A is one of the groups listed below



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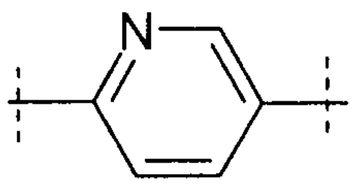

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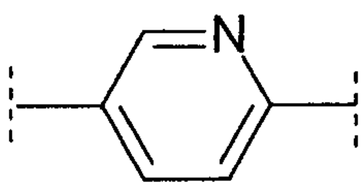
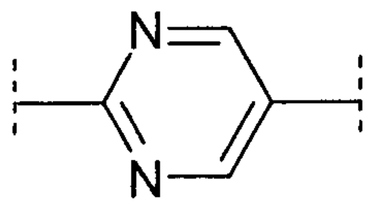
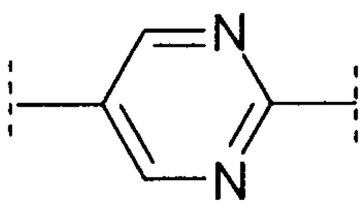
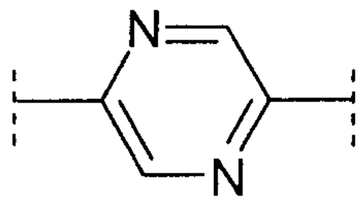
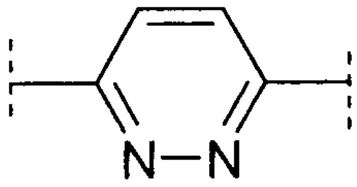
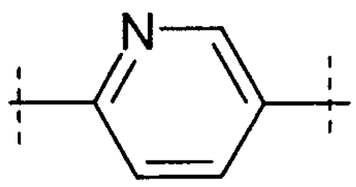
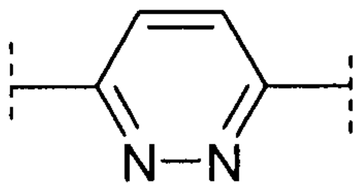
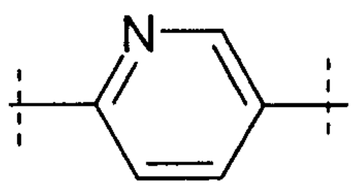






particularly  or 

most particularly preferably 

while the groups listed may be substituted as specified hereinbefore.

Particularly preferred substituents $R^{20}$ of the group A are, independently of one another, fluorine, chlorine, bromine, amino, $CF_3$, methoxy and $C_{1-3}$-alkyl.

Preferably the group A is unsubstituted or monosubstituted by $R^{20}$, as specified.

Preferred definitions of the group B according to a first preferred embodiment are selected from the group consisting of phenyl, pyridyl, thienyl and furanyl. Particularly preferably the group B denotes phenyl. The group B defined as specified may be mono- or polysubstituted by identical or different radicals $R^{20}$, while a phenyl group may additionally also be monosubstituted by nitro. Preferably the group B is unsubstituted or mono-, di or trisubstituted, particularly unsubstituted or mono- or disubstituted. In the case of a monosubstitution the substituent is preferably in the para position to the group A.

Preferred substituents $R^{20}$ of the group B are selected from the group consisting of fluorine, chlorine, bromine, cyano, nitro, $C_{1-4}$-alkyl, hydroxy, $CHF_2$, $CHF_2$-O- hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy, trifluoromethyl, trifluoromethoxy, $C_{2-4}$-alkynyl, carboxy, $C_{1-4}$-alkoxycarbonyl, ω-($C_{1-}$

$_4$-alkoxy)-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy-carbonylamino, amino, $C_{1-4}$-alkyl-amino, di-($C_{1-4}$-alkyl)-amino, cyclo-$C_{3-6}$-alkyleneimino, aminocarbonyl, $C_{1-4}$-alkyl-amino-carbonyl and di-($C_{1-4}$-alkyl)-amino-carbonyl.

Particularly preferred substituents $R^{20}$ of the group B are selected from the group consisting of fluorine, chlorine, bromine, cyano, $CF_3$, $C_{1-3}$-alkyl, $C_{1-4}$-alkoxy and trifluoromethoxy.

Most particularly preferred substituents $R^{20}$ of the group B are selected from the group consisting of chlorine and methoxy.

According to a second embodiment the definition of the group B is preferably selected from $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{5-7}$-cycloalkenyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkenyl-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkenyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkynyl, while one or more C atoms in the groups mentioned above for B may be mono- or polysubstituted by fluorine. In the cyclic groups according to the embodiment mentioned above one or more C atoms may be substituted by $R^{20}$.

Particularly preferred according to this embodiment are the groups $C_{3-6}$-alkyl, $C_{3-6}$-alkenyl, $C_{3-6}$-alkynyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclopentyl-$C_{1-3}$-alkyl, cyclopentenyl-$C_{1-3}$-alkyl, cyclohexyl-$C_{1-3}$-alkyl, cyclohexenyl-$C_{1-3}$-alkyl, cycloheptyl-$C_{1-3}$-alkyl, cycloheptenyl-$C_{1-3}$-alkyl, while one or more C atoms in the groups mentioned above for B may be mono- or polysubstituted by fluorine, and in cyclic groups one or more C atoms may be substituted by identical or different $R^{20}$.

Most particularly preferably, according to this second embodiment, B denotes cyclohexenyl, which is unsubstituted or contains 1, 2 or 3 identical or different substituents $R^{20}$, particularly methyl.

Some preferred definitions of other substituents according to the invention are listed below:

$R^4$ preferably denotes H, $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl and $C_{3-6}$-cycloalkyl-methyl, particularly H, methyl, ethyl, propyl, i-propyl, n-propyl, cylcopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexymethyl. Most particularly preferably $R^4$ denotes H or methyl.

Preferably the substituent $R^{13}$ has one of the meanings given for $R^{16}$. Particularly preferably $R^{13}$ denotes H, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, ω-hydroxy-$C_{2-3}$-alkyl, ω-($C_{1-4}$-alkoxy)-$C_{2-3}$-alkyl. Most particularly preferably $R^{13}$ denotes H or $C_{1-4}$-alkyl. The alkyl groups specified above may be monosubstituted by Cl or mono- or polysubstituted by F.

Preferred meanings of the substituent $R^{15}$ are H, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl and $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms may independently of one another additionally be monosubstituted by Cl or Br. Particularly preferably, $R^{15}$ denotes H, $CF_3$, methyl, ethyl, propyl or butyl.

The substituent $R^{16}$ preferably denotes H, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, ω-hydroxy-$C_{2-3}$-alkyl or ω-($C_{1-4}$-alkoxy)-$C_{2-3}$-alkyl, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms may independently of one another additionally be monosubstituted by Cl or Br. Particularly preferably $R^{16}$ denotes H, $CF_3$, $C_{1-3}$-alkyl, $C_{3-6}$-cycloalkyl or $C_{3-6}$-cycloalkyl-$C_{1-3}$-alkyl.

Preferably the substituent $R^{17}$ has one of the meanings given as preferred for $R^{16}$ or denotes phenyl, phenyl-$C_{1-3}$-alkyl, pyridinyl or $C_{1-4}$-alkylcarbonyl. Particularly preferably $R^{17}$ has one of the meanings given as preferred for $R^{16}$.

Preferably one or both of the substituents $R^{18}$ and $R^{19}$ independently of one another denote hydrogen or $C_{1-4}$-alkyl, particularly hydrogen.

The substituent $R^{20}$ preferably denotes halogen, hydroxy, cyano, $C_{1-4}$-alkyl, $C_{2-4}$-alkenyl, $C_{2-4}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl- $C_{1-3}$-alkyl, hydroxy-$C_{1-4}$-alkyl, $R^{22}$-$C_{1-3}$-alkyl or one of the meanings given as preferred for $R^{22}$, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br.

Particularly preferred definitions of the group $R^{20}$ are halogen, hydroxy, cyano, $C_{1-4}$-alkyl, $C_{1-4}$-alkylcarbonyl, $C_{3-7}$-cycloalkyl and $C_{1-4}$-alkoxy, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br. Most particularly preferably $R^{20}$ denotes F, Cl, Br, I, OH, cyano, methyl, difluoromethyl,

trifluoromethyl, ethyl, n-propyl, iso-propyl, acetyl, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy or iso-propoxy.

The substituent $R^{22}$ preferably denotes $C_{1-4}$-alkoxy, $C_{1-4}$-alkylthio, carboxy, $C_{1-4}$-alkylcarbonyl, $C_{1-4}$-alkoxycarbonyl, aminocarbonyl, $C_{1-4}$-alkylaminocarbonyl, di-($C_{1-4}$-alkyl)-aminocarbonyl, $C_{1-4}$-alkyl-sulphonyl, $C_{1-4}$-alkyl-sulphinyl, $C_{1-4}$-alkyl-sulphonylamino, amino, $C_{1-4}$-alkylamino, di-($C_{1-4}$-alkyl)-amino, $C_{1-4}$-alkyl-carbonyl-amino, hydroxy-$C_{1-3}$-alkylaminocarbonyl, aminocarbonylamino or $C_{1-4}$-alkylaminocarbonyl-amino, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms may independently of one another additionally be monosubstituted by Cl or Br. Most particularly preferred meanings of $R^{22}$ are $C_{1-4}$-alkoxy, $C_{1-4}$-alkylcarbonyl, amino, $C_{1-4}$-alkylamino, di-($C_{1-4}$-alkyl)-amino, wherein one or more H atoms may be replaced by fluorine.

Preferred definitions of the group $R^{21}$ are $C_{1-4}$-alkyl, $C_{1-4}$-alkylcarbonyl, $C_{1-4}$-alkylsulphonyl, -$SO_2$-$NH_2$, -$SO_2$-NH-$C_{1-3}$-alkyl, -$SO_2$-N($C_{1-3}$-alkyl)$_2$ and cyclo-$C_{3-6}$-alkyleneimino-sulphonyl, while, as hereinbefore defined, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br. Most particularly preferably $R^{21}$ denotes $C_{1-4}$-alkyl or $CF_3$.

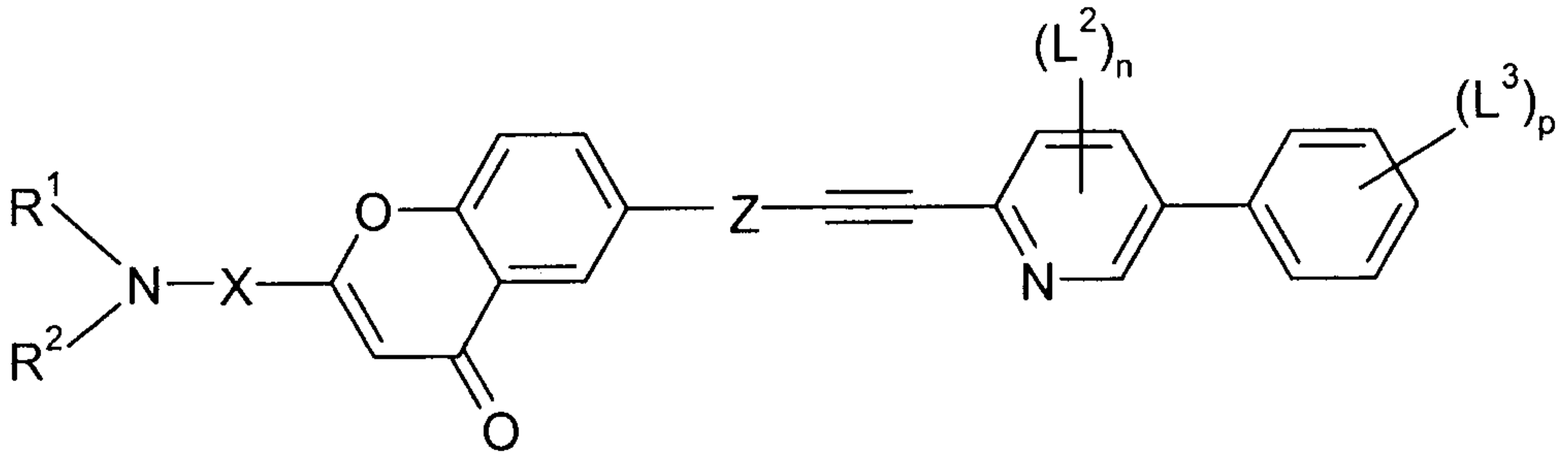
Cy preferably denotes a $C_{3-7}$-cycloalkyl, particularly a $C_{3-6}$-cycloalkyl group, a $C_{5-7}$-cycloalkenyl group, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, aryl or heteroaryl, and the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different radicals $R^{20}$, or in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$. Most particularly preferred definitions of the group Cy are $C_{3-6}$-cycloalkyl, pyrrolidinyl and piperidinyl, which may be substituted as specified.

The term aryl preferably denotes phenyl or naphthyl, particularly phenyl.

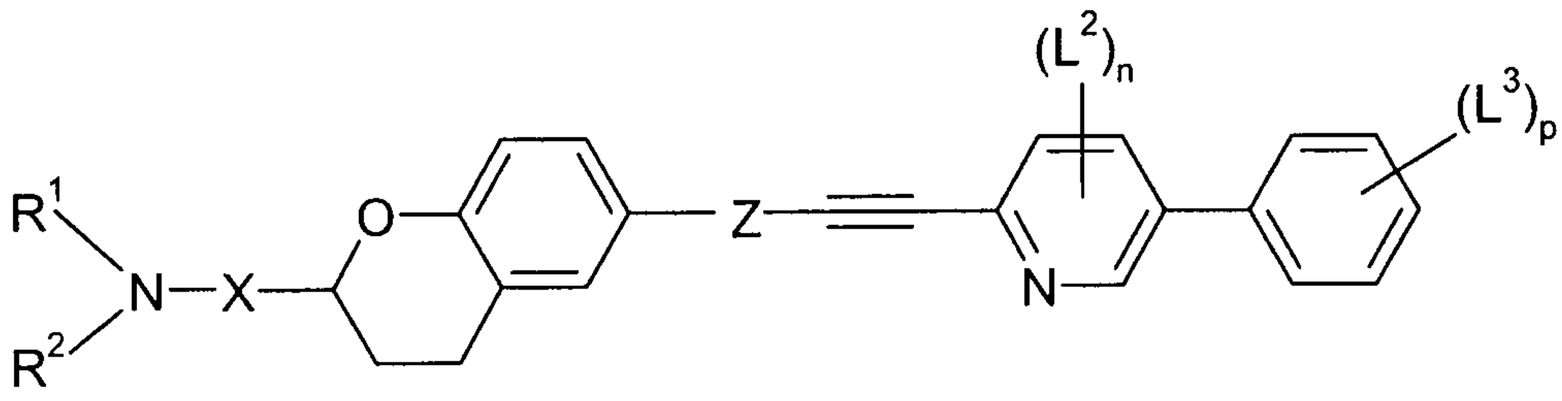
The term heteroaryl preferably includes pyridyl, indolyl, quinolinyl and benzoxazolyl.

Preferred compounds according to the invention are those wherein one or more of the groups, radicals, substituents and/or indices have one of the meanings specified hereinbefore as being preferred.

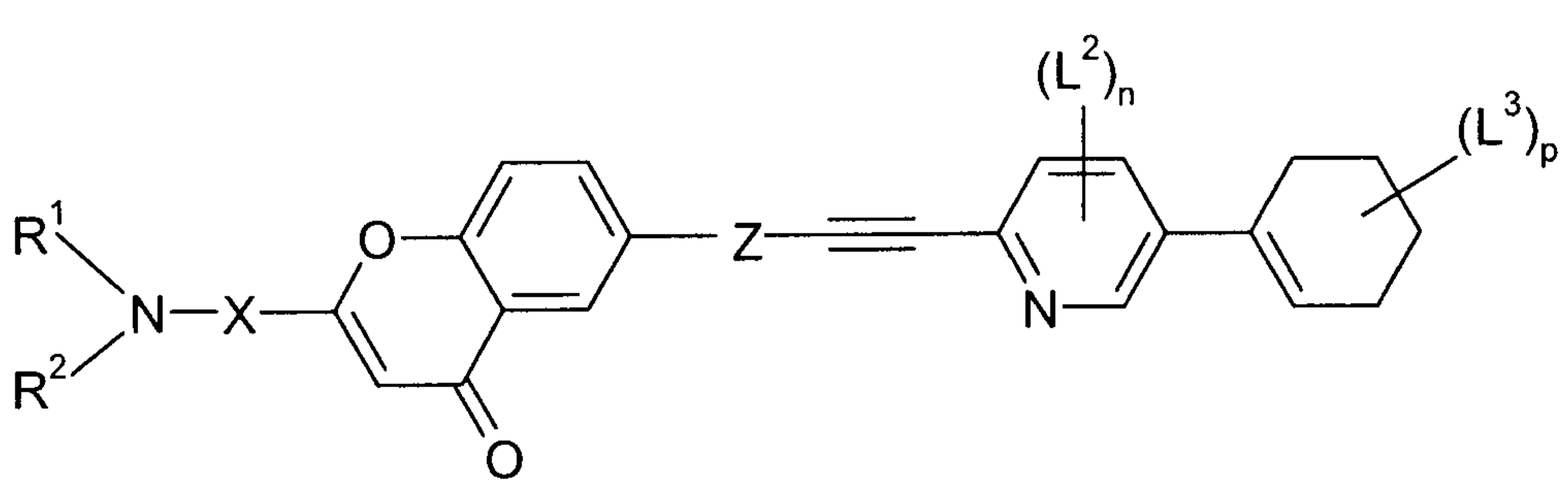
Particularly preferred compounds according to the invention may be described by one of the general formulae IIa to IId, particularly IIa and IIb



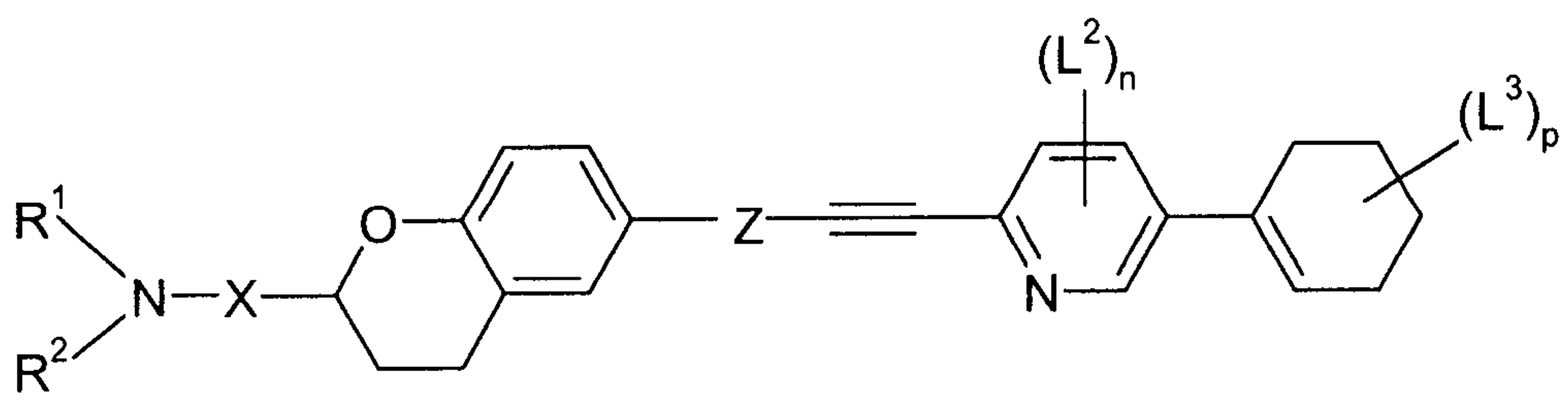
IIa



IIb



IIc



IId

wherein

the chromane and chromenone group is unsubstituted or mono- or disubstituted by $L^1$,

$R^1$, $R^2$, X and Z have one of the meanings given above and

$L^1$, $L^2$, $L^3$, independently of one another have one of the meanings given for $R^{20}$, and

n, p independently of one another represent the values 0, 1 or 2, and p may also denote 3.

Preferably in formulae IIa to IId, particularly IIa and IIb

X denotes an unsubstituted $-CH_2-$ bridge or

a $-CH_2-$ bridge which is mono- or disubstituted by $C_{1-3}$-alkyl, particularly methyl, while two alkyl substituents may be joined together, forming a $C_{3-6}$-cycloalkyl group, particularly cyclopropyl,

Z denotes a single bond,

$L^1$ denotes fluorine, chlorine, bromine, cyano, $C_{1-3}$-alkyl, $C_{1-3}$-alkoxy, $C_{1-4}$-alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, particularly $C_{1-3}$-alkyl,

$L^2$ denotes fluorine, chlorine, bromine, CN, amino, $CF_3$, methoxy and $C_{1-3}$-alkyl,

n denotes 0 or 1,

$L^3$ independently of one another have a meaning selected from among fluorine, chlorine, bromine, cyano, nitro, $C_{1-4}$-alkyl, hydroxy, ω-hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy, trifluoromethyl, trifluoromethoxy, $C_{2-4}$-alkynyl, carboxy, $C_{1-4}$-alkoxy-carbonyl, ω-($C_{1-4}$-alkoxy)-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy-carbonylamino, amino, $C_{1-4}$-alkyl-amino, di-($C_{1-4}$-alkyl)-amino, cyclo-$C_{3-6}$-alkyleneimino, aminocarbonyl, $C_{1-4}$-alkyl-amino-carbonyl or di-($C_{1-4}$-alkyl)-amino-carbonyl, particularly preferably fluorine, chlorine, bromine, cyano, $CF_3$, $C_{1-3}$-alkyl, $C_{1-4}$-alkoxy and trifluoromethoxy, with the proviso that a phenyl ring may only be monosubstituted by nitro, and

p denotes 0, 1, 2 or 3, particularly 1 or 2.

Most particularly preferably, in the formulae IIa, IIb, IIc, IId

$R^1$, $R^2$ independently of one another denote $C_{1-4}$-alkyl, hydroxy-$C_{1-4}$-alkyl, $C_{3-5}$-alkenyl, $C_{3-5}$-alkynyl, $C_{3-7}$-cycloalkyl, hydroxy-$C_{3-7}$-cycloalkyl, dihydroxy-$C_{3-6}$-alkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, (hydroxy-$C_{3-7}$-cycloalkyl)-$C_{1-3}$-alkyl, ω-($C_{1-4}$-alkoxy)-$C_{2-3}$-alkyl, pyridyl or benzyl, while an alkyl, cycloalkyl or cycloalkyl-alkyl group may additionally be mono- or disubstituted by hydroxy and/or hydroxy-$C_{1-3}$-alkyl, and/or mono- or polysubstituted by F or $C_{1-3}$-alkyl and/or monosubstituted by $CF_3$, Br, Cl or CN, and one of the groups $R^1$ and $R^2$ may also denote H, and phenyl and pyridyl rings may be mono- or polysubstituted by identical or different radicals $R^{20}$, while phenyl may also be monosubstituted by nitro, or

$R^1$, $R^2$ are joined together and form, together with the N atom to which they are bound, a heterocyclic group which is selected from pyrrolidine, piperidine, piperazine, wherein the free imine function is substituted by $R^{13}$, and morpholine,

wherein one or more H atoms may be replaced by identical or different groups $R^{14}$, and

while the heterocyclic group defined hereinbefore may be substituted through a single bond with a carbo- or heterocyclic group Cy, while Cy is selected from the group consisting of $C_{3-7}$-cycloalkyl and cyclo-$C_{3-6}$-alkyleneimino, while Cy may be mono- or polysubstituted by identical or different radicals $R^{20}$, where $R^{20}$ is as hereinbefore defined and is preferably selected from fluorine, $CF_3$, $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl and hydroxy, and

$R^{14}$ is selected from F, Cl, Br, $C_{1-4}$-alkyl, hydroxy, hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy, ω-($C_{1-4}$-alkoxy)-$C_{1-3}$-alkyl, amino-$C_{1-3}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkyl-amino-$C_{1-3}$-alkyl, N-($C_{3-7}$-cycloalkyl)-N-($C_{1-4}$-alkyl)-amino-$C_{1-3}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{1-3}$-alkyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{1-3}$-alkyl, aminocarbonyl and pyridylamino, while in the above-mentioned meanings one or more C atoms may each additionally be mono- or polysubstituted by F and/or in each case one or two C atoms may independently of one another additionally be monosubstituted by Cl or Br.

The compounds listed in the experimental section, including the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, are preferred according to the invention.

Some expressions used hereinbefore and below to describe the compounds according to the invention will now be defined more fully.

The term halogen denotes an atom selected from among F, Cl, Br and I, particularly F, Cl and Br.

The term $C_{1-n}$-alkyl, where n has a value of 3 to 8, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of such groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc.

The term $C_{1-n}$-alkylene, where n may have a value of 1 to 8, denotes a saturated, branched or unbranched hydrocarbon bridge with 1 to n C atoms. Examples of such groups include methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), 1-methyl-ethylene ($-CH(CH_3)-CH_2-$), 1,1-dimethyl-ethylene ($-C(CH_3)_2-CH_2-$), n-prop-1,3-ylene ($-CH_2-CH_2-CH_2-$), 1-methylprop-1,3-ylene ($-CH(CH_3)-CH_2-CH_2-$), 2-methylprop-1,3-ylene ($-CH_2-CH(CH_3)-CH_2-$), etc., as well as the corresponding mirror-symmetrical forms.

The term $C_{2-n}$-alkenyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C=C double bond. Examples of such groups include vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc.

The term $C_{2-n}$-alkynyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a C≡C triple bond. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 2-methyl-1-propynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 3-methyl-2-butynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc.

The term $C_{1-n}$-alkoxy denotes a $C_{1-n}$-alkyl-O- group, wherein $C_{1-n}$-alkyl is defined as above. Examples of such groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, iso-pentoxy, neo-pentoxy, tert-pentoxy, n-hexoxy, iso-hexoxy etc.

The term $C_{1-n}$-alkylthio denotes a $C_{1-n}$-alkyl-S- group, wherein $C_{1-n}$-alkyl is defined as above. Examples of such groups include methylthio, ethylthio, n-propylthio, iso-propylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, n-pentylthio, iso-pentylthio, neo-pentylthio, tert-pentylthio, n-hexylthio, iso-hexylthio, etc.

The term $C_{1-n}$-alkylcarbonyl denotes a $C_{1-n}$-alkyl -C(=O)- group, wherein $C_{1-n}$-alkyl is defined as above. Examples of such groups include methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, iso-propylcarbonyl, n-butylcarbonyl, iso-butylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, iso-pentylcarbonyl, neo-pentylcarbonyl, tert-pentylcarbonyl, n-hexylcarbonyl, iso-hexylcarbonyl, etc.

