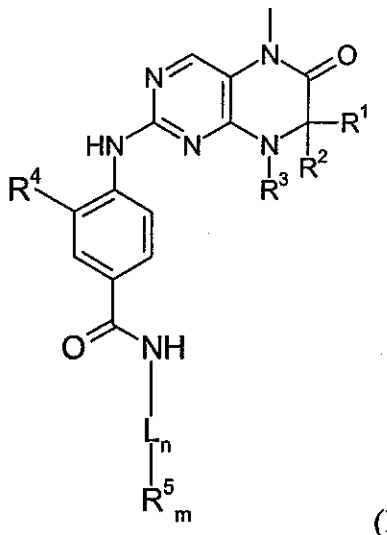
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Dihydropteridinone infusion solution having a long shelf life

The present invention relates to storage stable aqueous infusible or injectable solutions containing an active substance of formula (I)



(I)

wherein the groups L, R^1, R^2, R^3, R^4 and R^5 have the meanings given in the claims and in the specification, and an amount of a physiologically acceptable acid or mixture of acids sufficient to dissolve the active substance and act as a stabiliser, optionally together with other formulating excipients suitable for parenteral administration, and a process for preparing the infusible or injectable solutions according to the invention.

Background to the invention

The dihydropteridinones of formula (I) according to the invention are an innovative new cytostatic active substance in the oncological treatment of fast-growing types of cancer. Usually, cytostatic medications are administered as parenteral preparations, even though their oral bioavailability may be perfectly adequate. The reason for this is that treatment with cytostatics is generally accompanied by a range of gastrointestinal side-effects which is frequently characterised by nausea, vomiting and/or diarrhoea, and consequently effective treatment by oral route would be jeopardised thereby.

These circumstances also apply to the dihydropteridinones of formula (I) and make it essential to prepare a solution for parenteral infusion or injection.

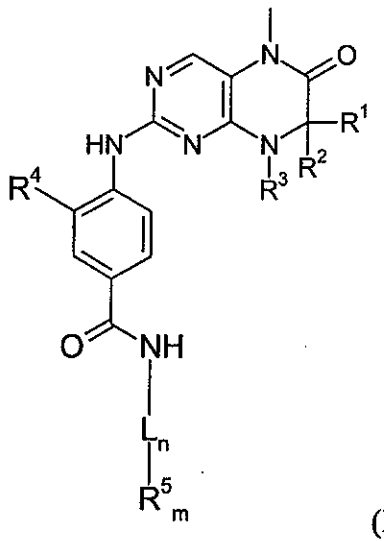
In the prior art EP 0219784 and WO 01/78732 describe methods of preparing and stabilising solutions for infusion containing ciprofloxacin by using one or more physiologically acceptable acid(s) of organic or inorganic origin. EP A 0287926 relates that the risk of particle formation can be greatly reduced by the use of highly pure grades of ciprofloxacin. EP 0143478 A1 describes the preparation of a stable hydrochloric acid solution of cisplatin, suitable for injection, which is particularly free from other additives. DE 197 03023 discloses that the stability of infusible solutions with regard to the formation of particulate impurities can be vastly improved by the use of glass containers with siliconised surfaces.

The aim of the present invention is to provide a stable infusible or injectable solution of dihydropteridinones of formula (I) for the desired dosage range tailored to treatment. As a further objective of the invention the stable infusible or injectable solution should be suitable both as a ready-to-use solution and as a concentrate for further dilution with solutions commonly used for parenteral administration such as for example isotonic NaCl solution, isotonic dextrose solution or Ringer lactate solution, to allow flexible adaptation of the dosage.

Description of the invention

It has been found that, surprisingly, storage stable aqueous infusible or injectable solutions containing an active substance of general formula (I), which contain an amount of a physiologically acceptable acid or mixture of acids sufficient to dissolve the active substance and act as a stabiliser, optionally together with other formulating excipients suitable for parenteral administration, can be produced free from particles and with long-term stability, irrespective of the quality of the active substance in each case, and in particular irrespective of the contamination profile.

The present invention therefore relates to storage stable aqueous infusible or injectable solutions containing the active substance of general formula (I)



(I)

wherein

R^1, R^2 which may be identical or different, denote hydrogen or optionally substituted C_1-C_6-alkyl, or

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

R^3 denotes hydrogen or a group selected from among optionally substituted C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkynyl and C_6-C_{14}-aryl, or a group selected from among optionally substituted and/or bridged C_3-C_{12}-cycloalkyl, C_3-C_{12}-cycloalkenyl, C_7-C_{12}-polycycloalkyl, C_7-C_{12}-polycycloalkenyl, C_5-C_{12}-spirocycloalkyl, C_3-C_{12}-heterocycloalkyl which contains 1 to 2 heteroatoms, and C_3-C_{12}-heterocycloalkenyl which contains 1 to 2 heteroatoms,

or

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

R^4 denotes a group selected from among hydrogen, -CN, hydroxy, $-NR_6R_7$ and halogen, or

a group selected from among optionally substituted C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_5-alkyloxy, C_2-C_5-alkenyloxy, C_2-C_5-alkynyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulphoxo and C_1-C_6-alkylsulphonyl,

L denotes a linker selected from among optionally substituted C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_6-C_{14}-aryl, -C_2-C_4-alkyl-C_6-C_{14}-aryl, -C_6-C_{14}-aryl-C_1-C_4-alkyl, optionally bridged C_3-C_{12}-cycloalkyl and heteroaryl which contains 1 or 2 nitrogen atoms,

n denotes 0 or 1,

m denotes 1 or 2,

R^5 denotes a group selected from among optionally substituted morpholinyl, piperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropenyl, R^8-diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, $-NR^8R^9$ and azacycloheptyl,

R^6, R^7 which may be identical or different, denote hydrogen or C_1-C_4-alkyl, and

R^8, R^9 denote unsubstituted nitrogen substituents at R^5, which may be identical or different, either hydrogen or a group selected from among C_1-C_6-alkyl, -C_1-C_4-alkyl-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl, C_6-C_{14}-aryl, -C_1-C_4-alkyl-C_6-C_{14}-aryl, pyranyl, pyridinyl, pyrimidinyl, C_1-C_4-alkyloxycarbonyl, C_6-C_{14}-arylcarbonyl, C_1-C_4-alkylcarbonyl, C_6-C_{14}-

arylmethyloxycarbonyl, C_6-C_{14}-arylsulphonyl, C_1-C_4-alkylsulphonyl- and C_6-C_{14}-aryl-C_1-C_4-alkylsulphonyl,

or the tautomers, racemates, enantiomers, diastereomers or optionally the physiologically effective derivatives or metabolites thereof and an amount of a physiologically acceptable acid or mixture of acids sufficient to dissolve the active substance and act as a stabiliser, optionally together with other formulating excipients suitable for parenteral administration.

Preferred storage stable solutions are those containing compounds of formula (I), wherein

R^1 to R^4, R^6 and R^7 are as hereinbefore defined, and

L denotes a linker selected from among optionally substituted C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_6-C_{14}-aryl, -C_2-C_4-alkyl-C_6-C_{14}-aryl, -C_6-C_{14}-aryl-C_1-C_4-alkyl, optionally bridged C_3-C_{12}-cycloalkyl and heteroaryl which contains 1 or 2 nitrogen atoms,

n denotes 1,

m denotes 1 or 2,

R^5 denotes a group bound to L via a nitrogen atom, selected from among optionally substituted morpholinyl, piperidinyl, R^8-piperazinyl, pyrrolidinyl, tropenyl, R^8-diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, -NR^8R^9 and azacycloheptyl,

and

R^8, R^9 denote unsubstituted nitrogen substituents at R^5, which may be identical or different, which denote hydrogen or a group selected from among C_1-C_6-alkyl, -C_1-C_4-alkyl-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl, C_6-C_{14}-aryl, -C_1-C_4-alkyl-C_6-C_{14}-aryl, pyranyl, pyridinyl, pyrimidinyl, C_1-C_4-

alkyloxycarbonyl, C_6-C_{14}-arylcarbonyl, C_1-C_4-alkylcarbonyl, C_6-C_{14}-arylmethyloxycarbonyl, C_6-C_{14}-arylsulphonyl, C_1-C_4-alkylsulphonyl- and C_6-C_{14}-aryl-C_1-C_4-alkylsulphonyl,

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

Also preferred are storage stable solutions containing compounds of formula (I), wherein R^1 to R^4, R^6 and R^7 are as hereinbefore defined,

and

L denotes a linker selected from among optionally substituted C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_6-C_{14}-aryl, -C_2-C_4-alkyl-C_6-C_{14}-aryl, -C_6-C_{14}-aryl-C_1-C_4-alkyl, optionally bridged C_3-C_{12}-cycloalkyl and heteroaryl which contains 1 or 2 nitrogen atoms,

n denotes 0 or 1,

m denotes 1 or 2,

R^5 denotes a group which is bound to L via a carbon atom, selected from among R^8 – piperidinyl, R^8R^9-piperazinyl, R^8-pyrrolidinyl, R^8-piperazinylcarbonyl, R^8-tropenyl, R^8-morpholinyl and R^8-azacycloheptyl,

and

R^8, R^9 denote unsubstituted nitrogen substituents at R^5, which may be identical or different, which denote hydrogen or a group selected from among C_1-C_6-alkyl, -C_1-C_4-alkyl-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl, C_6-C_{14}-aryl, -C_1-C_4-alkyl-C_6-C_{14}-aryl, pyranyl, pyridinyl, pyrimidinyl, C_1-C_4-alkyloxycarbonyl, C_6-C_{14}-arylcarbonyl, C_1-C_4-alkylcarbonyl, C_6-C_{14}-arylmethyloxycarbonyl, C_6-C_{14}-arylsulphonyl, C_1-C_4-alkylsulphonyl- and C_6-C_{14}-aryl-C_1-C_4-alkylsulphonyl,

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

Particularly preferred are storage stable solutions containing compounds of formula (I), wherein L, m, n and R^3 to R^9 are as hereinbefore defined,

and

R^1, R^2 which may be identical or different denote a group selected from among hydrogen, Me, Et and Pr,

or

R^1 and R^2 together form a C_2-C_4-alkyl bridge,

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

Particularly preferred are storage stable solutions containing compounds of formula I, wherein R^1, R^2, m, n and R^5 to R^8 are as hereinbefore defined,

and

R^3 denotes a group selected from among optionally substituted C_1-C_{10}-alkyl, C_3-C_7-cycloalkyl, C_3-C_6-heterocycloalkyl and C_6-C_{14}-aryl,

or

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

and

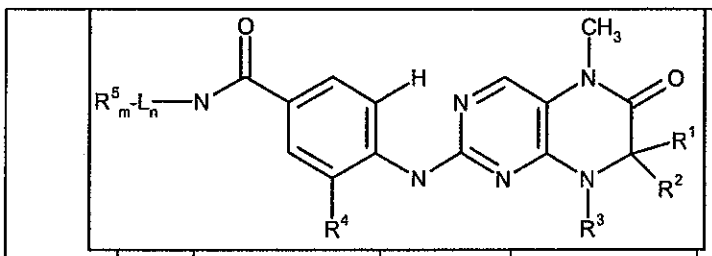
R^4 denotes a group selected from among hydrogen, OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, CL, Br, O-propargyl, O-butynyl, CN, SMe, NMe_2, $CONH_2$, ethynyl, propynyl, butynyl and allyl,

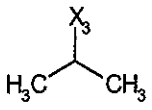
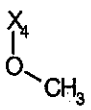
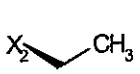
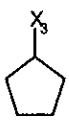
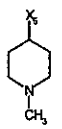
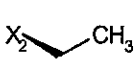
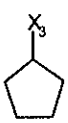
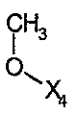
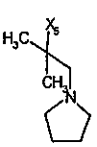
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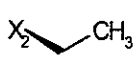
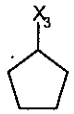
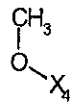
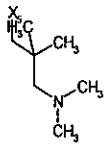
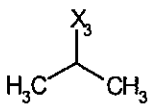
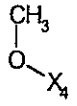
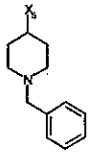
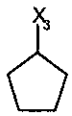
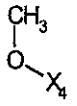
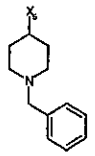
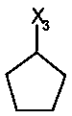
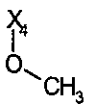
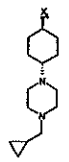
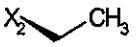
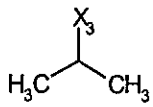
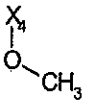
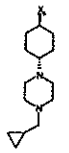
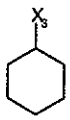
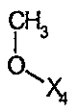
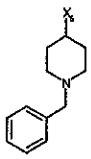
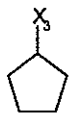
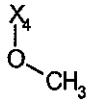
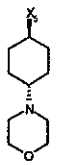
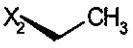
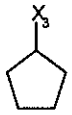
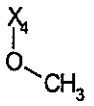
L denotes a linker selected from among optionally substituted phenyl, phenylmethyl, cyclohexyl and branched C_1-C_6-alkyl,

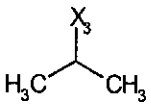
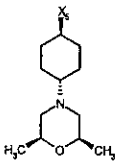
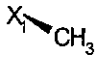
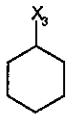
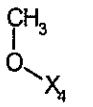
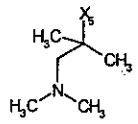
optionally in the form of the tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

The invention also relates to a storage stable solution containing a dihydropteridinone of general formula (I) as hereinbefore described, the dihydropteridinone being selected from among the following dihydropteridinones of general formula (I)



Ex.	R^1	R^2	Config. R^1 or R^2	R^3	R^4	L_n-$R^5{}_m$
27	H		R			
44	H		R		H	
55	H		R			

58	H		R			
102	H		R			
103	H		R			
105	H		R			
110	H		R			
115	H		R			
133	H		R			
134	H		R			

234	H		R			
240	H		R			

while the abbreviations X_1, X_2, X_3, X_4 and X_5 used in the Table in each case denote a link to a position in the general formula listed in the Table instead of the corresponding groups R^1, R^2, R^3, R^4 and L-R^5.

Long-term stability is defined as a shelf-life of at least 12 months at 25°C/60% r.h. and 30°C/70% r.h., preferably at least 36 months at 25°/60% r.h. and 30°C/70% r.h..

The infusible or injectable solutions according to the invention, apart from the addition of a physiologically acceptable acid or mixture of acids, may be free from solubilising additives or organic cosolvents, particularly organic cosolvents.

Preferred aqueous infusible or injectable solutions are those wherein the content of dissolved active substance of formula (I) is 0.1 mg to 10.0 mg, particularly preferably 0.5 to 5 mg, in 1 ml of infusible or injectable solution.

Also preferred are aqueous infusible or injectable solutions, wherein one or more acids used as storage and dilution stabilisers are selected from among hydrochloric acid, acetic acid, hydroxyacetic acid, methanesulphonic acid, ethanesulphonic acid, phosphoric acid, nitric acid, sulphuric acid, citric acid, tartaric acid, fumaric acid, succinic acid, glutaric acid, adipic acid, propionic acid, ascorbic acid, maleic acid, malic acid, glutamic acid, gluconic acid, glucuronic acid, galacturonic acid and lactic acid, preferably acetic acid, hydrochloric acid, phosphoric acid, tartaric acid, citric acid and fumaric acid, particularly preferably hydrochloric acid, citric acid and acetic acid.

For reasons of pH compatibility, as is evident from Figure 1, aqueous infusible or injectable solutions are preferred wherein the molar ratio of the physiologically acceptable acid or mixture of acids to the active substance is at most 3:1, preferably 1.25:1 to 3:1, particularly preferably 1.5 :1 to 3:1, in order to ensure that the pH is above 2.4.

Preferably the invention also relates to infusible or injectable solutions which contain 0.1 mg to 10.0 mg active substance per millilitre of aqueous solution and up to 3.0 mol of hydrochloric acid, based on one mol of active substance. The amounts of hydrochloric acid are preferably 1.25 mol to 3.0 mol, particularly 1.5 to 2.4 mol.

The invention also relates to infusible or injectable solutions of 4-[[(7*R*)-8-cyclopentyl-7-ethyl-5,6,7,8-tetrahydro-5-methyl-6-oxo-2-pteridinyl]amino]-3-methoxy-*N*-(1-methyl-4-piperidinyl)-benzamide which contain 1.6 to 2.0 mol hydrochloric acid per mol of active substance.

The infusible or injectable solutions according to the invention may also be modified so as to contain up to 10 mg/ml of the active substance, and up to 1 mol hydrochloric acid per mol of active substance, as well as one or more other physiologically acceptable acid(s), with the proviso that the total amount of acid is at least 1.25 mol per mol of active substance, but does not exceed 3.0 mol per mol active substance.

The minimum amount of acid needed per mol of active substance depends on the active substance concentration, and the acid(s) used, and is thus not constant. However, it may be determined within the limits according to the invention by simple tests as described for example in EP 0219784 and WO 01/78732.

Particularly preferred are aqueous infusible or injectable solutions which contain one or more other formulation aids selected from among complexing agents, crystallisation inhibitors, thickeners, isotonic agents, preservatives, light protecting agents and antioxidants.

Suitable complexing agents are e.g. genuine and substituted cyclodextrins, EDTA, albumins, as well as citric acid and the salts and derivatives thereof.

Suitable crystallisation inhibitors are e.g. PVP, cellulose derivatives, alginates, poloxamers and polysorbates.

Suitable thickeners are for example dextrans, glycerol and soluble cellulose derivatives, particularly carboxymethylcellulose and the salts thereof, as well as hydroxyalkyl celluloses.

Suitable isotonic agents are for example NaCl, mannitol, sorbitol, xylitol, saccharose, lactose, glucose and glycerol, preferably NaCl, mannitol, glucose, saccharose and glycerol, particularly preferably NaCl, mannitol and glucose.

Suitable preservatives are for example the esters of p-hydroxybenzoic acid, benzylalcohol, sorbic acid and benzoic acid.

Suitable light protecting agents are for example derivatives of p-hydroxybenzoic acid as well as cinnamic acid and the derivatives thereof.

A suitable antioxidant is for example ascorbic acid and the salts thereof.

Also particularly preferred are aqueous infusible or injectable solutions wherein the osmolality of the infusible or injectable solutions is 200 – 600 mOsmol/kg, preferably 260 – 350 mOsmol/ kg. They may be prepared using isotonic agents such as NaCl, mannitol, sorbitol, glucose, saccharose, xylitol, fructose and glycerol or mixtures of the above-mentioned substances. Preferred are infusible or injectable solutions which contain, in addition to the active substance, water, acid(s) and other formulation aids, an amount of NaCl or other isotonic agent such that a solution is obtained which is isotonic with the tissue fluid of the human or animal body or slightly hypotonic or hypertonic solution.

