(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2007 (21.12.2007)

PCT

(10) International Publication Number
WO 2007/144384 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/EP2007/055846

(22) International Filing Date: 13 June 2007 (13.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
06115504.0 14 June 2006 (14.06.2006) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

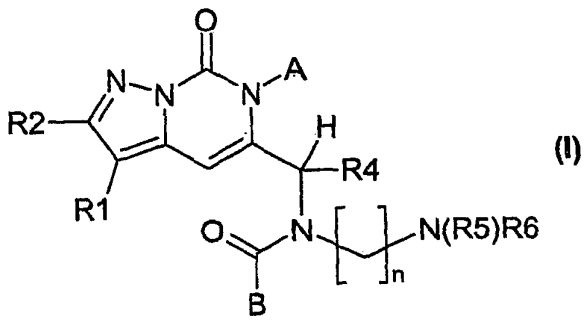
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** PYRAZOLOPYRIMIDONES



(I)

(57) **Abstract:** Compounds of a certain formula (I), in which R1, R2, A, R4, B, R5 and R6 have the meanings indicated in the description, are effective compounds with antiproliferative and/or apoptosis inducing activity.

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Pyrazolopyrimidones

Field of application of the invention

The invention relates to pyrazolopyrimidone derivatives, which can be used in the pharmaceutical industry for the production of pharmaceutical compositions.

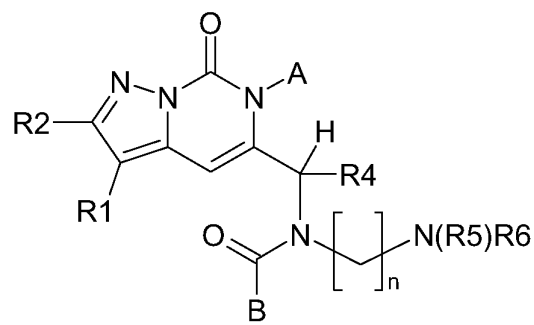
Known technical background

The US application US2004/0242596 contains pyrazolo[3,4-d]pyrimidones which are said to be useful as anti-cancer agents and to induce mitotic arrest.

Description of the invention

It has now been found, that the pyrazolo[1,5-c]pyrimidone derivatives, which are described in greater details below, differ from prior art compounds by unanticipated structural features and have surprising and particularly advantageous properties.
Thus, for example, the compounds according to this invention can act as inhibitors of Eg5 kinesin.
In more detail, it has been unexpectedly found that these derivatives are potent and highly efficacious inhibitors of cellular (hyper)proliferation and/or cell-cycle specific inducers of apoptosis in cancer cells.
Therefore, these compounds can be particular useful for treating (hyper)proliferative diseases and/or disorders responsive to the induction of apoptosis, notably cancer. By having a cell-cycle specific mode of action, these derivatives should have a higher therapeutic index compared to standard chemotherapeutic drugs targeting basic cellular processes like DNA replication or interfering with basic cellular molecules like DNA.
Thus, for example, the compounds according to this invention are expected to be useful in targeted cancer therapy.

The invention thus relates to compounds of formula I



(I)

in which

R1 is hydrogen or halogen,

R2 is 1-4C-alkyl,

A is Aryl-1-4C-alkyl, in which

Aryl is phenyl, or R3- and R31-substituted phenyl, in which

R3 is 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, hydroxyl, halogen, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R31 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R5 is hydrogen or 1-4C-alkyl,

R6 is hydrogen or 1-4C-alkyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is 1-4C-alkyl, trifluoromethyl, cyano, 1-4C-alkoxy, halogen, carboxyl, 1-4C-alkylcarbonyl, methylenedioxy, ethylenedioxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R71 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

n is 2, 3, 4, 5 or 6,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

As used herein, “alkyl” alone or as part of another group refers to both branched and straight chain saturated aliphatic hydrocarbon groups having the specified numbers of carbon atoms, such as for example:
1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals, of which propyl, isopropyl, ethyl and methyl are more worthy to be mentioned.

Halogen within the meaning of the present invention is iodine or, in particular, bromine, chlorine or fluorine.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals, of which propoxy, isopropoxy, and, particularly, ethoxy and methoxy are more worthy to be mentioned.

The term “cycloalkyl” alone or as part of another group refers to a monocyclic saturated aliphatic hydrocarbon group having the specified numbers of carbon atoms, such as for example:
3-7C-Cycloalkyl stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopentyl, cyclobutyl and, in particular, cyclopropyl are more worthy to be mentioned.

3-7C-Cycloalkyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be

mentioned are the 3-7C-cycloalkylmethyl radicals, of which cyclopentylmethyl, cyclobutylmethyl and, in particular, cyclopropylmethyl are more worthy to be mentioned.

1-4C-Alkoxy-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-isopropoxyethyl, 2-ethoxyethyl, 2-methoxyethyl and, in particular, isopropoxymethyl, ethoxymethyl and, in more particular, methoxymethyl radical.

Hydroxy-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by a hydroxyl radical. Examples which may be mentioned are the 3-hydroxypropoxy, 2-hydroxyethyl and, in particular, hydroxymethyl radical.

Completely or predominantly fluorine-substituted 1-4C-alkoxy is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the trifluoromethoxy and the difluoromethoxy radicals are preferred. “Predominantly” in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy groups are replaced by fluorine atoms.

1-4C-Alkylcarbonyl is a carbonyl group, to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example is the acetyl radical (CH_3CO-).

Aryl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by an Aryl radical as defined below, such as e.g. the Aryl-methyl or 2-Aryl-ethyl radical, of which the Aryl-methyl radical is to be emphasized.

Aryl stands for phenyl, or R3- and R31-substituted phenyl.

Examples of the Aryl-1-4C-alkyl radical include the phenethyl and, particularly, the benzyl radical, each of which is optionally substituted by R3 and R31 on the phenyl moiety.

Suitable salts for compounds according to this invention - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically and/or pharmaceutically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable include, but are not limited to, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, phenylsulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being

employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom. Preferred are the salts selected from hydrochlorides, mesylates, tartrates, citrates, fumarates or sulfates.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula I or their pharmaceutically acceptable salts, are also included.

Pharmaceutically unacceptable salts, which can be obtained, for example, as process products during the preparation of the compounds according to this invention on an industrial scale, are converted into pharmaceutically acceptable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of formula I according to this invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I according to this invention as well as all solvates and in particular all hydrates of the salts of the compounds of formula I according to this invention.

In one embodiment of this invention, salts of compounds of formula I include a salt of a compound of formula I with hydrochloric acid (hydrochloride).

The substituents R3 and R31 of compounds of formula I can be attached in the ortho, meta or para position with respect to the binding position in which the Aryl ring is bonded to the 1-4C-alkyl group, whereby emphasis is given to the attachment of R3 in the meta or para position. In one embodiment R31 is hydrogen.

The substituents R7 and R71 of compounds of formula I can be attached in the ortho, meta or para position with respect to the binding position in which the phenyl ring is bonded to the carbonyl group, whereby emphasis is given to the attachment of R7 in the meta or para position. In one embodiment R71 is hydrogen.

In the context of this invention, hyperproliferation and analogous terms are used to describe aberrant / dysregulated cellular growth, a hallmark of diseases like cancer. This hyperproliferation might be caused by single or multiple cellular / molecular alterations in respective cells and can be, in context

of a whole organism, of benign or malignant behaviour. Inhibition of cell proliferation and analogous terms is used herein to denote an ability of the compound to retard the growth of and/or kill a cell contacted with that compound as compared to cells not contacted with that compound. Most preferable this inhibition of cell proliferation is 100%, meaning that proliferation of all cells is stopped and/or cells undergo programmed cell death. In some preferred embodiments the contacted cell is a neoplastic cell. A neoplastic cell is defined as a cell with aberrant cell proliferation and/or the potential to metastasize to different tissues or organs. A benign neoplasia is described by hyperproliferation of cells, incapable of forming an aggressive, metastasizing tumor in-vivo. In contrast, a malignant neoplasia is described by cells with different cellular and biochemical abnormalities, e.g. capable of forming tumor metastasis. The aquired functional abnormalities of malignant neoplastic cells (also defined as "hallmarks of cancer") are replicative potential ("hyperproliferation"), self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion from apoptosis, sustained angiogenesis and tissue invasion and metastasis.

Inducer of apoptosis and analogous terms are used herein to identify a compound which executes programmed cell death in cells contacted with that compound. Apoptosis is defined by complex biochemical events within the contacted cell, such as the activation of cystein specific proteinases ("caspases") and the fragmentation of chromatin. Induction of apoptosis in cells contacted with the compound might not necessarily be coupled with inhibition of cell proliferation. Preferably, the inhibition of cell proliferation and/or induction of apoptosis is specific to cells with aberrant cell growth (hyperproliferation). Thus, compared to cells with aberrant cell growth, normal proliferating or arrested cells are less sensitive or even insensitive to the proliferation inhibiting or apoptosis inducing activity of the compound. Finally, cytotoxic is used in a more general sense to identify compounds which kill cells by various mechanisms, including the induction of apoptosis / programmed cell death in a cell cycle dependent or cell-cycle independent manner.

Cell cycle specific and analogous terms are used herein to identify a compound as inducing apoptosis only in continously proliferating cells actively passing a specific phase of the cell cycle, but not in resting, non-dividing cells. Continously proliferating cells are typical for diseases like cancer and characterized by cells in all phases of the cell division cycle, namely in the G ("gap") 1, S ("DNA synthesis"), G2 and M ("mitosis") phase.

Compounds according to this invention worthy to be mentioned are those compounds of formula I, in which

R1 is hydrogen or halogen,

R2 is 1-2C-alkyl,

A is Aryl-1-2C-alkyl, in which

Aryl is phenyl, or R3- and R31-substituted phenyl, in which

R3 is 1-2C-alkyl, trifluoromethyl, 1-2C-alkoxy, hydroxyl, halogen, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R31 is hydrogen, halogen, 1-2C-alkyl or 1-2C-alkoxy,

R4 is hydrogen, 1-4C-alkyl, cyclopropyl or cyclopropyl-1-2C-alkyl,

R5 is hydrogen or 1-3C-alkyl,

R6 is hydrogen or 1-3C-alkyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is 1-2C-alkyl, trifluoromethyl, cyano, 1-2C-alkoxy, halogen, carboxyl, 1-2C-alkylcarbonyl, methylenedioxy, ethylenedioxy, 1-2C-alkoxy-1-2C-alkyl, hydroxy-1-2C-alkyl, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R71 is hydrogen, halogen, 1-2C-alkyl or 1-2C-alkoxy,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention more worthy to be mentioned are those compounds of formula I, in which

R1 is hydrogen or halogen,

R2 is methyl or ethyl,

A is Arylmethyl, in which

Aryl is phenyl, or R3- and R31-substituted phenyl, in which

R3 is methyl, ethyl, trifluoromethyl, methoxy, ethoxy, hydroxyl, halogen, difluoromethoxy or trifluoromethoxy,

R31 is hydrogen, halogen, methyl, ethyl, methoxy or ethoxy,

R4 is methyl, ethyl, propyl, isopropyl, sec-butyl, cyclopropyl or cyclopropylmethyl,

R5 is hydrogen, methyl, ethyl, propyl or isopropyl,

R6 is hydrogen, methyl, ethyl, propyl or isopropyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, cyano, methoxy, ethoxy, halogen, carboxyl, acetyl, methylenedioxy, ethylenedioxy, methoxymethyl, hydroxymethyl, difluoromethoxy or trifluoromethoxy,