The term $C_{3-n}$-cycloalkyl denotes a saturated mono-, bi-, tri- or spirocarbocyclic, preferably monocarbocyclic group with 3 to n C atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclododecyl, bicyclo[3,2,1]octyl, spiro[4,5]decyl, norpinyl, norbonyl, norcaryl, adamantyl, etc.

The term $C_{5-n}$-cycloalkenyl denotes a monounsaturated mono-, bi-, tri- or spirocarbocyclic, preferably monocarboxylic group with 5 to n C atoms. Examples of such groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, etc.

The term $C_{3-n}$-cycloalkylcarbonyl denotes a $C_{3-n}$-cycloalkyl-C(=O) group, wherein $C_{3-n}$-cycloalkyl is as hereinbefore defined.

The term aryl denotes a carbocyclic, aromatic ring system, such as for example phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl, etc. A particularly preferred meaning of "aryl" is phenyl.

The term cyclo-$C_{3-6}$-alkyleneimino denotes a 4- to 7-membered ring which comprises 3 to 6 methylene units as well as an imino group, while the bond to the residue of the molecule is made via the imino group.

The term cyclo-$C_{3-6}$-alkyleneimino-carbonyl denotes a cyclo-$C_{3-6}$-alkyleneimino ring as hereinbefore defined which is linked to a carbonyl group via the imino group.

The term heteroaryl used in this application denotes a heterocyclic, aromatic ring system which comprises in addition to at least one C atom one or more heteroatoms selected from N, O and/or S. Examples of such groups are furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,3,5-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinozilinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, etc. The term heteroaryl also comprises the partially hydrogenated heterocyclic, aromatic ring systems, particularly those listed above. Examples of such partially hydrogenated ring systems are 2,3-dihydrobenzofuranyl, pyrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl, etc. Particularly preferably heteroaryl denotes a heteroaromatic mono- or bicyclic ring system.

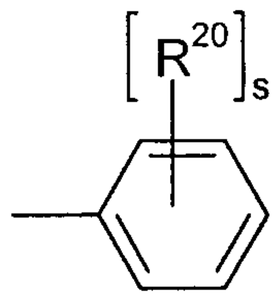
Terms such as $C_{3-7}$-cycloalkyl-$C_{1-n}$-alkyl, heteroaryl-$C_{1-n}$-alkyl, etc. refer to $C_{1-n}$-alkyl, as defined above, which is substituted with a $C_{3-7}$-cycloalkyl, aryl or heteroaryl group.

Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another. Thus, for example, in the group di-$C_{1-4}$-alkyl-amino, the two alkyl groups may have the same or different meanings.

The term "unsaturated", for example in "unsaturated carbocyclic group" or "unsaturated heterocyclic group", as used particularly in the definition of the group Cy, comprises in addition to the mono- or polyunsaturated groups, the corresponding, totally unsaturated groups, but particularly the mono- and diunsaturated groups.

The term "optionally substituted" used in this application indicates that the group thus designated is either unsubstituted or mono- or polysubstituted by the substituents specified. If the group in question is polysubstituted, the substituents may be identical or different.

The style used hereinbefore and hereinafter, according to which in a cyclic group a bond of a substituent is shown towards the centre of this cyclic group, indicates unless otherwise stated that this substituent may be bound to any free position of the cyclic group carrying an H atom.

Thus in the example 

the substituent $R^{20}$ where s = 1 may be bound to any of the free positions of the phenyl ring; where s = 2 selected substituents $R^{20}$ may independently of one another be bound to different free positions of the phenyl ring.

The H atom of any carboxy group present or an H atom bound to an N atom (imino or amino group) may in each case be replaced by a group which can be cleaved in vivo. By a group which can be cleaved in vivo from an N atom is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a $C_{1-16}$-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a $C_{1-16}$-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-$C_{1-6}$-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a $C_{1-3}$-alkylsulphonyl-$C_{2-4}$-alkoxycarbonyl, $C_{1-3}$-alkoxy-$C_{2-4}$-alkoxy-$C_{2-4}$-alkoxycarbonyl or $R_eCO$-O-($R_fCR_g$)-O-CO- group wherein

$R_e$ denotes a $C_{1-8}$-alkyl, $C_{5-7}$-cycloalkyl, phenyl or phenyl- $C_{1-3}$-alkyl group,

$R_f$ denotes a hydrogen atom, a $C_{1-3}$-alkyl, $C_{5-7}$-cycloalkyl or phenyl group and

$R_g$ denotes a hydrogen atom, a $C_{1-3}$-alkyl or $R_eCO$-O-($R_fCR_g$)-O-group wherein $R_e$ to $R_g$ are as hereinbefore defined,

while the phthalimido group is an additional possibility for an amino group, and the above-mentioned ester groups may also be used as a group which can be converted in vivo into a carboxy group.

The residues and substituents described above may be mono- or polysubstituted by fluorine as described. Preferred fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl. Preferred fluorinated alkoxy groups are fluoromethoxy, difluoromethoxy and trifluoromethoxy. Preferred fluorinated alkylsulphinyl and alkylsulphonyl groups are trifluoromethylsulphinyl and trifluoromethylsulphonyl.

The compounds of general formula I according to the invention may have acid groups, predominantly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula I may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine *inter alia*.

The compounds according to the invention may be obtained using methods of synthesis which are known in principle. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter.

The two reaction plans A and B that follow show the synthesis of the compounds A.5 and B.5 according to the invention, while $R^1$, $R^2$, X, Y, Z, W, A and B have one of the meanings described hereinbefore. Hal denotes chlorine, bromine or iodine, particularly bromine or iodine, particularly preferably iodine.

According to reaction plan A the halogen compound A.1 is reacted with the alkyne compound A.2 in a molar ratio of about 1.5 : 1 to 1 : 1.5 under a protective has atmosphere in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent.

A preferred amount of copper(I)iodide is in the range from 1 to 15 mol%, particularly 5 to 10 mol% based on the educt A.1.

Suitable palladium catalysts are for example $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$, $Pd(dppf)Cl_2$. The palladium catalyst is preferably used in an amount from 1 to 15 mol%, particularly 5 to 10 mol% based on the educt A.1.

Suitable bases are particularly amines, such as for example triethylamine or ethyldiisopropylamine, as well as $Cs_2CO_3$. The base is preferably used in an at least

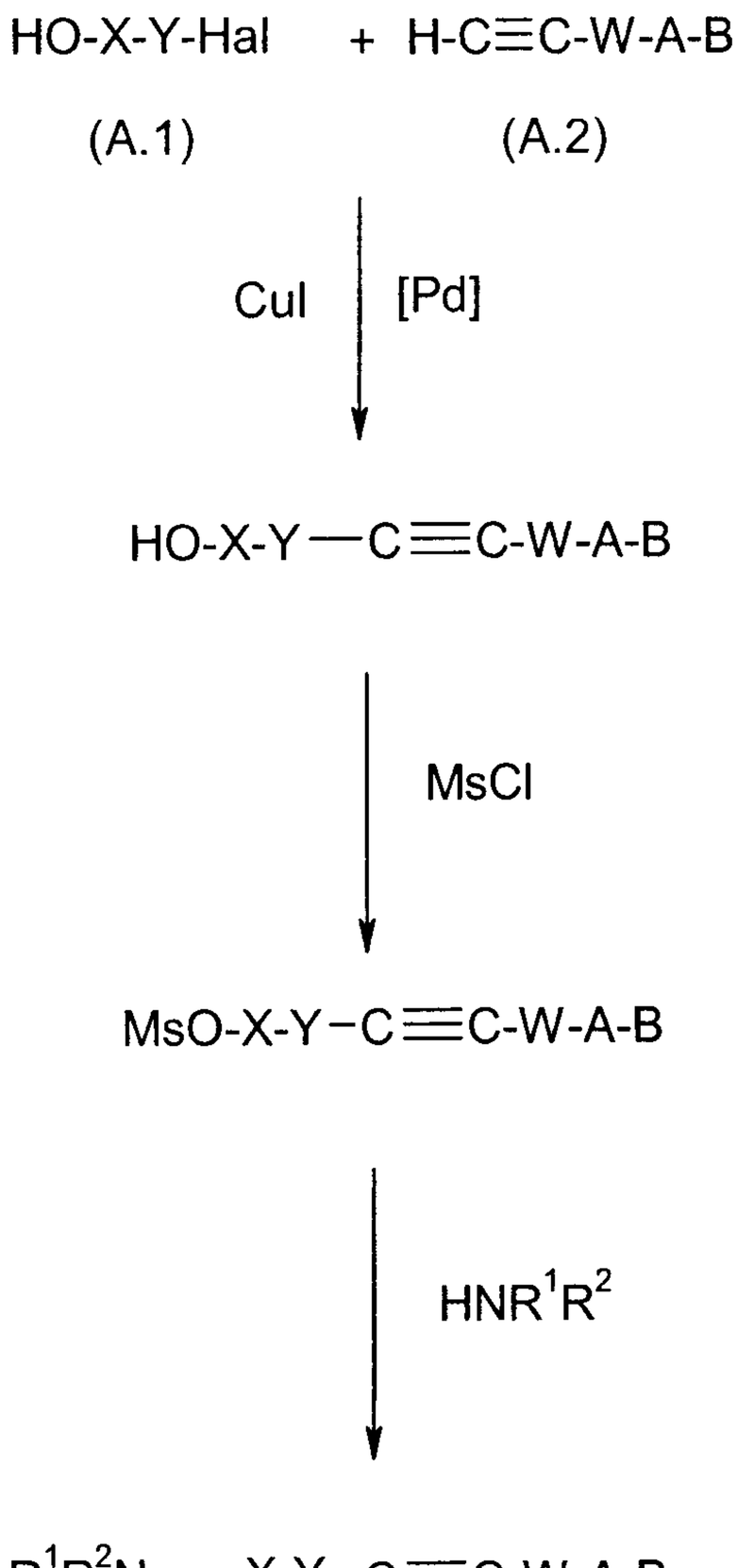
equimolar amount based on the educt A.1, in excess or as the solvent. Moreover, suitable solvents are dimethylformamide or ether, such as for example tetrahydrofuran, including the mixtures thereof. The reaction takes place over a period of about 2 to 24 hours in a temperature range of about 20 to 90°C.

The alkyne compound A.3 obtained is reacted directly or after prior purification with methanesulphonic acid chloride to form the methanesulphonate derivative A.4. The reaction conditions required are known to the skilled man as such. Advantageous solvents are halogenated hydrocarbons, such as for example dichloromethane. Suitable reaction temperatures are usually in the range from 0 to 30°C.

The reaction solution containing the methanesulphonate derivative A.4 or the purified methanesulphonate derivative A.4, dissolved in a suitable solvent, is reacted with an amine H-$NR^1R^2$ to yield the end product A.5 and then optionally purified. If the amine H-$NR^1R^2$ has another primary or secondary amino function, this is advantageously provided with a protective group beforehand, which can be cleaved again after the reaction has ended, using methods known from the literature. The product thus obtained may for example be converted into the salt form by reaction with a corresponding acid. A preferred molar ratio of the derivative A.4 to the amine compound is in the range from 1.5 : 1 to 1 : 1.5. Suitable solvents are dimethylformamide or ether, such as for example tetrahydrofuran, including the mixtures thereof.

The reaction to form the product A.5 is advantageously carried out in a temperature range from about 20 to 90°C.

Reaction plan A:

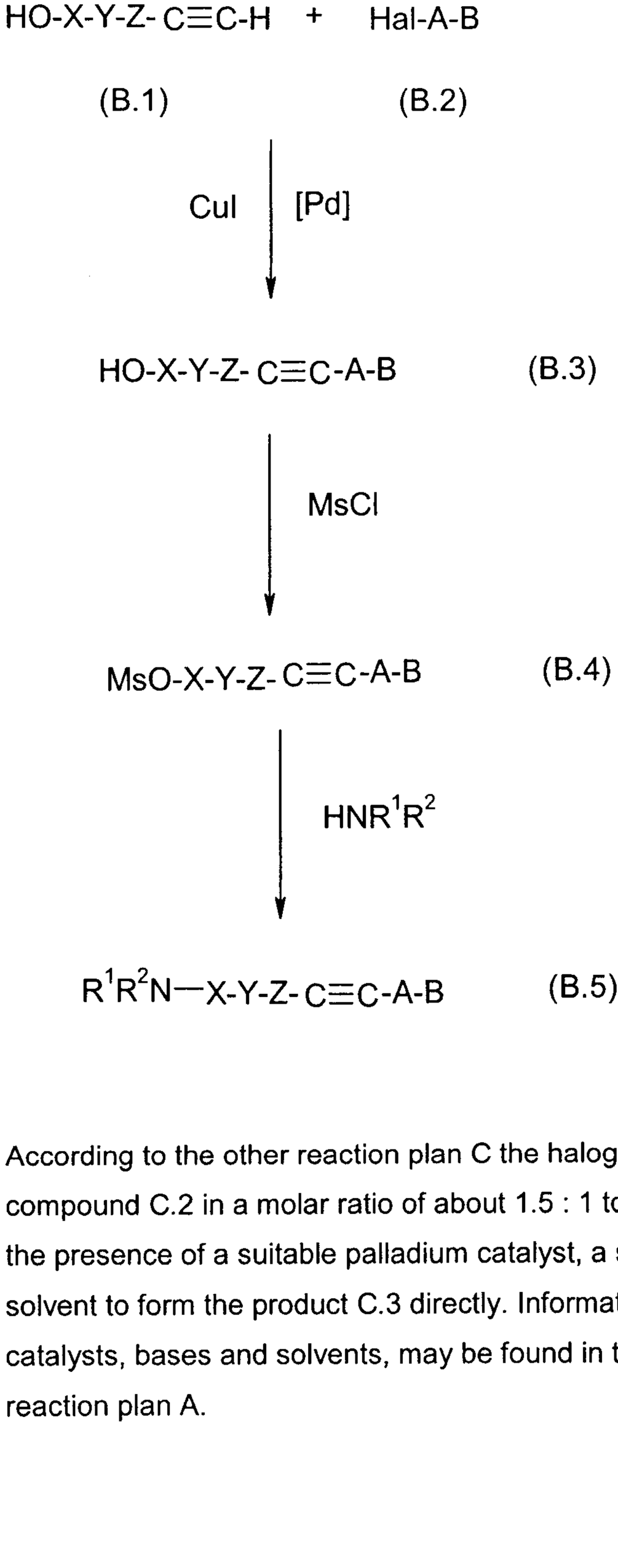



According to reaction plan B the halogen compound B.2 is reacted with the alkyne compound B.1 in a molar ratio of about 1.5 : 1 to 1 : 1.5 under a protective gas atmosphere in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent. Information on suitable reaction conditions, including catalysts, bases and solvents, may be found in the explanations of reaction plan A.

The alkyne compound B.3 obtained is reacted directly, or after prior purification, with methanesulphonic acid chloride to form the methanesulphonate derivative B.4. The reaction conditions to be respected can again be found in the remarks accompanying Diagram A.

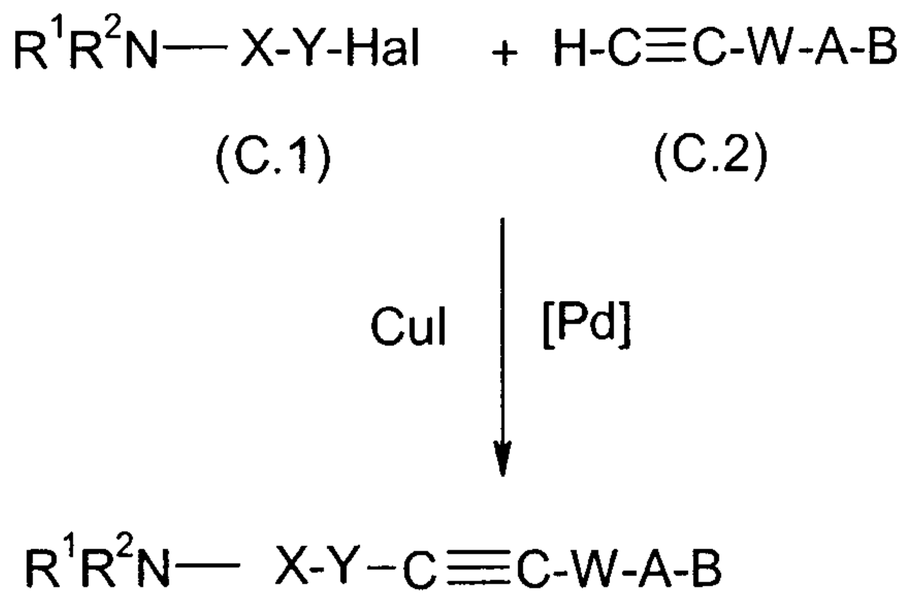
The reaction solution containing the methanesulphonate derivative B.4 or the purified methanesulphonate derivative B.4, dissolved in a suitable solvent, is reacted with an amine $H\text{-}NR^1R^2$ to form the end product B.5 and then optionally purified. Here again, the remarks concerning Diagram A apply.

Reaction plan B:



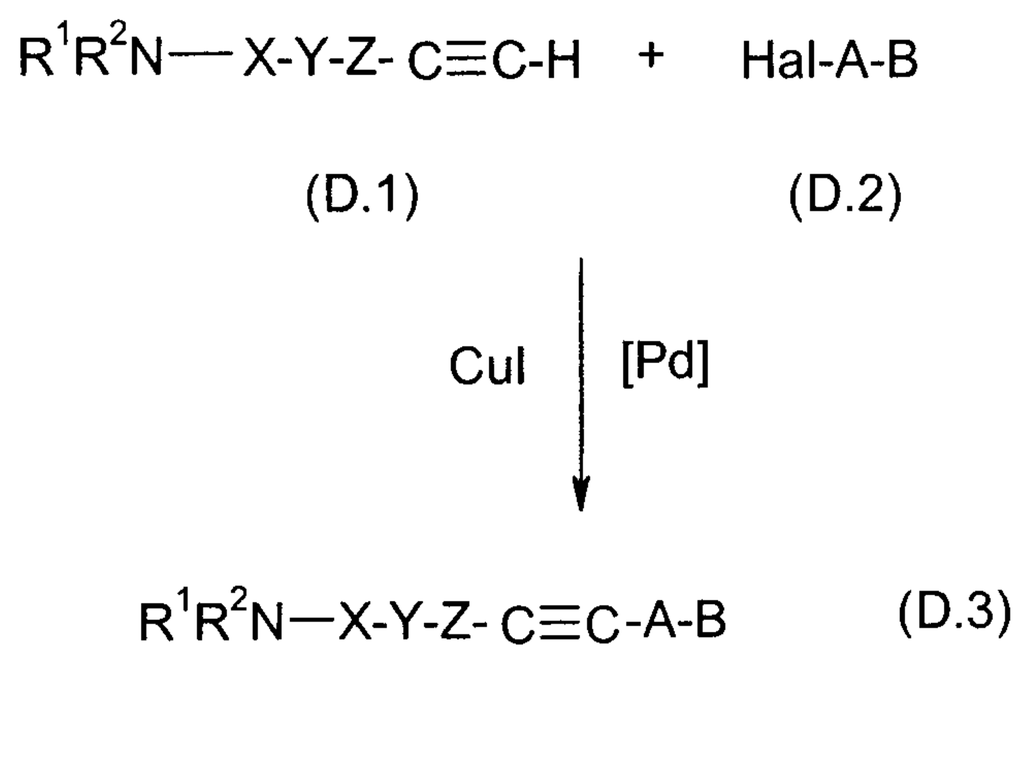

According to the other reaction plan C the halogen compound C.1 is reacted with the alkyne compound C.2 in a molar ratio of about 1.5 : 1 to 1 : 1.5 under a protective gas atmosphere in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent to form the product C.3 directly. Information on suitable reaction conditions, including catalysts, bases and solvents, may be found in the explanatory remarks accompanying reaction plan A.

Reaction plan C:




An alternative method of synthesis to this is shown in reaction plan D. According to this, the halogen compound D.2 is reacted with the alkyne compound D.1 in a molar ratio of about 1.5 : 1 to 1 : 1.5 under a protective gas atmosphere in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent to form the product D.3 directly. Once again, information on suitable reaction conditions, including catalysts, bases and solvents, may be found in the explanatory remarks accompanying reaction plan A.

Reaction plan D:




The reactions according to plans A, B, C and D are particularly advantageously carried out with the corresponding iodine compounds A.1, B.2, C.1 and D.2. In the event that Hal denotes bromine in compounds A.1, B.2, C.1 or D.2, it is advantageous to convert it into the corresponding iodine compound beforehand. One particularly advantageous method is the Aryl-Finkelstein reaction (Klapars, Artis; Buchwald, Stephen L.. Copper-Catalyzed Halogen

Exchange in Aryl Halides: An Aromatic Finkelstein Reaction. Journal of the American Chemical Society (2002), 124(50), 14844-14845). Thus, for example, the halogen compound A.1, B.2, C.1 or D.2 may be reacted with sodium iodide in the presence of *N,N'*-dimethyl-ethylenediamine and copper(I)iodide in a suitable solvent to form the corresponding iodine compound. An advantageous molar ratio of the halogen compound to sodium iodide is 1 : 1.8 to 1 : 2.3. *N,N'*-dimethyl-ethylenediamine is advantageously used in a molar ratio of 10 to 30 mol% based on the halogen compound A.1, B.2, C.1 or D.2. Preferred amounts of copper(I)iodide are in the range from 5 to 20 mol% based on the halogen compound A.1, B.2, C.1 or D.2. A suitable solvent is for example 1,4-dioxane. Suitable reaction temperatures are in the range from about 20 to 110°C. The reaction is substantially complete after 2 to 72 hours.

The compounds according to the invention may be obtained using methods of synthesis which are known in principle. Preferably the compounds are obtained analogously to the methods of preparation explained more fully in the experimental section.

Stereoisomeric compounds of formula (I) may chiefly be separated by conventional methods. The diastereomers are separated on the basis of their different physico-chemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

Racemates covered by general formula (I) may be separated for example by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+)-camphorsulphonic acid, or an optically active base, for example with (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound of formula (I) is reacted with one of the above-mentioned optically active acids or bases in equimolar amounts in a solvent and the resulting crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvent provided that it is sufficiently different in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised

with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. with dilute hydrochloric acid or aqueous methanesulphonic acid and in this way the corresponding free compound is obtained in the (+) or (-) form.

The (R) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds of general formula (I) may also be obtained by performing the syntheses described above with a suitable reaction component in the (R) or (S) configuration.

As already mentioned, the compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically and pharmacologically acceptable salts thereof. These salts may be present on the one hand as physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand, in the case of acidically bound hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter-ion. The acid addition salts may be prepared, for example, using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover, mixtures of the above mentioned acids may be used. To prepare the alkali and alkaline earth metal salts of the compound of formula (I) with acidically bound hydrogen the alkali and alkaline earth metal hydroxides and hydrides are preferably used, while the hydroxides and hydrides of the alkali metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are most preferred.

The compounds according to the present invention, including the physiologically acceptable salts, are effective as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit good affinity in MCH receptor binding studies. Pharmacological test systems for MCH-antagonistic properties are described in the following experimental section.

As antagonists of the MCH receptor the compounds according to the invention are advantageously suitable as pharmaceutical active substances for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. Generally the compounds according to the invention have low toxicity, they are well absorbed by oral route and have good intracerebral transitivity, particularly brain accessibility.

Therefore, MCH antagonists which contain at least one compound according to the invention are particularly suitable in mammals, such as for example rats, mice, guinea pigs, hares, dogs, cats, sheep, horses, pigs, cattle, monkeys and humans, for the treatment and/or prevention of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

Diseases caused by MCH or otherwise causally connected with MCH are particularly metabolic disorders, such as for example obesity, and eating disorders, such as for example bulimia, including bulimia nervosa. The indication obesity includes in particular exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, central obesity. This range of indications also includes cachexia, anorexia and hyperphagia.

Compounds according to the invention may be particularly suitable for reducing hunger, curbing appetite, controlling eating behaviour and/or inducing a feeling of satiation.

In addition, the diseases caused by MCH or otherwise causally connected with MCH also include hyperlipidaemia, cellulitis, fatty accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affectivity disorders, depression, anxiety states, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

Compounds according to the invention are also suitable as active substances for the prevention and/or treatment of other illnesses and/or disorders, particularly those which accompany obesity, such as for example diabetes, diabetes mellitus, particularly type II diabetes, hyperglycaemia, particularly chronic hyperglycaemia, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, etc., insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

MCH antagonists and formulations according to the invention may advantageously be used in combination with a dietary therapy, such as for example a dietary diabetes treatment, and exercise.

Another range of indications for which the compounds according to the invention are advantageously suitable is the prevention and/or treatment of micturition disorders, such as for example urinary incontinence, hyperactive bladder, urgency, nycturia, enuresis, while the hyperactive bladder and urgency may or may not be connected with benign prostatic hyperplasia.

Generally speaking, the compounds according to the invention are potentially suitable for preventing and/or treating dependencies, such as for example alcohol and/or nicotine dependency, and/or withdrawal symptoms, such as for example weight gain in smokers coming off nicotine. By "dependency" is generally meant here an irresistible urge to take an addictive substance and/or to perform certain actions, particularly in order to either achieve a feeling of wellbeing or to eliminate negative emotions. In particular, the term "dependency" is used here to denote a dependency on an addictive substance. By "withdrawal symptoms" are meant here, in general, symptoms which occur or may occur when addictive substances are withdrawn from patients dependent on one or more such substances. The compounds according to the invention are potentially suitable particularly as active substances for reducing or ending tobacco consumption, for the treatment or prevention of a nicotine dependency and/or for the treatment or prevention of nicotine withdrawal symptoms, for reducing the craving for tobacco and/or nicotine and generally as an anti-smoking agent. The compounds according to the invention may also be useful for preventing or at least reducing the weight gain typically seen when smokers are coming off nicotine. The substances may also be suitable as active substances which prevent or at least reduce the craving for and/or relapse into a dependency on addictive substances. The term addictive substances refers particularly but not exclusively to substances with a psycho-motor activity, such as narcotics or drugs, particularly alcohol, nicotine, cocaine, amphetamine, opiates, benzodiazepines and barbiturates.

The dosage required to achieve such an effect is conveniently, by intravenous or sub-cutaneous route, 0.001 to 30 mg/kg of body weight, preferably 0.01 to 5 mg/kg of body weight, and by oral or nasal route or by inhalation, 0.01 to 50 mg/kg of body weight, preferably 0.1 to 30 mg/kg of body weight, in each case 1 to 3 x daily.

For this purpose, the compounds prepared according to the invention may be formulated, optionally in conjunction with other active substances as described hereinafter, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose,

microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, lozenges, powders, granules, solutions, emulsions, syrups, aerosols for inhalation, ointments or suppositories.