Most preferred are aqueous infusible or injectable solutions which have a pH in the range from 2.4 to 5.3, preferably from 3.5 to 5.0, particularly preferably from 3.9 to 4.5.

The infusible or injectable solutions according to the invention are also suitable for dilution with standard commercial infusion or injection carrier solutions for supplying electrolyte without carbohydrates, such as isotonic NaCl solution, isotonic glucose solution, Ringer lactate solution and the like (Red List 2004, Verzeichnis des Bundesverbandes der Pharmazeutischen Industrie e.V., [Directory of Drug Products of the Members of the Federal Association of the Pharmaceutical Industry], Editio Cantor, Aulendorf/Württ., main groups 52.1 and 52.2.1) to give the desired concentration or dose without having any physical or chemical incompatibilities.

Also most preferred are aqueous infusible or injectable solutions which contain 1.25 to 3.0 mol, preferably 1.5 to 2.4 mol, of hydrochloric acid per mol of active substance, based on 100 ml of infusible or injectable solution, 0.75 to 1.2 g NaCl, preferably 0.85 to 0.95 g NaCl, and have an osmolality of 260 to 350 mOsmol/kg and a pH of 3.5 to 5.0.

The invention further relates to lyophilisates, concentrates and suspensions which by the addition of water yield one of the aqueous infusible or injectable solutions according to the invention.

The invention also relates to the infusible or injectable solutions according to the invention for use as pharmaceutical compositions with an antiproliferative activity.

The invention further relates to the use of the infusible or injectable solutions according to the invention for preparing a pharmaceutical composition for the treatment of tumoral diseases, infections, inflammatory and autoimmune diseases.

The invention further relates to a method for the treatment and/or prevention of tumoral diseases, infections, inflammatory and autoimmune diseases, preferably tumoral diseases, in which an effective amount of an infusible or injectable solution according to the invention is administered to a patient.

The invention further relates to the use of the infusible or injectable solutions according to the invention, which corresponds to a dosage range of from 0.1 to 50 mg active substance /kg body weight, preferably 0.5 to 25 mg active substance /kg body weight.

The infusible or injectable solutions according to the invention may be stored in suitable glass containers for parenteral preparations or in flexible plastic containers, preferably non-PVC materials based e.g. on polyolefin, with removable volumes of 20 to 1000 ml, preferably 50 to 500 ml. The containers may be designed so as to provide particular protection for the infusible or injectable solutions according to the invention, e.g. to protect them from light or oxygen. Special surface treatment of the primary packaging (e.g. (stoved) siliconisation of the surfaces of glass containers) to improve the stability of the infusible or injectable solutions according to the invention is neither necessary nor harmful. Flexible plastic containers may contain additional protection, e.g. in the form of aluminium packaging.

The infusible or injectable solutions according to the invention are suitable for terminal sterilisation, e.g. with pressurised steam, and can thus be made sterile and free from pyrogens in a particularly economical manner and with high product safety (low risk of contamination).

The infusible or injectable solution according to the invention may be prepared by methods of producing aqueous liquid formulations known from the literature.

Thus, the present invention relates to a process for preparing the infusible or injectable solutions according to the invention, containing 0.1 to 10 mg per millilitre of the active substance of formula (I). The process is characterised in that a suitable amount of active substance, optionally in the form of a salt, is combined with an anionic counter-ion, a hydrate or hydrates of a salt, or mixtures of these salts/hydrates with the quantity of a physiologically acceptable acid or mixture of acids which constitutes an excess in relation to the precise [amount needed] to dissolve the active substance or the salts or hydrates thereof and to prevent physical instabilities, other formulating excipients are

optionally added, and the preparation is made up with water (for injections) such that a range of concentrations of from 0.1 to 10 mg of active substance per millilitre of infusible or injectable solution is obtained.

When preparing the infusible or injectable solutions care should also be taken to ensure that the solution has the properties mentioned above regarding pH, amounts of acid, and osmolality. If a salt is used it is advantageous to use an acid the anion of which corresponds to the anion of the salt or salt hydrate of the active substance.

The active substance or the salt or hydrate thereof is optionally suspended in water, and up to 3.0 mol of physiologically acceptable acid or mixture of acids, preferably hydrochloric acid, are added per mol of active substance.

Finally, the other formulating excipients are added, particularly isotonic agents, preferably NaCl, which may optionally also be produced by a neutralising reaction in the formulation mixture, before it is adjusted to the desired active substance concentration with water.

The pH of the infusible or injectable solutions according to the invention can be adjusted to the pH values specified above with (physiologically) acceptable acids and/or bases, particularly NaOH.

To speed up the production process, particularly to dissolve the solid ingredients, the solutions may be heated slightly as a whole or in parts, preferably to temperatures between 20°C and 80°C.

The solutions according to the invention may be prepared particularly economically using concentrated solutions. The amount of active substance required for a preparation is combined with the majority (>90%) of the physiologically acceptable acid or mixture of acids and dissolved, optionally with gentle heating and/or the addition of a small amount of water. This concentrate is then diluted with water before the other

formulating excipients are added, and lastly made up to the nominal weight with the remainder of the acid(s) or water.

After the preparation of the solution it is generally filtered through a 0.2 µm membrane or deep filter, although finally it is terminally sterilised with pressurised steam in order to remove any particles and/or pyrogens which may be present.

Details of suitable filtration methods are known from the prior art (M. J. Groves, Parenteral Technology Manual, Interpharm Press Inc., 2. ed. 1988). The number of particles is limited to what the regulations specify and is economically viable, for example 6000 particles ≥ 10 µm and 600 particles ≥ 25 µm per package (package ≤ 100 mL) or 25 particles ≥ 10 µm and 3 particles ≥ 25 µm per millilitre (package > 100 mL), USP 27 <788>.

The solutions according to the invention have good stability on storage which is not limited either by the number of particles in the visible and subvisual range, or by significant active substance breakdown reactions.

The solutions according to the invention have sufficient local compatibility with respect to the pharmacodynamic properties of the active substance, and are not haemolytic.

The infusible or injectable solutions according to the invention are intended to be illustrated by the Examples that follow. The Examples serve purely as an illustration and are not to be construed in a limiting capacity.

Figure 1 shows the dependency of the pH of the ready-to-use solution on the molar ratio of acid/mixture of acids to active substance. The active substance here is 4-[[(7*R*)-8-cyclopentyl-7-ethyl-5,6,7,8-tetrahydro-5-methyl-6-oxo-2-pteridinyl]amino]-3-methoxy-*N*-(1-methyl-4-piperidinyl)-benzamide (Example 46 from Table 1).

For reasons of improved local compatibility for an iv infusion/injection the maximum molar ratio of acid(s) to active substance in the infusible or injectable solution according to the invention is restricted to a maximum of 3:1, in order to ensure a pH above 2.4.

Examples of parenteral solutions for infusion or injection

The abbreviation WFI denotes Water For Injections.

In the following general Example 1 the active substance is one of the dihydropteridinones of general formula (I) as hereinbefore described.

General Example 1

active substance	1-10 mg/ml
organic or inorganic acid, or acid mixture	1.0 – 3.0 mol (calculated on the basis of the active substance)
isotonic agent (e.g. NaCl/mannitol)	e.g. 9 mg/ml or 50 mg/ml
WFI ad	final volume, e.g. 1.0 ml
pH	3.0 – 4.5

In the following Examples the active substance is 4-[[(7*R*)-8-cyclopentyl-7-ethyl-5,6,7,8-tetrahydro-5-methyl-6-oxo-2-pteridinyl]amino]-3-methoxy-*N*-(1-methyl-4-piperidinyl)-benzamide (Example 46 from Table 1).

Example 2

active substance	2 mg/ml
hydrochloric acid 1N	6.8 µl
NaCl	0.009 g/ml
WFI ad	1 ml
pH	4.5
mOsmol / kg	295

Example 3

active substance	10.0000 g
hydrochloric acid 1N	36.6735 g
NaCl	45.0000 g
WFI	4934.8265 g
pH	4.3
mOsmol / kg	300

Example 4

active substance	500 mg
hydrochloric acid 1N	1.6 ml
NaCl	450.0 mg
WFI ad	50 ml
pH	4.0
mOsmol / kg	290

Example 5

active substance	0.5 mg
hydrochloric acid 1N	1,705 µl
NaCl	9 mg
WFI ad	1 ml
pH	4.8
mOsmol / kg	285

Example 6

active substance	1 mg
hydrochloric acid 1N	3.6125 µl
NaCl	0.009 g
WFI ad	1 ml
pH	4.8
mOsmol / kg	295

Example 7

active substance	2 mg
phosphoric acid (85%)	0,440 µl
NaCl	9 mg
WFI ad	1 ml
pH	4.0
mOsmol / kg	298

Example 8

active substance	100 mg
acetic acid	16,4 µl
dextrose	2.5 g
WFI ad	50 ml
pH	4.4
mOsmol / kg	305

Example 9

active substance	10 mg
tartaric acid	4.32 mg
mannitol	0,25 g
WFI ad	5 ml
pH	4.0
mOsmol / kg	298

Example 10

active substance	2 mg
citric acid	1,104 mg
NaCl	9 mg
WFI ad	1 ml
pH	4.5
mOsmol / kg	295

Example 11

active substance	2 mg
hydrochloric acid 1N	6.8 µl
acetic acid	0.501 mg
Na-acetate	0.2260 mg
NaCl	9 mg
WFI ad	1 ml
pH	4.0
mOsmol / kg	305

In the following Examples the active substance is N-[trans-4-[4-(cyclopropylmethyl)-1-piperazinyl]cyclohexyl]-4-[[(7R)-7-ethyl-5,6,7,8-tetrahydro-5-methyl-8-(1-methylethyl)-6-oxo-2-pteridinyl]amino]-3-methoxy-benzamide (Example 110 from Table 1).

Example 12

active substance * 3 HBr	2 mg/ml* (calculated as base)
NaCl	9 mg/ml
WFI ad	1.0 ml
pH	3.5

Example 13

active substance *3 HCl	2 mg/ml* (calculated as base)
NaCl	9 mg/ml
WFI ad	1.0 ml
pH	3.4

Example 14

active substance	500 mg
phosphoric acid 85%	157.5 mg
NaCl	2.250 g
WFI ad	250.0 ml
pH	3.2

Example 15

active substance	10 mg
tartaric acid	4.85 mg
NaCl	45 mg
WFI ad	5 ml
pH	3.5

Example 16

active substance	2 mg/ml
acetic acid	0.39 mg
NaCl	0.009 g
WFI ad	1 ml
pH	3.4

Example 17

active substance	2 mg
citric acid	1.24 mg
mannitol	50 mg
WFI ad	1 ml
pH	3.5

The compounds according to the invention may be prepared by the methods of synthesis A described hereinafter, whereby the substituents of general formulae (A1) to (A9) have

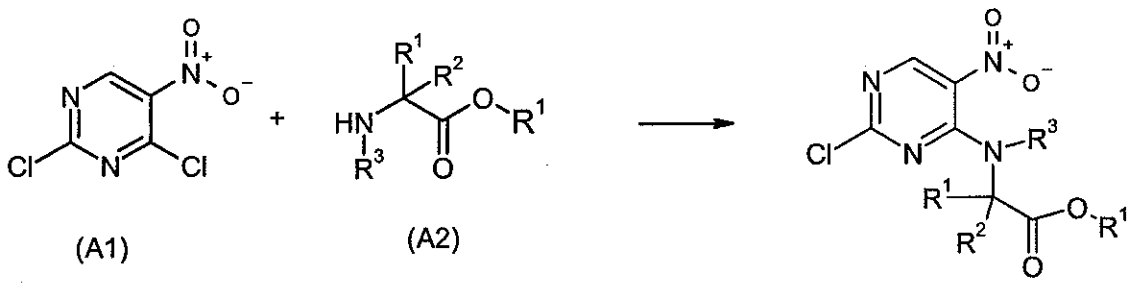
the above meanings. This method is to be understood as an illustration of the invention without limiting it to the content thereof.

Process A

Step 1A

A compound of formula (A1) is reacted with a compound of formula (A2) to yield a compound of formula (A3) (Diagram 1A). This reaction may be carried out according to WO 00/43369 or WO 00/43372. Compound (A1) is commercially available, for example from City Chemical LLC, 139 Allings Crossing Road, West Haven, CT, 06516, USA. Compound (A2) may be prepared by methods known from the literature, e.g. from (a) F. Effenberger, U. Burkhart, J. Willfahrt *Liebigs Ann. Chem.* **1986**, 314-333, (b) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373-6374, (c) R. K. Olsen, *J. Org. Chem.* **1970**, *35*, 1912-1915, (d) F.E. Dutton, B.H. Byung *Tetrahedron Lett.* **1998**, *30*, 5313-5316 or (e) J. M. Ranajuhi, M. M. Joullie *Synth. Commun.* **1996**, *26*, 1379-1384.

Diagram 1A



(A1) (A2) (A3)

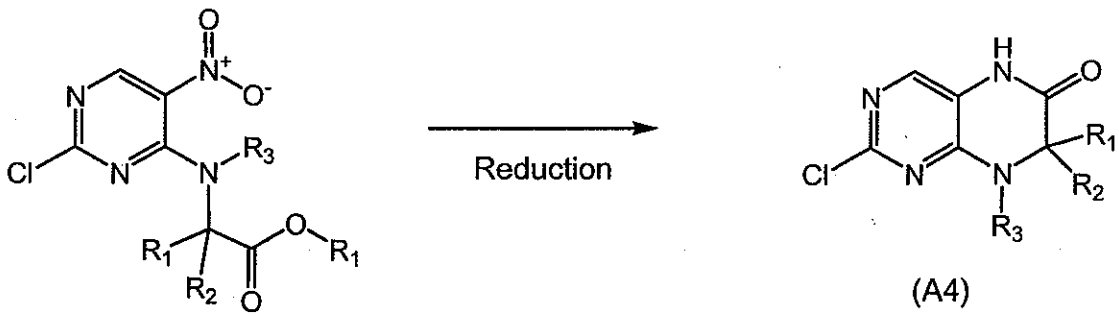
In Step 1A , 1 equivalent of the compound (A1) and 1 to 1.5 equivalents, preferably 1.1 equivalents of a base, preferably potassium carbonate, potassium hydrogen carbonate, sodium carbonate, sodium hydrogen carbonate or calcium carbonate, particularly preferably potassium carbonate, are stirred in a diluent, optionally mixed with water, for example acetone, tetrahydrofuran, diethyl ether, cyclohexane, petroleum ether or dioxane, preferably cyclohexane or diethyl ether.

At a temperature of 0 to 15 °C, preferably 5 to 10 °C, 1 equivalent of an amino acid of formula (A2) dissolved in an organic solvent, for example acetone, tetrahydrofuran, diethyl ether, cyclohexane or dioxane, is added dropwise. The reaction mixture is heated to a temperature of 18°C to 30 °C, preferably about 22°C, with stirring and then stirred for a further 10 to 24 hours, preferably about 12 hours. Then the diluent is distilled off, the residue is combined with water and the mixture is extracted two to three times with an organic solvent, for example, diethyl ether or ethyl acetate, preferably ethyl acetate. The combined organic extracts are dried and the solvent is distilled off. The residue (compound A3) may be used in Step 2 without any prior purification.

Step 2A

The compound (A3) obtained in Step 1A is reduced at the nitro group and cyclised to form the compound of formula (A4) (Diagram 2A).

Diagram 2A



(A3) (A4)

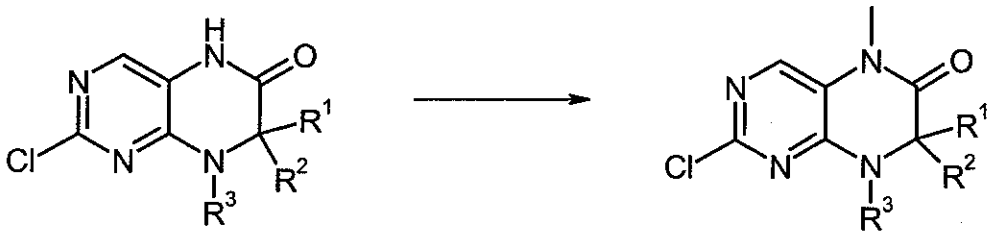
In Step 2A 1 equivalent of the nitro compound (A3) is dissolved in an acid, preferably glacial acetic acid, formic acid or aqueous hydrochloric acid, preferably glacial acetic acid, and heated to 50 to 70 °C, preferably about 60 °C. Then a reducing agent, for example zinc, tin or iron, preferably iron powder, is added until the exothermic reaction has ended and the mixture is stirred for 0.2 to 2 hours, preferably 0.5 hours, at 100 to 125 °C, preferably at about 117 °C. After cooling to ambient temperature the iron salt is filtered off and the solvent is distilled off. The residue is taken up in a solvent or mixture of solvents, for example ethyl acetate or dichloromethane/methanol 9/1 and semisaturated NaCl solution and filtered through kieselguhr for example. The organic

phase is dried and evaporated down. The residue (compound (A4)) may be purified by chromatography or by crystallisation or used as the crude product in Step 3A of the synthesis.

Step 3A

The compound (A4) obtained in Step 2A may be reacted by electrophilic substitution according to Diagram 3A to form the compound of formula (A5).

Diagram 3A



(A4) (A5)

In Step 3A 1 equivalent of the amide of formula (A4) is dissolved in an organic solvent, for example dimethylformamide or dimethylacetamide, preferably dimethylacetamide, and cooled to about -5 to 5 °C, preferably 0°C.