R71 is hydrogen, halogen, methyl, ethyl, methoxy or ethoxy,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention in particular worthy to be mentioned are those compounds of formula I, in which

R1 is hydrogen, fluorine, chlorine or bromine,

R2 is methyl or ethyl,

A is Arylmethyl, in which

Aryl is phenyl, or R3- and R31-substituted phenyl, in which

R3 is methyl, ethyl, trifluoromethyl, methoxy, ethoxy, hydroxyl or halogen,

R31 is hydrogen, halogen, methyl or methoxy,

R4 is ethyl, propyl, isopropyl, sec-butyl, cyclopropyl or cyclopropylmethyl,

R5 is hydrogen, methyl, ethyl, propyl or isopropyl,

R6 is hydrogen, methyl, ethyl, propyl or isopropyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, cyano, methoxy, ethoxy, halogen, carboxyl, methylenedioxy, ethylenedioxy, methoxymethyl or hydroxymethyl,

R71 is hydrogen, halogen, methyl, ethyl or methoxy,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention in more particular worthy to be mentioned are those compounds of formula I, in which

R1 is hydrogen, chlorine or bromine,

R2 is methyl or ethyl,

A is benzyl, halobenzyl (e.g. fluorobenzyl, chlorobenzyl or bromobenzyl), methylbenzyl, methylhalobenzyl, methoxybenzyl, hydroxybenzyl, dihalobenzyl (e.g. dichlorobenzyl), or dimethoxybenzyl,

R4 is ethyl, propyl, isopropyl, sec-butyl, cyclopropyl or cyclopropylmethyl,

R5 is hydrogen, methyl, ethyl, propyl or isopropyl,

R6 is hydrogen, methyl, ethyl, propyl or isopropyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, cyano, methoxy, ethoxy, halogen, carboxyl, methylenedioxy, ethylenedioxy, methoxymethyl or hydroxymethyl,

R71 is hydrogen, halogen, methyl or ethyl,

such as, for example,

B is phenyl, methylphenyl, ethylphenyl, halophenyl, methylhalophenyl, (hydroxymethyl)phenyl, methoxyphenyl, ethoxyphenyl, trifluoromethylphenyl, halo(trifluoromethyl)phenyl, dihalophenyl, methylenedioxyphenyl, ethylenedioxyphenyl, (methoxymethyl)phenyl, methoxychlorophenyl, carboxyphenyl or cyanophenyl,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention in further more particular worthy to be mentioned are those compounds of formula I, in which

R1 is hydrogen, chlorine or bromine,

R2 is methyl or ethyl,

A is benzyl, halobenzyl (e.g. fluorobenzyl, chlorobenzyl or bromobenzyl), methylbenzyl, methoxybenzyl or hydroxybenzyl,

R4 is ethyl, propyl, isopropyl, sec-butyl or cyclopropyl,

either

R5 and R6 are both hydrogen,

or

R5 is methyl, and

R6 is hydrogen,

or

R5 is ethyl, and

R6 is hydrogen,

or

R5 is propyl, and

R6 is hydrogen,

or

R5 is isopropyl, and

R6 is hydrogen,

or

R5 and R6 are both methyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, cyano, methoxy, ethoxy, halogen, carboxyl, methylenedioxy, ethylenedioxy, methoxymethyl or hydroxymethyl,

R71 is hydrogen, halogen, methyl or ethyl,

such as, for example,

B is phenyl, methylphenyl, ethylphenyl, halophenyl, dihalophenyl, methylhalophenyl, (hydroxymethyl)phenyl, halo(trifluoromethyl)phenyl, trifluoromethylphenyl, methoxyphenyl, methylenedioxyphenyl or cyanophenyl,

such as, for more detailed example,

B is phenyl, 4-methylphenyl, 3-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 3-fluoro-4-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl or 2,3-dichlorophenyl,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention to be emphasized are those compounds of formula I, in which

R1 is hydrogen, chlorine or bromine,

particularly

R1 is chlorine or bromine,

R2 is methyl,

A is benzyl, fluorobenzyl, chlorobenzyl, bromobenzyl, methylbenzyl, methoxybenzyl or hydroxybenzyl,

in particular

A is benzyl or fluorobenzyl (e.g. 3-fluorobenzyl or 4-fluorobenzyl),

R4 is ethyl, propyl, isopropyl, sec-butyl or cyclopropyl,

either

R5 and R6 are both hydrogen,

or

R5 is methyl, and

R6 is hydrogen,

or

R5 is ethyl, and

R6 is hydrogen,

or

R5 and R6 are both methyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, fluorine, chlorine or bromine,

R71 is hydrogen, methyl, fluorine, chlorine or bromine,

such as, for example,

B is phenyl, methylphenyl, trifluoromethylphenyl, methoxyphenyl, halophenyl, dihalophenyl or methylhalophenyl,

such as, for more detailed example,

B is phenyl, methylphenyl, trifluoromethylphenyl, methoxyphenyl, fluorophenyl, chlorophenyl, bromophenyl, dichlorophenyl, difluorophenyl, methylfluorophenyl, methylchlorophenyl or methylbromophenyl,

such as, for yet more detailed example,

B is phenyl, 4-methylphenyl, 3-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 3-fluoro-4-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl or 3,4-dichlorophenyl,

n is 2 or 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention to be more emphasized are those compounds of formula I, in which

R1 is chlorine or bromine,

R2 is methyl,

A is benzyl or fluorobenzyl (e.g. 3-fluorobenzyl or 4-fluorobenzyl),

R4 is ethyl, propyl, isopropyl, sec-butyl or cyclopropyl,

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl,

B is phenyl, methylphenyl, trifluoromethylphenyl, methoxyphenyl, halophenyl, dihalophenyl or methylhalophenyl,

such as, for example,

B is methylphenyl, trifluoromethylphenyl, methoxyphenyl, fluorophenyl, chlorophenyl, bromophenyl, dichlorophenyl, difluorophenyl, methylfluorophenyl, methylchlorophenyl or methylbromophenyl,

such as, for more detailed example,

B is 4-methylphenyl, 3-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 3-fluoro-4-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl or 3,4-dichlorophenyl,

n is 2 or 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention to be in particular emphasized are those compounds of formula I, in which

R1 is chlorine or bromine,

R2 is methyl,

A is benzyl, 3-fluorobenzyl or 4-fluorobenzyl,

R4 is ethyl, propyl, isopropyl or cyclopropyl,

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl,

B is methylphenyl, trifluoromethylphenyl, methoxyphenyl, chlorophenyl, dichlorophenyl, bromophenyl, fluorophenyl or methylfluorophenyl,

such as, for example,

B is 4-methylphenyl, 3-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl or 3-fluoro-4-methylphenyl,

n is 2 or 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

In a preferred embodiment, the invention relates to compounds of formula I according to the invention, in which

R1 is hydrogen, chlorine or bromine,

R2 is methyl,

A is benzyl or fluorobenzyl,

R4 is ethyl, propyl, isopropyl, sec-butyl or cyclopropyl,

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl,

B is phenyl, methylphenyl, trifluoromethylphenyl, methoxyphenyl, halophenyl, dihalophenyl or methylhalophenyl,

n is 2 or 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention to be in more particular emphasized are those compounds of formula I, in which

R1 is chlorine or bromine,

R2 is methyl,

A is benzyl,

R4 is ethyl or isopropyl,

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl,

B is methylphenyl, chlorophenyl, trifluoromethylphenyl, methoxyphenyl, bromophenyl or fluorophenyl,

such as, for example,

B is 4-methylphenyl, 3-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-bromophenyl or 4-fluorophenyl,

n is 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention to be particularly emphasized are those compounds of formula I comprising one or more of the following:

R1 is chlorine or bromine;

R2 is methyl;

A is benzyl;

R4 is ethyl or isopropyl;

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl;

B is 4-methylphenyl, 3-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl or 3-fluoro-4-methylphenyl; and

n is 3;

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

Compounds according to this invention to be in further more particular emphasized are those compounds of formula I, in which

R1 is chlorine or bromine,

R2 is methyl,

A is benzyl,

R4 is isopropyl,

R5 and R6 are both hydrogen,

B is methylphenyl, chlorophenyl, trifluoromethylphenyl, methoxyphenyl, bromophenyl or fluorophenyl,

such as, for example,

B is 4-methylphenyl, 4-chlorophenyl or 4-bromophenyl,

n is 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

The invention also relates to compounds of formula I according to the invention comprising one or more of the following:

R1 is chlorine or bromine;

R2 is methyl;

A is benzyl;

R4 is isopropyl;

R5 and R6 are both hydrogen;

B is 4-methylphenyl, 4-chlorophenyl or 4-bromophenyl; and

n is 3;

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

In a further preferred embodiment, the invention relates to compounds of formula I in which

R1 is hydrogen, chlorine, bromine or fluorine,

R2 is methyl,

A is benzyl,

R4 is ethyl, isopropyl, sec-butyl, cyclopropyl or cyclobutyl,

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl,

B is 4-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 4-bromophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 3-fluoro-4-methylphenyl, 2-fluoro-4-methylphenyl, 3,4-dichlorophenyl or 2,3-dichlorophenyl,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

In a further preferred embodiment, the invention relates to compounds of formula I according to the invention, in which

R1 is hydrogen, chlorine or bromine,

R2 is methyl,

A is benzyl,

R4 is ethyl or isopropyl,
either
R5 and R6 are both hydrogen,
or
R5 and R6 are both methyl,
B is 4-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 4-bromophenyl, 4-chlorophenyl, 4-methoxyphenyl,
n is 3,
and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

In a further preferred embodiment, the invention relates to compounds of formula I in which
R1 is chlorine, bromine or fluorine,
R2 is methyl,
A is benzyl,
R4 is ethyl, isopropyl, sec-butyl or cyclopropyl,
R5 and R6 are both hydrogen,
B is 4-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 4-bromophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-fluoro-4-methylphenyl, 2-fluoro-4-methylphenyl or 3,4-dichlorophenyl,
n is 3 or 4,
and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

A special interest in the compounds according to this invention refers to those compounds of formula I which are included -within the scope of this invention- by one or, when possible, by a combination of more of the following special embodiments:

Another special embodiment (embodiment 1) of the compounds of formula I according to this invention refers to those compounds of formula I, in which
R1 is hydrogen.

Another special embodiment (embodiment 2) of the compounds of formula I according to this invention refers to those compounds of formula I, in which
R1 is chlorine.

Another special embodiment (embodiment 3) of the compounds of formula I according to this invention refers to those compounds of formula I, in which
R1 is bromine.

Another special embodiment (embodiment 3a) of the compounds of formula I according to this invention refers to those compounds of formula I, in which
R1 is fluorine.

Another special embodiment (embodiment 4) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R2 is methyl.

Another special embodiment (embodiment 5) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R1 is chlorine, and R2 is methyl.

Another special embodiment (embodiment 6) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R1 is bromine, and R2 is methyl.

A special embodiment (embodiment 7) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

A is benzyl.

Another special embodiment (embodiment 8) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

A is fluorobenzyl, such as e.g. 3-fluorobenzyl or 4-fluorobenzyl.

Another special embodiment (embodiment 9) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

A is benzyl, halobenzyl (such as e.g. chlorobenzyl or bromobenzyl), methylbenzyl, hydroxybenzyl or methoxybenzyl.

Another special embodiment (embodiment 10) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R4 is ethyl.

Another special embodiment (embodiment 11) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R4 is isopropyl.

Another special embodiment (embodiment 11a) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R1 is chlorine, and R2 is methyl, and

R4 is isopropyl.

Another special embodiment (embodiment 11b) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

A is benzyl, and

R4 is isopropyl.