In addition to pharmaceutical compositions the invention also includes compositions containing at least one alkyne compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients. Such compositions may also be for example foodstuffs which may be solid or liquid, in which the compound according to the invention is incorporated.

For the above mentioned combinations it is possible to use as additional active substances particularly those which for example potentiate the therapeutic effect of an MCH antagonist according to the invention in terms of one of the indications mentioned above and/or which make it possible to reduce the dosage of an MCH antagonist according to the invention.
Preferably one or more additional active substances are selected from among

- active substances for the treatment of diabetes,
- active substances for the treatment of diabetic complications,
- active substances for the treatment of obesity, preferably other than MCH antagonists,
- active substances for the treatment of high blood pressure,
- active substances for the treatment of hyperlipidaemia, including arteriosclerosis,
- active substances for the treatment of dyslipidaemia, including arteriosclerosis,
- active substances for the treatment of arthritis,
- active substances for the treatment of anxiety states,
- active substances for the treatment of depression.

The above mentioned categories of active substances will now be explained in more detail by means of examples.

Examples of active substances for the treatment of diabetes are insulin sensitisers, insulin secretion accelerators, biguanides, insulins, $\alpha$-glucosidase inhibitors, $\beta$3 adreno-receptor agonists.

Insulin sensitisers include glitazones, particularly pioglitazone and its salts (preferably hydrochloride), troglitazone, rosiglitazone and its salts (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702 and GW-1929.

Insulin secretion accelerators include sulphonylureas, such as for example tolbutamide, chloropropamide, tolazamide, acetohexamide, glyclopyramide and its ammonium salts, glibenclamide, gliclazide, glimepiride. Further examples of insulin secretion accelerators are repaglinide, nateglinide, mitiglinide (KAD-1229) and JTT-608.

Biguanides include metformin, buformin and phenformin.

Insulins include those obtained from animals, particularly cattle or pigs, semisynthetic human insulins which are synthesised enzymatically from insulin obtained from animals, human insulin obtained by genetic engineering, e.g. from Escherichia coli or yeasts. Moreover, the term insulin also includes insulin-zinc (containing 0.45 to 0.9 percent by weight of zinc) and protamine-insulin-zinc obtainable from zinc chloride, protamine sulphate and insulin. Insulin may also be obtained from insulin fragments or derivatives (for example INS-1, etc.).

Insulin may also include different kinds, e.g. with regard to the onset time and duration of effect ("ultra immediate action type", "immediate action type", "two phase type", "intermediate type", "prolonged action type", etc.), which are selected depending on the pathological condition of the patient.

α-Glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate.

β3 Adreno receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

Active substances for the treatment of diabetes other than those mentioned above include ergoset, pramlintide, leptin, BAY-27-9955 as well as glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, protein tyrosine phosphatase 1B inhibitors, dipeptidyl protease inhibitors, glipazide, glyburide.

Active substances for the treatment of diabetic complications include for example aldose reductase inhibitors, glycation inhibitors and protein kinase C inhibitors, DPPIV blockers, GLP-1 or GLP-2 analogues and SGLT-2 inhibitors.

Aldose reductase inhibitors are for example tolrestat, epalrestat, imirestat, zenarestat, SNK-860, zopolrestat, ARI-50i, AS-3201.

An example of a glycation inhibitor is pimagedine.

Protein Kinase C inhibitors are for example NGF, LY-333531.

DPPIV blockers are for example LAF237 (Novartis), MK431 (Merck) as well as 815541, 823093 and 825964 (all GlaxoSmithkline).

GLP-1 analogues are for example Liraglutide (NN2211) (NovoNordisk), CJC1131 (Conjuchem), Exenatide (Amylin).

SGLT-2 inhibitors are for example AVE-2268 (Aventis) and T-1095 (Tanabe, Johnson&Johnson).

Active substances other than those mentioned above for the treatment of diabetic complications include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedine (ALT-711).

Active substances for the treatment of obesity, preferably other than MCH antagonists, include lipase inhibitors and anorectics.

A preferred example of a lipase inhibitor is orlistat.

Examples of preferred anorectics are phentermine, mazindol, dexfenfluramine, fluoxetine, sibutramine, baiamine, (S)-sibutramine, SR-141716, NGD-95-1.

Active substances other than those mentioned above for the treatment of obesity include lipstatin.

Moreover, for the purposes of this application, the active substance group of anti-

obesity active substances also includes the anorectics, of which the $\beta_3$ agonists, thyromimetic active substances and NPY antagonists should be emphasised. The range of substances which may be considered as preferred anti-obesity or anorectic active substances is indicated by the following additional list, by way of example: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as for example sibutramine), a sympathomimetic active substance, a serotonergic active substance (such as for example dexfenfluramine, fenfluramine, a 5-HT2C agonist such as BVT.933 or APD356, or duloxetine), a dopamine antagonist (such as for example bromocriptine or pramipexol), a melanocyte-stimulating hormone receptor agonist or mimetic, an analogue of melanocyte-stimulating hormone, a cannabinoid receptor antagonist (Rimonabant, ACOMPLIA TM), an MCH antagonist, the OB protein (hereinafter referred to as leptin), a leptin analogue, a fatty acid synthase (FAS) antagonist, a leptin receptor agonist, a galanine antagonist, a GI lipase inhibitor or reducer (such as for example orlistat). Other anorectics include bombesin agonists, dehydroepiandrosterone or its analogues, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the Glucagon-like Peptide-1 receptor, such as for example exendin, AC 2993, CJC-1131, ZP10 or GRT0203Y, DPPIV inhibitors and ciliary neurotrophic factors, such as for example axokines. In this context mention should also be made of the forms of therapy which produce weight loss by increasing the fatty acid oxidation in the peripheral tissue, such as for example inhibitors of acetyl-CoA carboxylase.

Active substances for the treatment of high blood pressure include inhibitors of angiotensin converting enzyme, calcium antagonists, potassium channel openers and angiotensin II antagonists.

Inhibitors of angiotensin converting enzyme include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride).

Examples of calcium antagonists are nifedipine, amlodipine, efonidipine, nicardipine.

Potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

Angiotensin II antagonists include telmisartan, losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

Active substances for the treatment of hyperlipidaemia, including arteriosclerosis, include HMG-CoA reductase inhibitors, fibrate compounds.

HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522 and their salts.

Fibrate compounds include bezafibrate, clinofibrate, clofibrate and simfibrate.

Active substances for the treatment of dyslipidaemia, including arteriosclerosis, include e.g. medicaments which raise the HDL level, such as e.g. nicotinic acid and derivatives and preparations thereof, such as e.g. niaspan, as well as agonists of the nicotinic acid receptor.

Active substances for the treatment of arthritis include NSAIDs (non-steroidal antiinflammatory drugs), particularly COX2 inhibitors, such as for example meloxicam or ibuprofen.

Active substances for the treatment of anxiety states include chlordiazepoxide, diazepam, oxozolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

Active substances for the treatment of depression include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The dosage for these active substances is conveniently 1/5 of the lowest normal recommended dose up to 1/1 of the normal recommended dose.

In another embodiment the invention also relates to the use of at least one alkyne compound according to the invention and/ or a salt according to the invention for influencing the eating behaviour of a mammal. This use is particularly based on the fact that compounds according to the invention may be suitable for reducing hunger, curbing appetite, controlling eating behaviour and/or inducing a feeling of satiety. The eating behaviour is advantageously influenced so as to reduce food intake. Therefore, the compounds according to the invention are advantageously used for reducing body weight. Another use according to the invention is the prevention of increases in body weight, for example in people who had previously taken

steps to lose weight and are interested in maintaining their lower body weight. According to this embodiment it is preferably a non-therapeutic use. Such a non-therapeutic use might be a cosmetic use, for example to alter the external appearance, or an application to improve general health. The compounds according to the invention are preferably used non-therapeutically for mammals, particularly humans, not suffering from any diagnosed eating disorders, no diagnosed obesity, bulimia, diabetes and/or no diagnosed micturition disorders, particularly urinary incontinence. Preferably, the compounds according to the invention are suitable for non-therapeutic use in people whose BMI (body mass index), defined as their body weight in kilograms divided by their height (in metres) squared, is below a level of 30, particularly below 25.

The Examples that follow are intended to illustrate the invention:

Preliminary remarks

As a rule, IR, $^1$H-NMR and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated the $R_f$ values were determined using ready-made silica gel 60 TLC plates $F_{254}$ (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation. The $R_f$ values obtained under the heading Alox were determined using ready-made aluminium oxide 60 TLC plates $F_{254}$ (E. Merck, Darmstadt, Item no. 1.05713) without chamber saturation. The ratios specified for the eluants are based on units by volume of the solvents in question. The units by volume specified in the case of $NH_3$ relate to a concentrated solution of $NH_3$ in water. Unless otherwise stated the acid, base and salt solutions used for working up the reaction solutions are aqueous systems of the concentrations specified.
In the asymmetric dihydroxylations the "AD-Mix Alpha“ (item number: 39,275-8) and "AD-Mix-Beta“ (item number: 39,276-6) sold by Messrs Aldrich are used.
For chromatographic purification, silica gel made by Messrs Millipore (MATREX$^{TM}$, 35-70 my) is used. For chromatographic purification, Alox (E. Merck, Darmstadt, standardised aluminium oxide 90, 63-200 µm, Item no.: 1.01097.9050) is used. The HPLC data specified were measured under the parameters indicated below:
Analytical columns: Zorbax column (Agilent Technologies), SB (Stable Bond) - C18; 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 0.8 mL / min; injection volume: 5 µL; detection at 254 nm (methods A, B and C).

Method A:

| time (min) | percent by volume of water (with 0.1% formic acid) | percent by volume of acetonitrile (with 0.1% formic acid) |
|---|---|---|
| 0 | 95 | 5 |
| 9 | 10 | 90 |
| 10 | 10 | 90 |
| 11 | 90 | 10 |

Method B:

| time (min) | percent by volume of water (with 0.1% formic acid) | percent by volume of acetonitrile (with 0.1% formic acid) |
|---|---|---|
| 0 | 95 | 5 |
| 4 | 10 | 90 |
| 10 | 10 | 90 |
| 11 | 90 | 10 |

Method C:

| time (min) | percent by volume of water (with 0.1% formic acid) | percent by volume of acetonitrile (with 0.1% formic acid) |
|---|---|---|
| 0 | 95 | 5 |
| 8 | 50 | 50 |
| 9 | 10 | 90 |
| 10 | 10 | 90 |
| 11 | 90 | 10 |

Preparative column: Zorbax-Säule (Agilent Technologies), SB (Stable Bond) - C18; 3.5 µm; 30 x 100 mm; column temperature: ambient temperature; flow: 30 mL / min; detection at 254 nm.

In preparative HPLC purification, as a rule the same gradients are used which were used when obtaining the analytical HPLC data.

The products are collected under mass control, the fractions containing the product are combined and freeze-dried.

Temperatures are given in degrees Celsius (°C) ; times are generally given in minutes (min), hours (h) or days (d). If there is no specific information as to the configuration, it is not clear

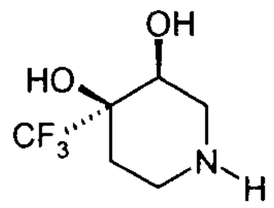
whether there are pure enantiomers or whether partial or even total racemisation has taken place.

The following abbreviations are used above and hereinafter:

| | |
|---|---|
| abs. | absolute |
| CDI | carbonyldiimidazole |
| cyc | cyclohexane |
| DCM | dichloromethane |
| DIPE | diisopropylether |
| DMF | dimethylformamide |
| DMSO | dimethylsulphoxide |
| dppf | 1,1´-bis(diphenylphosphino)ferrocene |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| i. vac. | in vacuo |
| MeOH | methanol |
| MTBE | methyl-tert-butylether |
| PE | petroleum ether |
| RT | ambient temperature (approx. 20°C) |
| TBAF | tetrabutylammonium fluoride trihydrate |
| THF | tetrahydrofuran |
| dil. | dilute |
| →* | denotes the binding site of a group |

Amine A1

(3S,4R)-4-trifluoromethyl-piperidin-3,4-diol




A1a 1-benzyl-4-trifluoromethyl-pyridinium chloride

A solution of 7.59 mL (65.94 mmol) benzylchloride in 10 mL acetonitrile is added to a solution of 10.0 g (65.94 mmol) 4-trifluoromethyl-pyridine in 40 mL acetonitrile and the mixture is stirred for 2 h at 80 °C stirred. A further 1.5 mL benzylchloride are added and the mixture is stirred for 22 h at 80 °C. The reaction mixture is cooled to RT and combined with MTBE. The precipitate is filtered off, washed with MTBE, dried i. vac. and stored in the desiccator.

Yield: 14.48 g (80% of theoretical)

$C_{13}H_{11}F_3N * Cl$ (M= 273.681)

Calc.: molpeak $(M+H)^+$: 238 Found: molpeak $(M+H)^+$: 238

A1b 1-benzyl-4-trifluoromethyl-1,2,3,6-tetrahydro-pyridine

3.0 g (79.36 mmol) $NaBH_4$ is added batchwise with intensive cooling at 0 °C to a solution of 14.48 g (52.91 mmol) 1-benzyl-4-trifluoromethyl-pyridiniumchloride in 100 mL EtOH, then the cooling is removed and the reaction mixture is stirred for 1.5 h at 14 °C. While cooling, 50 mL water and then 50 mL EtOH are added within 30 min. The reaction mixture is stirred for a further 30 min, the suspension formed is filtered and the filtrate is evaporated down i. vac..

Yield: 11.72 g (92% of theoretical)

$C_{13}H_{14}F_3N$ (M= 241.252)

Calc.: molpeak $(M+H)^+$: 242 Found: molpeak $(M+H)^+$: 242

HPLC-MS: 3.60 min (method B)

A1c (3S,4R)-1-benzyl-4-trifluoromethyl-piperidin-3,4-diol

43.80 g AD-Mix-Beta are placed in 3 L tert-butanol/water (1:1) and stirred for 20 min at RT. The mixture is cooled to 0 °C, 2.97 g (31.25 mmol) methanesulphonamide and 7.54 g (31.25 mmol) 1-benzyl-4-trifluoromethyl-1,2,3,6-tetrahydro-pyridine are added, the cooling bath is removed and the mixture is stirred for 8 d at RT. A further 22 g AD-Mix-Beta and 1.5 g methanesulphonamide are added and the mixture is again stirred for 7 d at RT. 11.2 g sodium sulphite are added and the mixture is stirred for 1 h. 200 mL of semisaturated $NaHCO_3$ solution are added and the aqueous phase is exhaustively extracted with DCM. The combined organic phases are dried over $Na_2SO_4$ and evaporated down i. vac.. The crude product is purified by MPLC-MS (Grom-Sil 120 ODS 4, 10 µm, gradient 0.15% formic acid in water / acetonitrile 90:10 → 10:90 in 10 Min). The eluates are combined, evaporated down i. vac. and neutralised with 100 mL halbsaturated $NaHCO_3$ solution. The aqueous phase is extracted with EtOAc, the combined organic phases are dried over $Na_2SO_4$ and evaporated down i. vac..

Yield: 1.51 g (17% of theoretical)

$C_{13}H_{16}F_3NO_2$ (M= 275.267)

Calc.: molpeak $(M+H)^+$: 276 Found: molpeak $(M+H)^+$: 276

$R_f$ value: 0.40 (silica gel, cyc/EtOAc 2:1)

A1d (3S,4R)-4-trifluoromethyl-piperidin-3,4-diol

A mixture of 1.50 g (5.45 mmol) (3S,4R)-1-benzyl-4-trifluoromethyl-piperidin-3,4-diol and 170 mg Pd/C (10%) in 17 mL MeOH is hydrogenated at RT and 3 bar hydrogen pressure for 5 h. The catalyst is filtered off and the filtrate is evaporated down i. vac..

Yield: 910 mg (90% of theoretical)

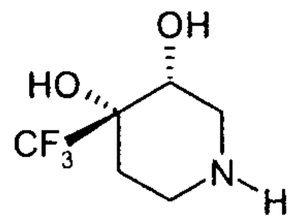
$C_6H_{10}F_3NO_2$ (M= 185.144)

Calc.: molpeak $(M+H)^+$: 186 Found: molpeak $(M+H)^+$: 186

$R_f$ value: 0.35 (silica gel, EtOAc/MeOH/$NH_3$ 7:3:0.3)

amine A2

(3R,4S)-4-trifluoromethyl-piperidin-3,4-diol




A2a (3R,4S)-1-benzyl-4-trifluoromethyl-piperidin-3,4-diol

The product is obtained analogously to A1c starting from intermediate product A1b and AD-Mix-Alpha. The crude product is purified by HPLC-MS.

Yield: 1.09 g (16% of theoretical)

$C_{13}H_{16}F_3NO_2$ (M= 275.267)

Calc.: molpeak $(M+H)^+$: 276 Found: molpeak $(M+H)^+$: 276

HPLC-MS: 3.70 min (method A)

A2b (3R,4S)-4-trifluoromethyl-piperidin-3,4-diol

The product is obtained analogously to A1d starting from (3R,4S)-1-benzyl-4-trifluoromethyl-piperidin-3,4-diol.

Yield: 665 mg (91% of theoretical)

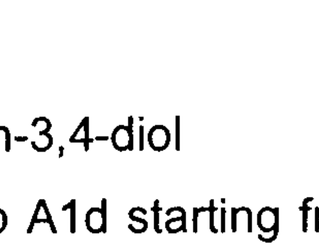
$C_6H_{10}F_3NO_2$ (M= 185.144)

Calc.: molpeak $(M+H)^+$: 186 Found: molpeak $(M+H)^+$: 186

$R_f$ value: 0.35 (silica gel, EtOAc/MeOH/$NH_3$ 7:3:0.3)

amine A3

(3R,4S)-4-methyl-piperidin-3,4-diol




A3a 1-benzyl-4-methyl-1,2,3,6-tetrahydro-pyridine

The product is obtained analogously to A1b starting from 10.0 g (45.5 mmol) 1-benzyl-4-methyl-pyridinium chloride.

Yield: 7.15 g (84% of theoretical)

$C_{13}H_{17}N$ (M= 187.281)

Calc.: molpeak $(M+H)^+$: 188 Found: molpeak $(M+H)^+$: 188

$R_f$ value: 0.95 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

A3b (3R,4S)-1-benzyl-4-methyl-piperidin-3,4-diol

Under a nitrogen atmosphere 14 g AD-Mix-Alpha are placed in 50 mL water and 50 mL tert-butanol and the mixture is stirred for 20 min at RT. Subsequently it is cooled to 0°C, 0.95 g (10.0 mmol) methanesulphonic acid amide and 1.87 g (10.0 mmol) 1-benzyl-4-methyl-1,2,3,6-tetrahydro-pyridine are added, the cooling bath is removed and the reaction mixture is stirred for 24 h at RT. 3.5 g sodium sulphite are added to the reaction mixture and it is stirred for 1 h. 200 mL DCM and 200 mL saturated $NaHCO_3$ solution are added, the organic phase is separated off and extracted with 100 mL $KHSO_4$ solution. The aqueous phase is made alkaline with saturated $K_2CO_3$ solution, extracted with 200 mL EtOAc and the organic phase is dried over $Na_2SO_4$. After the desiccant and solvent have been eliminated the crude product is purified by chromatography (silica gel, EtOAc/MeOH/$NH_3$ 19:1:0.1).

Yield: 1.23 g (56% of theoretical)

$C_{13}H_{19}NO_2$ (M= 221.296)

Calc.: molpeak $(M+H)^+$: 222 Found: molpeak $(M+H)^+$: 222

$R_f$ value: 0.56 (silica gel, EtOAc/MeOH/$NH_3$ 19:1:0.1)

A3c (3R,4S)-4-methyl-piperidin-3,4-diol

The product is obtained analogously to A1d starting from 1.23 g (5.57 mmol) (3R,4S)-1-benzyl-4-methyl-piperidin-3,4-diol.

Yield: 730 mg (quant. yield)

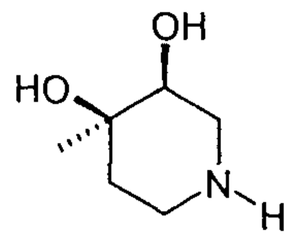
$C_6H_{13}NO_2$ (M= 131.173)

Calc.: molpeak $(M+H)^+$: 132 Found: molpeak $(M+H)^+$: 132

HPLC-MS: 0.93 min (method C)

amine A4

(3S,4R)-4-methyl-piperidin-3,4-diol



A4a (3S,4R)-1-benzyl-4-methyl-piperidin-3,4-diol

The product is obtained analogously to A3b starting from 5.0 g (26.7 mmol) 1-benzyl-4-methyl-1,2,3,6-tetrahydro-pyridine and AD-Mix-Beta.

Yield: 4.68 g (79% of theoretical)

$C_{13}H_{19}NO_2$ (M= 221.296)

Calc.: molpeak $(M+H)^+$: 222 Found: molpeak $(M+H)^+$: 222

$R_f$ value: 0.54 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

A4b (3S,4R)-4-methyl-piperidin-3,4-diol

The product is obtained analogously to A1d starting from 4.68 g (21.14 mmol) (3S,4R)-1-benzyl-4-methyl-piperidin-3,4-diol.

Yield: 2.33 g (84% of theoretical)

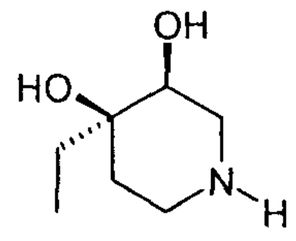
$C_6H_{13}NO_2$ (M= 131.173)

Calc.: molpeak $(M+H)^+$: 132 Found: molpeak $(M+H)^+$: 132

$R_f$ value: 0.05 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

<u>amine A5</u>

(3S,4R)-4-ethyl-piperidin-3,4-diol




A5a 1-*benzyl*-4-ethyl-*pyridinium* chloride

The product is obtained analogously to A1a starting from 100 mL (933 mmol) 4-ethylpyridine.

Yield: 143 g (66% of theoretical)

$C_{14}H_{16}N * Cl$ (M= 233.736)

Calc.: molpeak $(M+H)^+$: 198 Found: molpeak $(M+H)^+$: 198

$R_f$ value: 0.12 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

A5b 1-benzyl-4-ethyl-1,2,3,6-tetrahydro-pyridine

The product is obtained analogously to A1b starting from 143 g (614 mmol) 1-benzyl-4-ethyl-pyridinium chloride.

Yield: 99 g (80% of theoretical)

$C_{14}H_{19}N$ (M= 201.307)

Calc.: molpeak $(M+H)^+$: 202 Found: molpeak $(M+H)^+$: 202

$R_f$ value: 0.91 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

A5c (3S,4R)-1-benzyl-4-ethyl-piperidin-3,4-diol

The product is obtained analogously to A3b starting from 14.37 g (71.4 mmol) 1-benzyl-4-ethyl-1,2,3,6-tetrahydro-pyridine and AD-Mix-Beta.

Yield: 11.46 g (68% of theoretical)

$C_{14}H_{21}NO_2$ (M= 235.322)

Calc.: molpeak $(M+H)^+$: 236 Found: molpeak $(M+H)^+$: 236

$R_f$ value: 0.58 (silica gel, EtOAc/MeOH/$NH_3$ 95:5:0.5)

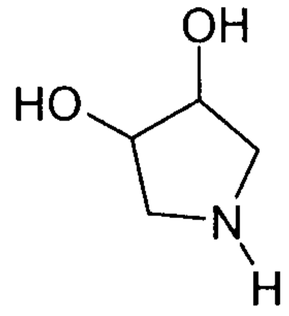
A5d (3S,4R)-4-ethyl-piperidin-3,4-diol

The product may be obtained analogously to A1d starting from (3S,4R)-1-benzyl-4-ethyl-piperidin-3,4-diol.

The enantiomer (3R,4S)-4-ethyl-piperidin-3,4-diol may be obtained analogously to the sequence described.

amine A6

cis-pyrrolidine-3,4-diol



A6a 1-benzyl-2,5-dihydro-1*H*-pyrrole

14.6 mL (127 mmol) benzyl chloride are added dropwise to a solution of 10 mL (127 mmol) 2,5-dihydro-1*H*-pyrrole in 100 mL acetonitrile, during which time the reaction mixture heats up to 45°C. After 1.5 h 300 mL MTBE is added to the suspension, the precipitate is filtered off and the filtrate is evaporated down. The residue is purified by chromatography (silica gel, EtOAc/MeOH/$NH_3$ 19:1:0.1).

Yield: 4.0 g (20% of theoretical)

$C_{11}H_{13}N$ (M= 159.228)

Calc.: molpeak $(M+H)^+$: 160 Found: molpeak $(M+H)^+$: 160

$R_f$ value: 0.60 (silica gel, EtOAc/MeOH/$NH_3$ 19:1:0.1)

A6b cis-1-benzyl-pyrrolidine-3,4-diol

The product is obtained analogously to A3b starting from 4.0 g (25.1 mmol) 1-benzyl-2,5-dihydro-1*H*-pyrrole and AD-Mix-Beta.

Yield: 0.97 g (20% of theoretical)

$C_{11}H_{15}NO_2$ (M= 193.242)

Calc.: molpeak $(M+H)^+$: 194 Found: molpeak $(M+H)^+$: 194

$R_f$ value: 0.15 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

A6c cis-pyrrolidine-3,4-diol

The product is obtained analogously to A1d starting from 0.97 g (5.04 mmol) cis-1-benzyl-pyrrolidine-3,4-diol.

Yield: 0.52 g (quant. yield)

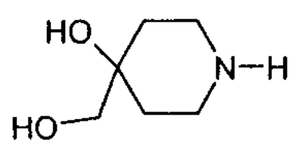
$C_4H_9NO_2$ (M= 103.120)

Calc.: molpeak $(M+H)^+$: 104 Found: molpeak $(M+H)^+$: 104

$R_f$ value: 0.05 (silica gel, EtOAc/MeOH/$NH_3$ 5:5:0.5)

amine A7

4-hydroxymethyl-piperidin-4-ol




A7a 1-benzyl-4-hydroxymethyl-piperidin-4-ol

The product is obtained analogously to A3b starting from 3.15 g (16.83 mmol) 1-benzyl-4-methylene-piperidine and AD-Mix-Alpha.

Yield: 2.92 g (79% of theoretical)

$C_{13}H_{19}NO_2$ (M= 221.296)

Calc.: molpeak $(M+H)^+$: 222 Found: molpeak $(M+H)^+$: 222

$R_f$ value: 0.12 (silica gel, EtOAc/MeOH/$NH_3$ 9:1:0.1)

A7b 4-hydroxymethyl-piperidin-4-ol

The product is obtained analogously to A1d starting from 2.92 g (13.21 mmol) 1-benzyl-4-hydroxymethyl-piperidin-4-ol.