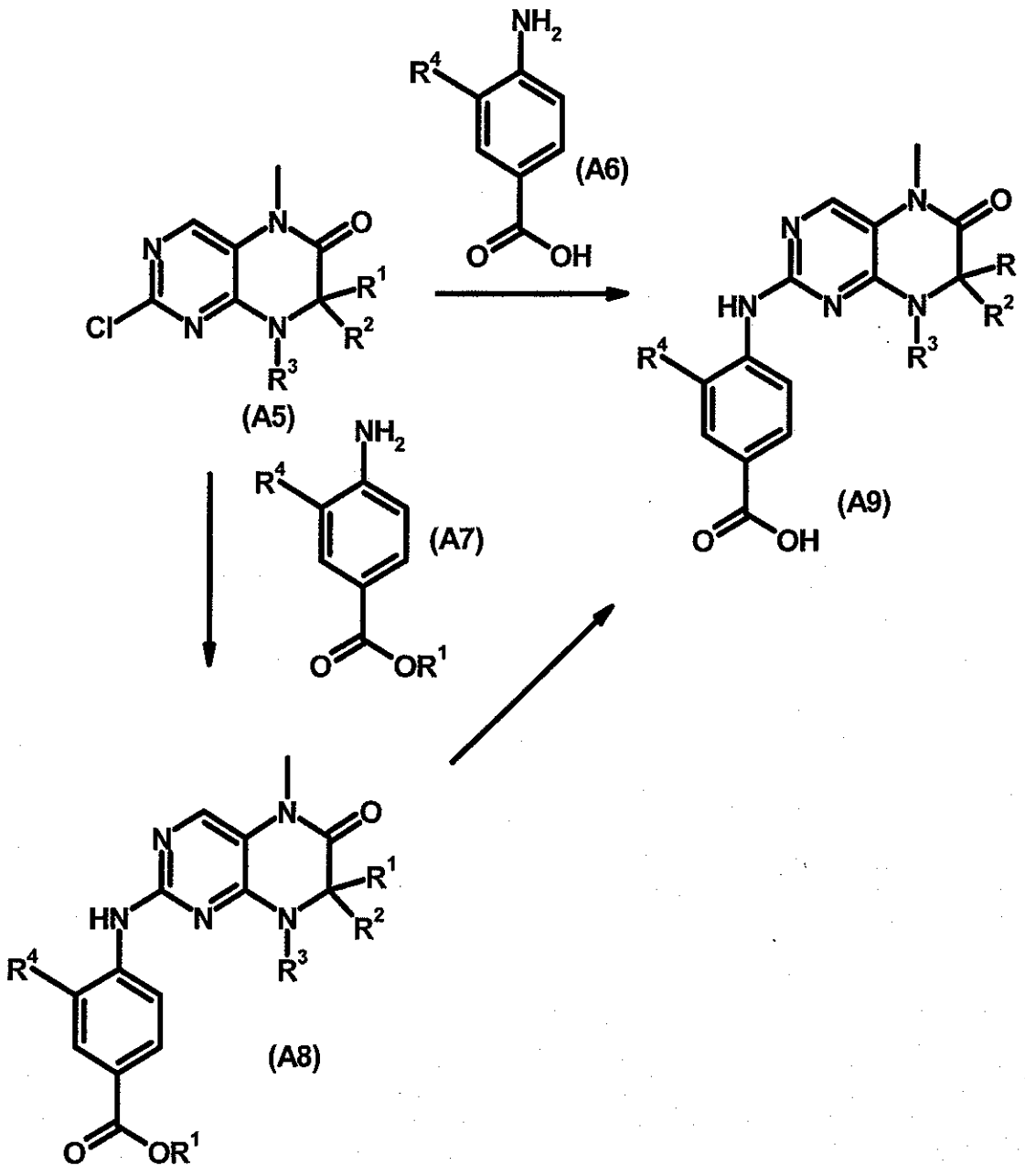
Then 0.9 to 1.3 equivalents of sodium hydride and 0.9 to 1.3 equivalents of a methylating reagent, for example methyliodide, are added. The reaction mixture is stirred for 0.1 – 3 hours, preferably about 1 hour, at about 0 to 10 °C, preferably at about 5 °C, and may optionally be left to stand for a further 12 hours at this temperature range. The reaction mixture is poured onto ice water and the precipitate is isolated. The residue (compound (A5)) may be purified by chromatography, preferably on silica gel, or by crystallisation or used as the crude product in Step 4A of the synthesis.

Step 4A

The amination of the compound (A5) obtained in Step 3A to form the compound of formula (A9) (Diagram 4A) may be carried out according to the methods of variants 4.1 A known from the literature from e.g. (a) M.P.V. Boarland, J.F.W. McOmie *J. Chem. Soc.* 1951, 1218-1221 or (b) F. H. S. Curd, F. C. Rose *J. Chem. Soc.* 1946, 343-348, and

4.2 A from e.g. (a) Banks *J. Am. Chem. Soc.* 1944, *66*, 1131, (b) Ghosh and Dolly *J. Indian Chem. Soc.* 1981, *58*, 512-513 or (c) N. P. Reddy and M. Tanaka *Tetrahedron Lett.* 1997, *38*, 4807-4810.

Diagram 4A



For example in variant 4.1 A, 1 equivalent of the compound (A5) and 1 to 3 equivalents, preferably about 2 equivalents of the compound (A6) may be heated without a solvent or with an organic solvent such as for example sulpholane, dimethylformamide, dimethylacetamide, toluene, N-methylpyrrolidone, dimethylsulphoxide, or dioxane, preferably sulpholane over 0.1 to 4 hours, preferably 1 hour, at 100 to 220°C, preferably at about 160 °C. After cooling the product (A9) is crystallised by the addition of org. solvents or mixtures of solvents, e.g. diethyl ether/methanol, ethyl acetate, methylene chloride, or diethyl ether, preferably diethyl ether/methanol 9/1, or purified by chromatography.

For example in variant 4.2 A, 1 equivalent of the compound (A5) and 1 to 3 equivalents of the compound (A6) are refluxed for 1 to 48 hours, preferably about 5 hours, with acid, for example 1-10 equivalents of 10-38% hydrochloric acid and/or an alcohol such as ethanol, propanol or butanol, preferably ethanol, with stirring.

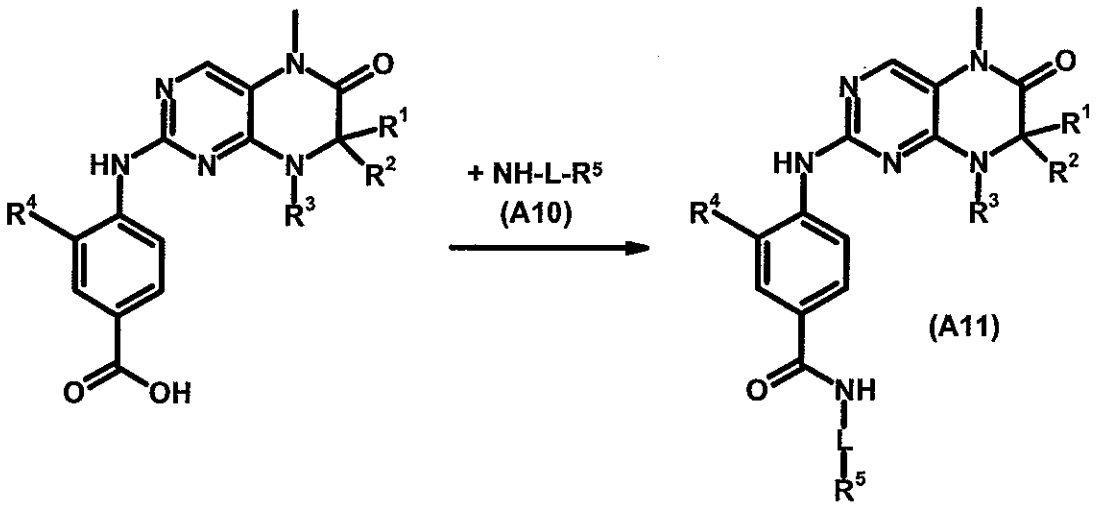
The precipitated product (A9) is filtered off and optionally washed with water, dried and crystallised from a suitable org. solvent.

For example in variant 4.3 A, 1 equivalent of the compound (A5) and 1 to 3 equivalents of the compound (A7) is dissolved in a solvent, for example toluene or dioxane and combined with a phosphine ligand, for example 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl and a palladium catalyst, for example tris(dibenzylideneacetone)-dipalladium(0) and a base, for example caesium carbonate, and refluxed for 1-24 h, preferably 17 h. The reaction mixture is purified on silica gel for example and the product (A8) is isolated from the solution or obtained by suitable crystallisation.

The product (A8) is dissolved in a suitable solvent, for example dioxane, and mixed with acid, for example semiconcentrated hydrochloric acid, for example in a solvent to an acid ratio of 3:1. Then the mixture is refluxed for 1 - 48 h, for example 12 h, and the precipitate formed is isolated. If desired the product (A9) is purified by crystallisation.

Step 5A

Diagram 5A



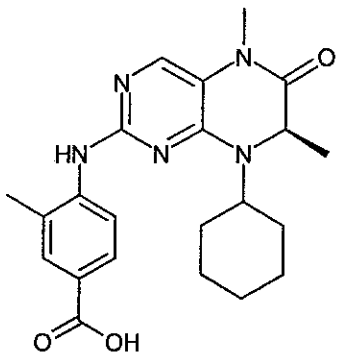
For example, 1 equivalent of the compound (A9) is dissolved with 1 equivalent of an activating reagent, for example O-benzotriazolyl-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU) and a base, for example about 1.5 equivalents, diisopropylethylamine (DIPEA) in an organic diluent, for example dichloromethane, tetrahydrofuran, dimethylformamide, N-methylpyrrolidone, dimethylacetamide, preferably dichloromethane or dimethylformamide. After the addition of 1 equivalent of the amine (A10) the reaction mixture is stirred for 0.1 to 24 hours, preferably about 2 hours at 20°C to 100°C. The product of formula (A11) is obtained for example by crystallisation or chromatographic purification.

The compounds of general formula (I) may be synthesised analogously to the following synthesis examples. These Examples should, however, only be regarded as an illustration of the procedures according to the invention without restricting the invention to their subject matter.

The preparation of some intermediate compounds used to synthesise the Examples will also be described hereinafter.

Preparation of the acids

In order to synthesise the compounds Ex. 94 and Ex. 95 first of all an intermediate compound Z1



Z1

is prepared as described hereinafter.

50.0 g (0.48 mol) D-alanine methylester x HCl and 49.1 g (0.50 mol) cyclohexanone are placed in 300 mL dichloromethane and then combined with 41.0 g (0.50 mol) sodium acetate and 159.0 g (0.75 mol) sodium triacetoxyborohydride. The mixture is stirred overnight and then 300 mL of 10% sodium hydrogen carbonate solution are added. The aqueous phase is extracted with dichloromethane. The combined organic phases are washed with 10% sodium hydrogen carbonate solution, dried over Na_2SO_4 and evaporated down.

Yield: 72.5 g of a compound Z1a (clear liquid)

72.5 g of the compound Z1a are placed in 500 mL water and 76.6 g (0.39 mol) 2,4-dichloro-5-nitropyrimidine in 500 mL diethyl ether are added. At a temperature of –5°C 100 mL 10% potassium hydrogen carbonate solution are added dropwise. The mixture is stirred for 3 h at –5°C and for a further 12 h at ambient temperature. The organic phase is separated off and dried over Na_2SO_4. During evaporation the product crystallises out.

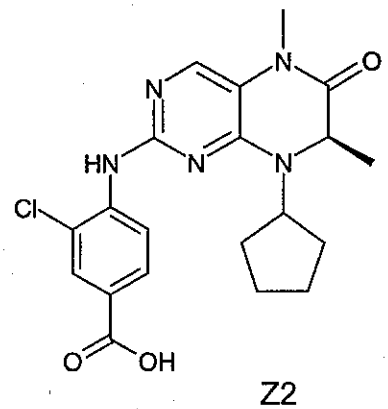
Yield: 48.0 g of a compound Z1b (yellow crystals)

48.0 g of the compound Z1b are dissolved in 350 mL glacial acetic acid and heated to 60°C. 47.5 g iron powder are added batchwise, while the temperature rises to 105°C. The reaction mixture is stirred for three hours at 80°C, then filtered hot through cellulose and evaporated down. The residue is stirred in water and ethyl acetate, suction filtered and the light grey precipitate is washed with ethyl acetate. The filtrate is washed with dilute ammonia and water, the organic phase is dried over Na_2SO_4, filtered through activated charcoal and evaporated down. More light grey solid is obtained.
Yield: 29.5 g of a compound Z1c (light grey crystals)

32.1 g of the compound Z1c are placed in 300 mL dimethylacetamide and combined with 13 mL (0.2 mol) methyliodide. At –5°C 6.4 g (0.16 mol) sodium hydride are added batchwise as a 60% dispersion in mineral oil. After 2 h the reaction mixture is poured onto 800 mL ice water. The precipitate formed is suction filtered and washed with petroleum ether.
Yield: 33.0 g of a compound Z1d (beige crystals)

4.0 g of the compound Z1d and 2.3 g (15 mmol) of 4-amino-3-methylbenzoic acid are suspended in 50 mL ethanol and 120 mL water, combined with 2 mL conc. hydrochloric acid and refluxed for 48 h. The precipitate formed on cooling is suction filtered and washed with water, ethanol and diethyl ether.
Yield: 2.9 g of a compound Z1 (colourless crystals)

To synthesise the compounds Ex. 188 and Ex. 203 first of all an intermediate compound Z2



Z2

is prepared as described below.

A solution of 128.2 g (0.83 mol) D-alanine ethylester x HCl and 71.5 g (0.85 mol) cyclopentanone in 1500 mL dichloromethane is combined with 70.1 (0.85 mol) sodium acetate and 265.6 g (1.25 mol) sodium triacetoxyborohydride. The reaction mixture is stirred for 12 h and then poured into 1.5 L of a 10% sodium hydrogen carbonate solution. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over Na_2SO_4 and evaporated down.
Yield: 143.4 g of a compound Z2a (colourless oil)

66.0 g of the compound Z2a are placed in 500 mL water and combined with 85.0 g (0.44 mol) 2,4-dichloro-5-nitropyrimidine in 500 mL diethyl ether. At –5°C 100 mL 10% potassium hydrogen carbonate solution are added dropwise and the reaction mixture is stirred for 48 h at ambient temperature. The aqueous phase is extracted with diethyl ether, the combined organic phases are dried over Na_2SO_4 and evaporated down. The dark red solid is extracted with petroleum ether and suction filtered.
Yield: 88.0 g of a compound Z2b (yellow crystals)

88.0 g of the compound Z2b are dissolved in 1000 mL glacial acetic acid and at 60°C 85 g iron powder are added batchwise, while the temperature rises to 110°C. The mixture is stirred for 1 h at 60°C, then suction filtered hot through cellulose and evaporated down. The brown solid is stirred with 700 mL water and suction filtered.
Yield: 53.3 g of a compound Z2c (light brown crystals)

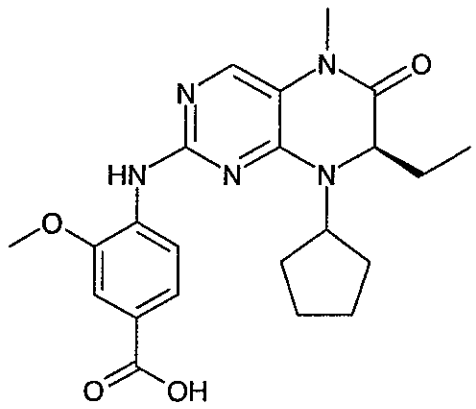
53.3 g of the compound Z2c are dissolved in 300 mL dimethylacetamide and combined with 13 mL (0.21 mol) methyl iodide. At –5°C 5.0 g (0.21 mol) sodium hydride are added batchwise as 60% dispersion in mineral oil. After 12 h the reaction mixture is poured onto 1000 mL ice water and the precipitate formed is suction filtered.
Yield: 40.0 g of a compound Z2d (colourless crystals)

4.0 g of the compound Z2d and 2.8 g (16 mmol) of 4-amino-3-chlorobenzoic acid are suspended in 25 mL ethanol and 60 mL water, combined with 3 mL conc. hydrochloric

acid and refluxed for 43 h. The precipitate formed on cooling is suction filtered and washed with water, ethanol and diethyl ether.

Yield: 0.9 g of a compound Z2 (colourless crystals)

In order to synthesise the compounds Ex. 19, 21, 22, 23, 45, 55, 58, 116, 128, 131, 133, 134, 136, 138, 177, 217, 231, 239, 46, 184, 166 and 187 first of all an intermediate compound Z3



Z3

is prepared as described below.

54.0 g (0.52 mol) D-2-aminobutyric acid are suspended in 540 mL methanol and 132 g (1.1 mol) thionyl chloride are slowly added while cooling with ice. The mixture is refluxed for 1.5 h and then evaporated down. The oil remaining is combined with 540 mL tert-butylmethylether and the colourless crystals obtained are suction filtered.
Yield: 78.8 g of a compound Z3a (colourless crystals)

74.2 g of the compound Z3a and 43.5 mL (0.49 mol) cyclopentanone are dissolved in 800 mL dichloromethane. After the addition of 40.0 g (0.49 mol) sodium acetate and 150.0 g (0.71 mol) sodium triacetoxyborohydride at 0°C the mixture is stirred for 12 h at ambient temperature and then 500 mL 20% sodium hydrogen carbonate solution are added. The aqueous phase is extracted with dichloromethane. The combined organic phases are washed with water, dried over $MgSO_4$ and evaporated down.

Yield: 85.8 g of a compound Z3b (light yellow oil)

40.0 g of the compound Z3b and 30.0 g (0.22 mol) potassium carbonate are suspended in 600 mL acetone and while cooling with ice combined with 45.0 g (0.23 mol) 2,4-dichloro-5-nitropyrimidine in 200 mL acetone. After 12 h a further 5.0 g of 2,4-dichloro-5-nitropyrimidine are added and the mixture is stirred for 3 h. The reaction mixture is evaporated down, taken up in 800 mL ethyl acetate and 600 mL water and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with water, dried over $MgSO_4$ and evaporated down.

Yield: 75.0 g of a compound Z3c (brown oil)

100 g of the compound Z3c are dissolved in 650 mL glacial acetic acid and at 70°C 20 g iron powder are added batchwise. The mixture is stirred for 1 h at 70°C, then for 1.5 h at 100°C and then filtered hot through kieselguhr. The reaction mixture is evaporated down, taken up in methanol/dichloromethane, applied to silica gel and purified by Soxhlet extraction with ethyl acetate. The solvent is removed and the residue is stirred with methanol.

Yield: 30.0 g of a compound Z3d (light brown crystals)

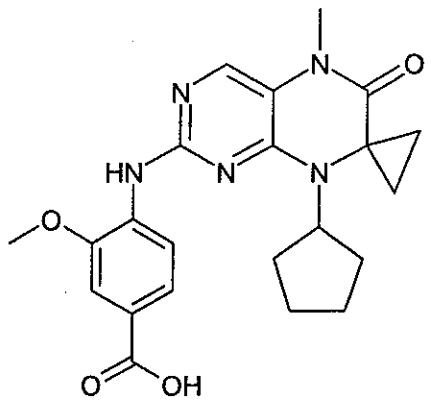
25.0 g of the compound Z3d and 6.5 mL (0.1 mol) methyl iodide are placed in 250 mL dimethylacetamide and at –10°C 3.8 g (0.95 mol) sodium hydride are added as a 60% dispersion in mineral oil. The mixture is stirred for 20 min. at 0°C, then 30 min. at ambient temperature and finally ice is added. The reaction mixture is evaporated down and combined with 300 mL water. The precipitate formed is suction filtered and washed with petroleum ether.

Yield: 23.0 g of a compound Z3e (colourless solid)

6.0 g of the compound Z3e and 5.1 g (31 mmol) of 4-amino-3-methoxybenzoic acid are suspended in 90 mL ethanol and 350 mL water, combined with 3.5 mL conc. hydrochloric acid and refluxed for 48 h. The reaction mixture is evaporated down, the residue is stirred with methanol/diethyl ether and the precipitate formed is suction filtered.