Another special embodiment (embodiment 11c) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R1 is chlorine, and R2 is methyl, and

A is benzyl, and

R4 is isopropyl.

Another special embodiment (embodiment 12) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R4 is propyl.

Another special embodiment (embodiment 13) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R4 is cyclopropyl.

Another special embodiment (embodiment 13a) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R4 is cyclobutyl.

Another special embodiment (embodiment 14) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R4 is sec-butyl.

Another special embodiment (embodiment 15) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

n is 2.

Another special embodiment (embodiment 16) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

n is 3.

Another special embodiment (embodiment 17) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 and R6 are the same and selected from hydrogen, methyl and ethyl.

Another special embodiment (embodiment 18) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 is methyl, ethyl, propyl or isopropyl, and R6 is hydrogen.

Another special embodiment (embodiment 19) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 is methyl or ethyl, and R6 is hydrogen.

Another special embodiment (embodiment 20) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 and R6 are both hydrogen, and n is 2.

Another special embodiment (embodiment 21) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 and R6 are both methyl, and n is 2.

Another special embodiment (embodiment 22) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 and R6 are both hydrogen, and n is 3.

Another special embodiment (embodiment 23) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R5 and R6 are both methyl, and n is 3.

Another special embodiment (embodiment 24) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is fluorine, chlorine, bromine, methyl, trifluoromethyl or ethyl,

R71 is hydrogen, fluorine, chlorine or methyl.

Another special embodiment (embodiment 25) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is phenyl, halophenyl, dihalophenyl, cyanophenyl, halo(trifluoromethyl)phenyl, (hydroxymethyl)phenyl, (methoxymethyl)phenyl, methoxyphenyl, ethoxyphenyl, carboxyphenyl, methylphenyl, ethylphenyl, methylenedioxyphenyl, ethylenedioxyphenyl, methoxychlorophenyl, methylhalophenyl or (trifluoromethyl)phenyl.

Another special embodiment (embodiment 26) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is phenyl, methylphenyl, halophenyl (e.g. chlorophenyl or bromophenyl), dihalophenyl (e.g. dichlorophenyl), methylhalophenyl (e.g. methylfluorophenyl), (hydroxymethyl)phenyl, halo(trifluoromethyl)phenyl, methylenedioxyphenyl, (trifluoromethyl)phenyl, methoxyphenyl or cyanophenyl.

Another special embodiment (embodiment 27) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is methylphenyl, chlorophenyl, dichlorophenyl, bromophenyl, fluorophenyl, (trifluoromethyl)phenyl, methoxyphenyl or methylfluorophenyl.

Another special embodiment (embodiment 28) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is 4-methylphenyl, 3-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl or 3-fluoro-4-methylphenyl.

Another special embodiment (embodiment 29) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is 4-methylphenyl, 4-chlorophenyl or 4-bromophenyl.

Another special embodiment (embodiment 30) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

B is 4-methylphenyl.

Another special embodiment (embodiment 31) of the compounds of formula I according to this invention refers to those compounds which are from formula I* as shown below.

Another special embodiment (embodiment 32) of the compounds of formula I according to this invention refers to those compounds which are from formula I** as shown below.

A respective another special embodiment (embodiment 33 to 92) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R1 is bromine, R2 is methyl, and

A, R4, n, R5 and R6 have the respective meanings indicated in Table 1 given below.

Table 1:

embodiment	A	R4	n	R5	R6
33	benzyl	ethyl	2	H	H
34	3-fluorobenzyl	ethyl	2	H	H
35	4-fluorobenzyl	ethyl	2	H	H
36	benzyl	isopropyl	2	H	H
37	3-fluorobenzyl	isopropyl	2	H	H
38	4-fluorobenzyl	isopropyl	2	H	H
39	benzyl	sec-butyl	2	H	H

embodiment	A	R4	n	R5	R6
40	3-fluorobenzyl	sec-butyl	2	H	H
41	4-fluorobenzyl	sec-butyl	2	H	H
42	benzyl	cyclopropyl	2	H	H
43	3-fluorobenzyl	cyclopropyl	2	H	H
44	4-fluorobenzyl	cyclopropyl	2	H	H
45	benzyl	propyl	2	H	H
46	3-fluorobenzyl	propyl	2	H	H
47	4-fluorobenzyl	propyl	2	H	H
48	benzyl	ethyl	3	H	H
49	3-fluorobenzyl	ethyl	3	H	H
50	4-fluorobenzyl	ethyl	3	H	H
51	benzyl	isopropyl	3	H	H
52	3-fluorobenzyl	isopropyl	3	H	H
53	4-fluorobenzyl	isopropyl	3	H	H
54	benzyl	sec-butyl	3	H	H
55	3-fluorobenzyl	sec-butyl	3	H	H
56	4-fluorobenzyl	sec-butyl	3	H	H
57	benzyl	cyclopropyl	3	H	H
58	3-fluorobenzyl	cyclopropyl	3	H	H
59	4-fluorobenzyl	cyclopropyl	3	H	H
60	benzyl	propyl	3	H	H
61	3-fluorobenzyl	propyl	3	H	H
62	4-fluorobenzyl	propyl	3	H	H
63	benzyl	ethyl	2	methyl	methyl
64	3-fluorobenzyl	ethyl	2	methyl	methyl
65	4-fluorobenzyl	ethyl	2	methyl	methyl
66	benzyl	isopropyl	2	methyl	methyl
67	3-fluorobenzyl	isopropyl	2	methyl	methyl
68	4-fluorobenzyl	isopropyl	2	methyl	methyl
69	benzyl	sec-butyl	2	methyl	methyl
70	3-fluorobenzyl	sec-butyl	2	methyl	methyl
71	4-fluorobenzyl	sec-butyl	2	methyl	methyl
72	benzyl	cyclopropyl	2	methyl	methyl
73	3-fluorobenzyl	cyclopropyl	2	methyl	methyl
74	4-fluorobenzyl	cyclopropyl	2	methyl	methyl
75	benzyl	propyl	2	methyl	methyl
76	3-fluorobenzyl	propyl	2	methyl	methyl
77	4-fluorobenzyl	propyl	2	methyl	methyl
78	benzyl	ethyl	3	methyl	methyl
79	3-fluorobenzyl	ethyl	3	methyl	methyl
80	4-fluorobenzyl	ethyl	3	methyl	methyl
81	benzyl	isopropyl	3	methyl	methyl
82	3-fluorobenzyl	isopropyl	3	methyl	methyl
83	4-fluorobenzyl	isopropyl	3	methyl	methyl
84	benzyl	sec-butyl	3	methyl	methyl
85	3-fluorobenzyl	sec-butyl	3	methyl	methyl
86	4-fluorobenzyl	sec-butyl	3	methyl	methyl
87	benzyl	cyclopropyl	3	methyl	methyl
88	3-fluorobenzyl	cyclopropyl	3	methyl	methyl
89	4-fluorobenzyl	cyclopropyl	3	methyl	methyl
90	benzyl	propyl	3	methyl	methyl
91	3-fluorobenzyl	propyl	3	methyl	methyl
92	4-fluorobenzyl	propyl	3	methyl	methyl

A respective another special embodiment (embodiment 93 to 152) of the compounds of formula I according to this invention refers to those compounds of formula I, in which

R1 is chlorine, R2 is methyl, and

A, R4, n, R5 and R6 have the respective meanings indicated in Table 2 given below.

Table 2:

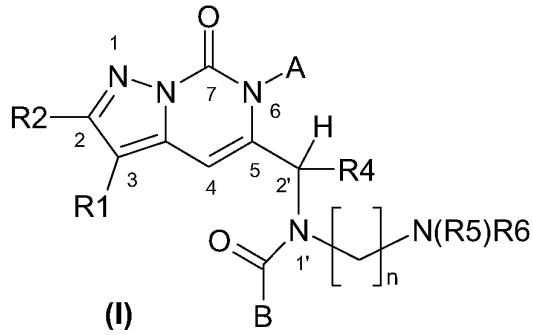
embodiment	A	R4	n	R5	R6
93	benzyl	ethyl	2	H	H
94	3-fluorobenzyl	ethyl	2	H	H
95	4-fluorobenzyl	ethyl	2	H	H
96	benzyl	isopropyl	2	H	H
97	3-fluorobenzyl	isopropyl	2	H	H
98	4-fluorobenzyl	isopropyl	2	H	H
99	benzyl	sec-butyl	2	H	H
100	3-fluorobenzyl	sec-butyl	2	H	H
101	4-fluorobenzyl	sec-butyl	2	H	H
102	benzyl	cyclopropyl	2	H	H
103	3-fluorobenzyl	cyclopropyl	2	H	H
104	4-fluorobenzyl	cyclopropyl	2	H	H
105	benzyl	propyl	2	H	H
106	3-fluorobenzyl	propyl	2	H	H
107	4-fluorobenzyl	propyl	2	H	H
108	benzyl	ethyl	3	H	H
109	3-fluorobenzyl	ethyl	3	H	H
110	4-fluorobenzyl	ethyl	3	H	H
111	benzyl	isopropyl	3	H	H
112	3-fluorobenzyl	isopropyl	3	H	H
113	4-fluorobenzyl	isopropyl	3	H	H
114	benzyl	sec-butyl	3	H	H
115	3-fluorobenzyl	sec-butyl	3	H	H
116	4-fluorobenzyl	sec-butyl	3	H	H
117	benzyl	cyclopropyl	3	H	H
118	3-fluorobenzyl	cyclopropyl	3	H	H
119	4-fluorobenzyl	cyclopropyl	3	H	H
120	benzyl	propyl	3	H	H
121	3-fluorobenzyl	propyl	3	H	H
122	4-fluorobenzyl	propyl	3	H	H
123	benzyl	ethyl	2	methyl	methyl
124	3-fluorobenzyl	ethyl	2	methyl	methyl
125	4-fluorobenzyl	ethyl	2	methyl	methyl
126	benzyl	isopropyl	2	methyl	methyl
127	3-fluorobenzyl	isopropyl	2	methyl	methyl
128	4-fluorobenzyl	isopropyl	2	methyl	methyl
129	benzyl	sec-butyl	2	methyl	methyl
130	3-fluorobenzyl	sec-butyl	2	methyl	methyl
131	4-fluorobenzyl	sec-butyl	2	methyl	methyl
132	benzyl	cyclopropyl	2	methyl	methyl
133	3-fluorobenzyl	cyclopropyl	2	methyl	methyl
134	4-fluorobenzyl	cyclopropyl	2	methyl	methyl
135	benzyl	propyl	2	methyl	methyl
136	3-fluorobenzyl	propyl	2	methyl	methyl
137	4-fluorobenzyl	propyl	2	methyl	methyl
138	benzyl	ethyl	3	methyl	methyl
139	3-fluorobenzyl	ethyl	3	methyl	methyl
140	4-fluorobenzyl	ethyl	3	methyl	methyl

embodiment	A	R4	n	R5	R6
141	benzyl	isopropyl	3	methyl	methyl
142	3-fluorobenzyl	isopropyl	3	methyl	methyl
143	4-fluorobenzyl	isopropyl	3	methyl	methyl
144	benzyl	sec-butyl	3	methyl	methyl
145	3-fluorobenzyl	sec-butyl	3	methyl	methyl
146	4-fluorobenzyl	sec-butyl	3	methyl	methyl
147	benzyl	cyclopropyl	3	methyl	methyl
148	3-fluorobenzyl	cyclopropyl	3	methyl	methyl
149	4-fluorobenzyl	cyclopropyl	3	methyl	methyl
150	benzyl	propyl	3	methyl	methyl
151	3-fluorobenzyl	propyl	3	methyl	methyl
152	4-fluorobenzyl	propyl	3	methyl	methyl

It is to be understood that the present invention includes any or all possible combinations and subsets of the special embodiments defined hereinabove.