Yield: 1.88 g (quant. yield)

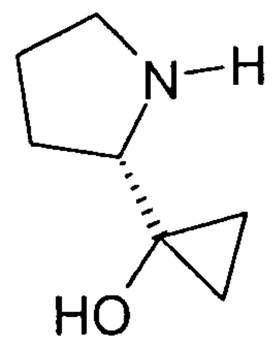
$C_6H_{13}NO_2$ (M= 131.173)

Calc.: molpeak $(M+H)^+$: 132 Found: molpeak $(M+H)^+$: 132

$R_f$ value: 0.06 (silica gel, EtOAc/MeOH/$NH_3$ 5:5:0.5)

amine A8

(S)-1-pyrrolidin-2-yl-cyclopropanol




A8a 1-((S)-1-benzyl-pyrrolidin-2-yl)-cyclopropanol

First 6.91 mL (23.57 mmol) Titanium(IV)-isopropoxide and then 14.3 mL (42. 9 mmol, 3 M in diethyl ether) ethylmagnesiumbromide are slowly added dropwise to a solution of 5.0 g (21.43 mmol) N-benzyl-L-prolinethylester in 80 mL dry diethyl ether cooled to -15°C and the reaction mixture is stirred for 30 min at this temperature. Subsequently at approx 10°C 5.4 mL (42.9 mmol) boron trifluoride-diethyl ether complex are added and the mixture is stirred for a further 75 h at RT. While cooling, the mixture is combined with 50 mL 1 M NaOH, stirred for 1 h at RT, combined with 100 mL diethyl ether, the organic phase is separated off and dried over $Na_2SO_4$. After the desiccant and solvent have been eliminated the residue is purified by chromatography (silica gel, EtOAc).

Yield: 0.745 g (16% of theoretical)

$C_{14}H_{19}NO$ (M= 217.307)

Calc.: molpeak $(M+H)^+$: 218 Found: molpeak $(M+H)^+$: 218

$R_f$ value: 0.17 (silica gel, EtOAc)

A8b (S)-1-pyrrolidin-2-yl-cyclopropanol

The product is obtained analogously to A1d starting from 745 mg (3.43 mmol) 1-((S)-1-benzyl-pyrrolidin-2-yl)-cyclopropanol.

Yield: 350 mg (80% of theoretical)

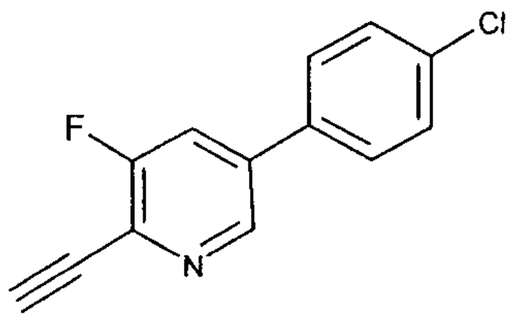
$C_7H_{13}NO$ (M= 127.184)

Calc.: molpeak $(M+H)^+$: 128 Found: molpeak $(M+H)^+$: 128

$R_f$ value: 0.10 (silica gel, EtOAc/MeOH/$NH_3$ 5:5:0.5)

intermediate product A9

5-(4-chloro-phenyl)-2-ethynyl-3-fluoro-pyridine



A9a 2,5-dibromo-3-fluoro-pyridine

A solution of 1.78 g (25.80 mmol) sodium nitrite in 3.5 mL water is added dropwise at -5 °C to a solution of 6.50 g (25.80 mmol) 2,5-dibromo-pyridin-3-ylamine and 15 mL conc. HCl (180.62 mmol) in 15 mL water and the mixture is stirred for 30 min. At 0 °C, 11.41 mL (77.41 mmol) hexafluorophosphoric acid (60% in water) are added and the mixture is stirred for 1 h at 0 °C. The diazonium salt formed is filtered off, washed with cold water, isopropanol and diethyl ether and dried i. vac. in the desiccator. Petroleum ether (100-140 °C) is heated to 90°C, the diazonium salt is added batchwise and the mixture is stirred until no further development of gas is detectable. The reaction mixture is cooled to RT, made alkaline with saturated $Na_2CO_3$ solution and the aqueous phase is exhaustively extracted with MTBE. The combined organic phases are washed with saturated $Na_2CO_3$ solution and water, dried over $MgSO_4$ and evaporated down i. vac.. The residue is dissolved in DCM, filtered through silica gel and the filtrate is evaporated down i. vac..

Yield: 3.30 (51% of theoretical)

$C_5H_2Br_2FN$ (M= 254.883)

Calc.: molpeak $(M+H)^+$: 253/255/257 ($Br_2$) Found: molpeak $(M+H)^+$: 253/255/257 ($Br_2$)

$R_f$ value: 0.63 (silica gel, PE/EtOAc 9:1)

A9b 5-bromo-2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-3-fluoro-pyridine

Under an argon atmosphere 2.62 mL (13.811 mmol) tert-butyl-ethynyl-dimethyl-silane is added to a solution of 3.20 g (12.56 mmol) 2,5-dibromo-3-fluoro-pyridine, 5.22 mL triethylamine (37.67 mmol), 59.8 mg (0.31 mmol) CuI and 220.3 mg (0.31 mmol) bis-triphenylphosphane-palladium(II)-chloride in 30 mL abs. THF at 15 °C and the mixture is stirred for 2 h at RT. Then a further 1 mL of tert-butyl-ethynyl-dimethyl-silane are added and the mixture is stirred for 1 h at RT. The reaction mixture is evaporated down i. vac. and the residue is taken up in EtOAc. The organic phase is washed with semisaturated $NaHCO_3$ solution, 5% $NH_3$ solution and water and dried over $MgSO_4$. After the desiccant and solvent have been eliminated the residue is purified by chromatography (silica gel, PE/DCM 9:1).

Yield: 1.62 g (41% of theoretical)

$C_{13}H_{17}BrFNSi$ (M= 314.269)

Calc.: molpeak $(M+H)^+$: 314/316 (Br) Found: molpeak $(M+H)^+$: 314/316 (Br)

HPLC-MS: 7.85 min (method B)

A9c 2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-5-(4-chloro-phenyl)-3-fluoro-pyridine

10 mL MeOH, 10 mL 2 N $Na_2CO_3$ solution and 94 mg (0.13 mmol) $PdCl_2$(dppf) are added to a solution of 1.61 g (5.14 mmol) 5-bromo-2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-3-fluoro-

pyridine and 0.90 g (5.65 mmol) 4-chlorophenylboric acid in 30 mL 1,4-dioxane and the mixture is refluxed for15 min. The reaction mixture is evaporated down i. vac. and diluted with EtOAc. The organic phase is washed with water and semisaturated $NaHCO_3$ solution and dried over $Na_2SO_4$. After the desiccant and solvent have been eliminated the residue is purified by chromatography (silica gel, PE/DCM 1:1).

Yield: 1.25 g (70% of theoretical)

$C_{19}H_{21}ClFNSi$ (M= 345.913)

Calc.: molpeak $(M+H)^+$: 346/348 (Cl) Found: molpeak $(M+H)^+$: 346/348 (Cl)

HPLC-MS: 8.83 min (method B)

A9d 5-(4-chloro-phenyl)-2-ethynyl-3-fluoro-pyridine

1.14 g (3.61 mmol) TBAF is added at RT to a solution of 1.25 g (3.61 mmol) 2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-5-(4-chloro-phenyl)-3-fluoro-pyridine in 30 mL DCM and the mixture is stirred for 2 h. The organic phase is washed with water and dried over $Na_2SO_4$. After the desiccant and solvent have been eliminated the residue is stirred with PE, the precipitate is filtered off, washed with PE and dried in the air.

Yield: 0.72 g (86% of theoretical)

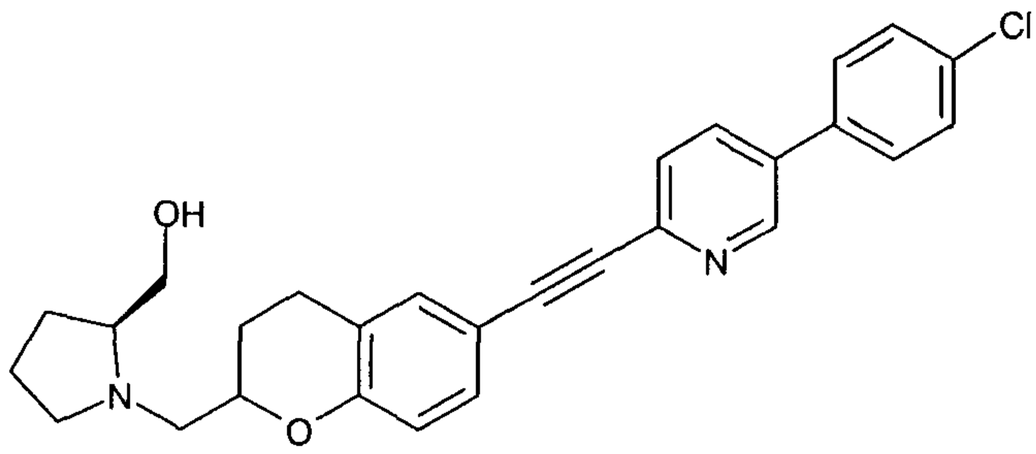
$C_{13}H_7ClFN$ (M= 231.653)

Calc.: molpeak $(M+H)^+$: 232/234 (Cl) Found: molpeak $(M+H)^+$: 232/234 (Cl)

HPLC-MS: 5.81 min (method B)

Example 1.1

((S)-1-{6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-ylmethyl}-pyrrolidin-2-yl)-methanol




1.1a (6-iodo-1-benzopyran-2-yl)-methanol

A finely triturated mixture of 4 g silica gel (0.2-0.5 mm) and 2.02 g (5.0 mmol) iron (III)nitrate nonahydrate is added to a solution of 1.64 g (10.00 mmol) 1-benzopyran-2-yl-methanol and 1.40 g (5.50 mmol) iodine in 15 mL DCM and stirred for 12 h at RT. A further 5 g of silica gel

are added and the reaction mixture is evaporated down i. vac.. Column chromatography (silica gel, PE/EtOAc 7:3) yielded the product.

Yield: 1.80 g (62% of theoretical)

$C_{10}H_{11}O_2$ (M= 290.098)

Calc.: molpeak $(M+H)^+$: 290 Found: molpeak $(M+H)^+$: 290

$R_f$ value: 0.45 (silica gel, PE/EtOAc 4:1)

1.1b 5-bromo-2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-pyridine

Under an argon atmosphere 0.80 g (4.20 mmol) CuI and 2.90 g (4.13 mmol) bis-triphenylphosphane-palladium(II)-chloride is added to a solution of 49.90 g (201.01 mmol) 2,5-dibromopyridine and 43.00 mL (225.57 mmol) tert-butyl-ethynyl-dimethyl-silane in 500 mL abs. THF and 120 mL triethylamine at -7 °C and the mixture is stirred for 30 min at 0 °C. The reaction mixture is stirred for 3.5 h at RT, then filtered and the filtrate is evaporated down i. vac.. The residue is dissolved in 1 L EtOAc, the organic phase is washed with water and saturated NaCl solution, dried over $Na_2SO_4$ and evaporated down i. vac.. The crude product is used in the next reaction step without any further purification.

Yield: 59.5 g (quant. yield)

$C_{13}H_{18}BrNSi$ (M= 296.278)

Calc.: molpeak $(M+H)^+$: 296/298 (Br) Found: molpeak $(M+H)^+$: 296/298 (Br)

$R_f$ value: 0.75 (silica gel, cyc/EtOAc 8:1)

1.1c 2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-5-(4-chloro-phenyl)-pyridine

250 mL MeOH, 220 mL 2 N $Na_2CO_3$ solution and 1.80 g (2.46 mmol) $PdCl_2$(dppf) are added to a solution of 59.5 g (201.01 mmol) 5-bromo-2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-pyridine and 36.5 g (233.40 mmol) 4-chlorophenylboric acid in 600 mL 1,4-dioxane and the mixture is refluxed for1 h. The reaction mixture is evaporated down i. vac. and diluted with EtOAc. The organic phase is washed with water and semisaturated $NaHCO_3$ solution, dried over $Na_2SO_4$ and evaporated down i. vac.. The residue is purified by column chromatography (silica gel, cyc/EtOAc 9:1).

Yield: 38.5 g (58% of theoretical)

$C_{19}H_{22}ClNSi$ (M= 327.923)

Calc.: molpeak $(M+H)^+$: 328/330 (Cl) Found: molpeak $(M+H)^+$: 328/330 (Cl)

$R_f$ value: 0.60 (silica gel, cyc/EtOAc 8:1)

1.1d 5-(4-chloro-phenyl)-2-ethynyl-pyridine

43.66 g (156.00 mmol) TBAF are added to a solution of 46.50 g (142.00 mmol) 2-[(tert-butyl-dimethyl-silanyl)-ethynyl]-5-(4-chloro-phenyl)-pyridine in 1 L DCM at RT and the mixture is stirred for 2 h. The organic phase is washed with water, dried over $Na_2SO_4$ and evaporated down i. vac.. The residue is stirred with DIPE, the precipitate is filtered off and washed with PE.

Yield: 26.0 g (86% of theoretical)

$C_{13}H_8ClN$ (M= 213.662)

Calc.: molpeak $(M+H)^+$: 214/216 (Cl) Found: molpeak $(M+H)^+$: 214/216 (Cl)

$R_f$ value: 0.30 (silica gel, cyc/EtOAc 4:1)

1.1e {6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-yl}-methanol

Under an argon atmosphere 48.6 mg (0.25 mmol) CuI is added to a solution of 1.62 g (5.58 mmol) (6-iodo-1-benzopyran-2-yl)-methanol, 1.20 g (5.60 mmol) 5-(4-chloro-phenyl)-2-ethynyl-pyridine, 204.1 mg (0.25 mmol) $PdCl_2$(dppf) and 2.36 mL (17.00 mmol) triethylamine in 50 mL acetonitrile and the mixture is stirred for 6 h at RT. The reaction mixture is poured onto water, the precipitate is filtered off and dried in the air. The residue is purified by column chromatography (silica gel, gradient DCM/EtOAc 100:0 → 50:50 in 30 min).

Yield: 0.85 g (41% of theoretical)

$C_{23}H_{18}ClNO_2$ (M= 375.847)

Calc.: molpeak $(M+H)^+$: 376/378 (Cl) Found: molpeak $(M+H)^+$: 376/378 (Cl)

$R_f$ value: 0.20 (silica gel, DCM/EtOAc 9:1)

1.1f 6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-ylmethyl methanesulphonate

389 µL (5.00 mmol) methanesulphonic acid chloride are added dropwise at 0 °C to a solution of 0.85 g (2.26 mmol) 6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-yl}-methanol and 403 µL (5.00 mmol) pyridine in 20 mL DCM and the mixture is stirred for 2 h at RT. A further 806 µL (10.00 mmol) methanesulphonic acid chloride are added and the mixture is stirred for 16 h. The reaction mixture is washed with water and dil. sodium bicarbonate solution, dried over $Na_2SO_4$, filtered through activated charcoal and evaporated down i. vac.. The crude product is purified by column chromatography (silica gel, DCM/EtOAc 4:1).

Yield: 0.70 g (68% of theoretical)

$C_{24}H_{20}ClNO_4S$ (M= 453.939)

Calc.: molpeak $(M+H)^+$: 454/456 (Cl) Found: molpeak $(M+H)^+$: 454/456 (Cl)

$R_f$ value: 0.53 (silica gel, DCM/EtOAc 9:1)

1.1g ((S)-1-{6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-ylmethyl}-pyrrolidin-2-yl)-methanol

A solution of 113.5 mg (0.25 mmol) 6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-ylmethyl methanesulphonate and 120 µL (1.10 mmol) (S)-1-pyrrolidin-2-yl-methanol in 2 mL DMF is stirred for 24 h at 80 °C and then poured onto water. The precipitate is washed with water, a little acetone and DIPE and dried in the air.

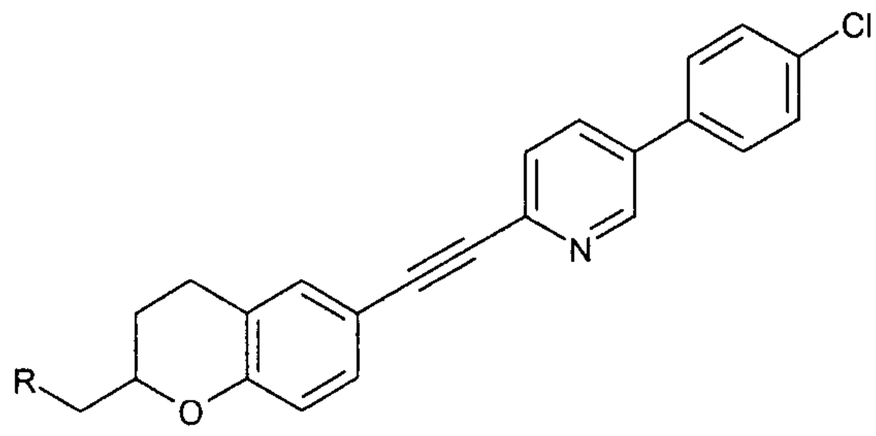
Yield: 80 mg (70% of theoretical)

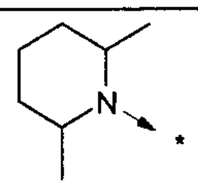
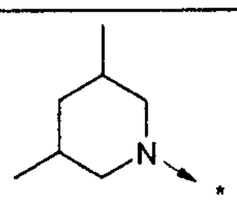
$C_{28}H_{27}ClN_2O_2$ (M= 458.979)

Calc.: molpeak $(M+H)^+$: 459/461 (Cl) Found: molpeak $(M+H)^+$: 459/461 (Cl)

$R_f$ value: 0.28 (silica gel, DCM/EtOAc 9:1)

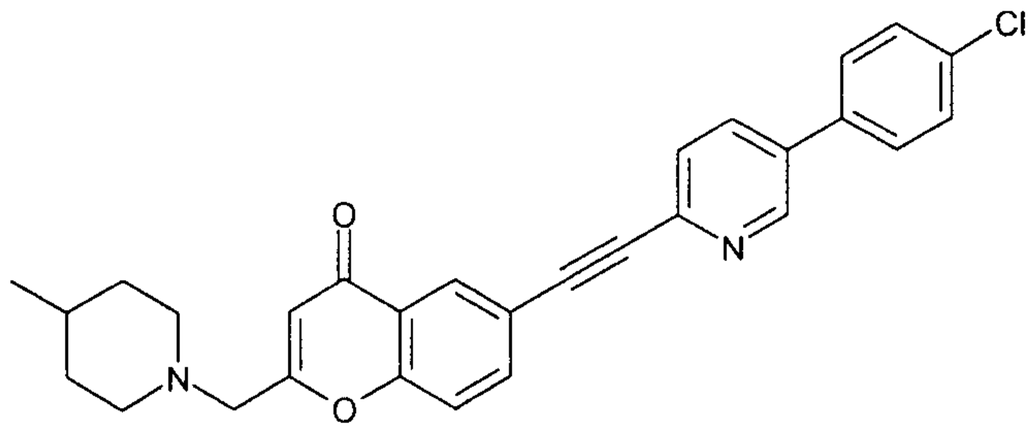
The following Examples are prepared analogously starting from 6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-ylmethyl methanesulphonate (Example 1.1f):




| Example | R | Yield (%) | empirical formula | mass spectrum | $R_f$ value (silica gel, DCM/MeOH 9:1) |
|---|---|---|---|---|---|
| 1.2 |  | 17 | $C_{30}H_{31}ClN_2O$ | 471/473 $[M+H]^+$ | 0.40 |
| 1.3 |  | 76 | $C_{30}H_{31}ClN_2O$ | 471/473 $[M+H]^+$ | 0.40 |

Example 2.1

6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one




2.1a 6-bromo-2-hydroxymethyl-1-benzopyran-4-on

17.03 g (105.00 mmol) CDI are added to a solution of 26.91 g (100.00 mmol) 6-bromo-4-oxo-4H-1-benzopyran-2-carboxylic acid in 250 mL THF and the mixture is heated in the water bath until the development of gas has ended. This mixture is poured onto a suspension of 1.89 g (50.00 mmol) sodium borohydride in 500 mL water, while keeping the temperature below 10 °C, and stirred for a further 2 h at RT. The reaction mixture is poured onto 500 mL of saturated ammonium chloride solution, stirred for 1 h at RT and the aqueous phase is exhaustively extracted with DIPE. The combined organic phases are washed with water, dried over $Na_2SO_4$ and evaporated down i. vac..

Yield: 19.50 g (76% of theoretical)

$C_{10}H_7BrO_3$ (M= 255.065)

Calc.: molpeak $(M+H)^+$: 255/257 (Br) Found: molpeak $(M+H)^+$: 255/257 (Br)

$R_f$ value: 0.40 (silica gel, DCM/MeOH 9:1)

2.1b 6-bromo-2-brommethyl-1-benzopyran-4-one

A solution of 0.47 mL (5.00 mmol) phosphorus tribromide in 2.5 mL of MTBE is added dropwise at 0 °C to a solution of 2.55 g (10.00 mmol) 6-bromo-2-hydroxymethyl-1-benzopyran-4-one in 50 mL MTBE and the mixture is stirred for 16 h at RT. Ice water is added and the organic phase is separated off. The organic phase is washed with ice water, dried over $MgSO_4$ and evaporated down i. vac.. The residue is purified by column chromatography (silica gel, gradient PE/EtOAc 80:20 → 50:50 in 20 min).

Yield: 1.69 g (53% of theoretical)

$C_{10}H_6Br_2O_2$ (M= 317.961)

Calc.: molpeak $(M+H)^+$: 317/319/321 (2Br) Found: molpeak $(M+H)^+$: 317/319/321 (2Br)

$R_f$ value: 0.63 (silica gel, PE/EtOAc 6:4)

2.1c 6-bromo-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one

A mixture of 0.60 g (1.89 mmol) 6-bromo-2-bromomethyl-1-benzopyran-4-one, 223µL (1.89 mmol) 4-methylpiperidine and 525 mg (3.80 mmol) potassium carbonate in 50 mL acetonitrile is stirred for 3 h at RT and then evaporated down i. vac.. The residue is taken up in MTBE,

the organic phase is washed with water, dried over $MgSO_4$, filtered through activated charcoal and evaporated down i. vac..

Yield: 450 mg (71% of theoretical)

$C_{16}H_{18}BrNO_2$ (M= 336.224)

Calc.: molpeak $(M+H)^+$: 336/338 (Br) Found: molpeak $(M+H)^+$: 336/338 (Br)

HPLC-MS: 3.90 min (method B)

2.1d 6-iodo-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one

Under an argon atmosphere a mixture of 450 mg (1.34 mmol) 6-bromo-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one, 26 mg (0.134 mmol) CuI, 400 mg (2.68 mmol) NaI and 28 µL (0.268 mmol) N,N'-dimethyl-ethan-1,2-diamine in 1.4 mL of 1,4-dioxane is heated to 110°C for 20 h. The reaction mixture is combined with dilute $NaHCO_3$ solution and the aqueous phase is exhaustively extracted with MTBE. The combined organic phases are dried over $MgSO_4$ and evaporated down i. vac.. The residue is purified by HPLC-MS (Zorbax Bonus C18 amide-phase 5 µm, gradient 0.15 % formic acid in water / acetonitrile 10 / 90 → 90 / 10 v/v). The eluates are evaporated down i. vac., combined with 5% $Na_2CO_3$ solution and the aqueous phase is exhaustively extracted with MTBE. The combined organic phases are dried over $MgSO_4$ and dried i. vac..

Yield: 220 mg (43% of theoretical)

$C_{16}H_{18}INO_2$ (M= 383.224)

Calc.: molpeak $(M+H)^+$: 384 Found: molpeak $(M+H)^+$: 384

HPLC-MS: 4.0 min (method B)

2.1e 6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one

The product is obtained analogously to Example 1.1e starting from 6-iodo-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one and 5-(4-chloro-phenyl)-2-ethynyl-pyridine (Example 1.1d). The crude product is purified by HPLC-MS (Zorbax Bonus C18 amide-phase 5 µm, gradient 0.15 % formic acid in water / acetonitrile 10 / 90 → 90 / 10 v/v).