Yield: 6.3 g of a compound Z3 (light beige crystals)

In order to synthesise the compound Ex. 81, 82, 93, 137 first of all an intermediate compound Z4



Z4

is prepared as described below.

25.0 g (0.19 mol) ethyl 1-aminocyclopropane-1-carboxylate x HCl and 16.8 g (0.20 mol) cyclopentanone are dissolved in 300 mL dichloromethane and combined with 16.4 g (0.20 mol) sodium acetate and 61.7 g (0.29 mol) sodium triacetoxyborohydride. The mixture is stirred overnight and the reaction mixture is then poured onto 400 mL 10% sodium hydrogen carbonate solution. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried over Na_2SO_4 and evaporated down.

Yield: 34.5 g of a compound Z4a (colourless oil)

42.5 g (0.22 mol) 2,4-dichloro-5-nitropyrimidine in 350 mL diethyl ether are added to a mixture of 34.5 g of the compound Z4a in 350 mL water. At –5°C 80 mL 10% potassium hydrogen carbonate solution are added and the mixture is stirred overnight at ambient temperature. The aqueous phase is extracted with diethyl ether. The combined organic phases are dried over Na_2SO_4 and evaporated down.

Yield: 53.8 g of a compound Z4b (brown oil)

20.1 g of the compound Z4b are dissolved in 200 mL glacial acetic acid and at 60°C 19.1 g of iron powder are added batchwise, while the temperature rises to 100°C. The mixture is stirred for 3 h at 60°C, then suction filtered through cellulose and evaporated down. The residue is extracted from water and ethyl acetate and the yellow precipitate is suction filtered. The filtrate is washed with dilute ammonia and water, the organic phase is dried over Na_2SO_4 and evaporated down. After the addition of diethyl ether the product crystallises out.

Yield: 4.0 g of a compound Z4c (yellow crystals)

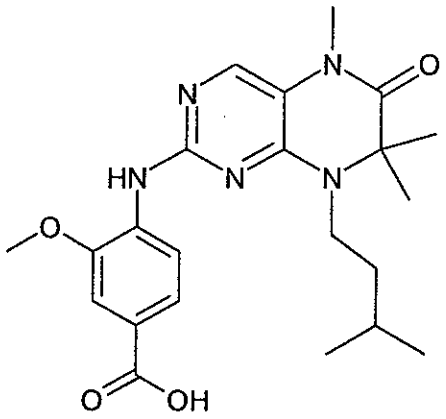
7.8 g of the compound Z4c and 2.6 mL (0.04 mol) methyl iodide are dissolved in 100 mL dimethylacetamide and at –5°C 1.5 g (0.04 mol) sodium hydride as a 60% dispersion in mineral oil are added batchwise. After 2 h the reaction mixture is poured onto ice water and the precipitate formed is suction filtered.

Yield: 7.5 g of a compound Z4d (light brown crystals)

3.0 g of the compound Z4d and 1.9 g (11 mmol) of 4-amino-3-methoxybenzoic acid are suspended in 40 mL ethanol and 80 mL water, combined with 2 mL conc. hydrochloric acid and refluxed for 20 h. A further 0.5 g 4-amino-3-methoxybenzoic acid is added and the mixture is refluxed for 48 h. The precipitate formed on cooling is suction filtered and washed with water, ethanol and diethyl ether.

Yield: 2.1 g of a compound Z4 (colourless crystals)

In order to synthesise the compounds Ex. 162, 43, 53, 161, 202, 211, 215 and 212 first of all an intermediate compound Z5



Z5

is prepared as described below.

A mixture of 73.4 mL (0.5 mol) ethyl 2-bromoisobutyrate, 87.1 mL (0.75 mol) 3-methyl-1-butylamine, 82.5 g (0.6 mol) sodium iodide and 76.0 g (0.6 mol) potassium carbonate in 1000 mL ethyl acetate is refluxed for 3 days. Any salts present are filtered off and the filtrate is evaporated down.

Yield: 97.0 g of a compound Z5a (red oil)

49.0 g (0.25 mol) 2,4-dichloro-5-nitropyrimidine and 38.3 g (0.28 mol) potassium carbonate are suspended in 500 mL acetone and at 0°C combined with 93.0 g of the compound Z5a in 375 mL acetone. The reaction mixture is stirred overnight at ambient temperature, filtered and evaporated down. The residue dissolved in ethyl acetate is washed with water and the organic phase is dried over $MgSO_4$ and evaporated down.

Yield: 102.7 g of a compound Z5b (brown oil)

22.7 g of the compound Z5b are dissolved in 350 mL glacial acetic acid and at 60°C 17.4 g of iron powder are added batchwise. After the addition has ended the mixture is refluxed for 0.5 h, filtered hot and evaporated down. The residue is taken up in 200 mL dichloromethane/methanol (9:1) and washed with sodium chloride solution. The organic phase is suction filtered through kieselguhr, dried over $MgSO_4$, evaporated down and purified by column chromatography (eluant: ethyl acetate/cyclohexane 1:1).

Yield: 1.9 g of a compound Z5c (colourless crystals)

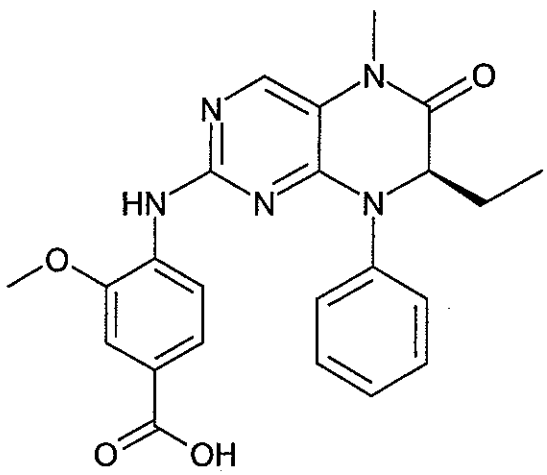
1.9 g of the compound Z5c are dissolved in 32 mL dimethylacetamide and while cooling with ice combined with 0.3 g (7 mmol) of sodium hydride as a 60% dispersion in mineral oil. After 10 min. 0.5 mL (7 mmol) of methyl iodide are added and the mixture is stirred for 3 h at ambient temperature. The reaction mixture is evaporated down and combined with water. The precipitate formed is suction filtered and washed with petroleum ether.

Yield: 1.6 g of a compound Z5d (colourless crystals)

14.0 g of the compound Z5d and 10.0 g (0.06 mol) 4-amino-3-methoxybenzoic acid are suspended in 200 mL dioxane and 80 mL water, combined with 10 mL conc. hydrochloric acid and refluxed for 40 h. The precipitate formed on cooling is suction filtered and washed with water, dioxane and diethyl ether.

Yield: 13.9 g of a compound Z5 (colourless crystals)

In order to synthesise the compounds Ex. 88, 194, 229 and 89 first of all an intermediate compound Z6



Z6

is prepared as described below.

6.0 g (0.06 mol) L-2-aminobutyric acid is placed in 80 mL of 0.5 M sulphuric acid and at 0°C combined with 5.5 g (0.08 mol) sodium nitrite in 15 mL water. The reaction mixture is stirred for 22 h at 0°C, combined with ammonium sulphate and filtered. The filtrate is extracted with diethyl ether and the combined organic phase is dried over $MgSO_4$ and evaporated down.

Yield: 6.0 g of a compound Z6a (yellow oil)

200 mL methanol are combined successively with 65.0 mL (0.89 mol) thionyl chloride and 76.0 g of the compound Z6a in 50 mL methanol while cooling with ice. The mixture is stirred for 1 h at 0°C and 2 h at ambient temperature and then the methanol and remaining thionyl chloride are eliminated in vacuo at 0°C.

Yield: 40.0 g of a compound Z6b (yellow oil)

30.0 mL (0.17 mol) trifluoromethanesulphonic acid anhydride are placed in 150 mL dichloromethane and while cooling with ice combined with a solution of 20.0 g of the compound Z6b and 14.0 mL (0.17 mol) pyridine in 50 mL dichloromethane within one hour. The mixture is stirred for 2 h at ambient temperature, any salts formed are suction filtered and then washed with 100 mL water. The organic phase is dried over $MgSO_4$ and evaporated down.

Yield: 42.0 g of a compound Z6c (bright yellow oil)

42.0 g of the compound Z6c in 200 mL dichloromethane is added dropwise to a solution of 15.5 mL (0.17 mol) aniline and 24.0 mL (0.17 mol) triethylamine in 400 mL dichloromethane within one hour while cooling with ice. The mixture is stirred for 1 h at ambient temperature and for a further 2 h at 35°C. The reaction mixture is washed with water, dried over $MgSO_4$ and evaporated down. The residue remaining is purified by distillation (95-100°C, $1*10^{-3}$ mbar).

Yield: 14.0 of a compound Z6d (colourless oil)

14.0 g of the compound Z6d and 16.0 g (0.1 mol) potassium carbonate are suspended in 100 mL acetone and at 10°C combined with 16.0 g (0.08 mol) 2,4-dichloro-5-nitropyrimidine. The mixture is stirred for 4 h at 40°C, any salts formed are suction

filtered and the filtrate is evaporated down. The residue is taken up in 300 mL ethyl acetate and washed with water. The organic phase is dried over $MgSO_4$ and evaporated down.

Yield: 31.0 g of a compound Z6e (brown oil)

31.0 g of the compound Z6e are dissolved in 200 mL glacial acetic acid and at 60°C 10 g of iron powder are added batchwise, while the temperature rises to 85°C. The mixture is stirred for a further hour at 60°C, filtered through kieselguhr and evaporated down. The residue is extracted with methanol.

Yield: 4.5 g of a compound Z6f (brown crystals)

0.6 g (16 mmol) of sodium hydride as a 60% dispersion in mineral oil are added batchwise at –20°C to a mixture of 4.5 g of the compound Z6f and 1.0 mL (16 mmol) methyl iodide in 100 mL dimethylacetamide. After 1 h the reaction mixture is combined with 50 mL water and evaporated down. The residue is stirred with 200 mL water, the precipitate is suction filtered and washed with petroleum ether.

Yield: 4.5 g of a compound Z6g (colourless crystals)

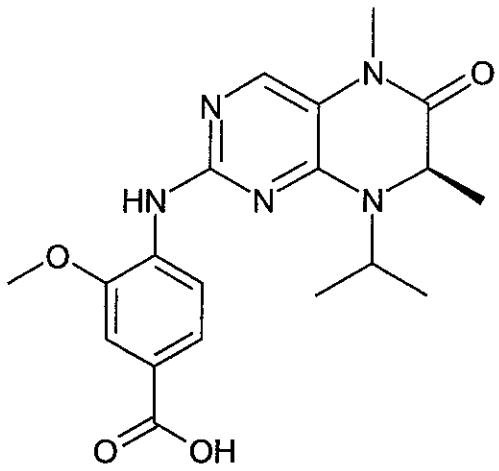
A suspension of 1.5 g of the compound Z6g and 1.4 g (8 mmol) of methyl 4-amino-3-methoxybenzoate in 30 mL toluene is combined with 0.4 g (0.6 mmol) of 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl, 0.23 g (0.3 mmol) of tris(dibenzylideneacetone)-dipalladium(0) and 7.0 g (21 mmol) of caesium carbonate and refluxed for 17 h. The reaction mixture is applied to silica gel and purified by column chromatography (eluant: dichloromethane/methanol 9:1).

Yield: 1.7 g of a compound Z6h (yellow crystals)

1.7 g of the compound Z6h are dissolved in 50 mL dioxane, combined with 15 mL semiconc. hydrochloric acid and refluxed for 12 h. After cooling the precipitate formed is suction filtered.

Yield: 1.1 g of a compound Z6 (colourless solid)

In order to synthesise the compound Ex. 26, 20, 32, 56, 101, 112, 209 first of all an intermediate compound Z7



Z7

is prepared as described below.

50.0 g (0.36 mol) D-alaninemethylester x HCl is suspended in 500 mL dichloromethane and 35 mL acetone and combined with 30.0 g (0.37 mol) sodium acetate and 80.0 g (0.38 mol) sodium triacetoxyborohydride. The mixture is stirred for 12 h and then poured onto 400 mL 10% sodium hydrogen carbonate solution. The organic phase is dried over Na_2SO_4 and evaporated down.
Yield: 51.0 g of a compound Z7a (yellow oil)

A suspension of 51.0 g of the compound Z7a in 450 mL water is combined with 80.0 g (0.41 mol) 2,4-dichloro-5-nitropyridine in 450 mL diethyl ether. At –5°C 100 mL 10% potassium hydrogen carbonate solution are added dropwise. The reaction mixture is stirred for 3 h, the organic phase is dried over Na_2SO_4 and evaporated down.
Yield: 74 g of a compound Z7b (yellow oil)

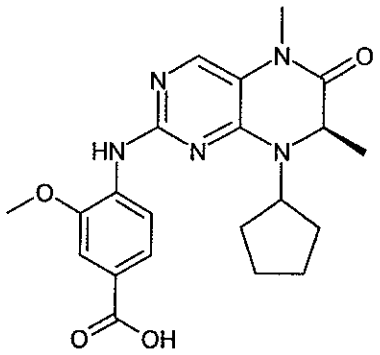
18.6 g of the compound Z7b are dissolved in 200 mL glacial acetic acid and at 60°C 20.0 g of iron powder are added batchwise. The mixture is stirred for 2 h at 60°C and

then suction filtered through cellulose. The residue is dissolved in ethyl acetate and washed with water and conc. ammonia. The organic phase is dried over Na_2SO_4 and evaporated down. The residue is crystallised from diethyl ether.
Yield: 9.8 g of a compound Z7c (colourless crystals)

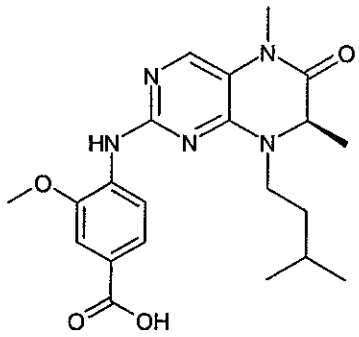
17.0 g of the compound Z7c and 7 mL (0.1 mol) methyl iodide are dissolved in 200 mL dimethylacetamide and at –5°C combined with 4.0 g (0.1 mol) sodium hydride as a 60% dispersion in mineral oil. The reaction mixture is stirred for 30 min. and then poured onto 300 mL ice water. The precipitate formed is suction filtered and extracted with petroleum ether.
Yield: 14.8 g of a compound Z7d (beige crystals)

0.9 g of the compound Z7d and 1.5 g (9 mmol) of 4-amino-3-methoxybenzoic acid are heated to 210°C for 30 min. After cooling the residue is extracted with ethyl acetate and the precipitate obtained is suction filtered.
Yield: 1.2 g of a compound Z7 (grey crystals)

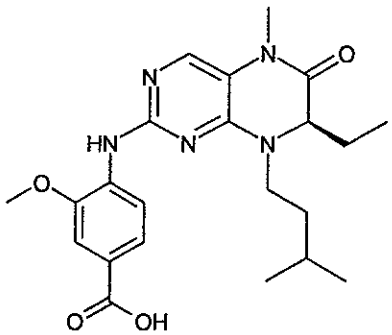
The following acids are prepared, for example, analogously to the syntheses described.



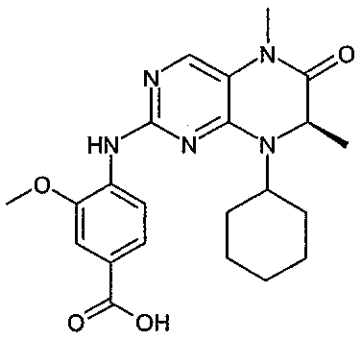
Z8



Z9



Z10

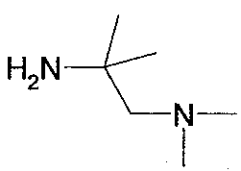


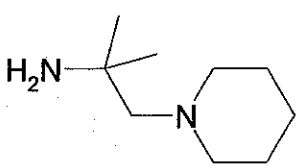
Z11

Synthesis of the amine components L-R5

The following amines are obtained as follows.

1,1-dimethyl-2-dimethylamino-1-yl-ethylamine and 1,1-dimethyl-2-piperidin-1-yl-ethylamine

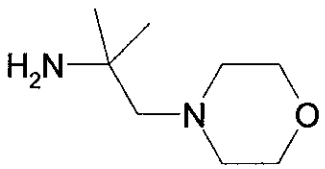




The compounds are prepared according to the following references: (a) S. Schuetz et al. *Arzneimittel-Forschung* **1971**, *21*, 739-763, (b) V. M. Belikov et al. *Tetrahedron* **1970**, *26*, 1199-1216 and (c) E.B. Butler and McMillan *J. Amer. Chem. Soc.* **1950**, *72*, 2978.

Other amines are prepared in a modified manner from that described in the above literature, as follows.

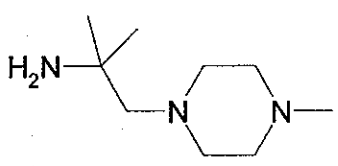
1,1-dimethyl-2-morpholin-1-yl-ethylamine



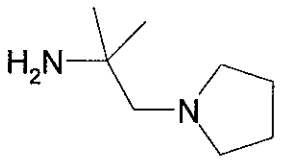
8.7 mL morpholine and 9.3 mL 2-nitropropane are taken, and cooled with ice, 7.5 mL formaldehyde (37%) and 4 mL of a 0.5 mol/L NaOH solution are slowly added dropwise (<10°C). Then the mixture is stirred for 1h at 25°C and 1h at 50°C. The solution is treated with water and ether and the aqueous phase is extracted 3x with ether. The combined org. phase is dried over $NaSO_4$ and combined with HCl in dioxane (4 mol/l), the precipitate formed is suction filtered.
Yield: 21.7 g white powder.
5 g of the white powder are dissolved in 80 mL methanol and with the addition of 2 g RaNi treated with hydrogen at 35°C and 50 psi for 40 minutes. This yielded 3.6 g of 1,1-dimethyl-2-morpholin-1-yl-ethylamine.

The following amines are prepared analogously to this method.