The compounds of formula I, in which R4 is different from hydrogen, are chiral compounds having a chiral center in position 2'.

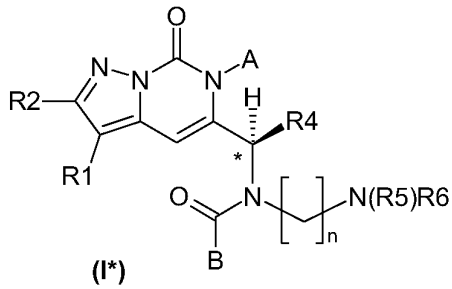
Numbering:



(I)

The invention includes all conceivable stereoisomers of the compounds of this invention, like e.g. diastereomers and enantiomers, in substantially pure form as well as in any mixing ratio, including the racemates, as well as the salts thereof.

In this connection, compounds of formula I worthy to be mentioned are those which have, with respect to the position 2', the same configuration as shown in formula I*:

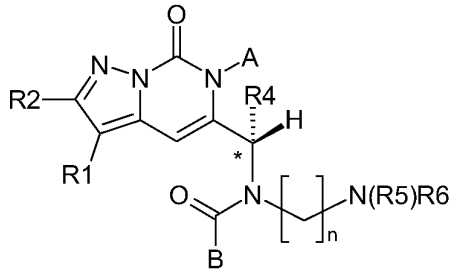


(I*)

In a preferred embodiment, the invention therefore relates to compounds of formula I as described in this application, wherein said compounds have the configuration as shown in formula I*, and the salts thereof.

If, for example, in compounds of formula I* R4 has the meaning methyl, ethyl, propyl, isopropyl, sec-butyl or cyclopropyl, then the configuration – according to the rules of Cahn, Ingold and Prelog – is R in the 2' position.

Further on, compounds of the formula I also worthy to be mentioned are those which have, with respect to the position 2', the same configuration as shown in formula I**:



(I**)

If, for example, in compounds of formula I** R4 has the meaning methyl, ethyl, propyl, isopropyl, sec-butyl or cyclopropyl, then the configuration – according to the rules of Cahn, Ingold and Prelog – is S in the position 2'.

In general, enantiomerically pure compounds of this invention may be prepared according to art-known processes, such as e.g. via asymmetric syntheses, for example by preparation and separation of appropriate diastereoisomeric compounds/intermediates, which can be separated by known methods (e.g. by chromatographic separation or (fractional) crystallization from a suitable solvent), or by using chiral synthons or chiral reagents; by chromatographic separation of the corresponding racemate on chiral separating columns; by means of diastereomeric salt formation of the racemic compounds with optically active acids (such as e.g. those mentioned below) or bases, subsequent resolution of the salts and release of the desired compound from the salt; by derivatization of the racemic compounds with chiral auxiliary reagents, subsequent diastereomer separation and removal

of the chiral auxiliary group; by resolution via diastereomeric inclusion compounds (e.g. complexes or clathrates); by kinetic resolution of a racemate (e.g. by enzymatic resolution); by enantioselective (preferential) crystallization (or crystallization by entrainment) from a conglomerate of enantiomorphous crystals under suitable conditions; or by (fractional) crystallization from a suitable solvent in the presence of a chiral auxiliary.

Thus, e.g. one possible alternative for enatiomer separation may be carried out at the stage of the compounds of formula I or of the starting compounds having a protonatable group, e.g. a free amino group, such as starting compounds of formula II as defined later. Hereby, separation of the enantiomers may be carried out, for example, by means of salt formation of the racemic compounds of formula II with optically active acids, preferably carboxylic acids, subsequent resolution of the salts and release of the desired compound from the salt. Examples of optically active carboxylic acids which may be mentioned in this connection, without being restricted thereto, are the enantiomeric forms of mandelic acid, tartaric acid, O,O'-dibenzoyltartaric acid, camphoric acid, quinic acid, glutamic acid, pyroglutamic acid, malic acid, camphorsulfonic acid, 3-bromocamphorsulfonic acid, α-methoxyphenylacetic acid, α-methoxy-α-trifluoromethylphenylacetic acid or 2-phenylpropionic acid or the like.

Another possible alternative for enantiomer separation may be carried out by chromatographic separation of a racemic mixture of compounds of formula I or of starting compounds thereof on a chiral separating column, such as e.g. described in the following examples or analogously or similarly thereto, using the appropriate separation conditions.

The enantiomers having the formula I* and the salts thereof are part of the invention.
The enantiomers having the formula I** and the salts thereof are also part of the invention.

Preference is given in this connection to those compounds of formula I which have with respect to the asymmetric -C(R4)H- atom (position 2') the same absolute configuration as the compound (+)-N-(3-amino-propyl)-N-[1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride having the specific optical rotation $[\alpha]_D^{20}$ = + 231 ° (c=0.4535, $CHCl_3$), as well as the salts thereof.

The invention therefore relates to compounds of formula I according to the invention, in which R4 is different from hydrogen, and which have with respect to the asymmetric -C(R4)H- atom the same absolute configuration as the compound (+)-N-(3-amino-propyl)-N-[1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride having the specific optical rotation $[\alpha]_D^{20}$= + 231 ° (c=0.4535, $CHCl_3$), as well as the salts thereof.

As exemplary compounds according to this invention the following compounds of formula I*, in which

R1 is bromine, and R2 is methyl,
and the salts thereof,
may be mentioned by means of the substituent meanings for A, R4, n, R5, R6 and B in the Table 3 given below.

As further exemplary compounds according to this invention the following compounds of formula I*, in which
R1 is chlorine, and R2 is methyl,
and the salts thereof,
may be mentioned by means of the substituent meanings for A, R4, n, R5, R6 and B in the Table 3 given below.

As further exemplary compounds according to this invention the following compounds of formula I*, in which
R1 is hydrogen, and R2 is methyl,
and the salts thereof,
may be mentioned by means of the substituent meanings for A, R4, n, R5, R6 and B in the Table 3 given below.

As further exemplary compounds according to this invention the following compounds of formula I**, in which
R1 is bromine, and R2 is methyl,
and the salts thereof,
may be mentioned by means of the substituent meanings for A, R4, n, R5, R6 and B in the Table 3 given below.

As further exemplary compounds according to this invention the following compounds of formula I**, in which
R1 is chlorine, and R2 is methyl,
and the salts thereof,
may be mentioned by means of the substituent meanings for A, R4, n, R5, R6 and B in the Table 3 given below.

As further exemplary compounds according to this invention the following compounds of formula I**, in which
R1 is hydrogen, and R2 is methyl,
and the salts thereof,
may be mentioned by means of the substituent meanings for A, R4, n, R5, R6 and B in the Table 3 given below.

Table 3:

	A	R4	n	R5	R6	B
1)	benzyl	ethyl	2	H	H	4-methylphenyl
2)	benzyl	ethyl	2	H	H	4-bromophenyl
3)	benzyl	ethyl	2	H	H	4-chlorophenyl
4)	benzyl	ethyl	2	H	H	4-methyl-3-fluorophenyl
5)	benzyl	ethyl	2	H	H	4-fluorophenyl
6)	benzyl	ethyl	2	H	H	4-trifluoromethylphenyl
7)	benzyl	ethyl	2	H	H	4-methoxyphenyl
8)	benzyl	ethyl	3	H	H	4-methylphenyl
9)	benzyl	ethyl	3	H	H	4-bromophenyl
10)	benzyl	ethyl	3	H	H	4-chlorophenyl
11)	benzyl	ethyl	3	H	H	4-methyl-3-fluorophenyl
12)	benzyl	ethyl	3	H	H	4-fluorophenyl
13)	benzyl	ethyl	3	H	H	4-trifluoromethylphenyl
14)	benzyl	ethyl	3	H	H	4-methoxyphenyl
15)	benzyl	ethyl	2	methyl	methyl	4-methylphenyl
16)	benzyl	ethyl	2	methyl	methyl	4-bromophenyl
17)	benzyl	ethyl	2	methyl	methyl	4-chlorophenyl
18)	benzyl	ethyl	2	methyl	methyl	4-methyl-3-fluorophenyl
19)	benzyl	ethyl	2	methyl	methyl	4-fluorophenyl
20)	benzyl	ethyl	2	methyl	methyl	4-trifluoromethylphenyl
21)	benzyl	ethyl	2	methyl	methyl	4-methoxyphenyl
22)	benzyl	ethyl	3	methyl	methyl	4-methylphenyl
23)	benzyl	ethyl	3	methyl	methyl	4-bromophenyl
24)	benzyl	ethyl	3	methyl	methyl	4-chlorophenyl
25)	benzyl	ethyl	3	methyl	methyl	4-methyl-3-fluorophenyl
26)	benzyl	ethyl	3	methyl	methyl	4-fluorophenyl
27)	benzyl	ethyl	3	methyl	methyl	4-trifluoromethylphenyl
28)	benzyl	ethyl	3	methyl	methyl	4-methoxyphenyl
29)	3-fluorobenzyl	ethyl	2	H	H	4-methylphenyl
30)	3-fluorobenzyl	ethyl	2	H	H	4-bromophenyl
31)	3-fluorobenzyl	ethyl	2	H	H	4-chlorophenyl
32)	3-fluorobenzyl	ethyl	2	H	H	4-methyl-3-fluorophenyl
33)	3-fluorobenzyl	ethyl	2	H	H	4-fluorophenyl
34)	3-fluorobenzyl	ethyl	2	H	H	4-trifluoromethylphenyl
35)	3-fluorobenzyl	ethyl	2	H	H	4-methoxyphenyl
36)	3-fluorobenzyl	ethyl	3	H	H	4-methylphenyl
37)	3-fluorobenzyl	ethyl	3	H	H	4-bromophenyl
38)	3-fluorobenzyl	ethyl	3	H	H	4-chlorophenyl
39)	3-fluorobenzyl	ethyl	3	H	H	4-methyl-3-fluorophenyl
40)	3-fluorobenzyl	ethyl	3	H	H	4-fluorophenyl
41)	3-fluorobenzyl	ethyl	3	H	H	4-trifluoromethylphenyl
42)	3-fluorobenzyl	ethyl	3	H	H	4-methoxyphenyl
43)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-methylphenyl
44)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-bromophenyl
45)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-chlorophenyl
46)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-methyl-3-fluorophenyl
47)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-fluorophenyl
48)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-trifluoromethylphenyl
49)	3-fluorobenzyl	ethyl	2	methyl	methyl	4-methoxyphenyl
50)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-methylphenyl
51)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-bromophenyl
52)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-chlorophenyl
53)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-methyl-3-fluorophenyl
54)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-fluorophenyl
55)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-trifluoromethylphenyl