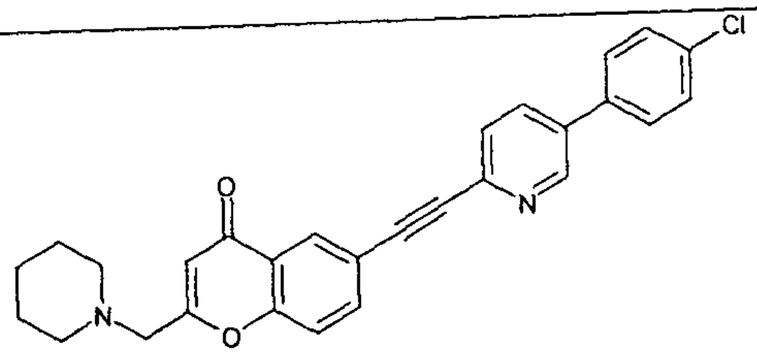
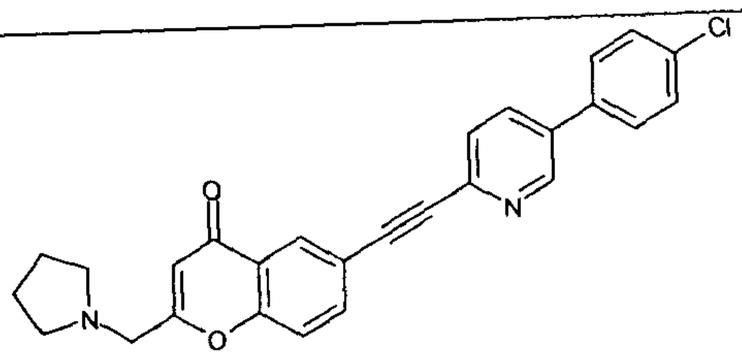
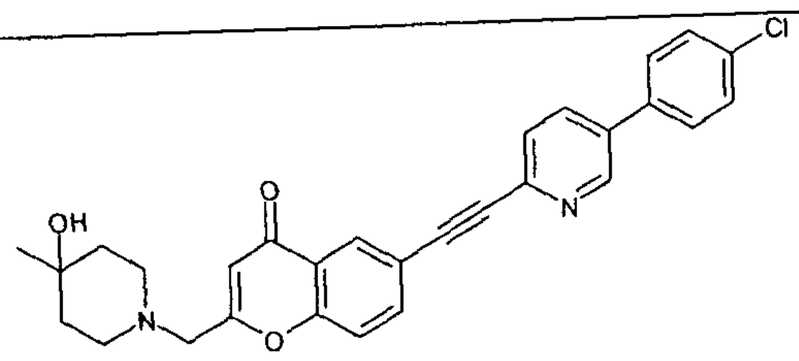
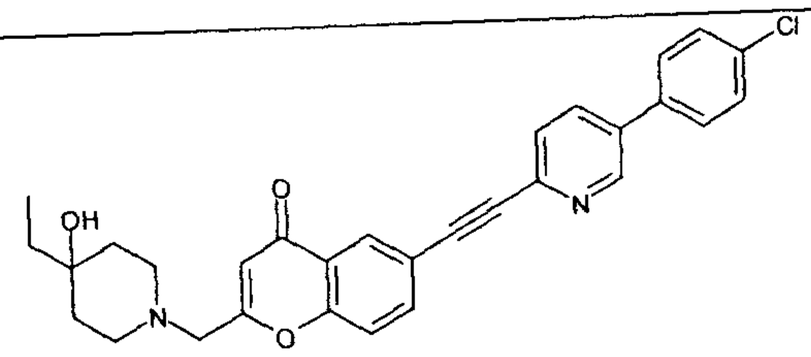
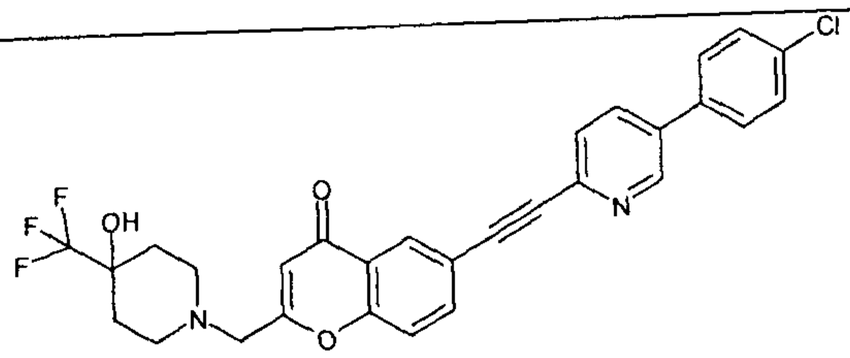
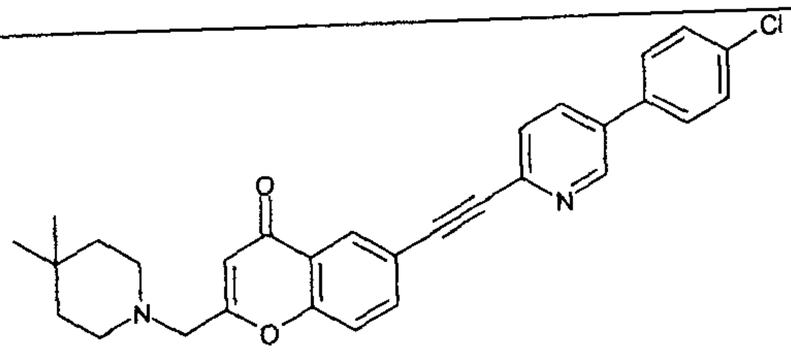
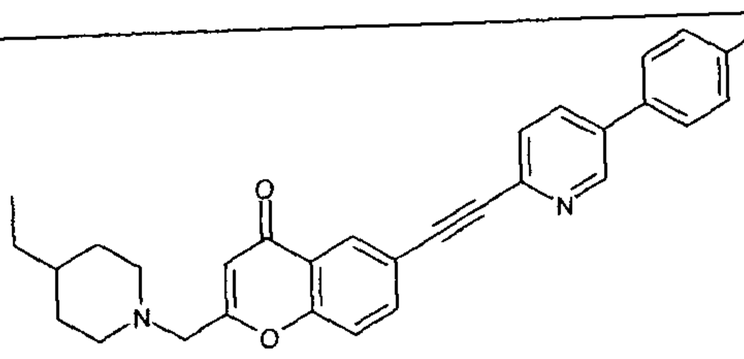
Yield: 20.5 mg (22% of theoretical)

$C_{29}H_{25}ClN_2O_2$ (M= 468.974)

Calc.: molpeak $(M+H)^+$: 469/471 (Cl) Found: molpeak $(M+H)^+$: 469/471 (Cl)

HPLC-MS: 5.1 min (method B)

The following compounds are obtained analogously to 2.1c, 2.1d and 2.1e:

| Example | structure | yield in % | mass spectrum | retention time HPLC (method) |
|---|---|---|---|---|
| 2.2 |  | | | |
| 2.3 |  | | | |
| 2.4 |  | 3 | 485/487 $[M+H]^+$ | 4.39 min (B) |
| 2.5 |  | 4 | 499/501 $[M+H]^+$ | 4.52 min (B) |
| 2.6 |  | | | |
| 2.7 |  | | | |
| 2.8 |  | | | |

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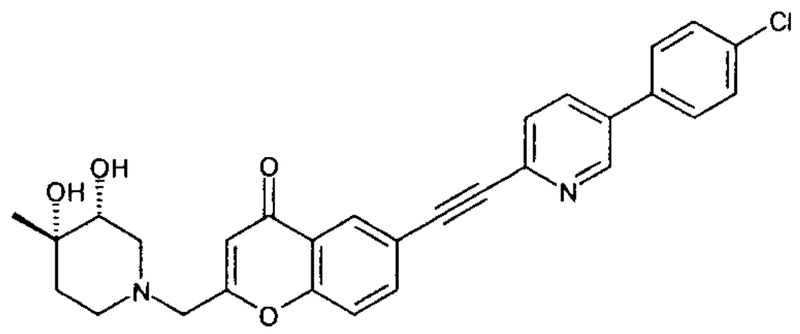
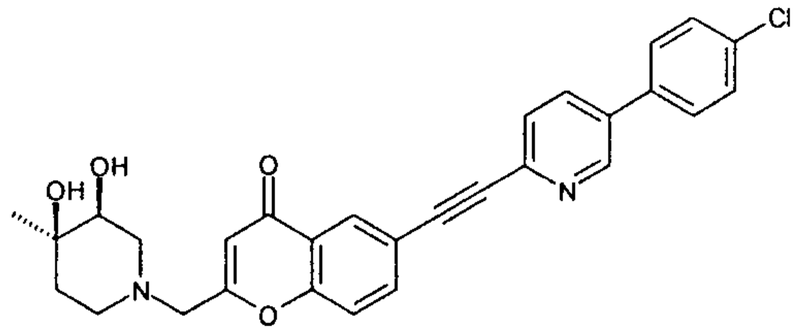
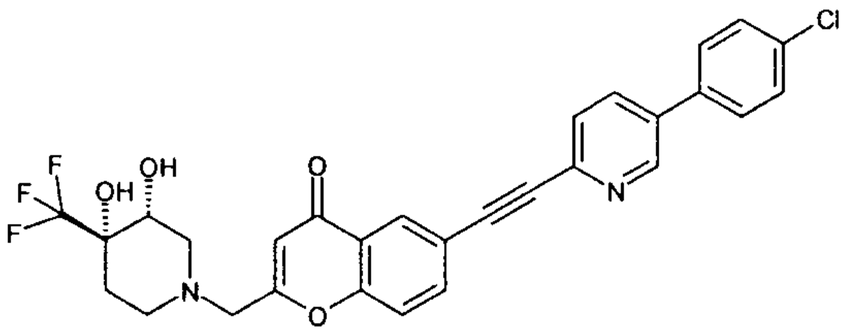
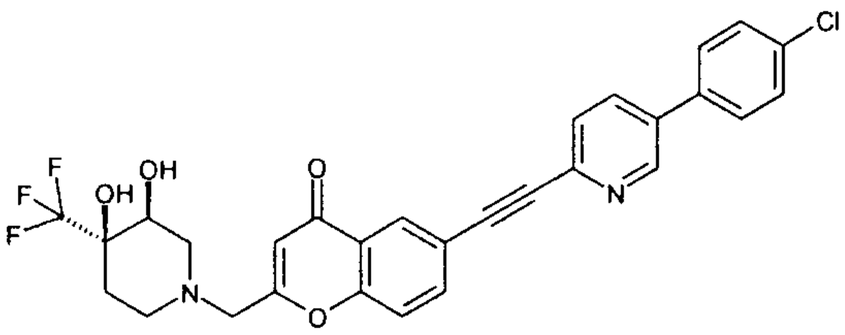
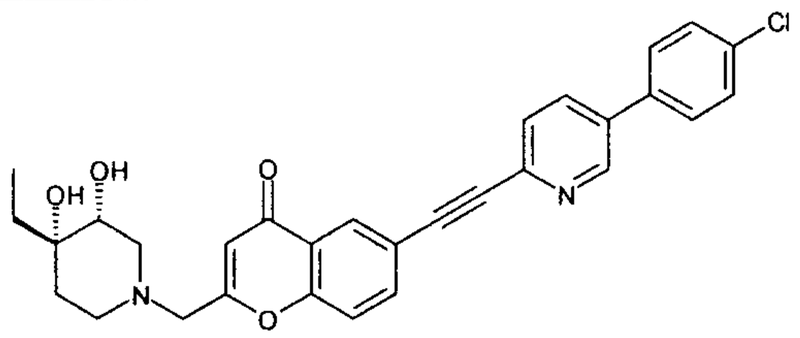
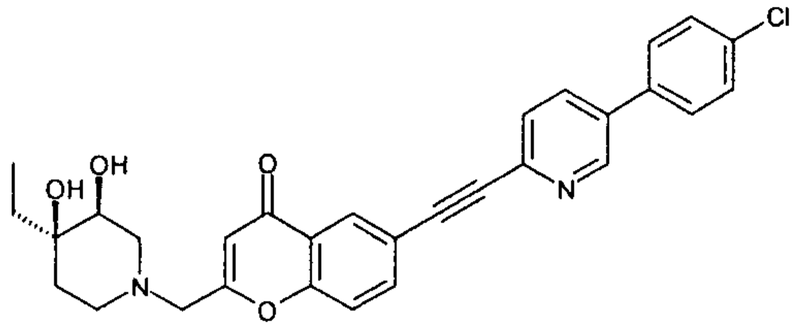
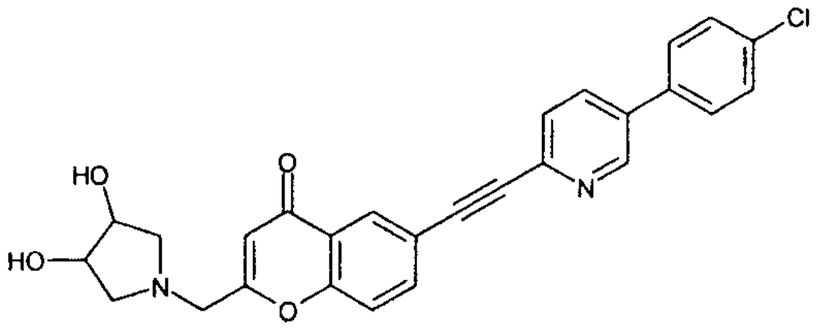
|---|---|---|---|---|
| 2.9 |  | | | |
| 2.10 |  | | | |
| 2.11 |  | | | |
| 2.12 |  | | | |
| 2.13 |  | | | |
| 2.14 |  | | | |
| 2.15 |  | | | |

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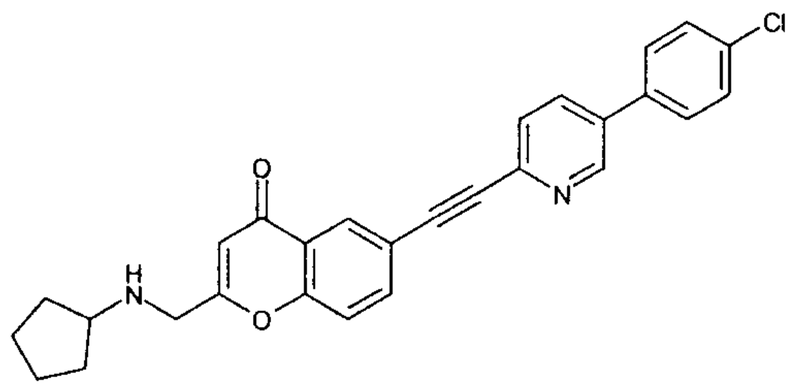
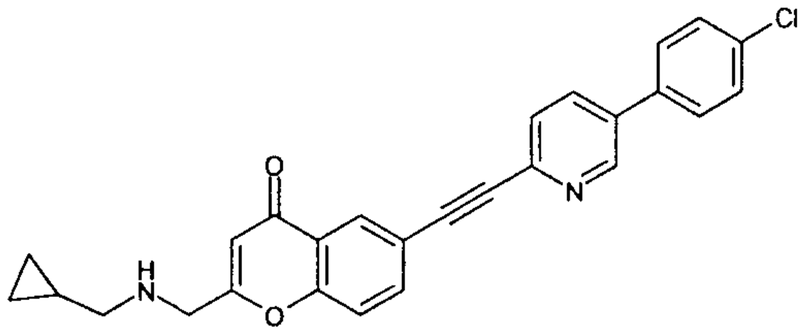
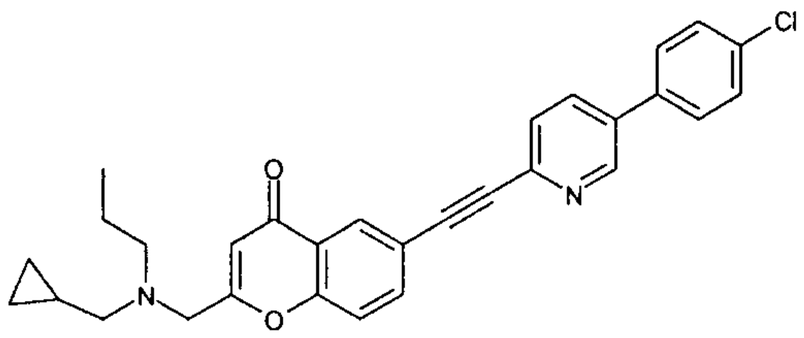
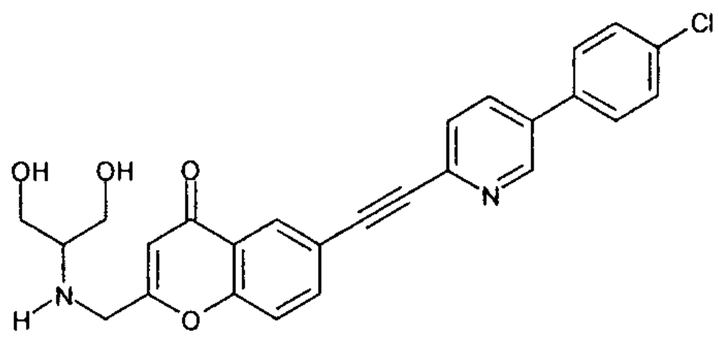
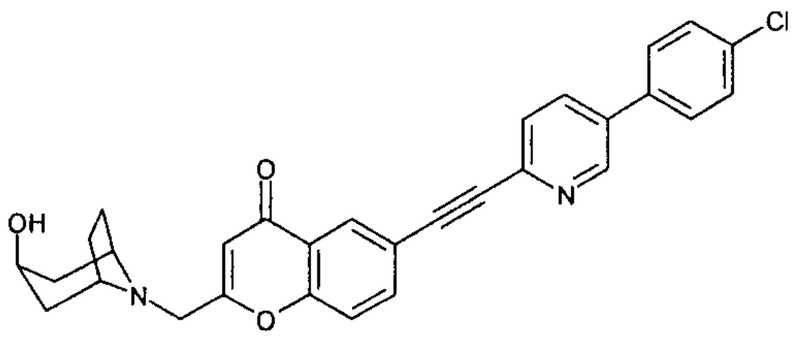
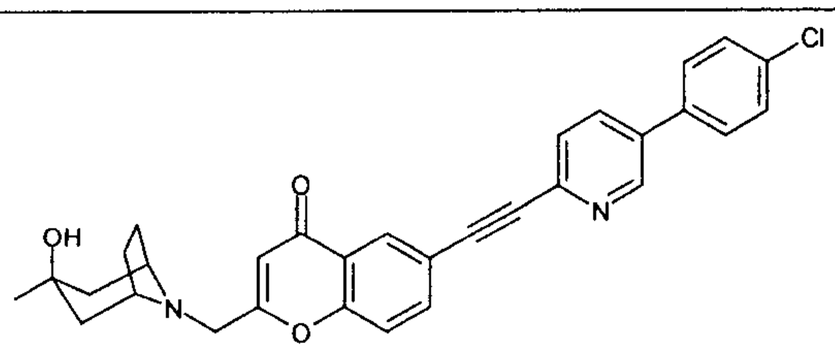
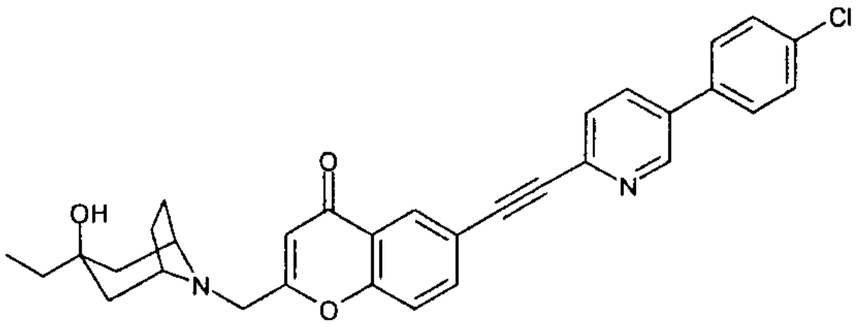
|---|---|---|---|---|
| 2.16 |  | | | |
| 2.17 |  | | | |
| 2.18 |  | | | |
| 2.19 |  | | | |
| 2.20 |  | | | |
| 2.21 |  | | | |
| 2.22 |  | | | |

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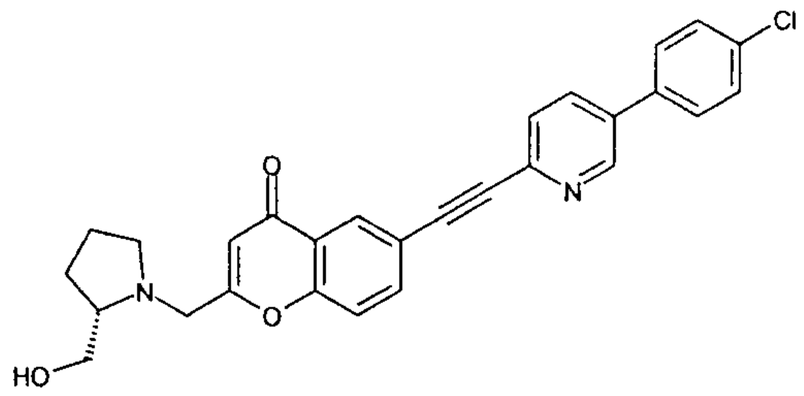
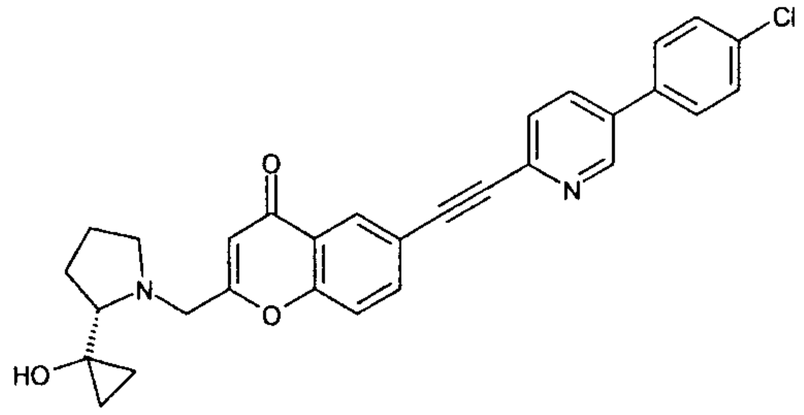
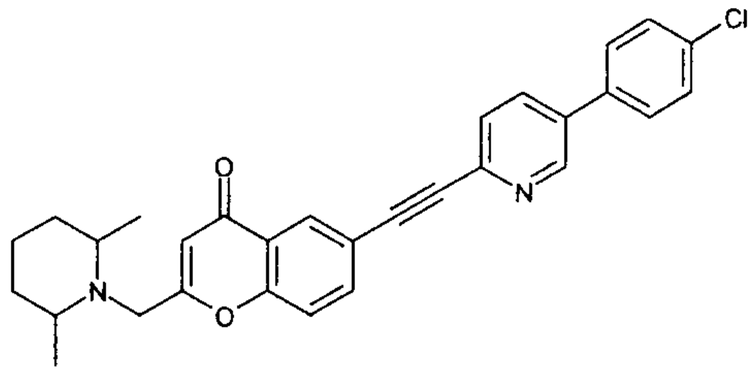
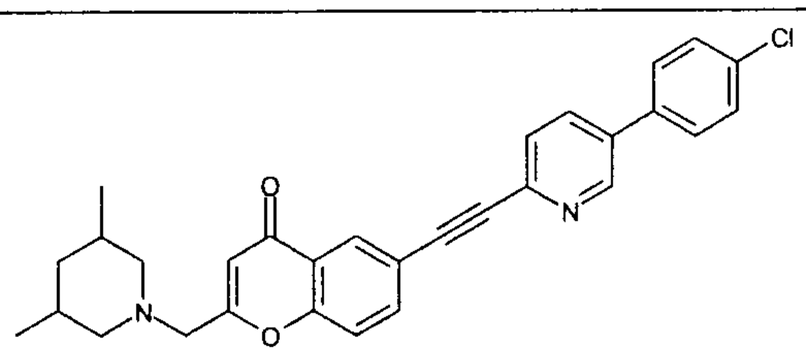
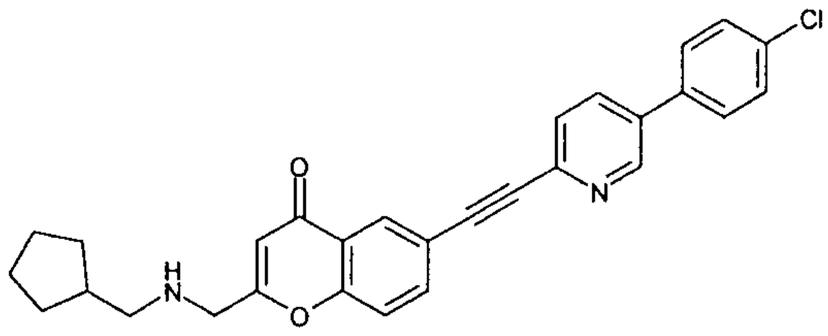
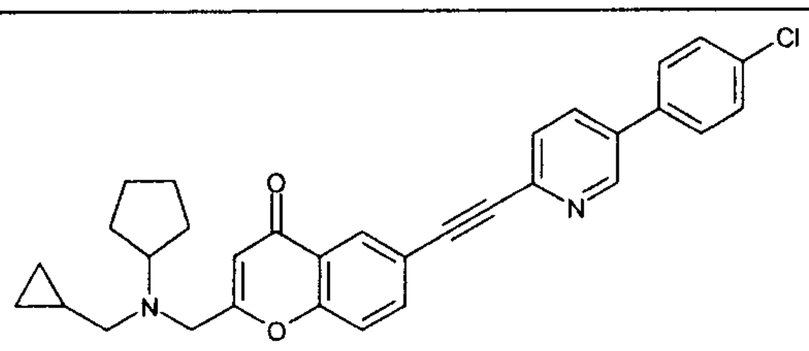
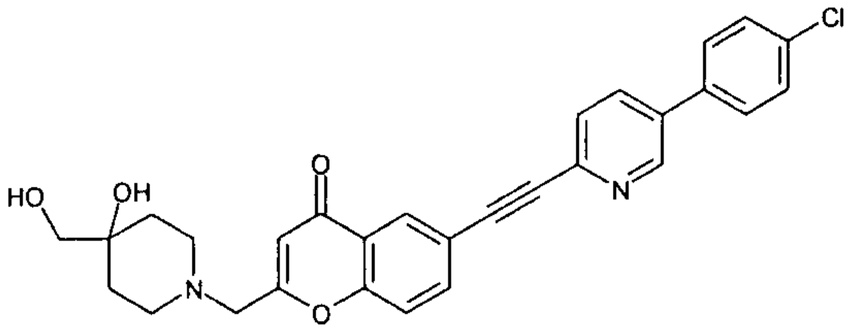
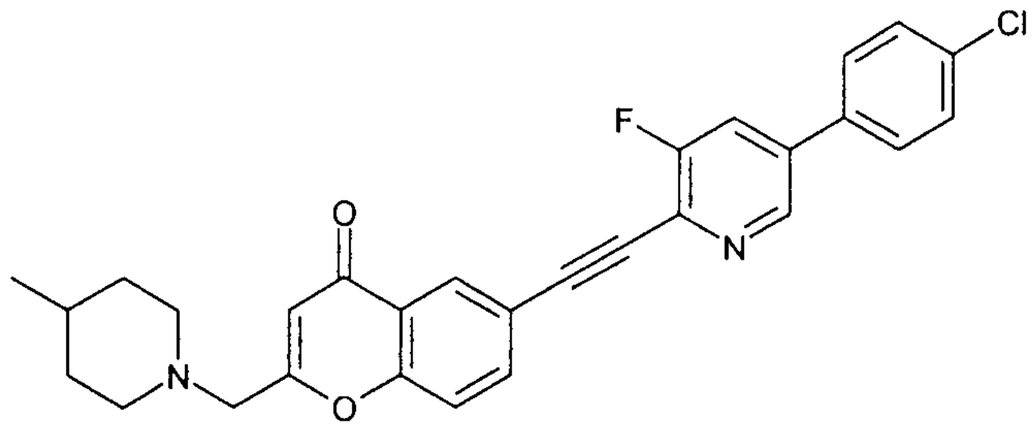
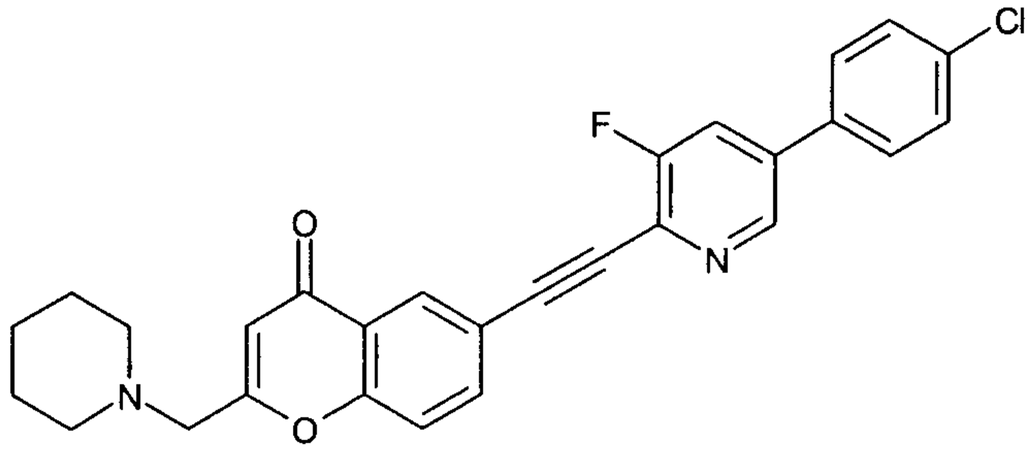
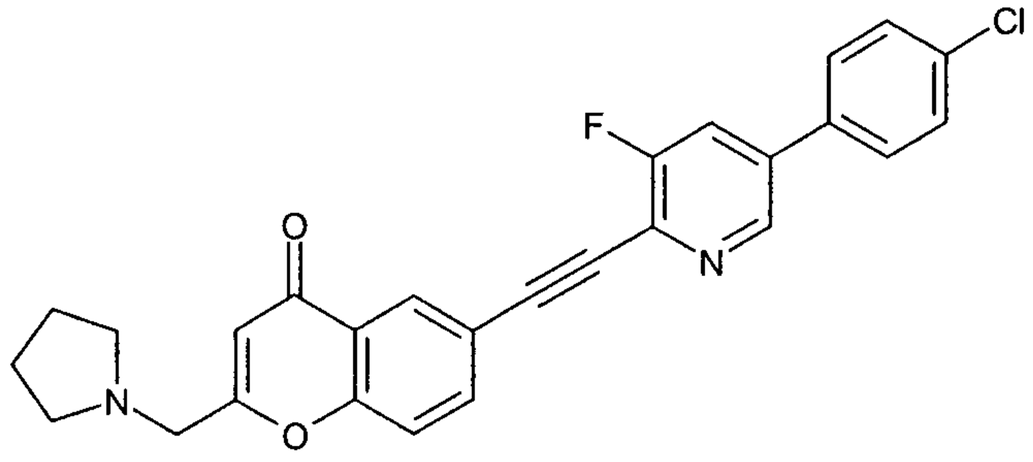
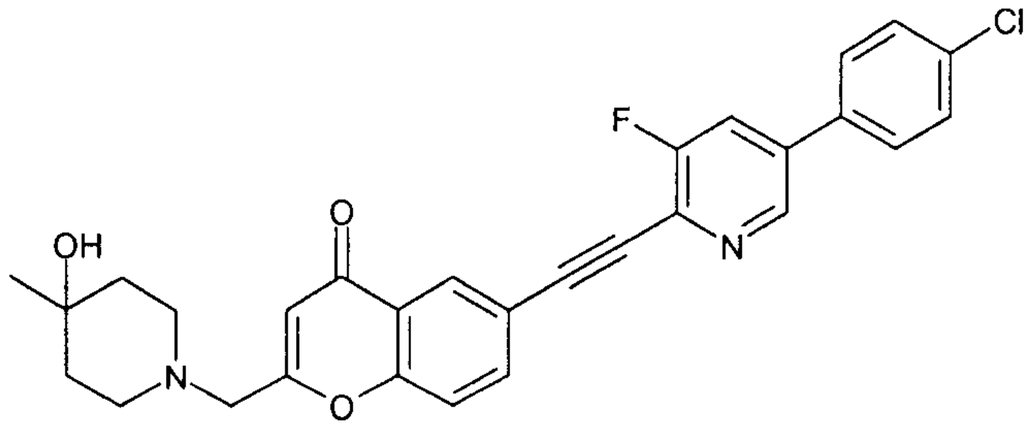
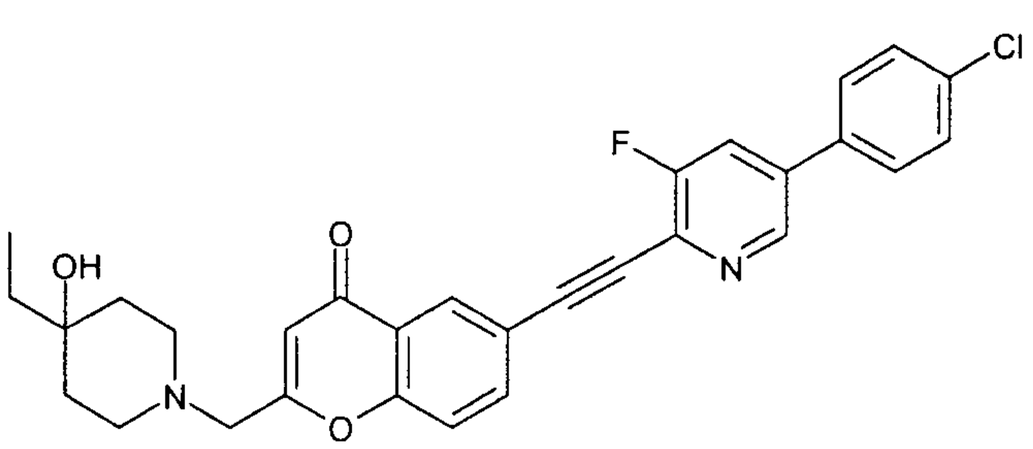
|---|---|---|---|---|
| 2.23 |  | | | |
| 2.24 |  | | | |
| 2.25 |  | 21 | 483/485<br>$[M+H]^+$ | 4.8 min<br>(B) |
| 2.26 |  | | | |
| 2.27 |  | | | |
| 2.28 |  | | | |
| 2.29 |  | | | |