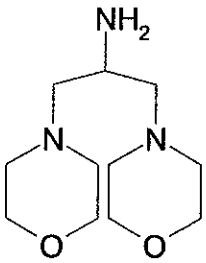
1,1-dimethyl-N-methylpiperazin-1-yl-ethylamine



1,1-dimethyl-2-pyrrolidin-1-yl-ethylamine

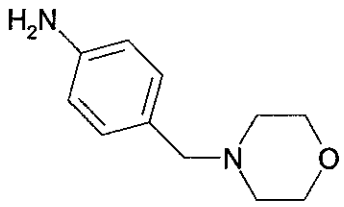


Synthesis of 1,3-dimorpholin-2-amino-propane



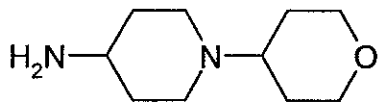
5 g of 1,3-dimorpholin-2-nitropropane made by Aldrich is dissolved in 80 mL methanol and with the addition of 2 g RaNi treated with hydrogen at 30°C and 50 psi for 5.5 h. 4.2 g of 1,3-dimorpholin-2-amino-propane was obtained.

4-aminobenzylmorpholine



The preparation of this amine is described in the following reference:
S. Mitsuru et al. *J. Med. Chem.* 2000, *43*, 2049-2063

4-amino-1-tetrahydro-4H-pyran-4-yl-piperidine



20 g (100 mmol) of 4-tert-butyloxycarbonyl-aminopiperidine are dissolved in 250 mL CH_2Cl_2 and stirred for 12 h at RT with 10 g (100 mmol) of tetrahydro-4H-pyran-4-one and 42 g (200 mmol) of $NaBH(OAc)_3$. Then the mixture is combined with water and potassium carbonate, the org. phase is separated off and dried and the solvent is eliminated in vacuo. The residue is dissolved in 200 mL CH_2Cl_2 and stirred for 12 h at RT with 100 mL trifluoroacetic acid. The solvent is eliminated in vacuo, the residue is taken up in $CHCl_3$ and again concentrated by evaporation, then taken up in acetone and the hydrochloride is precipitated with ethereal HCl. Yield: 14.3 g (56%).

cis- and trans-4-morpholino-cyclohexylamine



dibenzyl-4-morpholino-cyclohexylamine

3.9 g (30 mmol) of) 4-dibenzylcyclohexanone are dissolved in 100 mL CH_2Cl_2 and stirred with 3.9 g (45 mmol) of morpholine and 9.5 g (45 mmol) of $NaBH(OAc)_3$ for 12 h at RT. Then the mixture is combined with water and potassium carbonate, the org. phase is separated off, dried and the solvent is eliminated in vacuo. The residue is purified through a silica gel column (approx 20 mL silica gel; approx 500 mL ethyl acetate 90/methanol 10 + 1% conc. ammonia). The desired fractions are evaporated down in vacuo.

Yield 6.6 g (60%) cis-isomer and 2 g (18%) trans-isomer.

Alternatively the trans-dibenzyl-4-morpholino-cyclohexylamine may be prepared as follows:

33 g (112 mmol) of 4-dibenzylcyclohexanone are dissolved in 300 mL MeOH, combined with 17.4 g (250 mmol) of hydroxylamine hydrochloride and stirred for 4 h at 60°C. The solvent is evaporated down in vacuo, combined with 500 mL water and 50 g potassium carbonate and extracted twice with 300 mL dichloromethane. The org. phase is dried, evaporated down in vacuo, the residue is crystallised from petroleum ether, dissolved in 1.5 L EtOH and heated to 70°C. 166 g sodium are added batchwise and the mixture is refluxed until the sodium is dissolved. The solvent is eliminated in vacuo, the residue is combined with 100 mL water and extracted twice with 400 mL ether. The org. phase is washed with water, dried, evaporated down in vacuo and the trans-isomer is isolated using a column (approx. 1.5 L silica gel; approx. 2 L ethyl acetate 80/methanol 20 + 2 % conc. ammonia).
Yield: 12.6 g (41.2%).

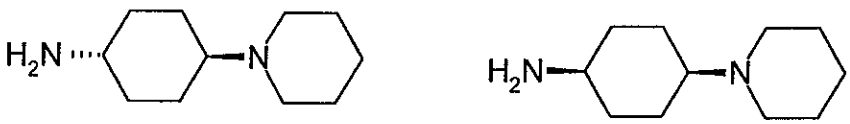
6.8 g (23 mmol) of trans-1-amino-4-dibenzylaminocyclohexane is dissolved in 90 mL DMF and stirred with 5 mL (42 mmol) of 2,2'-dichloroethylether and 5 g potassium carbonate for 8 h at 100°C. After cooling the mixture is combined with 30 mL water, the crystals precipitated are suction filtered and purified through a short column (approx. 20 mL silica gel, approx. 100 mL ethyl acetate). The residue is crystallised from methanol and conc. HCl as the dihydrochloride. Yield: 7.3 g (72.4%).

trans-4-morpholino-cyclohexylamine

7.2 g (16.4 mmol) of trans-dibenzyl-4-morpholino-cyclohexylamine are dissolved in 100 mL MeOH and hydrogenated on 1.4 g Pd/C (10%) at 30-50°C. The solvent is eliminated in vacuo and the residue is crystallised from ethanol and conc. HCl.
Yield: 3.9 g (93%).

The cis-isomer may be prepared analogously.

cis- and trans-4-piperidino-cyclohexylamine



trans-dibenzyl-4-piperidino-cyclohexylamine

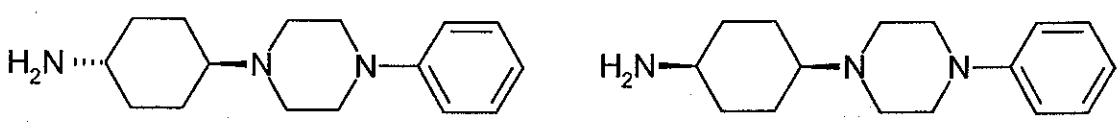
2.0 g (6.8 mmol) of trans-1amino-4-dibenzylaminocyclohexane (see Ex. 2) is dissolved in 50 mL DMF and stirred for 48 h at RT with 1.6 g (7 mmol) of 1,5-dibromopentane and 2 g of potassium carbonate. The mixture is cooled, combined with water, extracted twice with 100 mL dichloromethane, dried and the solvent is eliminated in vacuo. The residue is purified through a column (approx. 100 mL silica gel, approx. 500 mL ethyl acetate 80/methanol 20 +1% conc. ammonia). The desired fractions are evaporated down in vacuo and crystallised from petroleum ether. Yield: 1.2 g (49%).

trans-4-piperidino-cyclohexylamine

1.7 g (4.8 mmol) of trans-dibenzyl-4-piperidino-cyclohexylamine are dissolved in 35 mL MeOH and hydrogenated on 350 mg Pd/C (10%) at 20 °C. The solvent is eliminated in vacuo and the residue is crystallised from ethanol and conc. HCl. Yield: 1.1 g (78%).

The cis-isomer may be prepared analogously.

cis- and trans-4-(4-phenyl-piperazin-1-yl)-cyclohexylamine



4.1 g (25.3 mmol) of 4-dibenzylcyclohexanone is dissolved in 50 mL dichloromethane and stirred with 7.4 g (25.3 mmol) of N-phenylpyperazine and 7.4 g (35 mmol) of $NaBH(OAc)_3$ for 12 h at RT. Then the mixture is combined with water and potassium carbonate, the org. phase is separated off, dried and the solvent is eliminated in vacuo. The residue is purified on a silica gel column (ethyl acetate 80/ methanol 20 + 0.5% conc. ammonia).

Yield: 1.7 g (15.8%) cis-isomer and 0.27 (2.5%) trans-isomer.

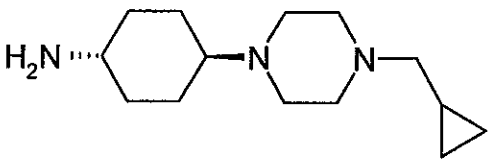
trans-4-(4-phenyl-piperazin-1-yl)-cyclohexylamine

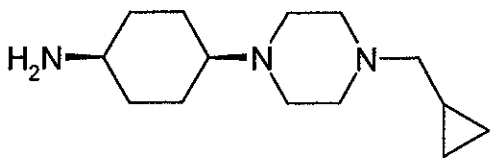
270 mg (0.61 mmol) of trans-dibenzyl-[4-(4-phenyl-piperazin-1-yl)-cyclohexyl]-amine are dissolved in 5 mL MeOH and hydrogenated on 40 mg Pd/C (10%) at 20-30 °C. The solvent is eliminated in vacuo and the residue is crystallised from ethanol and conc. HCl.

Yield: 110 mg (69%).

The cis-isomer may be prepared analogously.

cis- and trans-4-(4-cyclopropylmethyl-piperazin-1-yl)-cyclohexylamine





9.8 g (33.4 mmol) of 4-dibenzylcyclohexanone is dissolved in 100 mL dichloromethane and stirred with 5.6 g (40 mmol) of N-cyclopropylmethylpiperazine and 8.5 g (40 mmol) of $NaBH(OAc)_3$ for 12 h at RT. Then the mixture is combined with water and potassium carbonate, the org. phase is separated off and dried and the solvent is eliminated in vacuo. The residue is purified on a silica gel column (approx. 50 mL silica gel, approx. 3 L ethyl acetate 95/methanol 5 + 0.25% conc. ammonia). The desired fractions are evaporated down in vacuo. The faster eluting cis compound crystallises from ethyl acetate. The trans compound is crystallised from ethanol + conc. HCl.

Yield: 8.5 g (61%) cis-isomer and 2.2 g (13%) trans-isomer.

cis-4-(4-cyclopropylmethyl-piperazin-1-yl)-cyclohexylamine

8.5 g (20 mmol) of cis-dibenzyl-[4-(4-cyclopropylmethyl-piperazin-1-yl)-cyclohexyl]-amine are dissolved in 170 mL MeOH and hydrogenated on 1.7 g Pd/C (10%) at 30-50°C. The solvent is eliminated in vacuo and the residue is crystallised from ethanol and conc. HCl.
Yield: 4.4 g (91%).

The trans-isomer may be prepared analogously.

Synthesis of the Examples

Example 152

0.15g of the compound Z10, 0.14 g TBTU, 0.13 mL DIPEA are dissolved in dichloromethane and stirred for 20 minutes at 25°C. Then 90 µL 1-(3-aminopropyl)-4-methylpiperazine are added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with dichloromethane and extracted with water. The product is precipitated by the addition of petroleum ether, ether and ethyl acetate to the organic phase. Yield: 0.16 g of beige solid

Example 164

0.10g of the compound Z10, 0.1 g TBTU, 0.08 mL DIPEA are dissolved in 4 mL dichloromethane and stirred for 20 minutes at 25°C. Then 44 µL dimethylaminopropylamine are added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with dichloromethane and extracted with water. The product is precipitated by the addition of petroleum ether, ether and acetone to the organic phase. Yield: 0.08 g yellow solid.

Example 242

0.15g of the compound Z10, 0.14 g TBTU, 0.13 mL DIPEA are dissolved in 5 mL dichloromethane and stirred for 20 minutes at 25°C. Then 75 µL 1-(2-aminoethyl)piperidine are added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with dichloromethane and extracted with water. The product is precipitated by the addition of petroleum ether, ether and ethyl acetate to the organic phase. Yield: 0.14 g yellow solid.

Example 188

0.1 g of the compound Z2, 0.09 g TBTU, 0.05 mL DIPEA are dissolved in 15 mL dichloromethane and stirred for 20 minutes at 25°C. Then 33 mg 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 3 hours at 25°C. The solution is extracted with 20 mL water, then evaporated down in vacuo. The product is crystallised from ether. Yield: 0.047 g white crystals.

Example 203

0.1 g of the compound Z2, 0.09 g TBTU, 0.5 mL DIPEA are dissolved in 15 mL dichloromethane and stirred for 30 minutes at 25°C. Then 50 mg 4-amino-1-benzylpiperidine are added and the mixture is stirred for a further 3 hours at 25°C. The solution is extracted with 20 mL water, then evaporated down in vacuo. The residue is then chromatographed on silica gel and the product isolated is crystallised from ether. Yield: 0.015 g white crystals.

Example 94

0.17 g of the compound Z1, 0.19 g TBTU, 0.11 mL DIPEA are dissolved in 50 mL dichloromethane and stirred for 30 minutes at 25°C. Then 63 mg 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 17 hours at 25°C. 50 mL water and 1 g potassium carbonate are added to the solution and the organic phase is

separated off using a phase separation cartridge, then evaporated down in vacuo. The product is then purified by chromatography on silica gel and the purified product is crystallised using ether. Yield: 0.1 g white crystals.

Example 95

0.17 g of the compound Z1, 0.19 g TBTU, 0.11 mL DIPEA are dissolved in 50 mL dichloromethane and stirred for 30 minutes at 25°C. Then 77 mg exo-3-β-amino-tropane are added and the mixture is stirred for a further 17 hours at 25°C. 50 mL water and 1 g potassium carbonate are added to the solution and the organic phase is separated off using a phase separation cartridge, then evaporated down in vacuo. The product is then purified by chromatography on silica gel and the purified product is crystallised using ether. Yield: 0.03 g white crystals.

Example 46

0.15 g of the compound Z3, 0.12 g TBTU, 0.12 mL DIPEA are dissolved in 5 mL dichloromethane and stirred for 30 minutes at 25°C. Then 50 mg 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 2.5 hours at 25°C stirred. The solution is then extracted with water and then evaporated down. The residue is dissolved in warm ethyl acetate and crystallised using ether and petroleum ether. Yield: 0.025 g white crystals.

Example 80

0.2 g of the compound Z8, 0.2 g TBTU, 0.1 mL DIPEA are dissolved in 10 mL dichloromethane and stirred for 30 minutes at 25°C. Then 100 mg 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 17 hours at 25°C. The solution is then extracted with a dilute potassium carbonate solution and evaporated down. The residue is crystallised using ether. Yield: 0.12 g white crystals.

Example 190

0.2 g compound Z8, 0.2 g TBTU, 0.3 mL DIPEA are dissolved in 5 mL dichloromethane and the mixture is stirred for 1h at 25°C. Then 0.13 g 4-amino-1-benzylpiperidine is added and the mixture is stirred for a further hour at 25°C. The solution is then diluted with 10 mL methylene chloride and extracted with 20 mL water. Then the product is purified on silica gel and crystallised by means of ethyl acetate and ether.

Yield: 0.23 g of the compound Z8

0.23 g of the benzylamine Z8 are dissolved in 10 mL methanol, combined with 50 mg Pd/C and hydrogenated for 3h at 3 bar at 25°C. By the addition of petroleum ether and ethyl acetate white crystals are obtained. These are chromatographed on silica gel and crystallised using ethyl acetate and ether.

Yield: 0.075 g white crystals.

Example 196

0.1g compound Z10, 0.09 g TBTU, 0.3 mL DIPEA are dissolved in 4 mL dichloromethane and stirred for 20 minutes at 25°C. Then 67 mg 1,1-dimethyl-N-methylpiperazin-1-yl-ethylamine is added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with dichloromethane and extracted with water. It is then chromatographed on silica gel and the residue is dissolved in acetone, combined with ethereal HCl and the precipitate formed is isolated.

Yield: 0.09 g bright yellow solid

Example 166

0.1 g of the compound Z10, 0.11 g TBTU, 0.14 mL DIPEA are dissolved in 2 mL dimethylformamide and stirred for 3h at 50°C. Then 55 mg of 4-morpholinomethylphenylamine is added. Then the reaction is cooled to ambient temperature within 17 h. Then the dimethylformamide is eliminated in vacuo, the

residue is taken up in dichloromethane and extracted with water. It is then chromatographed on silica gel and the product is crystallised from ethyl acetate and ether.
Yield: 0.06 g yellowish crystals

Example 81

0.2 g of the compound Z4, 0.2 g TBTU, 0.1 mL DIPEA are dissolved in 10 mL dichloromethane and stirred for 30 minutes at 25°C. Then 0.1 g 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 17 hours at 25°C. The solution is then extracted with aqueous potassium carbonate solution and then evaporated down. The product is crystallised using ether.
Yield: 0.16 g white crystals.

Example 162

0.1 g of the compound Z5, 0.07 g TBTU, 0.15 mL DIPEA are dissolved in 5 mL dichloromethane and stirred for 20 minutes at 25°C. Then 0.04 g 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with 15 mL dichloromethane and extracted with 20 mL water. The residue is dissolved in MeOH and acetone, combined with 1 mL ethereal HCl and evaporated down. Using ether, ethyl acetate and a little MeOH a crystalline product is obtained.
Yield: 0.1 g white crystals.

Example 88

0.1 g of the compound Z6, 0.12 g TBTU, 0.12 mL DIPEA are dissolved in 10 mL dichloromethane and stirred for 30 minutes at 25°C. Then 0.04 g 1-methyl-4-aminopiperidine are added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with 10 mL dichloromethane and extracted with 10 mL water. Using ethyl acetate, ether and petroleum ether a crystalline product is obtained.

Yield: 0.6 g white crystals.

Example 89

0.1 g of the compound Z6, 0.08 g TBTU, 0.08 mL DIPEA are dissolved in 10 mL dichloromethane and stirred for 30 minutes at 25°C. Then 37 µL of N,N-dimethylneopentanediamine are added and the mixture is stirred for a further 2 hours at 25°C. The solution is then diluted with 10 mL dichloromethane and extracted with 10 mL water. The product is then chromatographed on silica gel and crystallised using ethyl acetate, ether and petroleum ether.
Yield: 0.005 g white crystals.

Example 26

0.15 g of the compound Z7, 0.16 g TBTU, 1 mL DIPEA are dissolved in 5 mL dichloromethane and stirred for 30 minutes at 25°C. Then 0.1 g of 4-morpholinocyclohexylamine are added and the mixture is stirred for a further 17 hours at 25°C. The residue is then combined with 10 mL 10% potassium carbonate solution, the precipitate is isolated and washed with water. Then it is dissolved in dichloromethane and again evaporated down. The product is crystallised using ethyl acetate.
Yield: 0.1 g white crystals.

Example 9

150 mg of the compound Z9 and 93 mg of cis-4-morpholino-cyclohexamine are dissolved in 5 mL dichloromethane and stirred with 160 mg TBTU and 1 mL DIPEA for 12 h at RT. The solvent is eliminated in vacuo, the residue is combined with 10 mL 10% potassium carbonate solution. The precipitate is suction filtered, washed with water, taken up in dichloromethane, dried and the solvent is eliminated in vacuo. The residue is crystallised from ethyl acetate.
Yield: 82.0 mg.

Example 16

150 mg of the compound Z8 and 73 mg trans-4-piperidino-cyclohexylamine are dissolved in 5 mL dichloromethane and stirred with 160 mg (0.50 mmol) of TBTU and 1 mL DIPEA for 12 h at RT. The solvent is eliminated in vacuo, the residue is combined with 10 mL 10% potassium carbonate solution. The precipitate is suction filtered, washed with water, taken up in dichloromethane, dried and the solvent is eliminated in vacuo. The residue is crystallised from ethyl acetate. Yield: 87.0 mg.