	A	R4	n	R5	R6	B
56)	3-fluorobenzyl	ethyl	3	methyl	methyl	4-methoxyphenyl
57)	4-fluorobenzyl	ethyl	2	H	H	4-methylphenyl
58)	4-fluorobenzyl	ethyl	2	H	H	4-bromophenyl
59)	4-fluorobenzyl	ethyl	2	H	H	4-chlorophenyl
60)	4-fluorobenzyl	ethyl	2	H	H	4-methyl-3-fluorophenyl
61)	4-fluorobenzyl	ethyl	2	H	H	4-fluorophenyl
62)	4-fluorobenzyl	ethyl	2	H	H	4-trifluoromethylphenyl
63)	4-fluorobenzyl	ethyl	2	H	H	4-methoxyphenyl
64)	4-fluorobenzyl	ethyl	3	H	H	4-methylphenyl
65)	4-fluorobenzyl	ethyl	3	H	H	4-bromophenyl
66)	4-fluorobenzyl	ethyl	3	H	H	4-chlorophenyl
67)	4-fluorobenzyl	ethyl	3	H	H	4-methyl-3-fluorophenyl
68)	4-fluorobenzyl	ethyl	3	H	H	4-fluorophenyl
69)	4-fluorobenzyl	ethyl	3	H	H	4-trifluoromethylphenyl
70)	4-fluorobenzyl	ethyl	3	H	H	4-methoxyphenyl
71)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-methylphenyl
72)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-bromophenyl
73)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-chlorophenyl
74)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-methyl-3-fluorophenyl
75)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-fluorophenyl
76)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-trifluoromethylphenyl
77)	4-fluorobenzyl	ethyl	2	methyl	methyl	4-methoxyphenyl
78)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-methylphenyl
79)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-bromophenyl
80)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-chlorophenyl
81)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-methyl-3-fluorophenyl
82)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-fluorophenyl
83)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-trifluoromethylphenyl
84)	4-fluorobenzyl	ethyl	3	methyl	methyl	4-methoxyphenyl
85)	benzyl	isopropyl	2	H	H	4-methylphenyl
86)	benzyl	isopropyl	2	H	H	4-bromophenyl
87)	benzyl	isopropyl	2	H	H	4-chlorophenyl
88)	benzyl	isopropyl	2	H	H	4-methyl-3-fluorophenyl
89)	benzyl	isopropyl	2	H	H	4-fluorophenyl
90)	benzyl	isopropyl	2	H	H	4-trifluoromethylphenyl
91)	benzyl	isopropyl	2	H	H	4-methoxyphenyl
92)	benzyl	isopropyl	3	H	H	4-methylphenyl
93)	benzyl	isopropyl	3	H	H	4-bromophenyl
94)	benzyl	isopropyl	3	H	H	4-chlorophenyl
95)	benzyl	isopropyl	3	H	H	4-methyl-3-fluorophenyl
96)	benzyl	isopropyl	3	H	H	4-fluorophenyl
97)	benzyl	isopropyl	3	H	H	4-trifluoromethylphenyl
98)	benzyl	isopropyl	3	H	H	4-methoxyphenyl
99)	benzyl	isopropyl	2	methyl	methyl	4-methylphenyl
100)	benzyl	isopropyl	2	methyl	methyl	4-bromophenyl
101)	benzyl	isopropyl	2	methyl	methyl	4-chlorophenyl
102)	benzyl	isopropyl	2	methyl	methyl	4-methyl-3-fluorophenyl
103)	benzyl	isopropyl	2	methyl	methyl	4-fluorophenyl
104)	benzyl	isopropyl	2	methyl	methyl	4-trifluoromethylphenyl
105)	benzyl	isopropyl	2	methyl	methyl	4-methoxyphenyl
106)	benzyl	isopropyl	3	methyl	methyl	4-methylphenyl
107)	benzyl	isopropyl	3	methyl	methyl	4-bromophenyl
108)	benzyl	isopropyl	3	methyl	methyl	4-chlorophenyl
109)	benzyl	isopropyl	3	methyl	methyl	4-methyl-3-fluorophenyl
110)	benzyl	isopropyl	3	methyl	methyl	4-fluorophenyl
111)	benzyl	isopropyl	3	methyl	methyl	4-trifluoromethylphenyl

	A	R4	n	R5	R6	B
112)	benzyl	isopropyl	3	methyl	methyl	4-methoxyphenyl
113)	3-fluorobenzyl	isopropyl	2	H	H	4-methylphenyl
114)	3-fluorobenzyl	isopropyl	2	H	H	4-bromophenyl
115)	3-fluorobenzyl	isopropyl	2	H	H	4-chlorophenyl
116)	3-fluorobenzyl	isopropyl	2	H	H	4-methyl-3-fluorophenyl
117)	3-fluorobenzyl	isopropyl	2	H	H	4-fluorophenyl
118)	3-fluorobenzyl	isopropyl	2	H	H	4-trifluoromethylphenyl
119)	3-fluorobenzyl	isopropyl	2	H	H	4-methoxyphenyl
120)	3-fluorobenzyl	isopropyl	3	H	H	4-methylphenyl
121)	3-fluorobenzyl	isopropyl	3	H	H	4-bromophenyl
122)	3-fluorobenzyl	isopropyl	3	H	H	4-chlorophenyl
123)	3-fluorobenzyl	isopropyl	3	H	H	4-methyl-3-fluorophenyl
124)	3-fluorobenzyl	isopropyl	3	H	H	4-fluorophenyl
125)	3-fluorobenzyl	isopropyl	3	H	H	4-trifluoromethylphenyl
126)	3-fluorobenzyl	isopropyl	3	H	H	4-methoxyphenyl
127)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-methylphenyl
128)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-bromophenyl
129)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-chlorophenyl
130)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-methyl-3-fluorophenyl
131)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-fluorophenyl
132)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-trifluoromethylphenyl
133)	3-fluorobenzyl	isopropyl	2	methyl	methyl	4-methoxyphenyl
134)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-methylphenyl
135)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-bromophenyl
136)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-chlorophenyl
137)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-methyl-3-fluorophenyl
138)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-fluorophenyl
139)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-trifluoromethylphenyl
140)	3-fluorobenzyl	isopropyl	3	methyl	methyl	4-methoxyphenyl
141)	4-fluorobenzyl	isopropyl	2	H	H	4-methylphenyl
142)	4-fluorobenzyl	isopropyl	2	H	H	4-bromophenyl
143)	4-fluorobenzyl	isopropyl	2	H	H	4-chlorophenyl
144)	4-fluorobenzyl	isopropyl	2	H	H	4-methyl-3-fluorophenyl
145)	4-fluorobenzyl	isopropyl	2	H	H	4-fluorophenyl
146)	4-fluorobenzyl	isopropyl	2	H	H	4-trifluoromethylphenyl
147)	4-fluorobenzyl	isopropyl	2	H	H	4-methoxyphenyl
148)	4-fluorobenzyl	isopropyl	3	H	H	4-methylphenyl
149)	4-fluorobenzyl	isopropyl	3	H	H	4-bromophenyl
150)	4-fluorobenzyl	isopropyl	3	H	H	4-chlorophenyl
151)	4-fluorobenzyl	isopropyl	3	H	H	4-methyl-3-fluorophenyl
152)	4-fluorobenzyl	isopropyl	3	H	H	4-fluorophenyl
153)	4-fluorobenzyl	isopropyl	3	H	H	4-trifluoromethylphenyl
154)	4-fluorobenzyl	isopropyl	3	H	H	4-methoxyphenyl
155)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-methylphenyl
156)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-bromophenyl
157)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-chlorophenyl
158)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-methyl-3-fluorophenyl
159)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-fluorophenyl
160)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-trifluoromethylphenyl
161)	4-fluorobenzyl	isopropyl	2	methyl	methyl	4-methoxyphenyl
162)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-methylphenyl
163)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-bromophenyl
164)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-chlorophenyl
165)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-methyl-3-fluorophenyl
166)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-fluorophenyl
167)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-trifluoromethylphenyl

	A	R4	n	R5	R6	B
168)	4-fluorobenzyl	isopropyl	3	methyl	methyl	4-methoxyphenyl
169)	benzyl	cyclopropyl	2	H	H	4-methylphenyl
170)	benzyl	cyclopropyl	2	H	H	4-bromophenyl
171)	benzyl	cyclopropyl	2	H	H	4-chlorophenyl
172)	benzyl	cyclopropyl	2	H	H	4-methyl-3-fluorophenyl
173)	benzyl	cyclopropyl	2	H	H	4-fluorophenyl
174)	benzyl	cyclopropyl	2	H	H	4-trifluoromethylphenyl
175)	benzyl	cyclopropyl	2	H	H	4-methoxyphenyl
176)	benzyl	cyclopropyl	3	H	H	4-methylphenyl
177)	benzyl	cyclopropyl	3	H	H	4-bromophenyl
178)	benzyl	cyclopropyl	3	H	H	4-chlorophenyl
179)	benzyl	cyclopropyl	3	H	H	4-methyl-3-fluorophenyl
180)	benzyl	cyclopropyl	3	H	H	4-fluorophenyl
181)	benzyl	cyclopropyl	3	H	H	4-trifluoromethylphenyl
182)	benzyl	cyclopropyl	3	H	H	4-methoxyphenyl
183)	benzyl	cyclopropyl	2	methyl	methyl	4-methylphenyl
184)	benzyl	cyclopropyl	2	methyl	methyl	4-bromophenyl
185)	benzyl	cyclopropyl	2	methyl	methyl	4-chlorophenyl
186)	benzyl	cyclopropyl	2	methyl	methyl	4-methyl-3-fluorophenyl
187)	benzyl	cyclopropyl	2	methyl	methyl	4-fluorophenyl
188)	benzyl	cyclopropyl	2	methyl	methyl	4-trifluoromethylphenyl
189)	benzyl	cyclopropyl	2	methyl	methyl	4-methoxyphenyl
190)	benzyl	cyclopropyl	3	methyl	methyl	4-methylphenyl
191)	benzyl	cyclopropyl	3	methyl	methyl	4-bromophenyl
192)	benzyl	cyclopropyl	3	methyl	methyl	4-chlorophenyl
193)	benzyl	cyclopropyl	3	methyl	methyl	4-methyl-3-fluorophenyl
194)	benzyl	cyclopropyl	3	methyl	methyl	4-fluorophenyl
195)	benzyl	cyclopropyl	3	methyl	methyl	4-trifluoromethylphenyl
196)	benzyl	cyclopropyl	3	methyl	methyl	4-methoxyphenyl
197)	3-fluorobenzyl	cyclopropyl	2	H	H	4-methylphenyl
198)	3-fluorobenzyl	cyclopropyl	2	H	H	4-bromophenyl
199)	3-fluorobenzyl	cyclopropyl	2	H	H	4-chlorophenyl
200)	3-fluorobenzyl	cyclopropyl	2	H	H	4-methyl-3-fluorophenyl
201)	3-fluorobenzyl	cyclopropyl	2	H	H	4-fluorophenyl
202)	3-fluorobenzyl	cyclopropyl	2	H	H	4-trifluoromethylphenyl
203)	3-fluorobenzyl	cyclopropyl	2	H	H	4-methoxyphenyl
204)	3-fluorobenzyl	cyclopropyl	3	H	H	4-methylphenyl
205)	3-fluorobenzyl	cyclopropyl	3	H	H	4-bromophenyl
206)	3-fluorobenzyl	cyclopropyl	3	H	H	4-chlorophenyl
207)	3-fluorobenzyl	cyclopropyl	3	H	H	4-methyl-3-fluorophenyl
208)	3-fluorobenzyl	cyclopropyl	3	H	H	4-fluorophenyl
209)	3-fluorobenzyl	cyclopropyl	3	H	H	4-trifluoromethylphenyl
210)	3-fluorobenzyl	cyclopropyl	3	H	H	4-methoxyphenyl
211)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-methylphenyl
212)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-bromophenyl
213)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-chlorophenyl
214)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-methyl-3-fluorophenyl
215)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-fluorophenyl
216)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-trifluoromethylphenyl
217)	3-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-methoxyphenyl
218)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-methylphenyl
219)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-bromophenyl
220)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-chlorophenyl
221)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-methyl-3-fluorophenyl
222)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-fluorophenyl
223)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-trifluoromethylphenyl