The following compounds are obtained analogously to 2.1c, 2.1d and 2.1e (with compound A9 as educt):

| Example | Structure |
|---|---|
| 3.1 |  |
| 3.2 |  |
| 3.3 |  |
| 3.4 |  |
| 3.5 |  |

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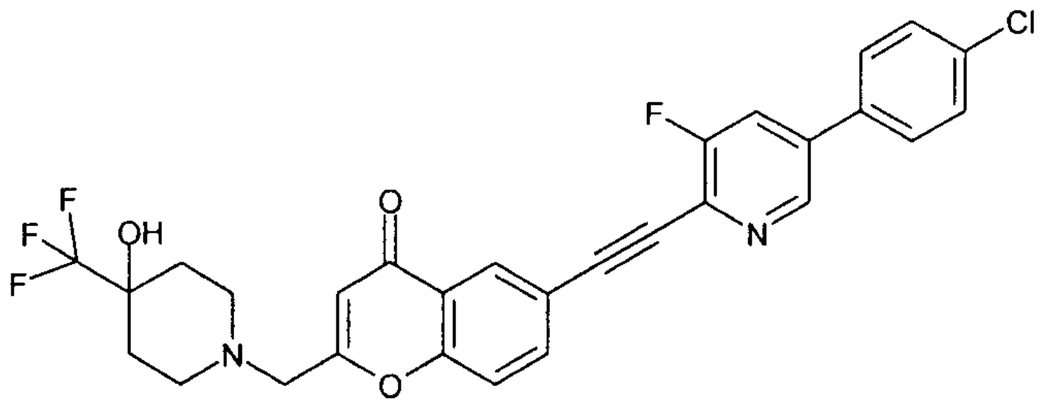

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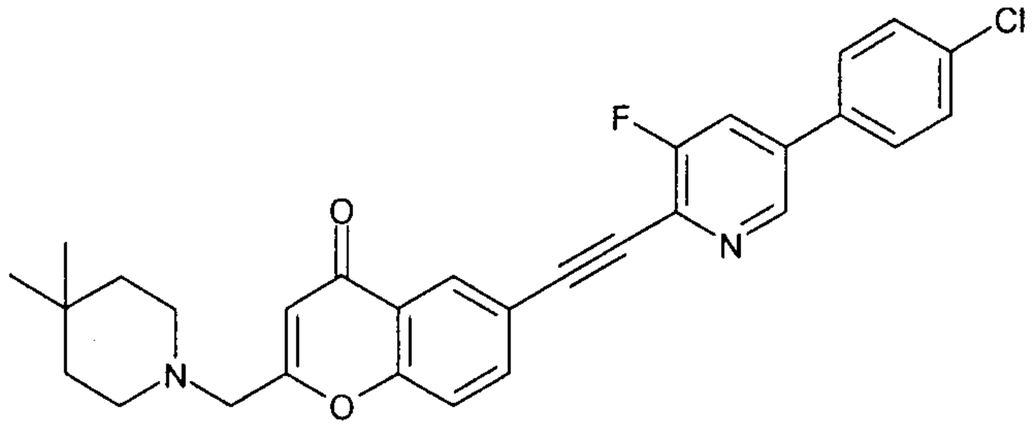

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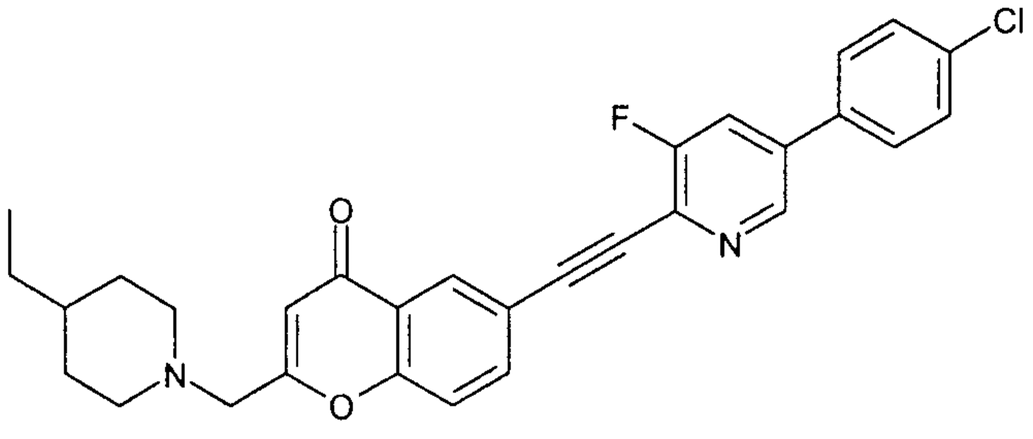

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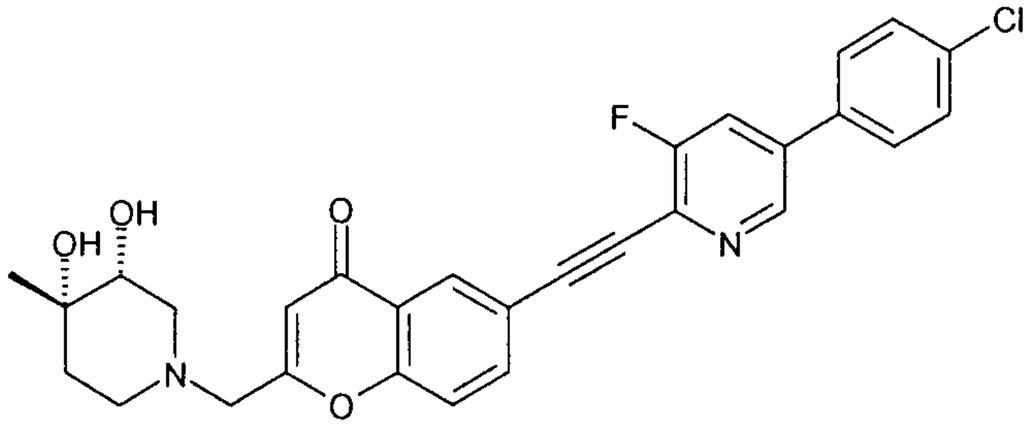

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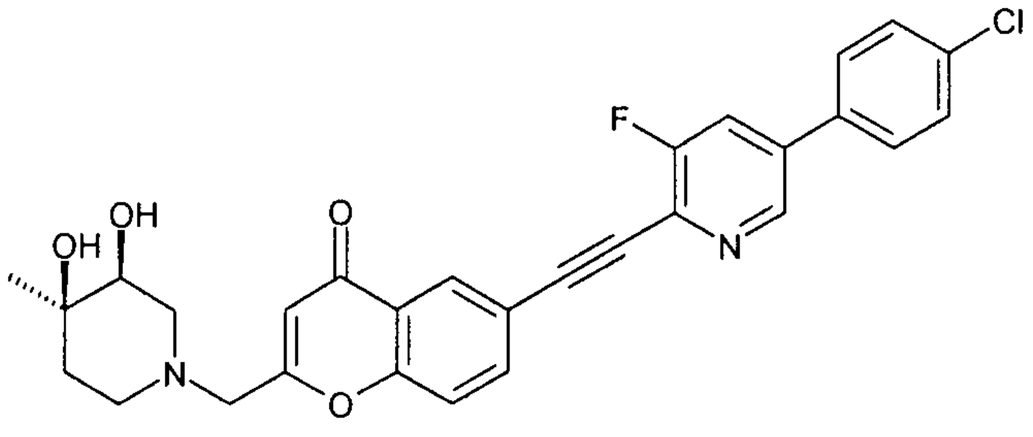

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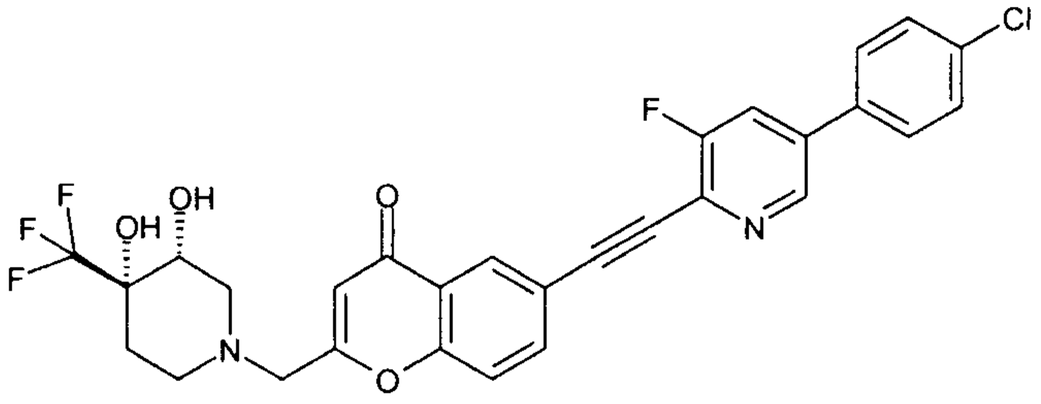

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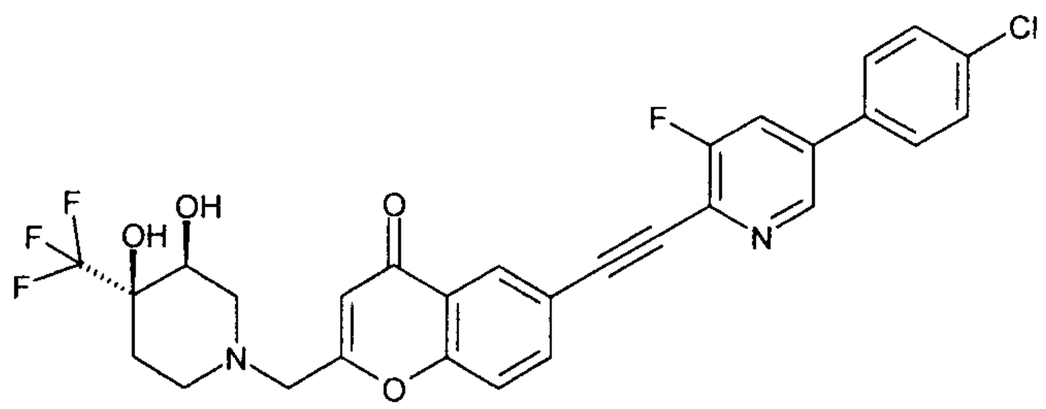

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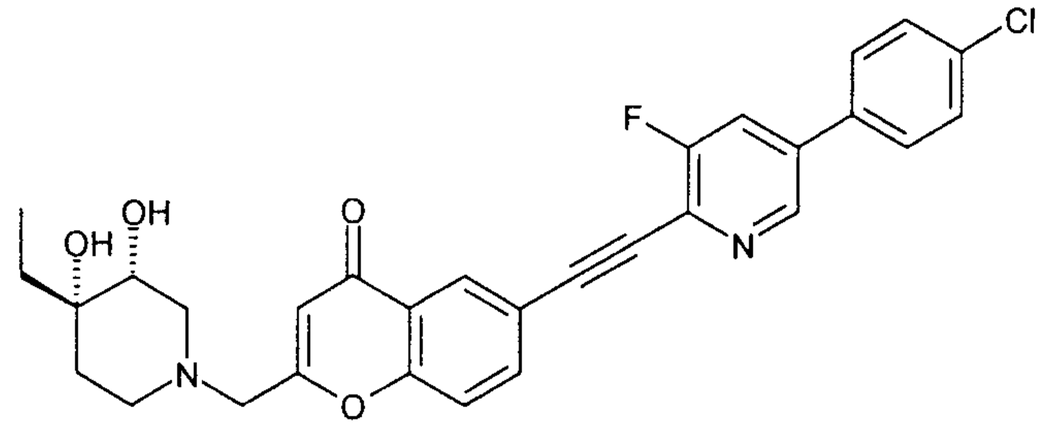

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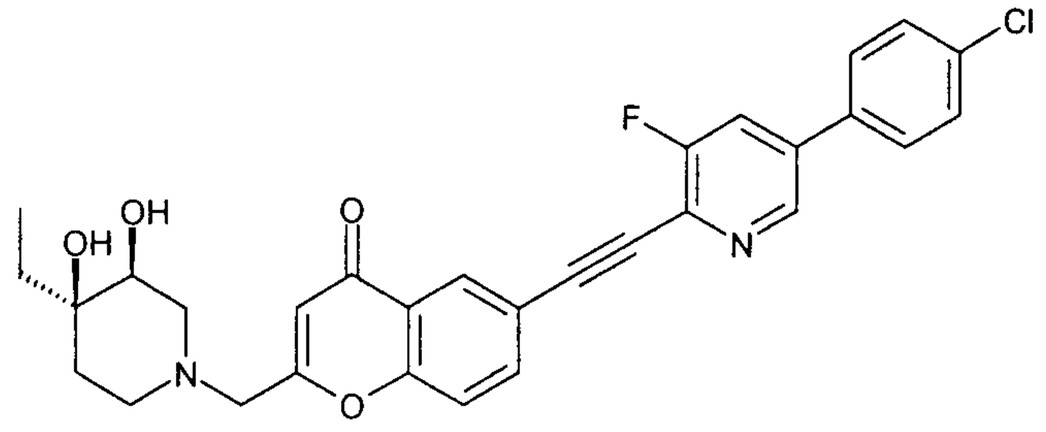

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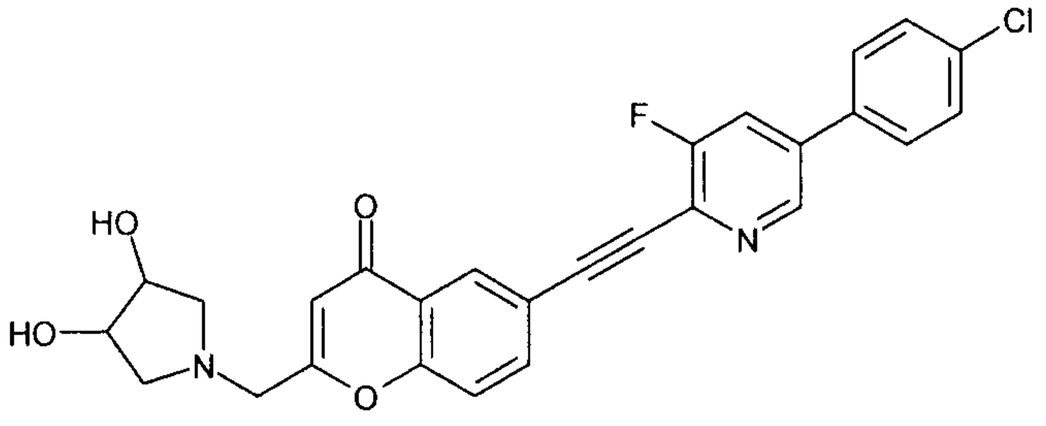

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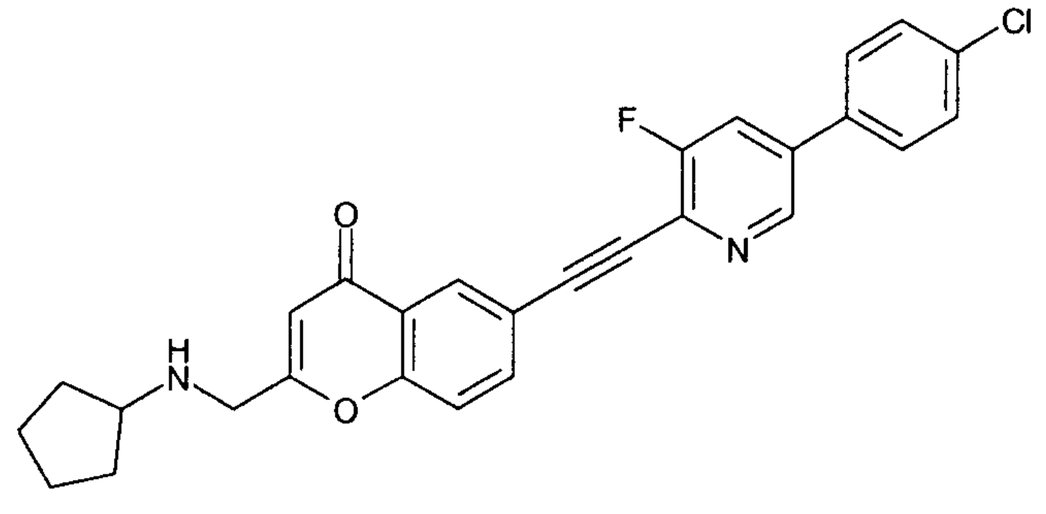

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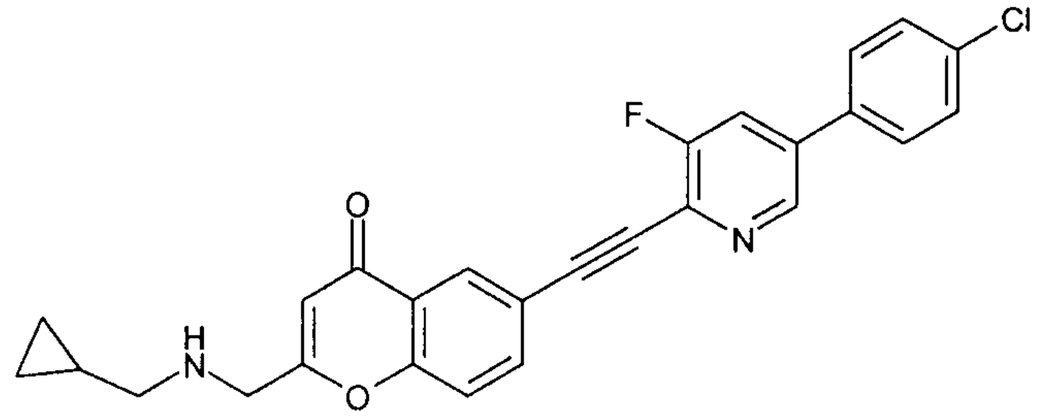

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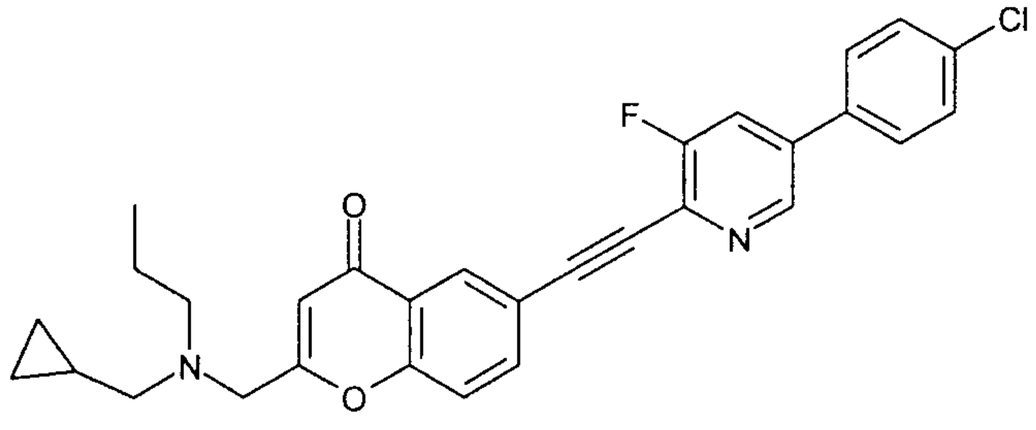

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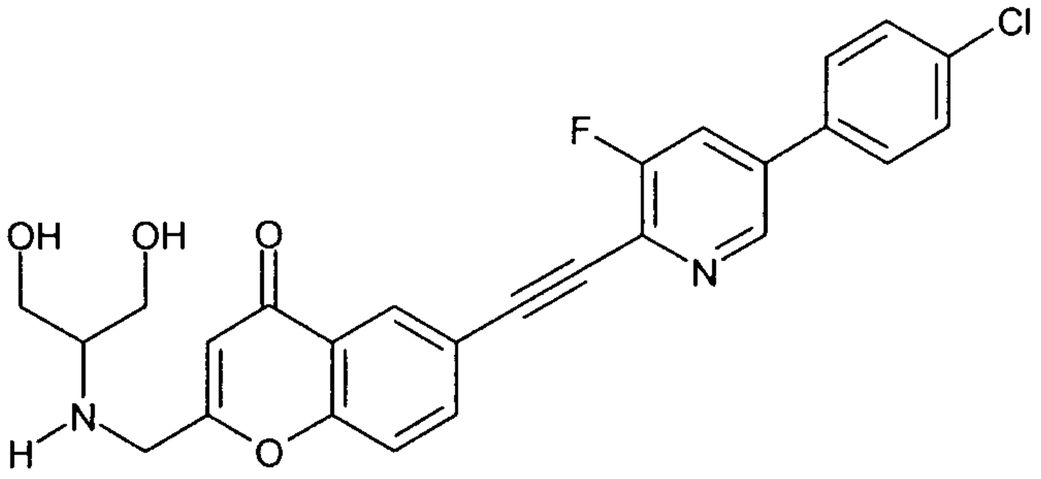