Example 37

100 mg of the compound Z9 and 42 mg of 3-amino-1-ethyl-pyrolidine are dissolved in 10 mL dichloromethane and stirred with 90 mg of TBTU and 0.5 mL of DIPEA for 12 h at RT. The solvent is eliminated in vacuo, the residue is combined with 10 mL of 10% potassium carbonate solution. The precipitate is suction filtered, washed with water, taken up in dichloromethane, dried and the solvent is eliminated in vacuo. The residue is crystallised from ethyl acetate/petroleum ether. Yield: 24.0 mg.

Example 120

100 mg of the compound Z11 and 73 mg of 4-amino-1-tetrahydro-4H-pyran-4-yl-piperidine are dissolved in 10 mL dichloromethane and this is stirred with 90 mg of TBTU and 0.5 mL DIPEA for 1 h at RT. The solvent is eliminated in vacuo, the residue is combined with 10 mL 10% potassium carbonate solution. The precipitate is suction filtered, washed with water, taken up in dichloromethane, dried and the solvent is eliminated in vacuo. The residue is crystallised from ethyl acetate/petroleum ether. Yield: 89 mg.

Example 212

150 mg of the compound Z5 and 150 mg of trans-4-(4-cyclopropylmethyl-piperazin-1-yl)-cyclohexylamine (as the hydrochloride) are dissolved in 5 mL dichloromethane and

stirred with 160 mg of TBTU and 2 mL DIPEA for 2 h at RT. The solvent is eliminated in vacuo, the residue is combined with 10 mL 10% potassium carbonate solution. The precipitate is suction filtered, washed with water, taken up in dichloromethane, dried and the solvent is eliminated in vacuo. The residue is purified through a column (20 mL silica gel, 300 mL ethyl acetate 90/ methanol 10 + 2% conc. ammonia). The desired fractions are evaporated down in vacuo and crystallised from ethyl acetate.
Yield: 140 mg.

Example 232

390 mg of the compound Z11 and 240 mg trans-4-(4-t-butyloxycarbonyl-piperazin-1-yl)-cyclohexylamine are dissolved in 2.5 mL NMP and stirred with 482 mg of TBTU and 1 mL triethylamine for 2 h at RT. Then the mixture is combined with 100 mL water and 200 mg potassium carbonate, the precipitate is suction filtered, washed with water and purified through a silica gel column. The suitable fractions are evaporated down in vacuo, dissolved in 2 mL dichloromethane, combined with 2 mL trifluoroacetic acid and stirred for 2 h at RT, again combined with 100 ml water and 200 mg potassium carbonate and the precipitate is suction filtered and washed with water. Then the precipitate is purified through a silica gel column. The desired fractions are evaporated down in vacuo and the residue is crystallised from ethanol and conc. hydrochloric acid.
Yield: 95 mg.

Example 213

60 mg of the compound Example 232 is dissolved in 10 mL ethyl acetate and stirred with 1 mL acetic anhydride and 1 mL triethylamine for 30 min. at RT. The solvent is eliminated in vacuo, the residue is combined with water and ammonia, the precipitated crystals are suction filtered and washed with water and a little cold acetone.

Yield: 40 mg.

Example 218

1.2 g of the compound Z9 and 0.5g of 1,4-dioxaspiro[4.5]dec-8-ylamine are dissolved in 20 mL dichloromethane and stirred with 1.28 g TBTU and 4 mL triethylamine for 12 h at RT. Then 50 mL water and 0.5 g potassium carbonate are added, the org. phase is separated off, dried and evaporated down in vacuo. The residue is crystallised from ethyl acetate, combined with 25 mL 1 N hydrochloric acid and 20 mL methanol and stirred for 30 min. at 50°C. The methanol is eliminated in vacuo, the precipitate is suction filtered, washed with water and dried. The residue is taken up in 20 mL dichloromethane and stirred with 0.5 g thiomorpholine and 0.5 g $NaBH(OAc)_3$ for 12 h at RT. Then the mixture is combined with water and potassium carbonate, the org. phase is separated off, dried and the solvent is eliminated in vacuo. The residue is purified on a silica gel column. The desired fractions are evaporated down in vacuo and the hydrochloride is precipitated with ethereal HCl.

Yield: 86 mg trans-isomer; amorphous powder.

Example 187

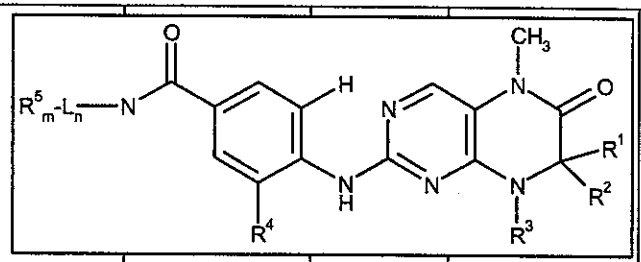
200 mg of the compound Z3 in 5 mL dichloromethane is combined with 0.1 mL diisopropylethylamine and 180 mg TBTU and stirred for 30 min.. Then 191 mg of 4-(4-methyl-piperazin-1-yl)-phenylamine are added and the mixture is stirred overnight. The reaction mixture is combined with water and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried over Na_2SO_4 and evaporated down. The residue is purified by column chromatography (eluant: dichloromethane/methanol 100:7).

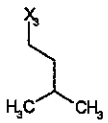
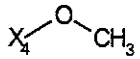
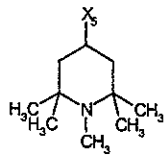
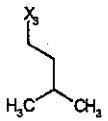
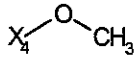
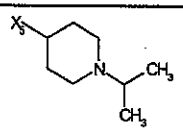
Yield: 128 mg (light yellow crystals)

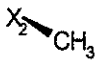
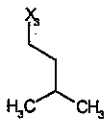
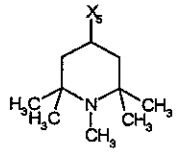
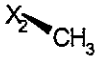
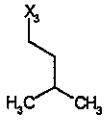
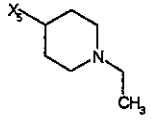
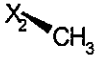
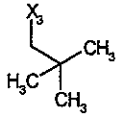
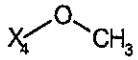
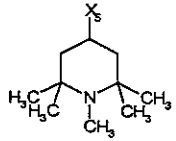
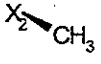
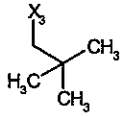
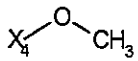
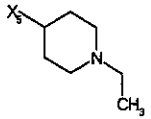
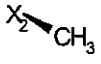
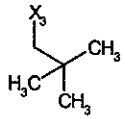
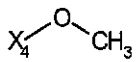
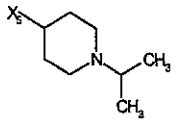
The compounds of formula (I) listed in Table 1 may be obtained *inter alia* analogously to the method described hereinbefore.

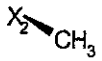
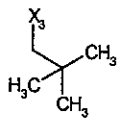
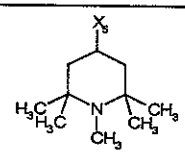
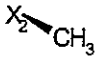
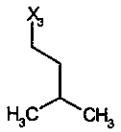
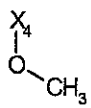
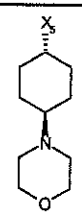
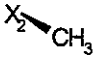
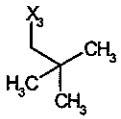
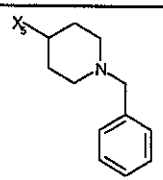
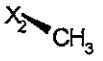
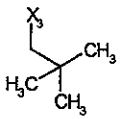
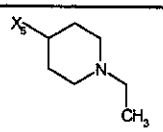
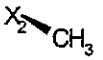
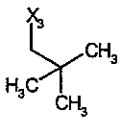
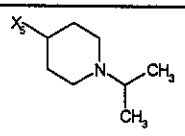
The abbreviations X_1, X_2, X_3, X_4 and X_5 used in Table 1 in each case denote a link to a position in the general formula listed in the Table instead of the corresponding groups R^1, R^2, R^3, R^4 and L-R^5.

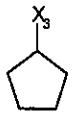
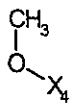
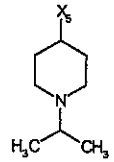
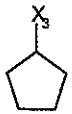
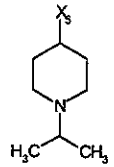
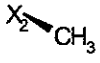
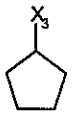
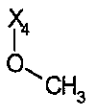
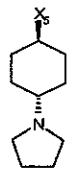
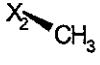
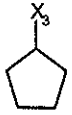
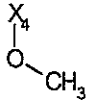
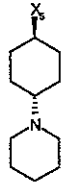
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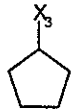
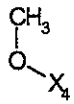
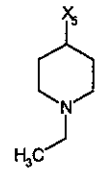
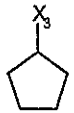
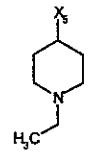
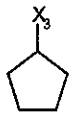
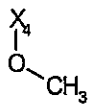
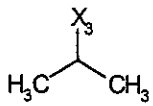
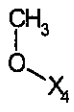
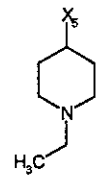
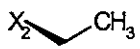
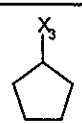
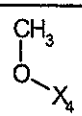
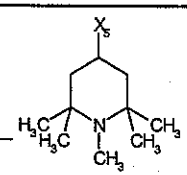


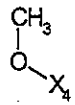
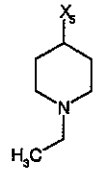
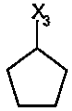
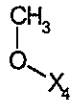
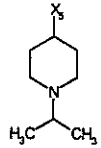
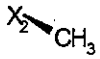
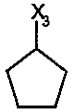
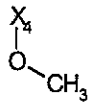
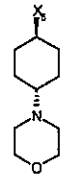
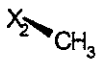
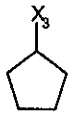
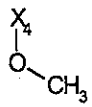
Ex.	R^1	R^2	Config. R^1 or R^2	R^3	R^4	L_n-$R^5{}_m$
1	H		R			
2	H		R			

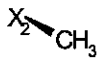
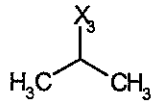
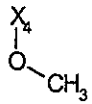
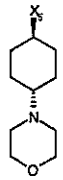
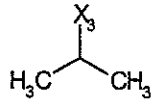
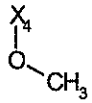
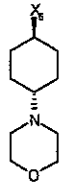
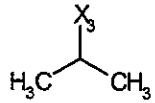
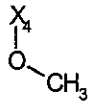
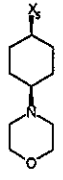
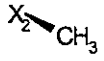
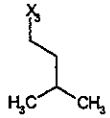
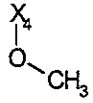
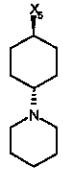
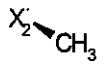
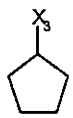
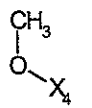
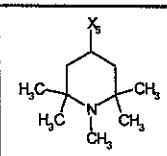
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5	H		R			
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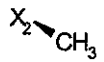
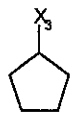
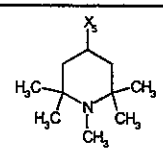
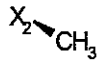
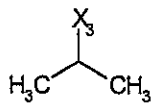
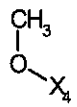
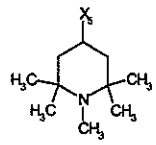
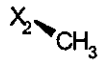
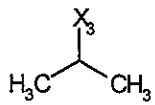
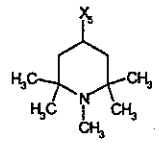
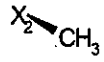
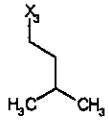
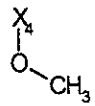
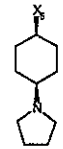
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9	H		R			
10	H		R		H	
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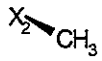
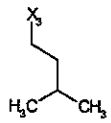
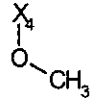
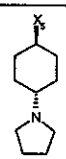
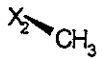
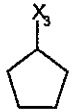
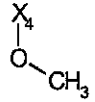
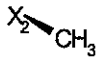
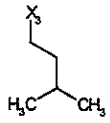
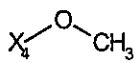
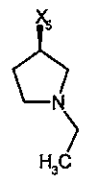
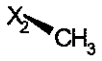
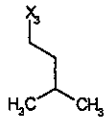
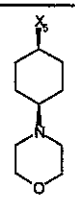
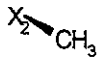
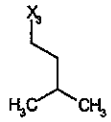
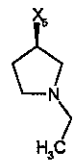
13	H		R			
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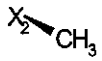
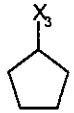
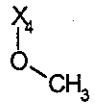
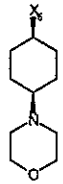
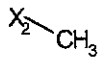
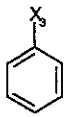
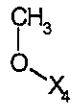
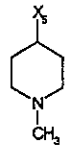
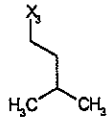
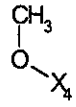
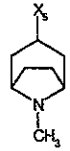
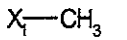
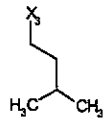
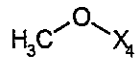
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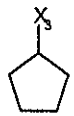
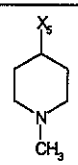
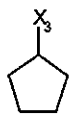
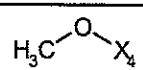
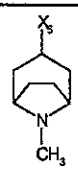
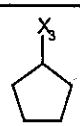
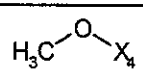
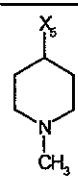
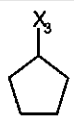
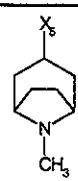
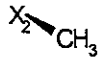
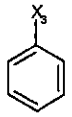
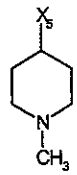
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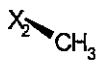
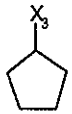
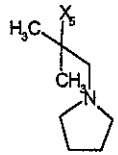
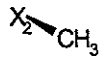
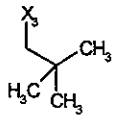
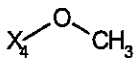
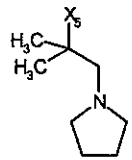
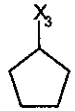
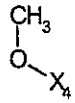
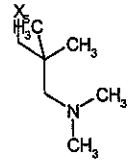
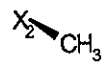
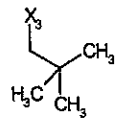
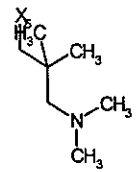
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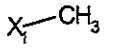
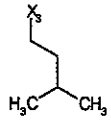
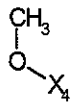
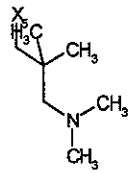
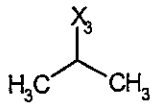
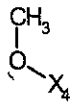
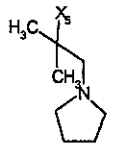
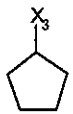
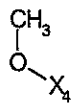
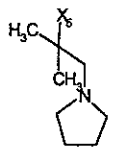
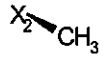
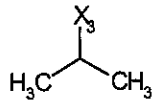
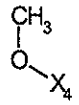
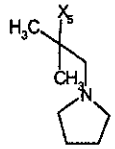
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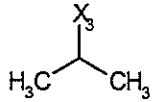
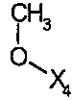
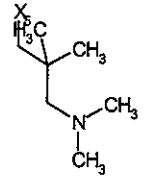
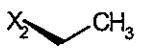
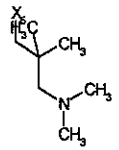
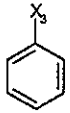
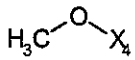
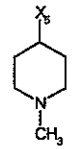
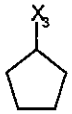
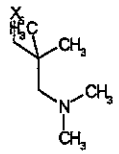
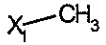
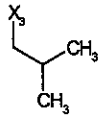
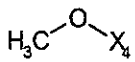
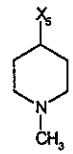
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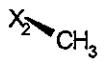
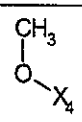
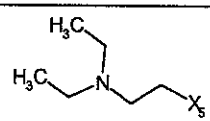
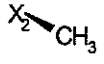
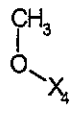
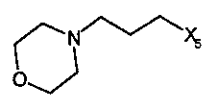
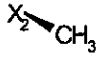
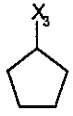
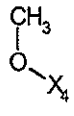
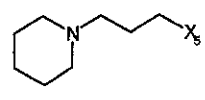
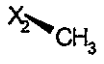
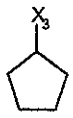
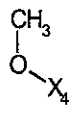
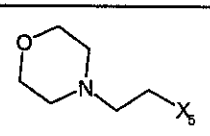
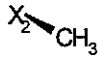
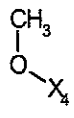
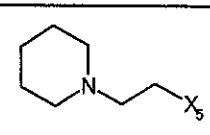
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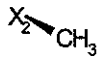
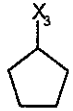
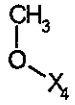
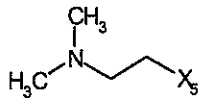
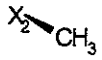
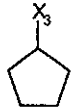
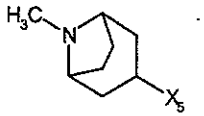
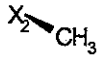
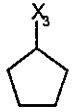
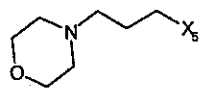
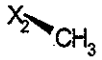
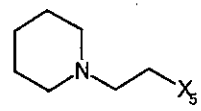
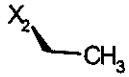
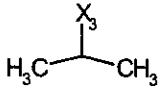
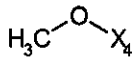
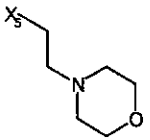
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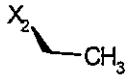
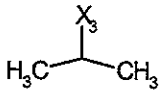
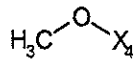
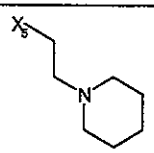
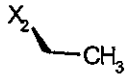
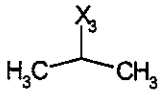
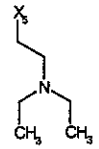
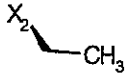
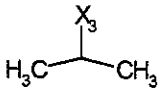
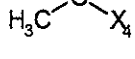
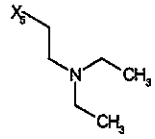
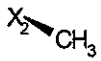
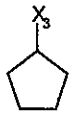
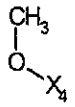
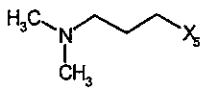
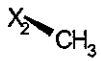
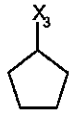
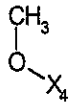
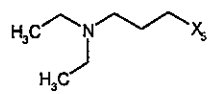
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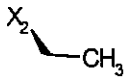
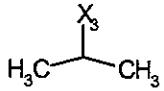
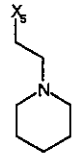
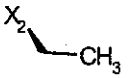
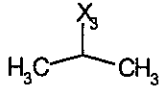
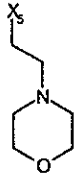
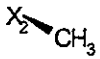
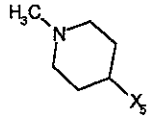
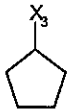
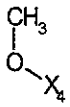
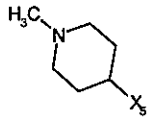
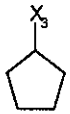
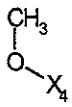
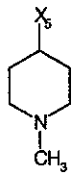
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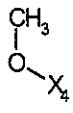
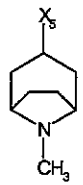
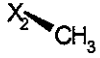
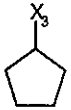
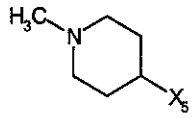
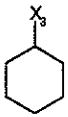
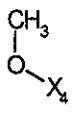
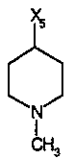
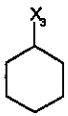
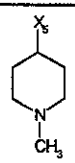
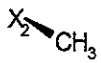
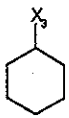
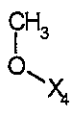
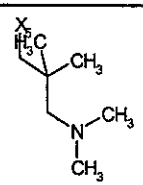
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61						