	A	R4	n	R5	R6	B
224)	3-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-methoxyphenyl
225)	4-fluorobenzyl	cyclopropyl	2	H	H	4-methylphenyl
226)	4-fluorobenzyl	cyclopropyl	2	H	H	4-bromophenyl
227)	4-fluorobenzyl	cyclopropyl	2	H	H	4-chlorophenyl
228)	4-fluorobenzyl	cyclopropyl	2	H	H	4-methyl-3-fluorophenyl
229)	4-fluorobenzyl	cyclopropyl	2	H	H	4-fluorophenyl
230)	4-fluorobenzyl	cyclopropyl	2	H	H	4-trifluoromethylphenyl
231)	4-fluorobenzyl	cyclopropyl	2	H	H	4-methoxyphenyl
232)	4-fluorobenzyl	cyclopropyl	3	H	H	4-methylphenyl
233)	4-fluorobenzyl	cyclopropyl	3	H	H	4-bromophenyl
234)	4-fluorobenzyl	cyclopropyl	3	H	H	4-chlorophenyl
235)	4-fluorobenzyl	cyclopropyl	3	H	H	4-methyl-3-fluorophenyl
236)	4-fluorobenzyl	cyclopropyl	3	H	H	4-fluorophenyl
237)	4-fluorobenzyl	cyclopropyl	3	H	H	4-trifluoromethylphenyl
238)	4-fluorobenzyl	cyclopropyl	3	H	H	4-methoxyphenyl
239)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-methylphenyl
240)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-bromophenyl
241)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-chlorophenyl
242)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-methyl-3-fluorophenyl
243)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-fluorophenyl
244)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-trifluoromethylphenyl
245)	4-fluorobenzyl	cyclopropyl	2	methyl	methyl	4-methoxyphenyl
246)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-methylphenyl
247)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-bromophenyl
248)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-chlorophenyl
249)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-methyl-3-fluorophenyl
250)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-fluorophenyl
251)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-trifluoromethylphenyl
252)	4-fluorobenzyl	cyclopropyl	3	methyl	methyl	4-methoxyphenyl
253)	benzyl	sec-butyl	2	H	H	4-methylphenyl
254)	benzyl	sec-butyl	2	H	H	4-bromophenyl
255)	benzyl	sec-butyl	2	H	H	4-chlorophenyl
256)	benzyl	sec-butyl	2	H	H	4-methyl-3-fluorophenyl
257)	benzyl	sec-butyl	2	H	H	4-fluorophenyl
258)	benzyl	sec-butyl	2	H	H	4-trifluoromethylphenyl
259)	benzyl	sec-butyl	2	H	H	4-methoxyphenyl
260)	benzyl	sec-butyl	3	H	H	4-methylphenyl
261)	benzyl	sec-butyl	3	H	H	4-bromophenyl
262)	benzyl	sec-butyl	3	H	H	4-chlorophenyl
263)	benzyl	sec-butyl	3	H	H	4-methyl-3-fluorophenyl
264)	benzyl	sec-butyl	3	H	H	4-fluorophenyl
265)	benzyl	sec-butyl	3	H	H	4-trifluoromethylphenyl
266)	benzyl	sec-butyl	3	H	H	4-methoxyphenyl
267)	benzyl	sec-butyl	2	methyl	methyl	4-methylphenyl
268)	benzyl	sec-butyl	2	methyl	methyl	4-bromophenyl
269)	benzyl	sec-butyl	2	methyl	methyl	4-chlorophenyl
270)	benzyl	sec-butyl	2	methyl	methyl	4-methyl-3-fluorophenyl
271)	benzyl	sec-butyl	2	methyl	methyl	4-fluorophenyl
272)	benzyl	sec-butyl	2	methyl	methyl	4-trifluoromethylphenyl
273)	benzyl	sec-butyl	2	methyl	methyl	4-methoxyphenyl
274)	benzyl	sec-butyl	3	methyl	methyl	4-methylphenyl
275)	benzyl	sec-butyl	3	methyl	methyl	4-bromophenyl
276)	benzyl	sec-butyl	3	methyl	methyl	4-chlorophenyl
277)	benzyl	sec-butyl	3	methyl	methyl	4-methyl-3-fluorophenyl
278)	benzyl	sec-butyl	3	methyl	methyl	4-fluorophenyl
279)	benzyl	sec-butyl	3	methyl	methyl	4-trifluoromethylphenyl

	A	R4	n	R5	R6	B
280)	benzyl	sec-butyl	3	methyl	methyl	4-methoxyphenyl
281)	3-fluorobenzyl	sec-butyl	2	H	H	4-methylphenyl
282)	3-fluorobenzyl	sec-butyl	2	H	H	4-bromophenyl
283)	3-fluorobenzyl	sec-butyl	2	H	H	4-chlorophenyl
284)	3-fluorobenzyl	sec-butyl	2	H	H	4-methyl-3-fluorophenyl
285)	3-fluorobenzyl	sec-butyl	2	H	H	4-fluorophenyl
286)	3-fluorobenzyl	sec-butyl	2	H	H	4-trifluoromethylphenyl
287)	3-fluorobenzyl	sec-butyl	2	H	H	4-methoxyphenyl
288)	3-fluorobenzyl	sec-butyl	3	H	H	4-methylphenyl
289)	3-fluorobenzyl	sec-butyl	3	H	H	4-bromophenyl
290)	3-fluorobenzyl	sec-butyl	3	H	H	4-chlorophenyl
291)	3-fluorobenzyl	sec-butyl	3	H	H	4-methyl-3-fluorophenyl
292)	3-fluorobenzyl	sec-butyl	3	H	H	4-fluorophenyl
293)	3-fluorobenzyl	sec-butyl	3	H	H	4-trifluoromethylphenyl
294)	3-fluorobenzyl	sec-butyl	3	H	H	4-methoxyphenyl
295)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-methylphenyl
296)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-bromophenyl
297)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-chlorophenyl
298)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-methyl-3-fluorophenyl
299)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-fluorophenyl
300)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-trifluoromethylphenyl
301)	3-fluorobenzyl	sec-butyl	2	methyl	methyl	4-methoxyphenyl
302)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-methylphenyl
303)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-bromophenyl
304)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-chlorophenyl
305)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-methyl-3-fluorophenyl
306)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-fluorophenyl
307)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-trifluoromethylphenyl
308)	3-fluorobenzyl	sec-butyl	3	methyl	methyl	4-methoxyphenyl
309)	4-fluorobenzyl	sec-butyl	2	H	H	4-methylphenyl
310)	4-fluorobenzyl	sec-butyl	2	H	H	4-bromophenyl
311)	4-fluorobenzyl	sec-butyl	2	H	H	4-chlorophenyl
312)	4-fluorobenzyl	sec-butyl	2	H	H	4-methyl-3-fluorophenyl
313)	4-fluorobenzyl	sec-butyl	2	H	H	4-fluorophenyl
314)	4-fluorobenzyl	sec-butyl	2	H	H	4-trifluoromethylphenyl
315)	4-fluorobenzyl	sec-butyl	2	H	H	4-methoxyphenyl
316)	4-fluorobenzyl	sec-butyl	3	H	H	4-methylphenyl
317)	4-fluorobenzyl	sec-butyl	3	H	H	4-bromophenyl
318)	4-fluorobenzyl	sec-butyl	3	H	H	4-chlorophenyl
319)	4-fluorobenzyl	sec-butyl	3	H	H	4-methyl-3-fluorophenyl
320)	4-fluorobenzyl	sec-butyl	3	H	H	4-fluorophenyl
321)	4-fluorobenzyl	sec-butyl	3	H	H	4-trifluoromethylphenyl
322)	4-fluorobenzyl	sec-butyl	3	H	H	4-methoxyphenyl
323)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-methylphenyl
324)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-bromophenyl
325)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-chlorophenyl
326)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-methyl-3-fluorophenyl
327)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-fluorophenyl
328)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-trifluoromethylphenyl
329)	4-fluorobenzyl	sec-butyl	2	methyl	methyl	4-methoxyphenyl
330)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-methylphenyl
331)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-bromophenyl
332)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-chlorophenyl
333)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-methyl-3-fluorophenyl
334)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-fluorophenyl
335)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-trifluoromethylphenyl

	A	R4	n	R5	R6	B
336)	4-fluorobenzyl	sec-butyl	3	methyl	methyl	4-methoxyphenyl

The compounds according to the invention can be prepared e.g. as described as follows and according to the following specified reaction steps, or, particularly, in a manner as described by way of example in the following examples, or analogously or similarly thereto according to preparation procedures or synthesis strategies known to the person skilled in the art.

As shown in the synthesis route outlined in scheme 1 below, the trione compound of formula IX, in which R2 has the meanings given above (particularly, R2 is methyl), is condensed and cyclized with semicarbazide (H_2N-C(O)-$NHNH_2$*HCl) to give the corresponding pyrazolopyrimidone compounds of formula VIII. Said cyclocondensation reaction can be carried out as it is habitual for the skilled person or as described in the following examples or analogously or similarly thereto, in the presence of a suitable base (e.g. sodium carbonate) in a suitable solvent, for example water, at elevated temperature.

Compounds of formula IX, in which R2 has the meanings given above, particularly methyl, are known or can be prepared according to known procedures or as described in the following examples, or analogously or similarly thereto. Thus, e.g. compounds of formula IX can be obtained from corresponding compounds of formula X by alkaline hydrolysis

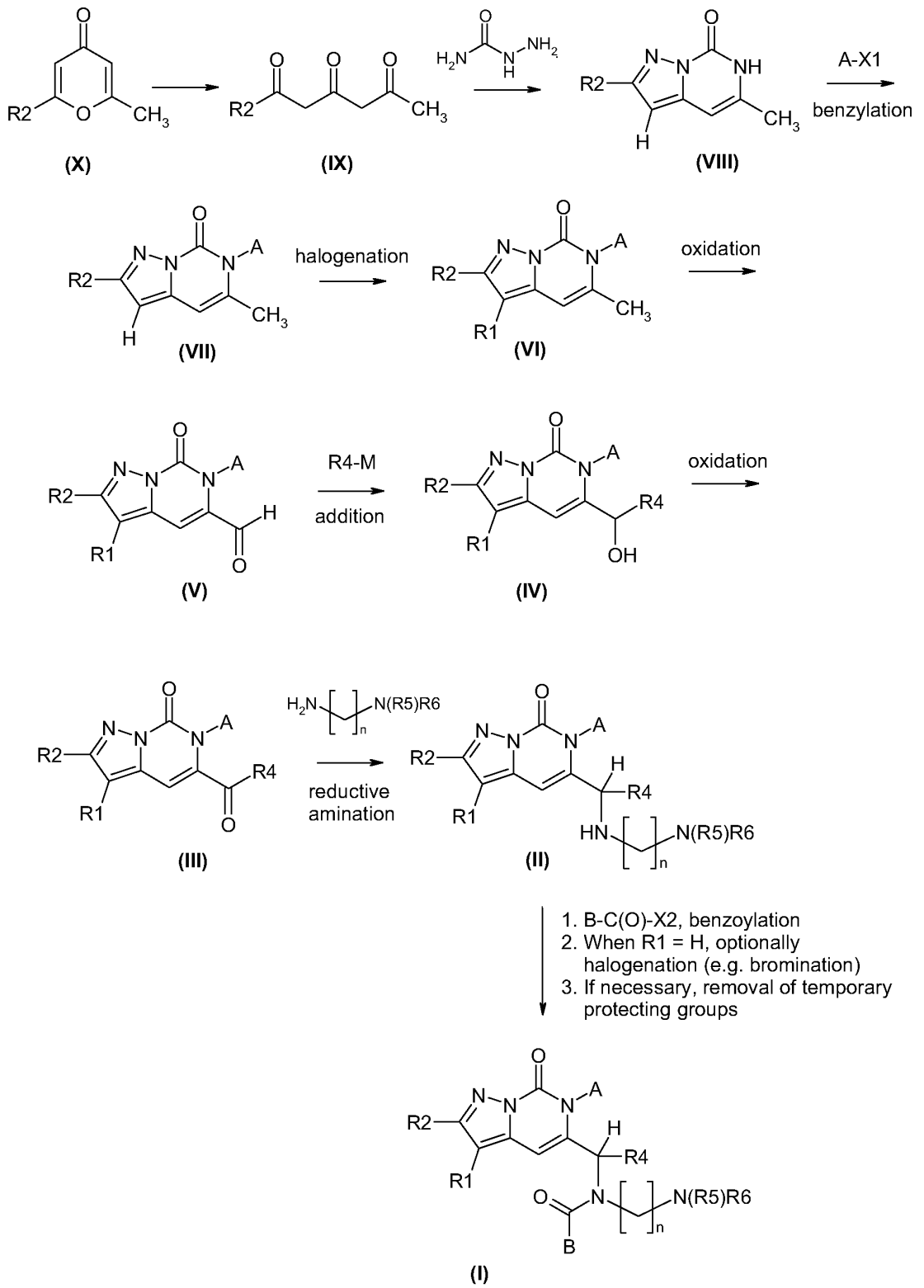
Compounds of formula X are known or can be obtained according to known procedures.