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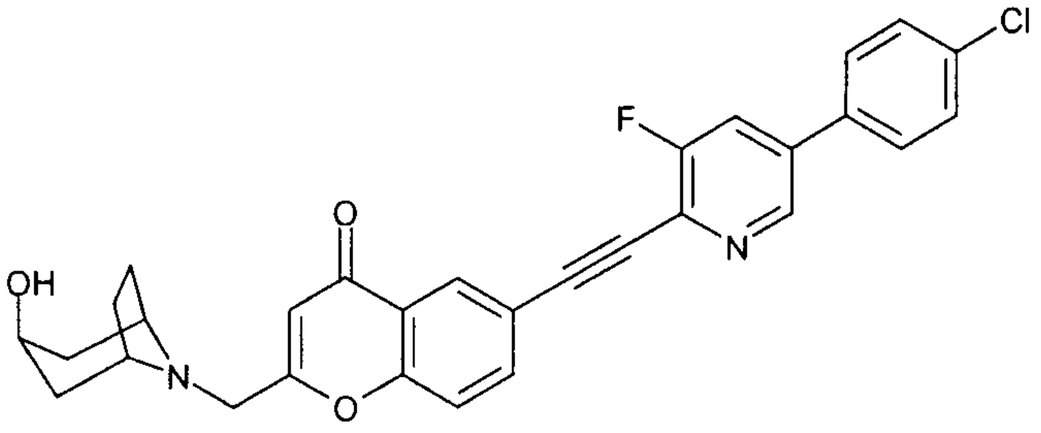

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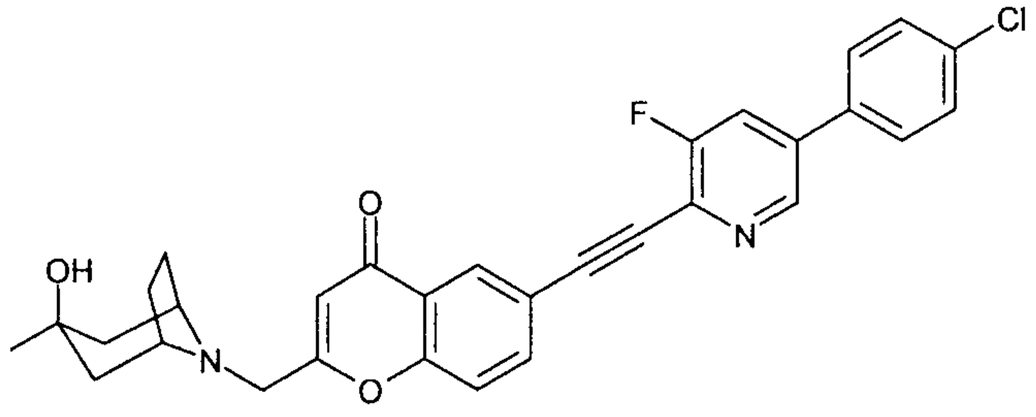

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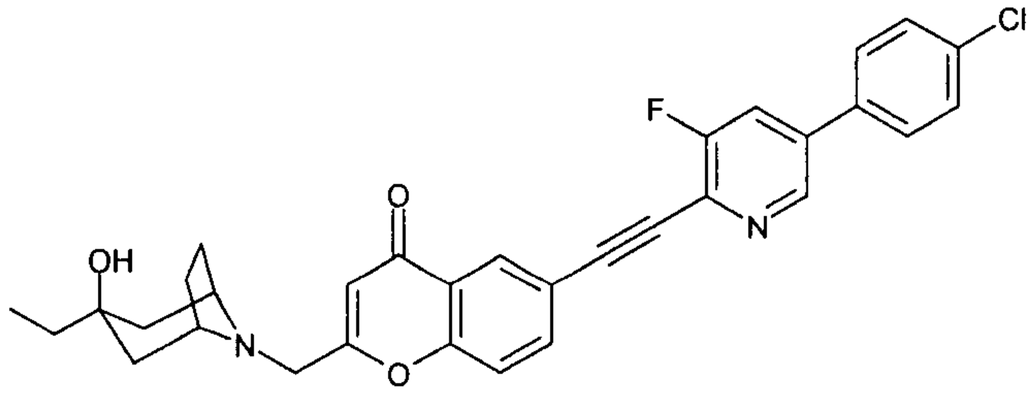

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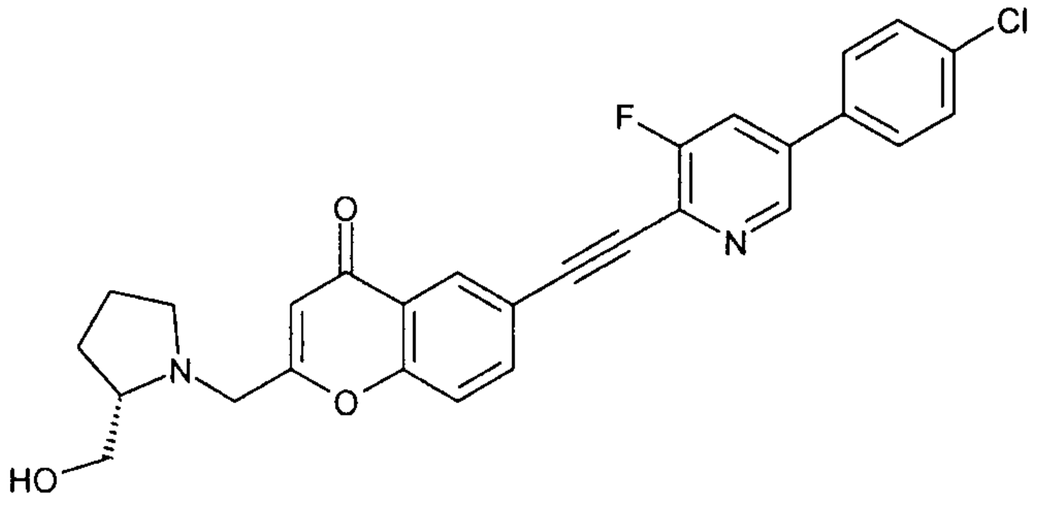

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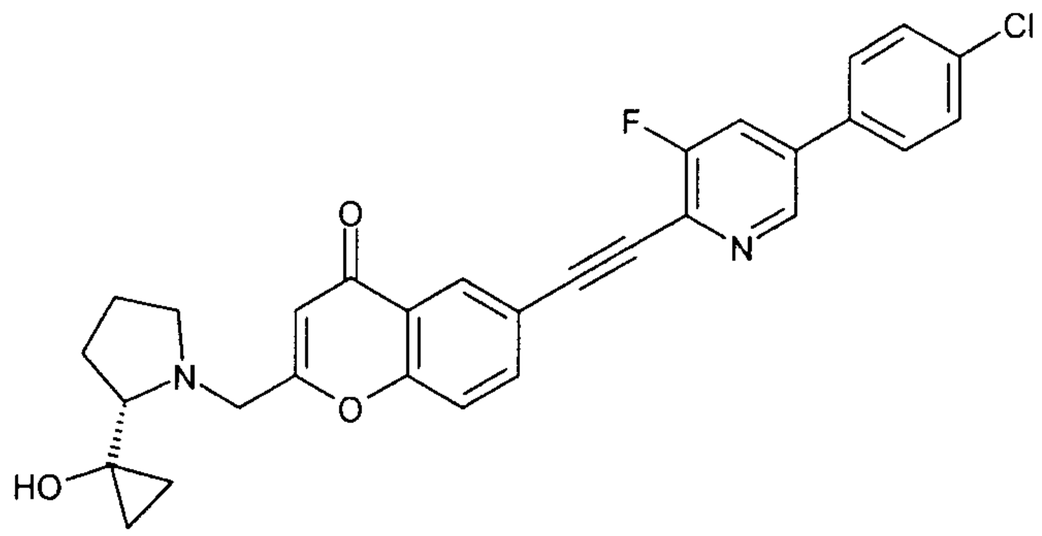

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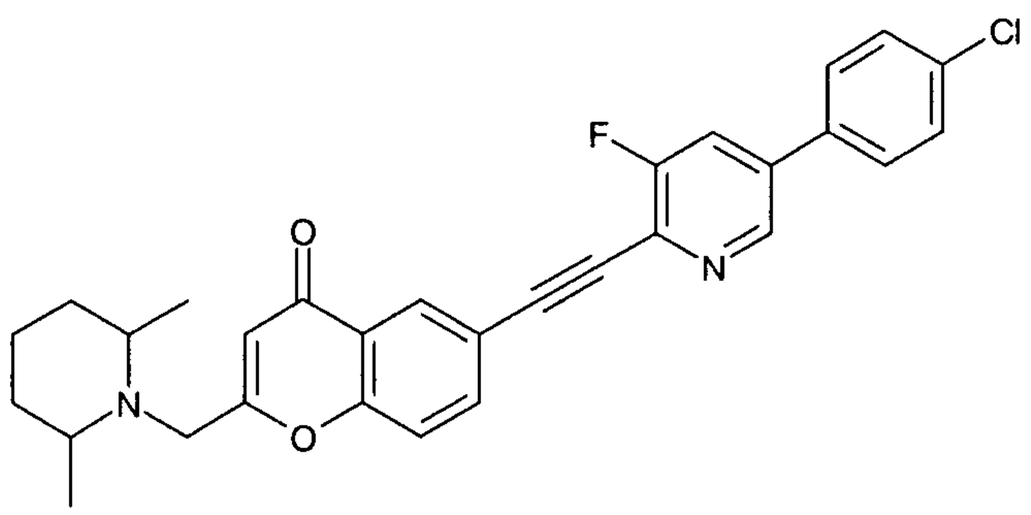

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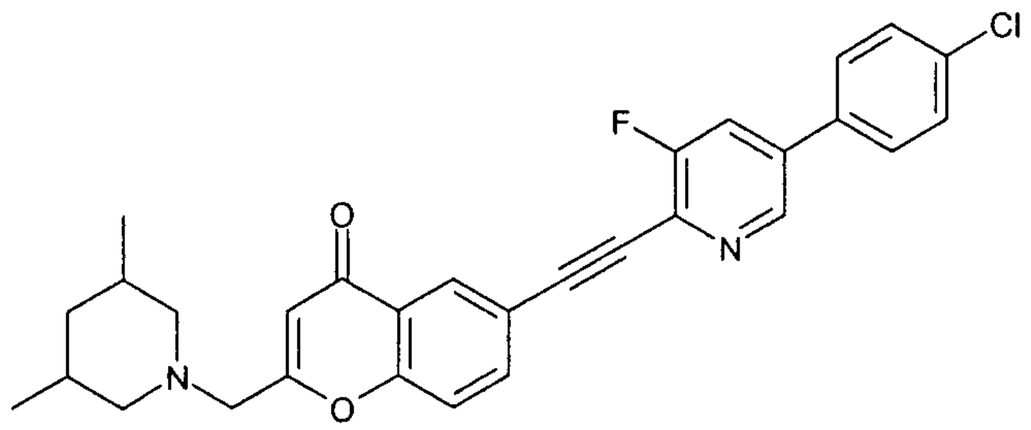

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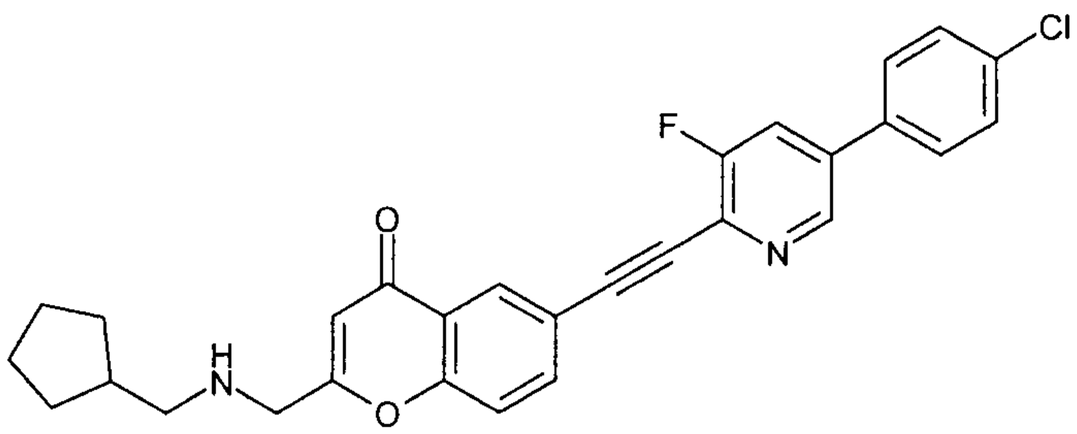

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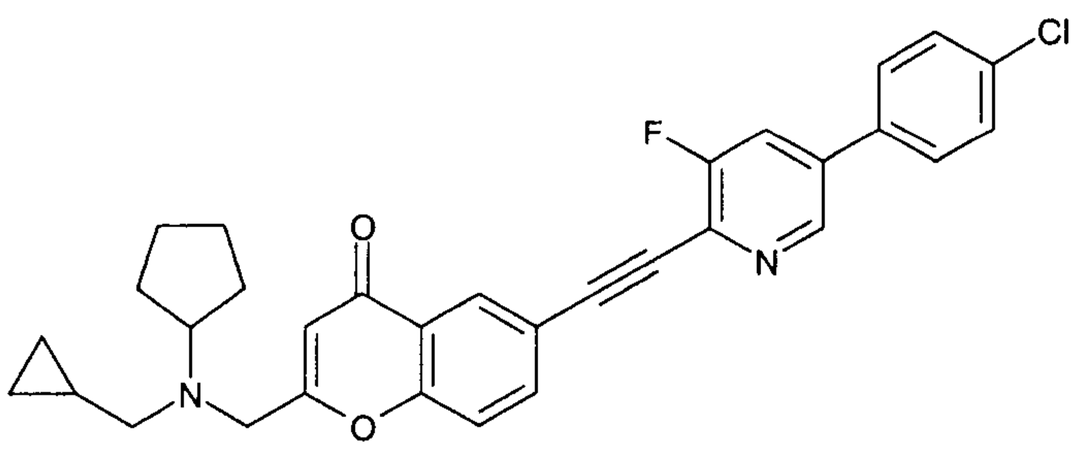

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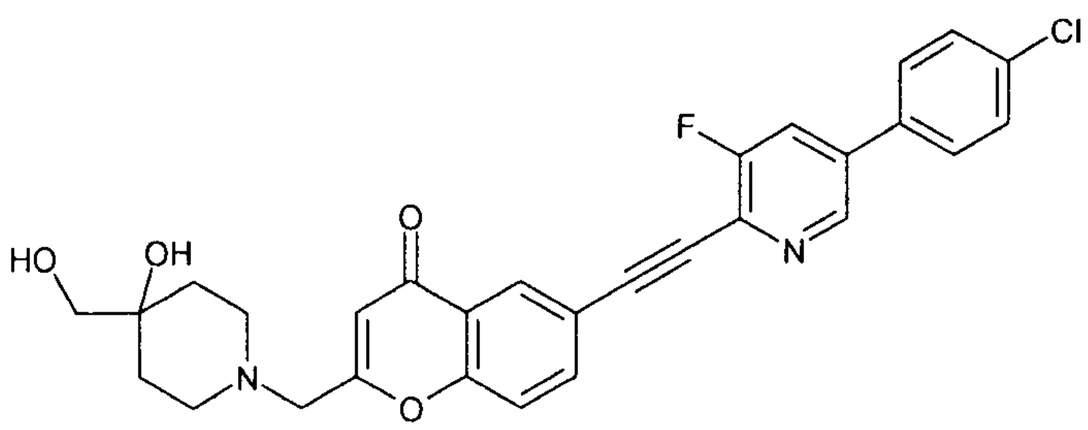


Some test methods for determining an MCH-receptor antagonistic activity will now be described. In addition, other test methods known to the skilled man may be used, e.g. by inhibiting the MCH-receptor-mediated inhibition of cAMP production, as described by Hoogduijn M et al. in "Melanin-concentrating hormone and its receptor are expressed and functional in human skin", Biochem. Biophys. Res Commun. 296 (2002) 698-701 and by biosensory measurement of the binding of MCH to the MCH receptor in the presence of antagonistic substances by plasmon resonance, as described by Karlsson OP and Lofas S. in "Flow-Mediated On-Surface Reconstitution of G-Protein Coupled Receptors for Applications in Surface Plasmon Resonance Biosensors", Anal. Biochem. 300 (2002), 132-138. Other methods of testing antagonistic activity to MCH receptors are contained in the references and patent documents mentioned hereinbefore, and the description of the test methods used is hereby incorporated in this application.

**MCH-1 receptor binding test**

Method: MCH binding to hMCH-1R transfected cells

Species: Human

Test cell: hMCH-1R stably transfected into CHO/Galpha16 cells

Results: IC50 values

Membranes from CHO/Galpha16 cells stably transfected with human hMCH-1R are resuspended using a syringe (needle 0.6 x 25 mm) and diluted in test buffer (50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, pH 7.00; 0.1 % bovine serum albumin (protease-free), 0.021 % bacitracin, 1 µg/ml aprotinin, 1 µg/ml leupeptin and 1 µM phosphoramidone) to a concentration of 5 to 15 µg/ml.

200 microlitres of this membrane fraction (contains 1 to 3 µg of protein) are incubated for 60 minutes at ambient temperature with 100 pM of $^{125}$I-tyrosyl melanin concentrating hormone ($^{125}$I-MCH commercially obtainable from NEN) and increasing concentrations of the test compound in a final volume of 250 microlitres. After the incubation the reaction is filtered using a cell harvester through 0.5% PEI treated fibreglass filters (GF/B, Unifilter Packard).

The membrane-bound radioactivity retained on the filter is then determined after the addition of scintillator substance (Packard Microscint 20) in a measuring device (TopCount of Packard).

The non-specific binding is defined as bound radioactivity in the presence of 1 micromolar MCH during the incubation period.

The analysis of the concentration binding curve is carried out on the assumption of one receptor binding site.

Standard:

Non-labelled MCH competes with labelled $^{125}$I-MCH for the receptor binding with an IC50 value of between 0.06 and 0.15 nM.

The KD value of the radioligand is 0.156 nM.

## MCH-1 receptor-coupled $Ca^{2+}$ mobilisation test

| | |
|---|---|
| Method: | Calcium mobilisation test with human MCH (FLIPR$^{384}$) |
| Species: | Human |
| Test cells: | CHO/ Galpha 16 cells stably transfected with hMCH-R1 |
| Results: | 1st measurement:: % stimulation of the reference (MCH $10^{-6}$M) |
| | 2nd measurement: pKB value |

| Reagents: | | |
|---|---|---|
| | HBSS (10x) | (GIBCO) |
| | HEPES buffer (1M) | (GIBCO) |
| | Pluronic F-127 | (Molecular Probes) |
| | Fluo-4 | (Molecular Probes) |
| | Probenecid | (Sigma) |
| | MCH | (Bachem) |
| | bovine serum albumin (protease-free) | (Serva) |
| | DMSO | (Serva) |
| | Ham's F12 | (BioWhittaker) |
| | FCS | (BioWhittaker) |
| | L-Glutamine | (GIBCO) |
| | Hygromycin B | (GIBCO) |
| | PENStrep | (BioWhittaker) |
| | Zeocin | (Invitrogen) |

Clonal CHO/Galpha16 hMCH-R1 cells are cultivated in Ham's F12 cell culture medium (with L-glutamine; BioWhittaker; Cat.No.: BE12-615F). This contains per 500 ml 10% FCS, 1% PENStrep, 5 ml L-glutamine (200 mM stock solution), 3 ml hygromycin B (50 mg/ml in PBS) and 1.25 ml zeocin (100 µg/ml stock solution). One day before the experiment the cells are

plated on a 384-well microtitre plate (black-walled with a transparent base, made by Costar) in a density of 2500 cells per cavity and cultivated in the above medium overnight at 37°C, 5% $CO_2$ and 95% relative humidity. On the day of the experiment the cells are incubated with cell culture medium to which 2 mM Fluo-4 and 4.6 mM Probenicid have been added, at 37°C for 45 minutes. After charging with fluorescent dye the cells are washed four times with Hanks buffer solution (1 x HBSS, 20 mM HEPES), which has been combined with 0.07% Probenicid. The test substances are diluted in Hanks buffer solution, combined with 2.5% DMSO. The background fluorescence of non-stimulated cells is measured in the presence of substance in the 384-well microtitre plate five minutes after the last washing step in the FLIPR$^{384}$ apparatus (Molecular Devices; excitation wavelength: 488 nm; emission wavelength: bandpass 510 to 570 nm). To stimulate the cells MCH is diluted in Hanks buffer with 0.1% BSA, pipetted into the 384-well cell culture plate 35 minutes after the last washing step and the MCH-stimulated fluorescence is then measured in the FLIPR$^{384}$ apparatus.

**Data analysis:**

1st measurement: The cellular $Ca^{2+}$ mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH $10^{-6}$M). This measurement serves to identify any possible agonistic effect of a test substance.

2nd measurement: The cellular $Ca^{2+}$ mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH $10^{-6}$M, signal is standardised to 100%). The EC50 values of the MCH dosage activity curve with and without test substance (defined concentration) are determined graphically by the GraphPad Prism 2.01 curve program. MCH antagonists cause the MCH stimulation curve to shift to the right in the graph plotted.

The inhibition is expressed as a pKB value:

$$pKB=\log(EC_{50(testsubstance+MCH)} / EC_{50(MCH)} -1) -\log c_{(testsubstance)}$$

The compounds according to the invention, including their salts, exhibit an MCH-receptor antagonistic activity in the tests mentioned above. Using the MCH-1 receptor binding test described above an antagonistic activity is obtained in a dosage range from about $10^{-10}$ to $10^{-5}$ M, particularly from $10^{-9}$ to $10^{-6}$ M.

The following IC50 values were determined using the MCH-1 receptor binding test described above:

| Compound according to Example no. | name of substance | IC50 value |
|---|---|---|
| 1.1 | ((S)-1-{6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-benzopyran-2-ylmethyl}-pyrrolidin-2-yl)-methanol | 6 nM |
| 2.1 | 6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-2-(4-methyl-piperidin-1-ylmethyl)-1-benzopyran-4-one | 3 nM |

Some examples of formulations will be described hereinafter, wherein the term "active substance" denotes one or more compounds according to the invention, including their salts. In the case of one of the combinations with one or more active substances described, the term "active substance" also includes the additional active substances.

Example A

Capsules for powder inhalation containing 1 mg active substance

Composition:

1 capsule for powder inhalation contains:

| | |
|---|---|
| active substance | 1.0 mg |
| lactose | 20.0 mg |
| hard gelatine capsules | 50.0 mg |
| | 71.0 mg |

Method of preparation:

7The active substance is ground to the particle size required for inhalation. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

Example B

Inhalable solution for Respimat® containing 1 mg active substance

Composition:

1 spray contains:

| | |
|---|---|
| active substance | 1.0 mg |
| benzalkonium chloride | 0.002 mg |
| disodium edetate | 0.0075 mg |
| purified water ad | 15.0 µl |

Method of preparation:

The active substance and benzalkonium chloride are dissolved in water and packed into Respimat® cartridges.

Example C

Inhalable solution for nebulisers containing 1 mg active substance

Composition:

1 vial contains:

| | |
|---|---|
| active substance | 0.1 g |
| sodium chloride | 0.18 g |
| benzalkonium chloride | 0.002 g |
| purified water ad | 20.0 ml |

Method of preparation:

The active substance, sodium chloride and benzalkonium chloride are dissolved in water.

Example D

Propellant type metered dose aerosol containing 1 mg active substance

Composition:

1 spray contains:

| | |
|---|---|
| active substance | 1.0 mg |
| lecithin | 0.1 % |

| | |
|---|---|
| propellant gas ad | 50.0 µl |

Method of preparation:

The micronised active substance is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

Example E

Nasal spray containing 1 mg active substance

Composition:

| | |
|---|---|
| active substance | 1.0 mg |
| sodium chloride | 0.9 mg |
| benzalkonium chloride | 0.025 mg |
| disodium edetate | 0.05 mg |
| purified water ad | 0.1 ml |

Method of preparation:

The active substance and the excipients are dissolved in water and transferred into a corresponding container.

Example F

Injectable solution containing 5 mg of active substance per 5 ml

Composition:

| | |
|---|---|
| active substance | 5 mg |
| glucose | 250 mg |
| human serum albumin | 10 mg |
| glycofurol | 250 mg |
| water for injections ad | 5 ml |

Preparation:

Glycofurol and glucose are dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules under nitrogen gas.

Example G

Injectable solution containing 100 mg of active substance per 20 ml

Composition:

| | |
|---|---|
| active substance | 100 mg |
| monopotassium dihydrogen phosphate = $KH_2PO_4$ | 12 mg |
| disodium hydrogen phosphate = $Na_2HPO_4 \cdot 2H_2O$ | 2 mg |
| sodium chloride | 180 mg |
| human serum albumin | 50 mg |
| Polysorbate 80 | 20 mg |
| water for injections ad | 20 ml |

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into ampoules.

Example H

Lyophilisate containing 10 mg of active substance

Composition:

| | |
|---|---|
| Active substance | 10 mg |
| Mannitol | 300 mg |
| human serum albumin | 20 mg |

Preparation:

Mannitol is dissolved in water for injections (Wfl); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfl; transferred into vials; freeze-dried.

Solvent for lyophilisate:

| | |
|---|---|
| Polysorbate 80 = Tween 80 | 20 mg |
| mannitol | 200 mg |

| | |
|---|---|
| water for injections ad | 10 ml |

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (Wfl); transferred into ampoules.

Example I

Tablets containing 20 mg of active substance

| Composition: | |
|---|---|
| active substance | 20 mg |
| lactose | 120 mg |
| maize starch | 40 mg |
| magnesium stearate | 2 mg |
| Povidone K 25 | 1 8 mg |

Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

Example J

Capsules containing 20 mg active substance

| Composition: | |
|---|---|
| active substance | 20 mg |
| maize starch | 80 mg |
| highly dispersed silica | 5 mg |
| magnesium stearate | 2.5 mg |

Preparation:

Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example K

Suppositories containing 50 mg of active substance

Composition:

| | |
|---|---|
| active substance | 50 mg |
| hard fat (Adeps solidus) q.s. ad | 1700 mg |

Preparation:

Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

Example L

Injectable solution containing 10 mg of active substance per 1 ml

Composition:

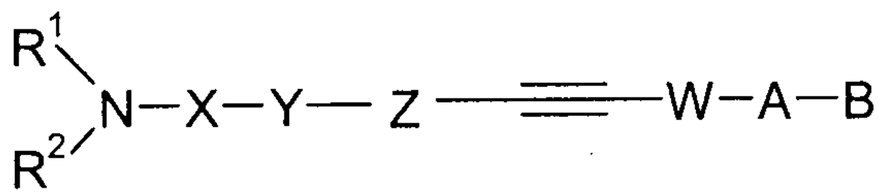
| | |
|---|---|
| active substance | 10 mg |
| mannitol | 50 mg |
| human serum albumin | 10 mg |
| water for injections ad | 1 ml |

Preparation:

Mannitol is dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules under nitrogen gas.