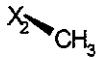
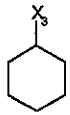
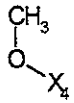
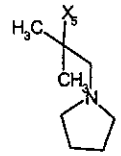
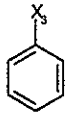
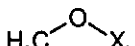
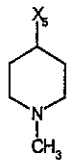
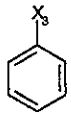
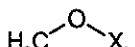
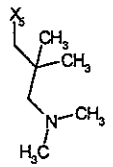
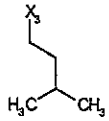
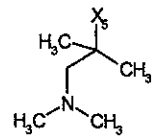
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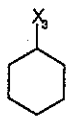
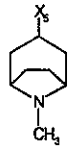
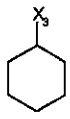
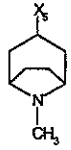
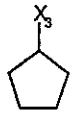
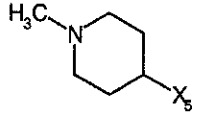
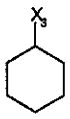
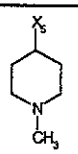
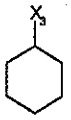
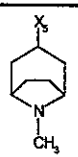
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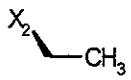
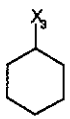
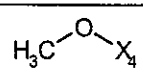
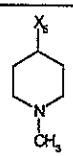
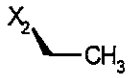
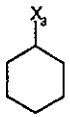
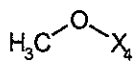
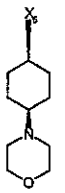
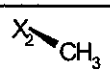
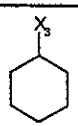
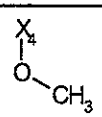
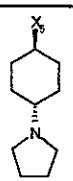
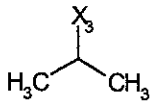
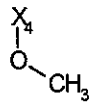
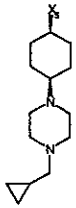
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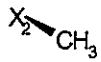
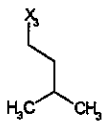
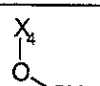
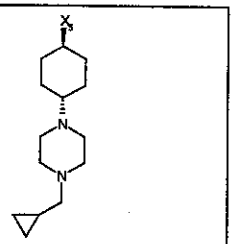
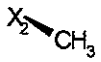
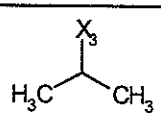
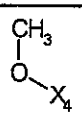
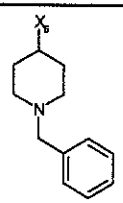
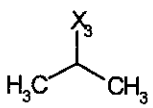
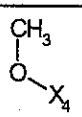
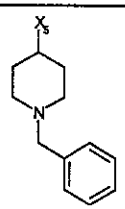
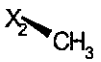
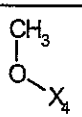
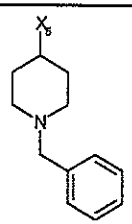
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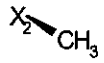
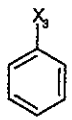
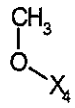
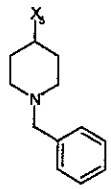
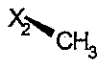
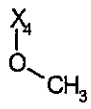
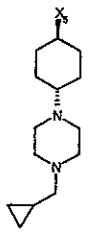
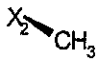
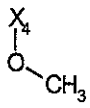
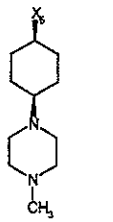
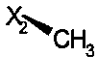
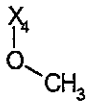
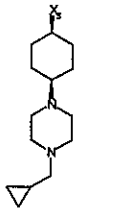
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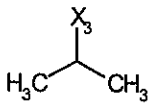
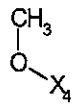
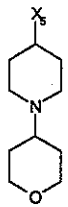
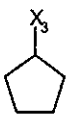
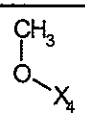
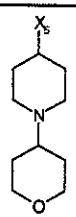
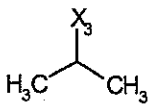
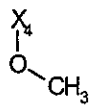
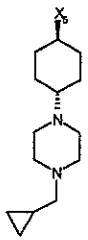
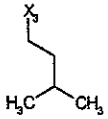
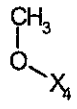
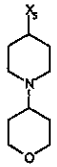
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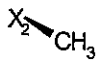
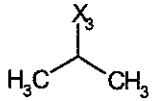
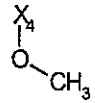
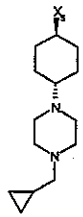
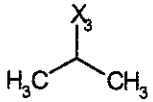
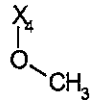
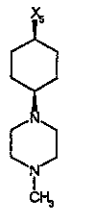
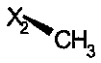
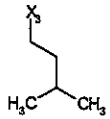
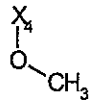
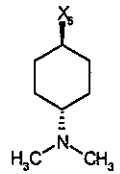
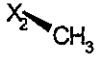
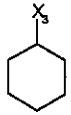
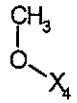
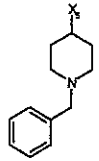
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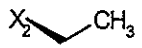
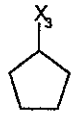
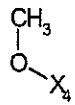
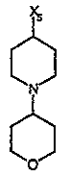
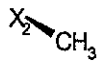
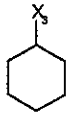
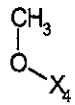
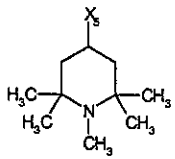
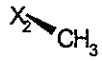
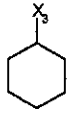
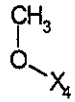
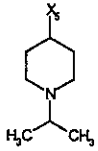
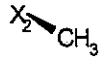
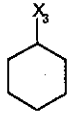
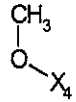
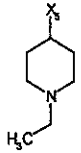
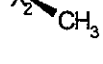
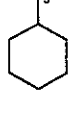
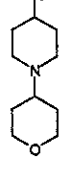
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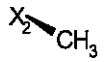
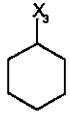
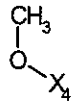
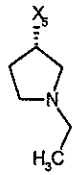
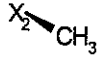
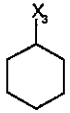
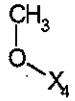
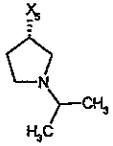
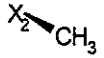
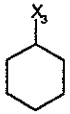
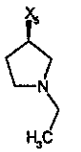
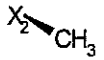
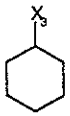
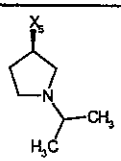
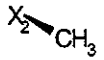
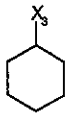
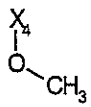
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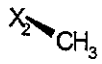
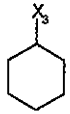
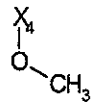
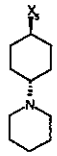
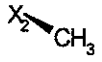
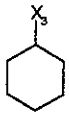
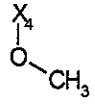
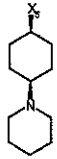
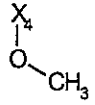
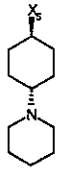
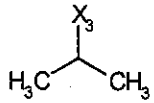
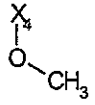
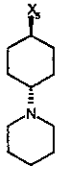
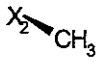
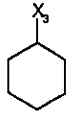
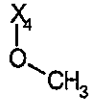
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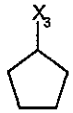
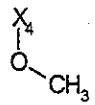
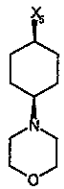
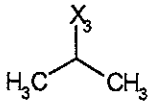
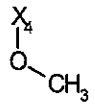
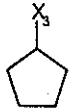
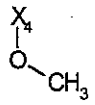
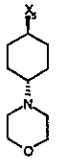
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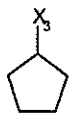
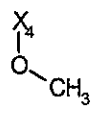
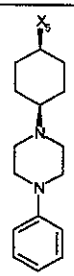
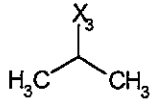
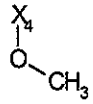
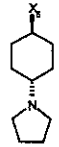
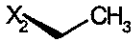
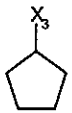
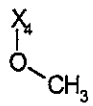
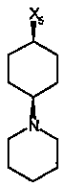
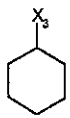
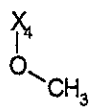
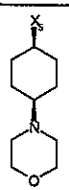
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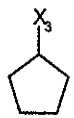
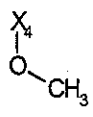
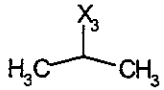
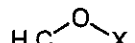
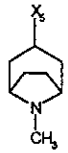
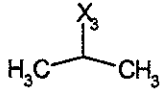
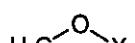
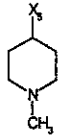
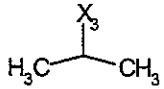
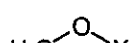
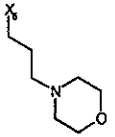
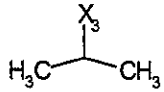
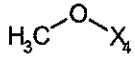
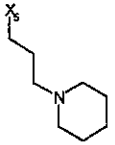
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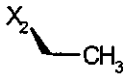
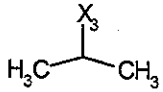
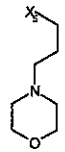
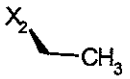
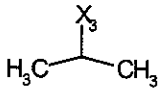
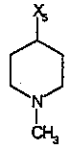
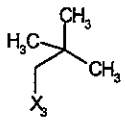
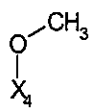
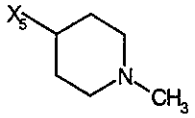
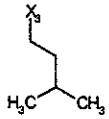
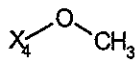
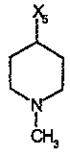
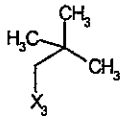
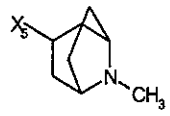
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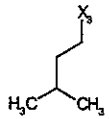
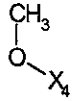
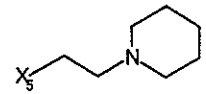
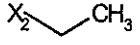
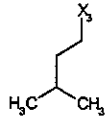
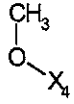
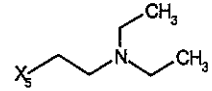
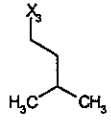
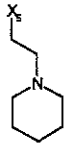
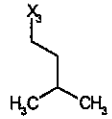
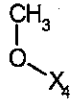
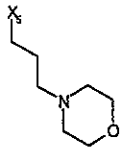
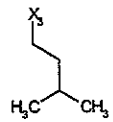
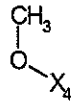
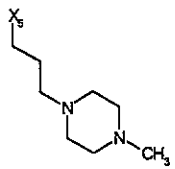
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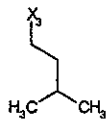
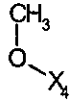
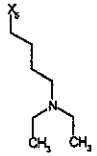
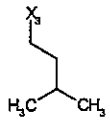
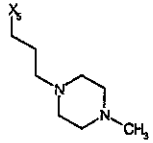
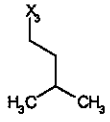
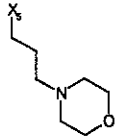
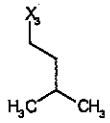
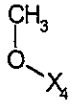
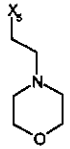
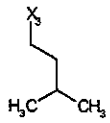
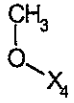
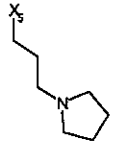
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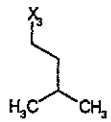
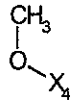
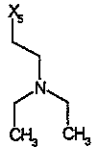
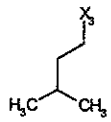
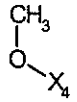
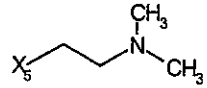
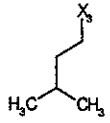
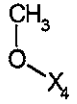
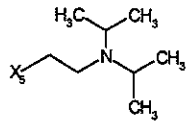
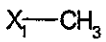
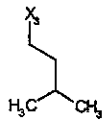
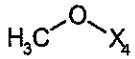
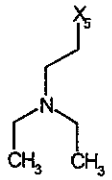
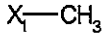
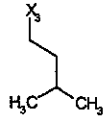
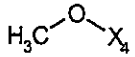
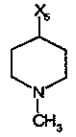
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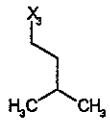
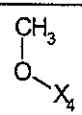
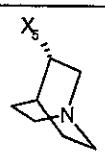
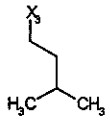
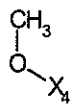
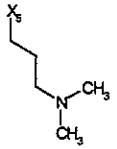
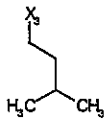
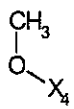
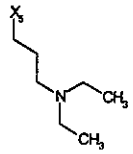
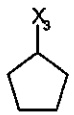
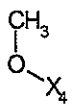
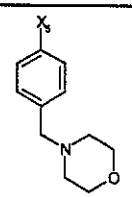
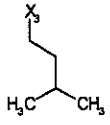
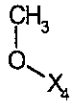
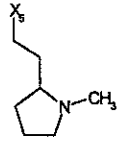
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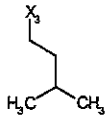
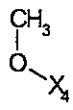
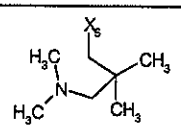
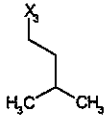
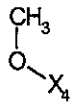
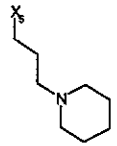
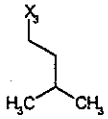
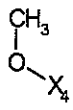
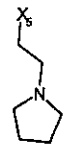
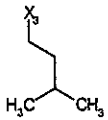
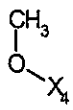
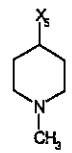
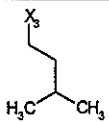
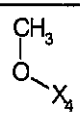
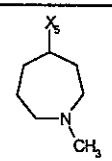
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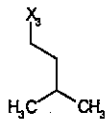
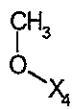
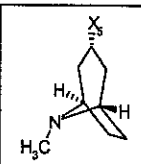
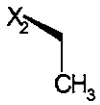
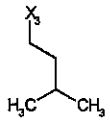
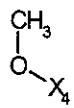
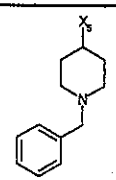
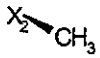
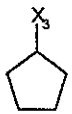
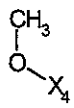
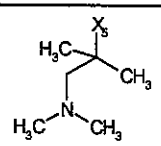
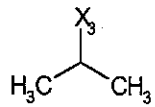
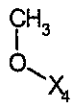
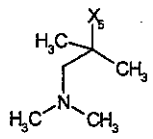
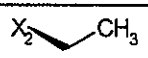
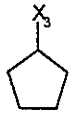
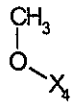
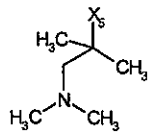
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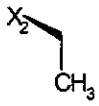
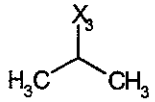
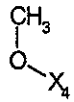
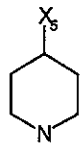
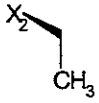
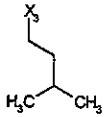
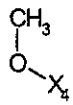
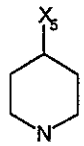
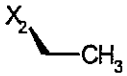
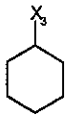
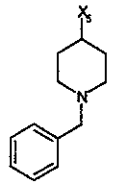
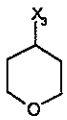
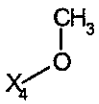
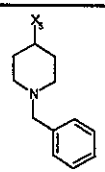
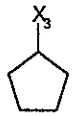
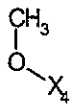
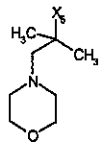
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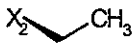
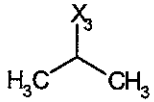
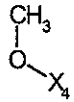
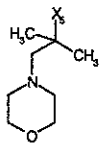
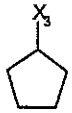
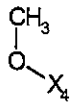
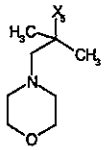
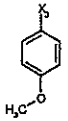
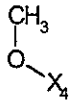
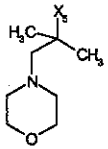
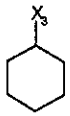
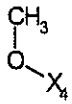
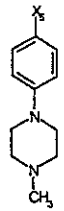
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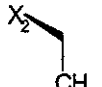
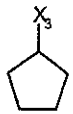
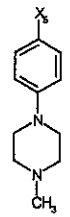
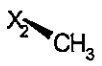
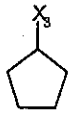
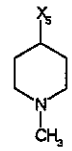
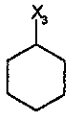
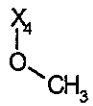
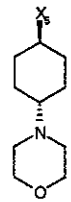
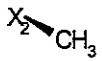
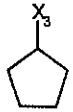
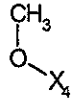
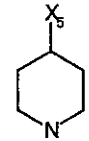
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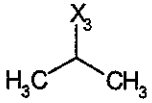
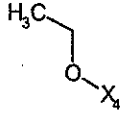
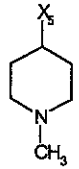
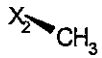
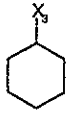
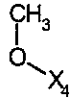
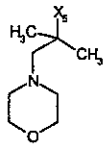
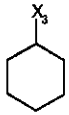
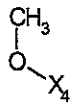
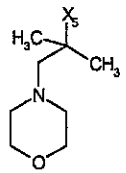
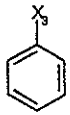
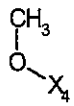
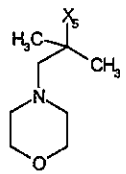
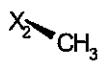
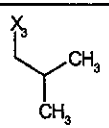
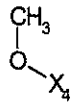
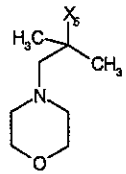
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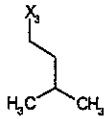
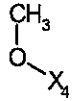
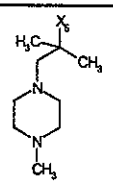
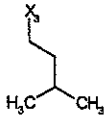
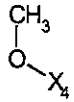
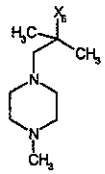
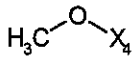
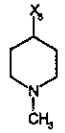
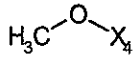
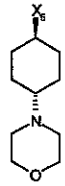
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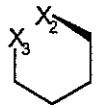
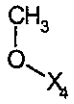
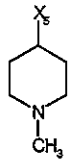
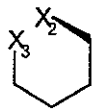
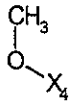
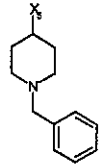
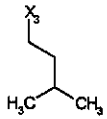
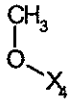
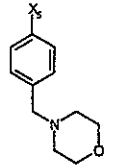
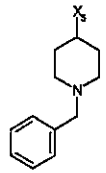
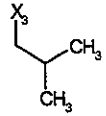
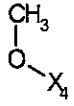
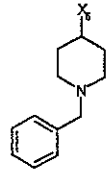
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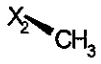
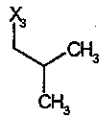
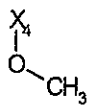
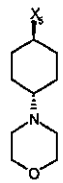
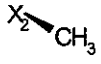
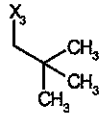
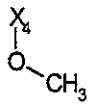
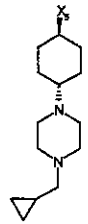
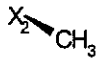
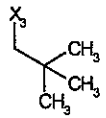
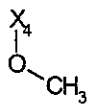
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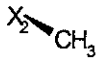
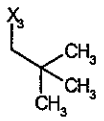
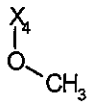
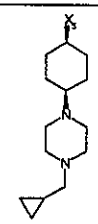
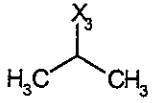
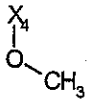
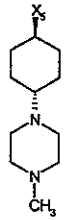
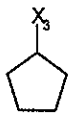
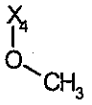
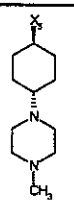
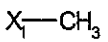
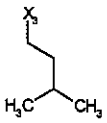
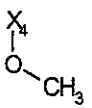
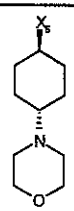
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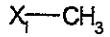
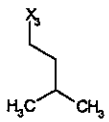
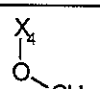
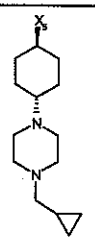
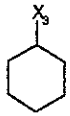
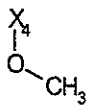
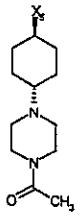
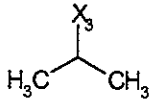
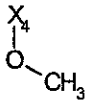
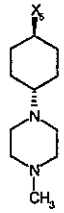
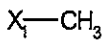
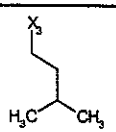
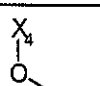
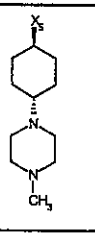
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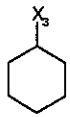
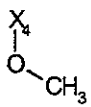
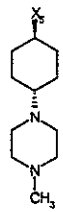
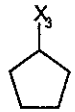
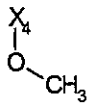
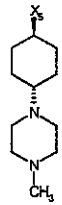
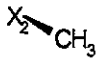
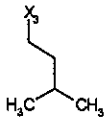
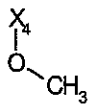
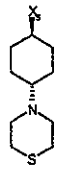
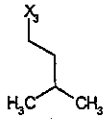
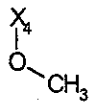
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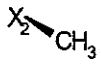
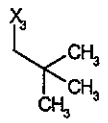
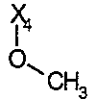
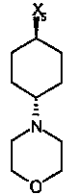
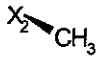
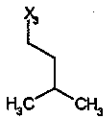
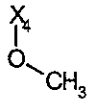
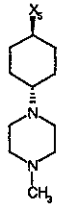
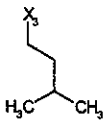
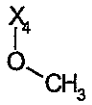
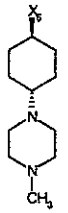
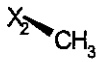
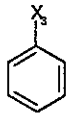
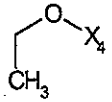
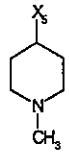
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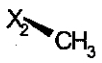
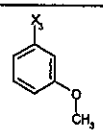
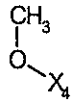
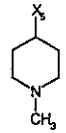
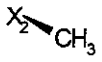
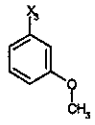
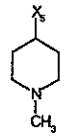
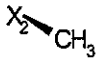
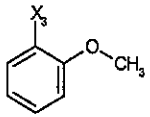
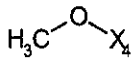
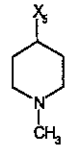
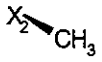
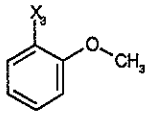
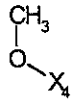
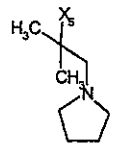
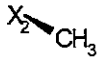
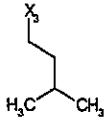
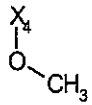
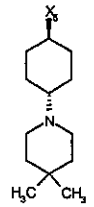
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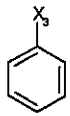
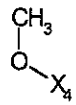
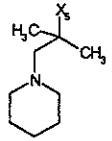
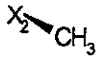
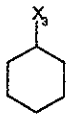
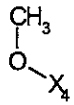
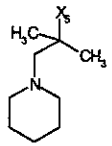
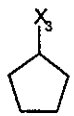
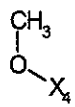
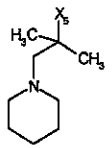
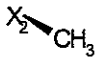
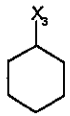
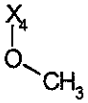
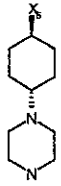
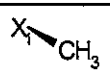
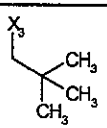
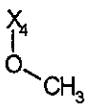
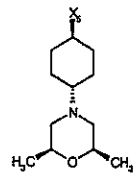
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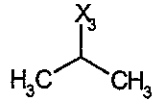
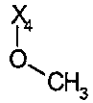
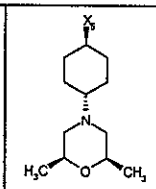
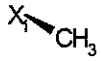
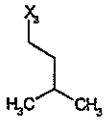
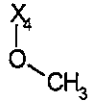
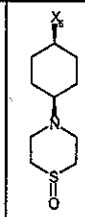
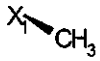
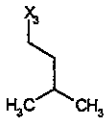
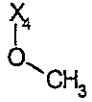
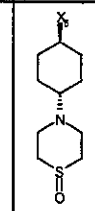
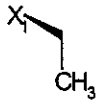
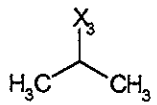
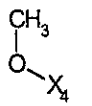
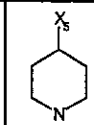
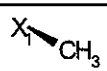
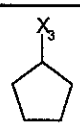
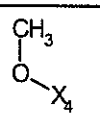
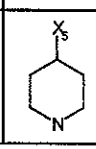
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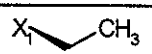
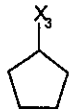
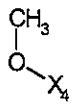
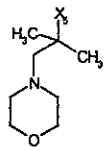
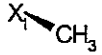
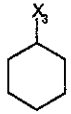
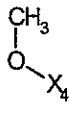
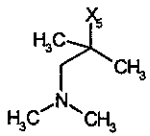
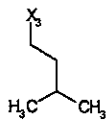
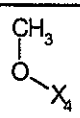
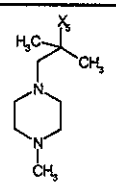
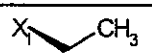
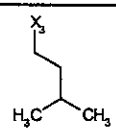
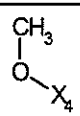
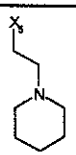
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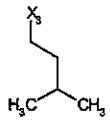
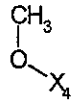
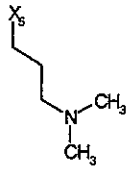
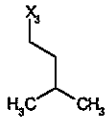
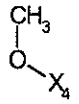
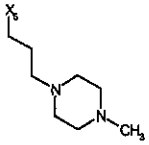
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221	H		R			
222	H		R			
223	H		R			