Compounds of formula VIII are benzylated with compounds of formula A-X1, in which A has the meanings given above and X1 is a suitable leaving group (e.g. halogen or the like), in a standard manner or as described exemplarily in the following examples to give corresponding compounds of formula VII.

Compounds of formula VII, in which R2 and A have the meanings given above, are halogenated using a suitable halogenating reagent under appropriate conditions to obtain corresponding compounds of formula VI, in which R2 and A have the meanings given above and R1 is halogen, in particular fluorine or, in more particular, chlorine or bromine. Said halogenation reaction can be carried out according to customary procedures or as described in the following examples, or analogously or similarly thereto.

Thus, chlorination or bromination reaction can be carried out using an appropriate electrophilic chlorinating or brominating reagent, e.g. N-chlorosuccinimide (NCS) or N-bromosuccinimide (e.g. NBS / AIBN), respectively, under conditions customary for the skilled person or as described in the following examples.

Reaction scheme 1:



Fluorination reaction may be carried out using a suitable electrophilic fluorinating reagent, such as e.g. 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (Selectfluor I) or 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (Selectfluor II) or the like, under appropriate conditions.

Using appropriate conditions, said halogenation reaction is carried out largely regioselectively to obtain halogenation on the pyrazole moiety of the pyrazolopyrimidone scaffold, i.e. the 3-position of the pyrazolopyrimidone scaffold.

The methyl group attached to the pyrimidone moiety of the pyrazolopyrimidone of compounds of formula VI, in which R1 is halogen and A and R2 have the meanings given above, is oxidized under suitable conditions to obtain corresponding compounds of formula V. Said oxidation is carried out in a manner habitual for the skilled person or as described in the following examples using a suitable oxidation reagent, e.g. selenium dioxide, to give largely regioselectively the 5-formyl derivative of formula V.

Compounds of formula V, in which R1 is halogen and A and R2 have the meanings given above, are reacted in a nucleophilic addition reaction with compounds of formula R4-M, in which R4 is different from hydrogen and has the meanings given above and M is a suitable metal or metal complex, to give corresponding compounds of formula IV. Said nucleophilic addition reaction can be obtained using organomagnesium halides (Grignard reagents) of formula R4-Mg-X (X = Halogen) with or without further additives (e.g. LiCl or alkyl lithium reagents). Advantageously said reaction is carried out in the presence of alkyl lithium reagents, e.g. methyl lithium, forming in situ more reactive organomagnesium reagents, e.g. lithium trialkyl magnesiates such as $R4Me_2MgLi$ from 2 equiv. LiMe and 1 equiv. R4-Mg-X. The nucleophilic addition reaction can be carried out in a manner customary for the skilled person or as described in the following examples.

When compounds of formula V, in which R1 is bromine, are reacted with Grignard reagents in said nucleophilic addition reaction, debromination of the 3-bromo substituent can be obtained depending on the reaction conditions to give corresponding compounds of formula IV, in which R1 is hydrogen. Said debromination is performed as described in the following examples.

Alcohols of formula IV, in which R1 is hydrogen, fluorine or chlorine and A, R2 and R4 have the meanings given above, are converted into the corresponding ketones of formula III by oxidation reaction using an appropriate oxidation reagent, such as e.g. NMO (N-methylmorpholine-N-oxide) / TPAP (tetrapropylammonium perruthenate) or the like, under conditions known for the skilled person or as described in the following examples.

Compounds of formula III, in which R1 is hydrogen, fluorine or chlorine and A, R2 and R4 have the meanings given above, are subjected to a reductive amination reaction with amines of formula H_2N-$(CH_2)_n$-N(R5)R6, in which n has the meanings indicated above and R5 and R6 stand for a suitable temporary protective group PG1 or for the meanings given above with the exception that R5 and R6 are not hydrogen, to afford corresponding compounds of formula II in a manner which is habitual for the skilled person or which is described in the following examples. In more detail, in a first step of the reductive amination reaction the reaction partners are reacted in the presence of a suitable Lewis acid, e.g. a suitable titanium reagent like titanium(IV)isopropoxide, to give the corresponding imine compounds, which are reduced in a second step, such as with the aid of a suitable reducing reagent, e.g. a suitable hydride like a borohydride (e.g. $NaCNBH_3$, $NaBH_4$ or $Na(OAc)_3BH$) or the like, Raney-Ni or in the presence of hydrogen/transition metal catalyst (e.g. H_2/Pd).

PG1 stands for a suitable temporary protective group for the amino group, for example tert-butoxycarbonyl, benzyloxycarbonyl or 4-methoxy-benzyloxycarbonyl or one of those art-known protective groups mentioned in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

Compounds of formula II, in which R1 is hydrogen, fluorine or chlorine and A, n, R2 and R4 have the meanings given above and R5 and R6 stand for a suitable temporary protective group PG1 as defined above or for the meanings given above with the exception that R5 and R6 are not hydrogen, are benzoylated with compounds of formula B-C(O)-X2, in which B has the meanings given above and X2 is a suitable leaving group (e.g. chlorine), to give corresponding compounds of formula I.

Compounds of formula I, in which R1 is hydrogen and A, n, B, R2 and R4 have the meanings given above and R5 and R6 stand for a suitable temporary protective group PG1 as defined above or for the meanings given above with the exception that R5 and R6 are not hydrogen, can be halogenated, particularly brominated, using a suitable halogenating reagent (for bromination e.g. NBS) under appropriate conditions to obtain corresponding further compounds of formula I, in which R1 is halogen. Said halogenation reaction can be carried out according to customary procedures, such as those mentioned above, or as described in the following examples, or analogously or similarly thereto.

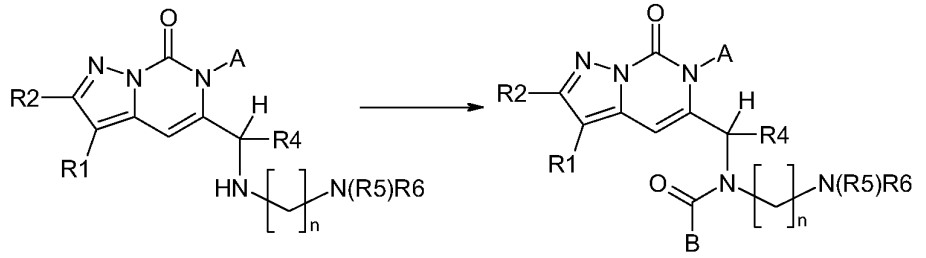
Compounds of formula I, in which R1, A, n, B, R2 and R4 have the meanings given above and R5 and R6 stand for a suitable temporary protective group PG1 as defined above, are deprotected by removal of said protecting group PG1 in a manner known to the person skilled in the art or as described in the following examples to give corresponding deprotected compounds of formula I.

Compounds of formula I, in which R5 and R6 are 1-4C-alkyl, e.g. methyl, and in which R1, A, n, B, R2 and R4 have the meanings given above, can be obtained by the methods described above, starting from compounds of formula I, in which R5 and R6 are 1-4C-alkyl, e.g. methyl, and in which R1, A, n,

B, R2 and R4 have the meanings given above. Alternatively, compounds of formula I, in which R5 and R6 are 1-4C-alkyl, e.g. methyl, and in which R1, A, n, B, R2 and R4 have the meanings given above, can be obtained by alkylation, e.g. methylation, of compounds of formula I, in which R5 and R6 are hydrogen. Alternatively, these compounds of formula I, in which R5 and R6 are 1-4C-alkyl, e.g. methyl, can be obtained by any other method that is known to the person skilled in the art.

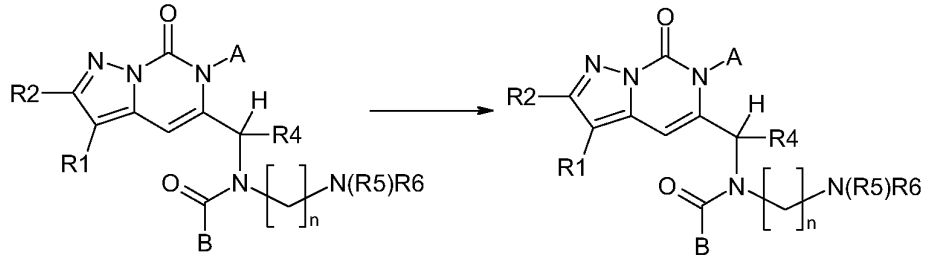
The invention therefore relates to a process for preparing a compound as described in this application, comprising at least one of the steps

(i) benzoylation of a compound of formula II, with the meanings of R1, R2, A, R4, R5 and R6 as indicated for the compounds according to the invention, or with at least one of R5 and R6 being part of a protective group,



(II) **(I)**

(ii) halogenation of a compound of formula I wherein R1 = H to give a compound of formula I wherein R1 = halogen, or



(I) R1 = H **(I)** R1 = halogen

(iii) optionally the removal of protecting groups represented by at least one of R5 and R6 as indicated under (i).

Optionally, compounds of the formula I can be converted into their salts, or, optionally, salts of the compounds of the formula I can be converted into the free compounds. Corresponding processes are customary for the skilled person.

When one of the final steps or purification is carried out under the presence of an inorganic or organic acid (e.g. hydrochloric, trifluoroacetic, acetic or formic acid or the like), the compounds of formula I may be obtained - depending on their individual chemical nature and the individual nature of the acid used - as free base or containing said acid in an stoechiometric or non-stoechiometric quantity. The amount of the acid contained can be determined according to art-known procedures, e.g. by titration.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

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

Salts can be obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low-molecular-weight aliphatic alcohol, such as methanol, ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts can be obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted into the free compounds, which can in turn be converted into salts, by alkalization or by acidification. In this manner, pharmacologically and/or pharmaceutically unacceptable salts can be converted into pharmacologically and/or pharmaceutically acceptable salts.

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art.

The person skilled in the art may know on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds according to this invention. All these other possible synthesis routes are also part of this invention.