## Patent Claims

1. Alkyne compounds of general formula I



I

wherein

$R^1$, $R^2$ independently of one another denote H, $C_{1-8}$-alkyl, $C_{3-7}$-cycloalkyl or a phenyl or pyridinyl group optionally mono- or polysubstituted by identical or different groups $R^{20}$ and/or monosubstituted by nitro, while the alkyl or cycloalkyl group may be mono- or polysubstituted by identical or different groups $R^{11}$, and a $-CH_2-$ group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by -O-, -S- or $-NR^{13}-$, or

$R^1$ and $R^2$ form a $C_{3-8}$-alkylene bridge, wherein a $-CH_2-$ group not adjacent to the N atom of the $R^1R^2N-$ group may be replaced by -CH=N-, -CH=CH-, -O-, -S-, -SO-, $-(SO_2)-$, -CO-, $-C(=CH_2)-$ or $-NR^{13}-$,

while in the alkylene bridge defined hereinbefore one or more H atoms may be replaced by identical or different groups $R^{14}$, and

the alkylene bridge defined hereinbefore may be substituted by one or two identical or different carbo- or heterocyclic groups Cy such that the bond between the alkylene bridge and the group Cy is made

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system;

X denotes a $C_{1-4}$-alkylene bridge, while in the definition $C_{2-4}$-alkylene one or two C atoms may be monosubstituted by $R^{10}$, or

denotes a $C_{3-4}$-alkylene bridge, wherein a $-CH_2-CH_2-$ group not immediately adjacent to the N atom of the $R^1R^2N-$ group is replaced by -CH=CH- or $-C\equiv C-$,

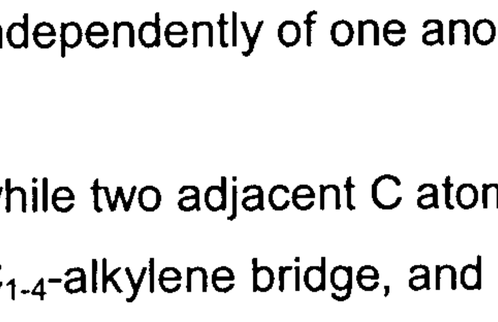
while the meanings given above for X may include a substituent selected from $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-7}$-cycloalkyl and $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl as well as, independently, one, two or three identical or different $C_{1-4}$-alkyl substituents, while two alkyl groups may be joined together forming a 3- to 7-membered cyclic group or an alkyl and an alkenyl group may be joined together forming a 5- to 7-membered cyclic group, and

W, Z independently of one another denote a single bond or a $C_{1-2}$-alkylene bridge,

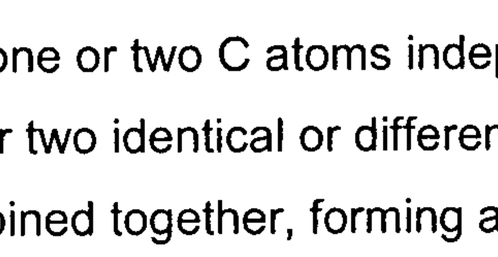
while two adjacent C atoms may be joined together by an additional $C_{1-4}$-alkylene bridge, and

one or two C atoms independently of one another may be substituted by one or two identical or different $C_{1-3}$-alkyl groups, while two alkyl groups may be joined together, forming a carbocyclic ring, and

Y is selected from the definitions of the partial formulae Y1 and Y2



Y1



Y2

wherein the group M denotes O, S or $NR^M$, where $R^M$ has a meaning selected from among H, $C_{1-6}$-alkyl, $C_{3-6}$-alkenyl, $C_{3-6}$-alkynyl, $C_{3-7}$-cycloalkyl and $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, and

in the partial formulae Y1 and Y2 one or more C atoms may be substituted independently of one another by $R^{20}$, and

A independently of one another are selected from among the bivalent cyclic groups phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, tetrahydronaphthyl, indolyl, dihydroindolyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, dihydroisoquinolinyl, tetrahydro-isoquinolinyl, benzimidazolyl, benzoxazolyl, thienyl, furanyl, benzothienyl or benzofuranyl, while the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different groups $R^{20}$, and in the case of a phenyl ring may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$,

B has one of the meanings given for Y, A or denotes

$C_{1-6}$-alkyl, $C_{1-6}$-alkenyl, $C_{1-6}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{5-7}$-cycloalkenyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkenyl-$C_{1-3}$-alkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkenyl or $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkynyl, wherein one or more C atoms independently of one another may be mono- or polysubstituted by halogen and/ or monosubstituted by hydroxy or cyano and/ or cyclic groups may be mono- or polysubstituted by identical or different groups $R^{20}$,

Cy denotes a carbo- or heterocyclic group selected from one of the following meanings

- a saturated 3- to 7-membered carbocyclic group,
- an unsaturated 4- to 7-membered carbocyclic group,
- a phenyl group,
- a saturated 4- to 7-membered or unsaturated 5- to 7-membered heterocyclic group with an N, O or S atom as heteroatom,
- a saturated or unsaturated 5- to 7-membered heterocyclic group with two or more N atoms or with one or two N atoms and an O or S atom as heteroatoms,
- an aromatic heterocyclic 5- or 6-membered group with one or more identical or different heteroatoms selected from N, O and/or S,

while the saturated 6- or 7-membered groups mentioned above may also be present as bridged ring systems with an imino, ($C_{1-4}$-alkyl)-imino, methylene, ($C_{1-4}$-alkyl)-methylene or di-($C_{1-4}$-alkyl)-methylene bridge, and

the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different groups $R^{20}$, and in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by $R^{21}$,

$R^{10}$ denotes hydroxy, ω-hydroxy-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxy or $C_{1-4}$-alkoxy-$C_{1-3}$-alkyl,

$R^{11}$ denotes halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $R^{15}$-O-, $R^{15}$-O-CO-, $R^{15}$-CO-O- cyano, $R^{16}R^{17}N$, $R^{18}R^{19}N$-CO- or Cy, while in the above-mentioned groups one or more C atoms may be substituted independently of one another by substituents selected from halogen, OH, CN, $CF_3$, $C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl;

$R^{13}$ has one of the meanings given for $R^{17}$,

$R^{14}$ denotes halogen, cyano, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $R^{15}$-O- $R^{15}$-O-CO-, $R^{15}$-CO-, $R^{15}$-CO-O- $R^{16}R^{17}N$, $R^{18}R^{19}N$-CO-,$R^{15}$-O-$C_{1-3}$-alkyl, $R^{15}$-O-CO-$C_{1-3}$-alkyl, $R^{15}$-$SO_2$-NH-, $R^{15}$-O-CO-NH-$C_{1-3}$-alkyl, $R^{15}$-$SO_2$-NH-$C_{1-3}$-alkyl, $R^{15}$-CO-$C_{1-3}$-alkyl, $R^{15}$-CO-O-$C_{1-3}$-alkyl, $R^{16}R^{17}N$-$C_{1-3}$-alkyl, $R^{18}R^{19}N$-CO-$C_{1-3}$-alkyl or Cy-$C_{1-3}$-alkyl,

$R^{15}$ denotes H, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, phenyl, phenyl-$C_{1-3}$-alkyl, pyridinyl or pyridinyl-$C_{1-3}$-alkyl,

$R^{16}$ denotes H, $C_{1-6}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, $C_{4-7}$-cycloalkenyl, $C_{4-7}$-cycloalkenyl-$C_{1-3}$-alkyl, ω-hydroxy-$C_{2-3}$-alkyl, ω-($C_{1-4}$-alkoxy)-$C_{2-3}$-alkyl, amino-$C_{2-6}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{2-6}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{2-6}$-alkyl or cyclo-$C_{3-6}$-alkyleneimino-$C_{2-6}$-alkyl,

$R^{17}$ has one of the meanings given for $R^{16}$ or denotes phenyl, phenyl-$C_{1-3}$-alkyl, pyridinyl, $C_{1-4}$-alkylcarbonyl, hydroxycarbonyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkoxycarbonyl, $C_{1-4}$-alkoxycarbonyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkylcarbonylamino-$C_{2-3}$-alkyl, N-($C_{1-4}$-alkylcarbonyl)-N-($C_{1-4}$-alkyl)-amino-$C_{2-3}$-alkyl, $C_{1-4}$-alkylsulphonyl, $C_{1-4}$-alkylsulphonylamino-$C_{2-3}$-alkyl or N-($C_{1-4}$-alkylsulphonyl)-N(-$C_{1-4}$-alkyl)-amino-$C_{2-3}$-alkyl;

$R^{18}$, $R^{19}$ independently of one another denote H or $C_{1-6}$-alkyl,

$R^{20}$ denotes halogen, hydroxy, cyano, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, hydroxy-$C_{1-3}$-alkyl, $R^{22}$-$C_{1-3}$-alkyl or has one of the meanings given for $R^{22}$,

$R^{21}$ denotes $C_{1-4}$-alkyl, ω-hydroxy-$C_{2-6}$-alkyl, ω-$C_{1-4}$-alkoxy-$C_{2-6}$-alkyl, ω-$C_{1-4}$-alkyl-amino-$C_{2-6}$-alkyl, ω-di-($C_{1-4}$-alkyl)-amino-$C_{2-6}$-alkyl, ω-cyclo-$C_{3-6}$-alkyleneimino-$C_{2-6}$-alkyl, phenyl, phenyl-$C_{1-3}$-alkyl, $C_{1-4}$-alkyl-carbonyl, $C_{1-4}$-alkoxy-carbonyl, $C_{1-4}$-alkylsulphonyl, aminosulphonyl, $C_{1-4}$-alkylaminosulphonyl, di-$C_{1-4}$-alkylaminosulphonyl or cyclo-$C_{3-6}$-alkylene-imino-sulphonyl,

$R^{22}$ denotes pyridinyl, phenyl, phenyl-$C_{1-3}$-alkoxy, cyclo-$C_{3-6}$-alkyleneimino-$C_{2-4}$-alkoxy, OHC-, HO-N=HC-, $C_{1-4}$-alkoxy-N=HC-, $C_{1-4}$-alkoxy, $C_{1-4}$-alkylthio, carboxy, $C_{1-4}$-alkylcarbonyl, $C_{1-4}$-alkoxycarbonyl, aminocarbonyl, $C_{1-4}$-alkylaminocarbonyl, di-($C_{1-4}$-alkyl)-aminocarbonyl, cyclo-$C_{3-6}$-alkyl-amino-carbonyl, cyclo-$C_{3-6}$-alkyleneimino-carbonyl, phenylaminocarbonyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{2-4}$-alkyl-aminocarbonyl, $C_{1-4}$-alkyl-sulphonyl, $C_{1-4}$-alkyl-sulphinyl, $C_{1-4}$-alkyl-sulphonylamino, amino, $C_{1-4}$-alkylamino, di-($C_{1-4}$-alkyl)-amino, $C_{1-4}$-alkyl-carbonyl-amino, cyclo-$C_{3-6}$-alkyleneimino, phenyl-$C_{1-3}$-alkylamino, N-($C_{1-4}$-alkyl)-phenyl-$C_{1-3}$-alkylamino, acetylamino, propionylamino, phenylcarbonyl, phenylcarbonylamino, phenylcarbonylmethylamino, hydroxy-$C_{2-3}$-alkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or $C_{1-4}$-alkylaminocarbonylamino,

while in the above-mentioned groups and residues, particularly in W, X, Z, $R^{13}$ to $R^{22}$, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may additionally be monosubstituted by Cl or Br and/or in each case one or more phenyl rings may independently of one another additionally contain one, two or three substituents selected from among F, Cl, Br, I, cyano, $C_{1-4}$-alkyl, $C_{1-4}$-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, $C_{1-3}$-alkylamino, di-($C_{1-3}$-alkyl)-amino, acetylamino, aminocarbonyl, difluoromethoxy, trifluoromethoxy, amino-$C_{1-3}$-alkyl, $C_{1-3}$-alkylamino-$C_{1-3}$-alkyl- and di-($C_{1-3}$-alkyl)-amino-$C_{1-3}$-alkyl and/or may be monosubstituted by nitro, and

the H atom of any carboxy group present or an H atom bound to an N atom may each be replaced by a group which can be cleaved *in vivo*,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

while the following compounds are not included according to the invention:

6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-2-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-quinoline,

6-[5-(4-chloro-phenyl)-pyridin-2-ylethynyl]-1-methyl-2-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydro-quinoline and

5-(4-chloro-phenyl)-2-[2-(4-methyl-piperidin-1-ylmethyl)-chroman-6-ylethynyl]-pyridine.

2. Alkyne compounds according to claim 1, characterised in that the groups $R^1$, $R^2$ are selected independently of one another from the group consisting of H, $C_{1-6}$-alkyl, $C_{3-5}$-alkenyl, $C_{3-5}$-alkynyl, $C_{3-7}$-cycloalkyl, hydroxy-$C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl, (hydroxy-$C_{3-7}$-cycloalkyl)-$C_{1-3}$-alkyl, hydroxy-$C_{2-4}$-alkyl, ω-NC-$C_{2-3}$-alkyl, $C_{1-4}$-alkoxy-$C_{2-4}$-alkyl, hydroxy-$C_{1-4}$-alkoxy-$C_{2-4}$-alkyl, $C_{1-4}$-alkoxy-carbonyl-$C_{1-4}$-alkyl, carboxyl-$C_{1-4}$-alkyl, amino-$C_{2-4}$-alkyl, $C_{1-4}$-alkyl-amino-$C_{2-4}$-alkyl, di-($C_{1-4}$-alkyl)-amino-$C_{2-4}$-alkyl, cyclo-$C_{3-6}$-alkyleneimino-$C_{2-4}$-alkyl, pyrrolidin-3-yl, N-($C_{1-4}$-alkyl)-pyrrolidin-3-yl, pyrrolidinyl-$C_{1-3}$-alkyl, N-($C_{1-4}$-alkyl)-pyrrolidinyl-$C_{1-3}$-alkyl, piperidin-3-yl, piperidin-4-yl, N-($C_{1-4}$-alkyl)-piperidin-3-yl, N-($C_{1-4}$-alkyl)-piperidin-4-yl, piperidinyl-$C_{1-3}$-alkyl, N-($C_{1-4}$-alkyl)-piperidinyl-$C_{1-3}$-alkyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, phenyl, phenyl-$C_{1-3}$-alkyl, pyridyl or pyridyl-$C_{1-3}$-alkyl, while in the above-mentioned groups and radicals one or more C atoms may be mono- or polysubstituted independently of one another by F, $C_{1-3}$-alkyl or hydroxy-$C_{1-3}$-alkyl, and/or one or two C atoms may be monosubstituted independently of one another by Cl, Br, OH, $CF_3$ or CN, and the phenyl or pyridyl group may be mono- or polysubstituted by identical or different groups $R^{20}$, and in the case of a phenyl group may also additionally be monosubstituted by nitro, and

the group $R^{20}$ has the meaning given in claim 1.

3. Alkyne compounds according to claim 1, characterised in that $R^1$ and $R^2$ together with the N atom to which they are bound form a heterocyclic group which is selected from the meanings pyrrolidine, piperidine, piperazine, wherein the free imine function is substituted by $R^{13}$, and morpholine,

while one or more H atoms may be replaced by identical or different groups $R^{14}$, and/or

the heterocyclic groups specified may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in such a way that the bond between the alkylene bridge and the group Cy is made

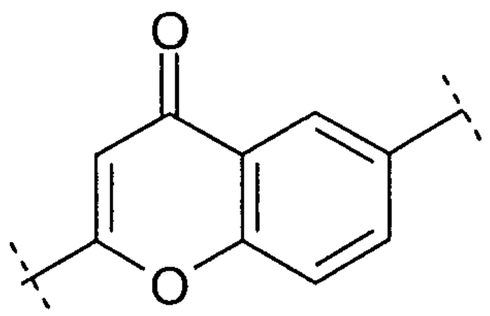
- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common adjacent C- and/or N atoms forming a fused bicyclic ring system or
- via three or more C- and/or N atoms forming a bridged ring system;

and the groups $R^{13}$, $R^{14}$ and the group Cy are defined as in claim 1.

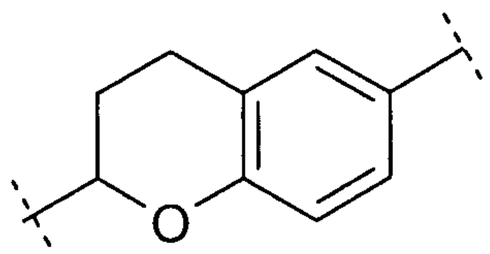
4. Alkyne compounds according to one or more of the preceding claims, characterised in that X denotes a methylene or ethylene bridge which is unsubstituted or substituted by one or two identical or different $C_{1-3}$-alkyl-substituents and/or a substituent selected from $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{3-6}$-cycloalkyl and $C_{3-6}$-cycloalkyl-$C_{1-3}$-alkyl, while two alkyl substituents may be joined together, forming a 3- to 6-membered carbocyclic ring system.

5. Alkyne compounds according to one or more of the preceding claims, characterised in that Z denotes a single bond or ethylene and W denotes a single bond.

6. Alkyne compounds according to one or more of the preceding claims, characterised in that the group Y is selected from the group of partial formulae



Y1.1



Y2.1

while in the partial formulae Y1.1 and Y2.1 one or more C atoms may be substituted independently of one another with $R^{20}$, and

$R^{20}$ is defined as in claim 1.

7. Alkyne compounds according to one or more of the preceding claims, characterised in that the group A is selected from the group of bivalent cyclic groups phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, which may be mono- or polysubstituted at one or more C atoms by identical or different groups $R^{20}$, or in the case of a phenyl ring may also additionally be monosubstituted by nitro, and

$R^{20}$ is defined as in claim 1.

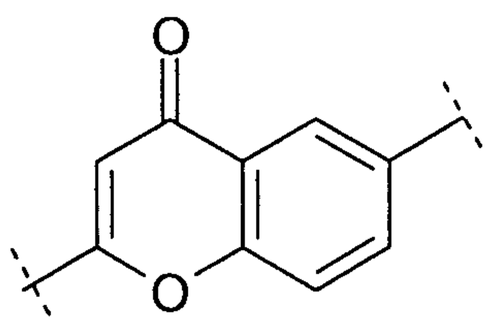
8. Alkyne compounds according to one or more of the preceding claims, characterised in that the group B is selected from phenyl, cyclohexenyl, pyridyl, thienyl and furanyl, and

the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms by identical or different groups $R^{20}$, or in the case of a phenyl group may also additionally be monosubstituted by nitro, and

$R^{20}$ is defined as in claim 1.

9. Alkyne compounds according to one or more of the preceding claims, characterised in that

Y denotes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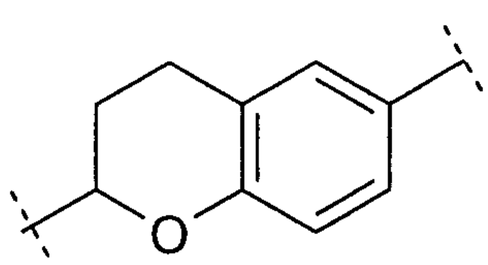
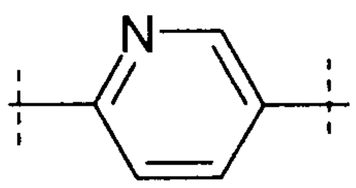

,

A has a meaning selected from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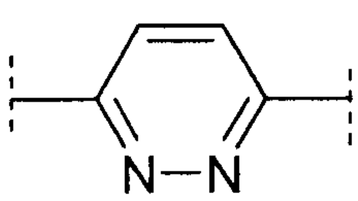
, and/or

B denotes phenyl, cyclohexenyl, pyridyl, thienyl and furanyl, preferably phenyl,

while Y and A are unsubstituted or monosubstituted by $R^{20}$, and B is unsubstituted or mono-, di- or trisubstituted independently of one another by $R^{20}$, or in the case of a phenyl ring may also be additionally monosubstituted by nitro, and $R^{20}$ has the meaning given in claim 1.

10. Alkyne compounds according to one or more of the preceding claims, characterised in that

$R^{20}$ denotes F, Cl, Br, I, OH, cyano, methyl, difluoromethyl, trifluoromethyl, ethyl, n-propyl, iso-propyl, amino, acetyl, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy or iso-propoxy, while substituents $R^{20}$ which occur repeatedly may have the same or different meanings.

11. Physiologically acceptable salts of the alkyne compounds according to one or more of claims 1 to 10.

12. Composition, containing at least one alkyne compound according to one or more of claims 1 to 10 and/ or a salt according to claim 11, optionally together with one or more physiologically acceptable excipients.

13. Pharmaceutical compositions, containing at least one alkyne compound according to one or more of claims 1 to 10 and/ or a salt according to claim 11, optionally together with one or more inert carriers and/or diluents.

14. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/ or a salt according to claim 11 for influencing the eating behaviour of a mammal.

15. Use of at least one amide compound according to one or more of claims 1 to 10 and/or a salt according to claim 11, for reducing the body weight and/ or for preventing an increase in the body weight of a mammal.

16. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition with an MCH-receptor-antagonistic activity.

17. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition which is suitable for preventing and/or treating symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

18. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition which is suitable for preventing and/or treating metabolic disorders and/or eating disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia.

19. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition which is suitable for preventing and/or treating diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

20. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition which is suitable for preventing and/or treating hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, sleep disorders, reproductive disorders, sexual disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

21. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition which is suitable for preventing and/or treating micturition disorders, such as for example urinary incontinence, hyperactive urinary bladder, urgency, nycturia and enuresis.

22. Use of at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 for preparing a pharmaceutical composition which is suitable for preventing and/or treating dependencies and/or withdrawal symptoms.

23. Process for preparing a composition or a pharmaceutical composition according to one or more of claims 12, 13 and 16 to 22, characterised in that at least one alkyne compound according to one or more of claims 1 to 10 and/or a salt according to claim 11 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

24. Pharmaceutical composition, containing

a first active substance which is selected from the alkyne compounds according to one or more of claims 1 to 10 and/or a salt according to claim 11, and

a second active substance selected from the group consisting of active substances for the treatment of diabetes, active substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active substances for the treatment of depression,

optionally together with one or more inert carriers and/or diluents.

25. Process for preparing alkyne compounds of formula A.5

$R^1R^2N$-X-Y-C≡C-W-A-B (A.5)

while in formulae A.1, A.2, A.3, A.4 and A.5 $R^1$, $R^2$, Y, X, W, A and B have one of the meanings given in claims 1 to 10,

wherein a halogen compound of formula A.1

HO-X-Y-Hal (A.1)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine, is reacted with an alkyne compound of formula A.2

H-C≡C-W-A-B(A.2)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent, and

the compound of formula A.3 obtained

HO-X-Y-C≡C-W-A-B (A.3)

is reacted with methanesulphonic acid chloride (MsCl) to produce the methanesulphonate derivative A.4,

MsO-X-Y-C≡C-W-A-B (A.4)

which is further reacted with an amine of formula H-$NR^1R^2$ to form the end product A.5.

26. Process process for preparing alkyne compounds of formula B.5

$R^1R^2N$-X-Y-Z-C≡C-A-B (B.5)

while in formulae B.1, B.2, B.3, B.4 and B.5 $R^1$, $R^2$, X, Y, Z, A and B have one of the meanings given in claims 1 to 10,

wherein a halogen compound of formula B.1

Hal-A-B (B.1)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine, is reacted with an alkyne compound of formula B.2

HO-X-Y-Z-C≡C-H (B.2)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent, and

the resulting compound of formula B.3

HO-X-Y-Z-C≡C-A-B (B.3)

is reacted with methanesulphonic acid chloride (MsCl) to form the methanesulphonate derivative B.4,

MsO-X-Y-Z-C≡C-A-B (B.4)

which is reacted further with an amine of formula H-$NR^1R^2$ to form the end product B.5.

27. Process for preparing alkyne compounds of formula C.3

$R^1R^2N$-X-Y-C≡C-W-A-B (C.3)

while in formulae C.1, C.2 and C.3 $R^1$, $R^2$, X, Y, W, A and B have one of the meanings given in claims 1 to 10,

wherein a halogen compound of formula C.1

$R^1R^2N$-X-Y-Hal (C.1)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine, is further reacted with an alkyne compound of formula C.2

H-C≡C-W-A-B(C.2)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent to yield the end product C.3.

28. Process for preparing alkyne compounds of formula D.3

$R^1R^2N$-X-Y-Z-C≡C-A-B (D.3)

while in formulae D.1, D.2 and D.3 $R^1$, $R^2$, X, Y, Z, A and B have one of the meanings given in claims 1 to 10,

wherein a halogen compound of formula D.2

Hal-A-B (D.2)

wherein Hal denotes chlorine, bromine or iodine, preferably bromine or iodine, is reacted with an alkyne compound of formula D.1

$R^1R^2N$-X-Y-Z-C≡C-H (D.1)

in the presence of a suitable palladium catalyst, a suitable base and copper(I)iodide in a suitable solvent to form the end product D.3.

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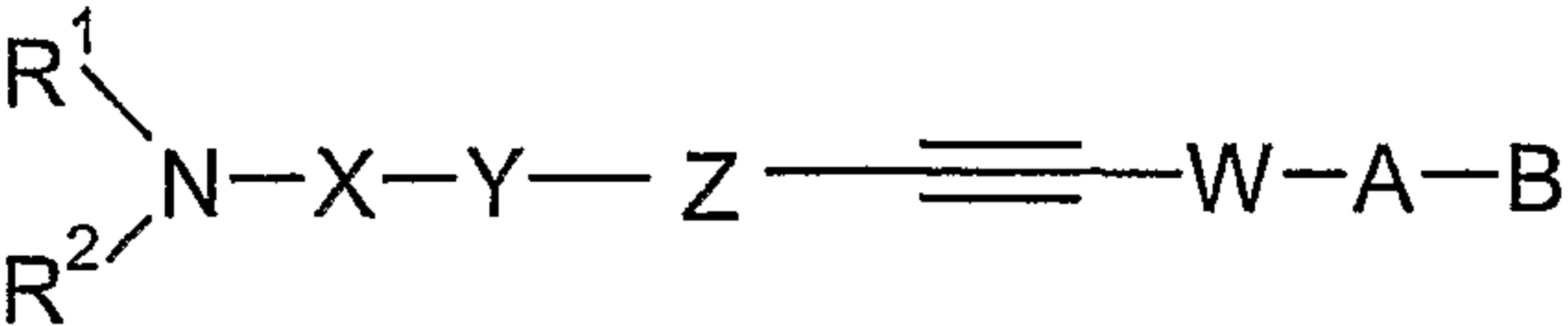

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