224	H		R			
225	H		R		H	
226	H		R			
227	H		R			
228	H		R			

229	H		R			
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232	H		R			
233	H		R			

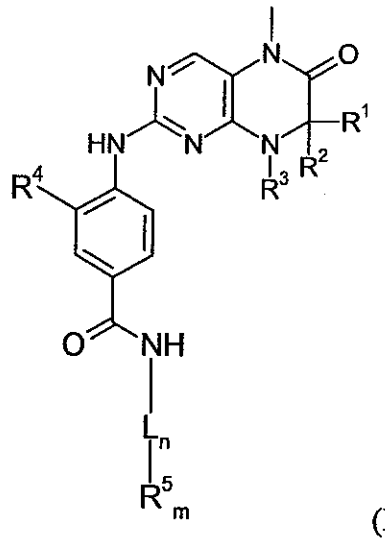
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236	H		R			
237	H		R			
238	H		R			

239	H		R			
240	H		R			
241	H		R			
242	H		R			

243	H		R			
244	H		R			

Patent Claims

1. Storage stable aqueous infusible or injectable solutions containing an active substance of general formula (I)



(I)

wherein

R^1, R^2 which may be identical or different, denote hydrogen or optionally substituted C_1-C_6-alkyl,

or

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

R^3 denotes hydrogen or a group selected from among optionally substituted C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, C_2-C_{12}-alkynyl and C_6-C_{14}-aryl, or
a group selected from among optionally substituted and/or bridged C_3-C_{12}-cycloalkyl, C_3-C_{12}-cycloalkenyl, C_7-C_{12}-polycycloalkyl, C_7-C_{12}-polycycloalkenyl, C_5-C_{12}-

spirocycloalkyl, C_3-C_{12}-heterocycloalkyl which contains 1 to 2 heteroatoms, and C_3-C_{12}-heterocycloalkenyl which contains 1 to 2 heteroatoms,

or

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

R^4 denotes a group selected from among hydrogen, -CN, hydroxy, $-NR_6R_7$ and halogen,

or

a group selected from among optionally substituted C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_5-alkyloxy, C_2-C_5-alkenyloxy, C_2-C_5-alkynyloxy, C_1-C_6-alkylthio, C_1-C_6-alkylsulphoxo and C_1-C_6-alkylsulphonyl,

L denotes a linker selected from among optionally substituted C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_6-C_{14}-aryl, $-C_2$-C_4-alkyl-C_6-C_{14}-aryl, $-C_6$-C_{14}-aryl-C_1-C_4-alkyl, optionally bridged C_3-C_{12}-cycloalkyl and heteroaryl which contains 1 or 2 nitrogen atoms,

n denotes 0 or 1,

m denotes 1 or 2,

R^5 denotes a group selected from among optionally substituted morpholinyl, piperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropenyl, R^8-diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, $-NR^8R^9$ and azacycloheptyl,

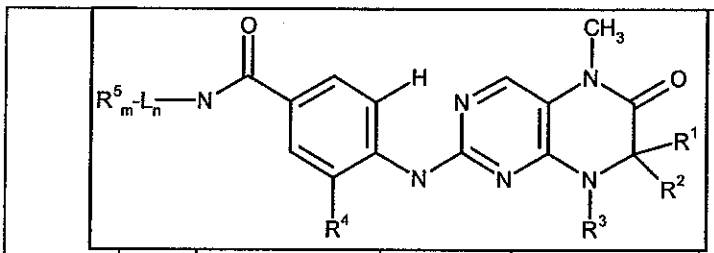
R^6, R^7, which may be identical or different, denote hydrogen or C_1-C_4-alkyl,

and

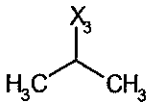
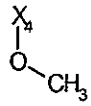
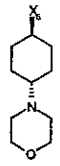
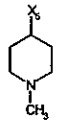
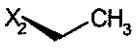
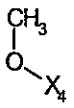
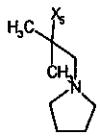
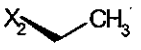
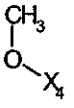
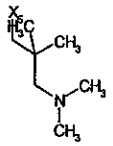
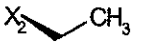
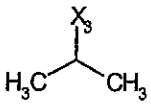
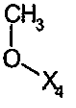
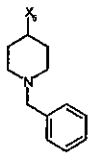
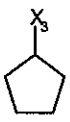
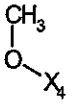
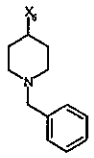
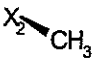
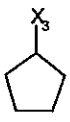
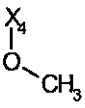
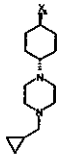
R^8, R^9 denote unsubstituted nitrogen substituents at R^5, which may be identical or different, either hydrogen or a group selected from among C_1-C_6-alkyl, -C_1-C_4-alkyl-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl, C_6-C_{14}-aryl, -C_1-C_4-alkyl-C_6-C_{14}-aryl, pyranyl, pyridinyl, pyrimidinyl, C_1-C_4-alkyloxycarbonyl, C_6-C_{14}-arylcarbonyl, C_1-C_4-alkylcarbonyl, C_6-C_{14}-arylmethyloxycarbonyl, C_6-C_{14}-arylsulphonyl, C_1-C_4-alkylsulphonyl- and C_6-C_{14}-aryl-C_1-C_4-alkylsulphonyl,

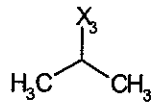
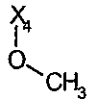
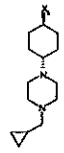
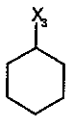
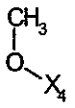
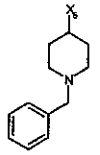
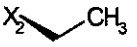
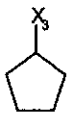
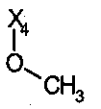
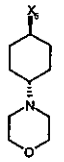
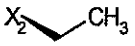
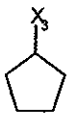
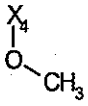
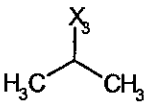
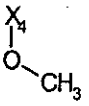
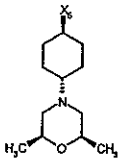
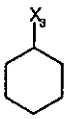
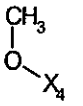
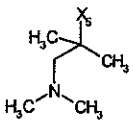
or the tautomers, racemates, enantiomers, diastereomers or optionally the physiologically effective derivatives or metabolites thereof and an amount of a physiologically acceptable acid or mixture of acids sufficient to dissolve the active substance and act as a stabiliser, optionally together with other formulating excipients suitable for parenteral administration.

2. Storage stable aqueous infusible or injectable solutions according to claim 1, characterised in that the dihydropteridinone is selected from among the following dihydropteridinones of general formula (I)



Ex.	R^1	R^2	Config. R^1 or R^2	R^3	R^4	L_n-$R^5{}_m$

27	H		R			
44	H		R		H	
55	H		R			
58	H		R			
102	H		R			
103	H		R			
105	H		R			

110	H		R			
115	H		R			
133	H		R			
134	H		R			
234	H		R			
240	H		R			

whereby the abbreviations X_1, X_2, X_3, X_4 and X_5 used in the Table in each case denote a link to a position in the general formula listed in the Table instead of the corresponding groups R^1, R^2, R^3, R^4 and L-R^5.

3. Aqueous infusible or injectable solutions according to claim 1 or 2, characterised in that the content of dissolved active substance is 0.1 mg to 10.0 mg in 1

ml of infusible or injectable solution.

4. Aqueous infusible or injectable solutions according to one of claims 1 to 3, characterised in that one or more acids used as storage and dilution stabilisers are selected from among hydrochloric acid, acetic acid, hydroxyacetic acid, methanesulphonic acid, ethanesulphonic acid, phosphoric acid, nitric acid, sulphuric acid, citric acid, tartaric acid, fumaric acid, succinic acid, glutaric acid, adipic acid, propionic acid, ascorbic acid, maleic acid, malic acid, glutamic acid, gluconic acid, glucuronic acid, galacturonic acid and lactic acid.

5. Aqueous infusible or injectable solutions according to one of claims 1 to 4, characterised in that the molar ratio of the physiologically acceptable acid or mixture of acids to the active substance is at most 3:1.

6. Aqueous infusible or injectable solutions according to one of claims 1 to 5, characterised in that they contain one or more other formulating excipients selected from among complexing agents, light protecting agents, crystallisation inhibitors, thickeners, isotonic agents, antioxidants and euhydration agents.

7. Aqueous infusible or injectable solutions according to one of claims 1 to 6, characterised in that the osmolality of the infusible or injectable solutions is 200 – 600 mOsmol/kg.

8. Aqueous infusible or injectable solutions according to one of claims 1 to 7, characterised in that they have a pH of 2.4 to 5.3.

9. Aqueous infusible or injectable solutions according to one of claims 1 to 8, characterised in that they contain 1.25 to 3.0 mol hydrochloric acid per mol active substance, based on 100 ml infusible or injectable solution, 0.75 to 1.2 g NaCl, and have an osmolality of 260 to 350 mOsmol/kg and a pH of 3.5 to 5.0.

10. Lyophilisates, concentrates and suspensions, characterised in that by the addition of water they yield an aqueous infusible or injectable solution according to one of claims 1 to 9.

11. Infusible or injectable solutions according to one of claims 1 to 9 for use as pharmaceutical compositions with an antiproliferative activity.

12. Use of an infusible or injectable solution according to one of claims 1 to 9 for preparing a pharmaceutical composition for the treatment of tumoral diseases, infections, inflammatory and autoimmune diseases

13. Method of treating and/or preventing tumoral diseases, infections, inflammatory and autoimmune diseases, characterised in that an effective amount of an infusible or injectable solution according to claim 1 to 9 is administered to a patient.

14. Use of an infusible or injectable solution according to one of claims 1 to 9, which corresponds to a dosage range of from 0.1 mg to 50 mg of active substance/ kg body weight.

15. Glass containers or flexible plastic containers suitable for parenteral preparations, containing infusible or injectable solutions according to one of claims 1 to 9.