The present invention also relates to intermediates (including their salts, stereosiomers as well as salts of these stereoisomers), methods and processes useful in synthesizing compounds according to this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivatizations, homologisations and adaptations to the described invention can be made on the base of art-known knowledge and/or, particularly, on the base of the

disclosure (e.g. the explicite, implicite or inherent disclosure) of the present invention without departing from the spirit and scope of this invention as defined by the appended claims.

The following examples illustrate the invention in greater detail without restricting it. Likewise, further compounds according to this invention, of which the preparation is not explicitly described, can be prepared in an analogous or similar manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

Any or all of the compounds of formula I according to the present invention which are mentioned as final compounds in the following examples, as well as the salts, stereoisomers and salts of the stereoisomers thereof, are a preferred subject of the present invention.

In the examples, m.p. stands for melting point, h for hour(s), min for minutes, conc. for concentrated, calc. for calculated, fnd. for found, EF for elemental formula, MS for mass spectrometry, M for molecular ion in mass spectrometry, TFA for trifluoroacetic acid, and other abbreviations have their meanings customary per se to the skilled person.

Further on, according to common practice in stereochemistry, the term "(RS)" characterizes a racemate comprising the one enantiomer having the configuration R and the other enantiomer having the configuration S; each of these enantiomers and their salts in pure form as well as their mixtures including the racemic mixtures is part of this invention.

Examples

Final compounds

1. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride

150 mg {3-[[1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (0.26 mmol) are solved in 1 ml diethylether. 10 ml HCl in diethylether (ca. 4 N) are added and the suspension is stirred 1 h at ambient temperature. Afterwards the suspension is evaporated, the colorless solid is washed twice with diethylether and dried in vacuo. By this method 120 mg (91%) of a colorless solid are obtained.

M.p.: 235–250 °C (decomposition).

MS: m/z (MH^+) = 472.1.

2. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride

150 mg {3-[[1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert butyl ester (0.26 mmol) are solved in 1 ml diethylether, 4 ml HCl in diethylether (ca. 4N) are added and the mixture is stirred 1 h at ambient temperature. Afterwards the suspension is evaporated, the colorless solid is washed twice with diethylether and dried in vacuo. By this method 135 mg (88%) of a colorless solid are obtained.

M.p.: > 190 °C (decomposition).

MS: m/z (MH^+) = 550.0, 552.0.

3. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3-methyl-benzamide; isolated as trifluoroacetate salt

0.144 g (1.0 eq) {3-[[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-m-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester is dissolved in 8 mL dichloromethane and treated with 2 mL trifluoro acetic acid. After stirring 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and yields after drying 0.108 g (73%) of the title compound as a trifluoroacetate.

M.p. 162 °C.

MS: m/z (MH^+) = 520.1, 522.1.

4. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-fluoro-benzamide; isolated as trifluoroacetate salt

0.090 g (1.0 eq) (3-{[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-fluoro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester is dissolved in 6 mL dichloromethane and treated with 1.5 mL trifluoro acetic acid. After stirring 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and yields after drying 0.068 g (75%) of the title compound as a trifluoroacetate.

M.p. 182 °C.

MS: m/z (MH^+) = 524.1, 526.1.

5. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methoxy-benzamide; isolated as trifluoroacetate salt

0.014 g (1.0 eq) (3-{[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-methoxy-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester is dissolved in 0.8 mL dichloromethane and treated with 0.2 mL trifluoro acetic acid. After stirring 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and yields after drying 0.007 g (48%) of the title compound as a trifluoroacetate.

M.p. 149 °C.

MS: m/z (MH^+) = 536.1, 538.1.

6. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-bromo-benzamide; isolated as trifluoroacetate salt

0.153 g (1.0 eq) (3-{[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester is dissolved in 10 mL dichloromethane and treated with 2.5 mL trifluoro acetic acid. After stirring 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and yields after drying 0.086 g (55%) of the title compound as a trifluoroacetate.

M.p. 204-205 °C (decomposition).

MS: m/z (MH^+) = 584.0, 585.9, 587.9.

7. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-chloro-benzamide; isolated as trifluoroacetate salt

0.130 g (1.0 eq) (3-{[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-chloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester is dissolved in 8 mL dichloromethane and treated with 2 mL trifluoro acetic acid. After stirring 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and yields after drying 0.075 g (56%) of the title compound as a trifluoroacetate.

M.p. 199-201 °C (decomposition).

MS: m/z (MH^+) = 540.0, 542.0, 544.0.

8. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride

0.129 g (1.0 eq) {3-[[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (compound A8) is dissolved in 20 mL of a 1 M solution of hydrochloric acid in diethylether at ambient temperature. After stirring for 16 hours the precipitate is filtered off and washed with diethylether. This yields after drying 0.083 g (71%) of the title compound as a hydrochloride salt.

M.p. 183 °C.

MS: m/z (MH^+) = 520.0, 522.1.

Separation of enantiomers:

8a. (+)-N-(3-Amino-propyl)-N-[1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride (assumed (R)-isomer) and

8b. (-)-N-(3-Amino-propyl)-N-[1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride (assumed (S)-isomer)

1.79 g of racemic N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride are separated into its enantiomers by preparative HPLC (column: CHIRALPAK AD 10 µm, 250 x 20 mm; mobile phase: n-Heptane / ethanol / diethylamine 80:20:0.1 (v/v/v); flow rate: 30 ml/min; detection: UV 230 nm; temperature: 25 °C).

The enantiomers elute at 7.49 min and 13.95 min. Both isomers are isolated by solving in dichloromethane and treatment with 4M solution of HCl in dioxane. After stirring for 6 hours at ambient temperature, the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo.

The HCl-salt of the first eluting enantiomer (τ = 7.49 min, > 99.5 % ee, 94 % purity, 556 mg, example 8a) has an optical rotation of $[\alpha]_D^{20}$ = +225 ° (c = 1.02, dichloromethane), a melting point of 203-263 °C (decomposition) and MS: m/z (MH^+) = 519.8, 521.9.

The HCl-salt of the second eluting enantiomer (τ = 13.95 min, > 98 % ee, > 99 % purity, 870 mg, example 8b) has an optical rotation of $[\alpha]_D^{20}$ = -205 ° (c = 0.725, dichloromethane), a melting point of 206-233 °C (decomposition) and MS: m/z (MH^+) = 520.1, 522.0.

The absolute stereochemistry of (+)-N-(3-Amino-propyl)-N-[1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride (8a) is tentatively assigned to the enantiomer with the R-configuration (+)-N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride. Consequently, the S-configuration is assigned to the (-)-enantiomer.

Furthermore, a variety of salts of compound 8, 8a and 8b is prepared:

8c. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide phosphate

100 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) are suspended in 1 mL ethanol and heated at reflux until the amine is completely dissolved. 13.1 µL phosphoric acid (85% in water, 1.0 eq) are added and the mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded (after 30 min ultrasonification) in a white slurry that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 63 mg (53%) of the title compound. There are slight impurities of diethylether and diethylammonium phosphate.

M.p.: foaming at 123 °C, melting 160-205 °C (decomposition).

MS: m/z (MH^+) = 519.9, 522.1.

8d. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide semi fumarate

100 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) and 22.3 mg of fumaric acid (1.0 eq) are suspended in 1 mL ethanol and heated at reflux for 2 minutes. The mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 61 mg (55%) of the title compound. There are slight impurities of diethylether and diethylammonium fumarate. The semi fumarate is elucidated by NMR spectroscopy.

M.p.: sinter from 140 °C on, melting 195-215 °C (decomposition).

MS: m/z (MH^+) = 519.9, 522.1.

8e. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide sulfate

100 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) are suspended in 1 mL ethanol and heated at reflux until the amine is completely dissolved. 10.2 µL sulfuric acid (1.0 eq) are added and the mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry (after 15 min ultrasonification) that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 73 mg (62%) of the title compound. There are slight impurities of diethylether and diethylammonium sulfate.

M.p.: foaming at 130 °C, melting 198-209 °C (decomposition).

MS: m/z (MH^+) = 519.9, 522.1.

8f. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide sesqui citrate

100 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) and 37 mg of citric acid (1.0 eq) are suspended in 1 mL ethanol and heated at reflux for 2 minutes. The mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded (after 15 min ultrasonification) in a white slurry that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 85 mg (55%) of the title compound. There are slight impurities of diethylether and diethylammoniu**m citrate. The sesqui citrate is** elucidated by NMR spectroscopy.

M.p.: sinter from 110 °C on, melting 160-191 °C (decomposition).

MS: m/z (MH^+) = 520.0, 522.0.

8g. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (D)-tartrate

100 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) and 29 mg of D-tartaric acid (1.0 eq) are suspended in 1 mL ethanol and heated at reflux for 2 minutes. The mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded (after 20 min ultrasonification) in a white slurry that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 98 mg (76%) of the title compound. There are slight impurities of diethylether and diethylammonium tartrate. The mono tartrate is elucidated by NMR spectroscopy.

M.p.: foaming at 100 °C, melting 162-176 °C (decomposition).

MS: m/z (MH^+) = 519.9, 522.0.

8h. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide mesylate

100 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) are suspended in 1 mL ethanol and heated at reflux until the amine is completely dissolved. 12.5 µL methane sulfonic acid (1.0 eq) are added and the mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry (after 15 min ultrasonification) that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 63 mg (53%) of the title compound. There are slight impurities of diethylether and diethylammonium mesylate. The mono mesylate is elucidated by NMR spectroscopy.

M.p.: melting 150-214 °C (decomposition).

MS: m/z (MH^+) = 520.0, 522.0.

8i. N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide benzoate

50 mg of (-)-N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8b) are suspended in 1 mL ethanol and heated at reflux until the amine is completely dissolved. 11.8 mg benzoic acid (1.0 eq) are added and the mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry (after 10 min ultrasonification) that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 29 mg (47%) of the title compound. There are slight impurities of diethylether and diethylammonium benzoate. The mono benzoate is elucidated by NMR spectroscopy.

M.p.: sinter from 145 °C, melting 160-175 °C (decomposition).

MS: m/z (MH^+) = 520.0, 522.0.

8j. N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide mesylate

60 mg of (-)-N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8a) are suspended in 1 mL ethanol and heated at reflux until the amine is completely dissolved. 7.5 µL methane sulfonic acid (1.0 eq) are added and the mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry (after 10 min ultrasonification) that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 63 mg (89%) of the title compound. The mono mesylate is elucidated by NMR spectroscopy.

M.p.: foaming at 125 °C, melting 190-198 °C (decomposition).

MS: m/z (MH^+) = 519.9, 521.9.

8k. N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide fumarate

59 mg of (-)-N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8a) and 13.2 mg of fumaric acid (1.0 eq) are suspended in 1 mL ethanol and heated at reflux for 2 minutes. The mixture is stirred for 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 73 mg (quant.) of the title compound. The mono fumarate is elucidated by NMR spectroscopy.

M.p.: sinter from 165 °C on, melting 190-200 °C (decomposition).

MS: m/z (MH^+) = 520.0, 522.0.

8l. N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide tosylate

58 mg of (-)-N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (example 8a) and 21.2 mg of p-toluenesulfonic acid monohydrate (1.0 eq) are suspended in 1 mL ethanol and heated at reflux for 2 minutes. The mixture is stirred for another 5 minutes without heating anymore. Evaporation of the solvent and subsequent addition of diethylether yielded in a white slurry that is filtered and washed with several portions of diethylether. The colorless solid is dried in vacuo to yield 65 mg (85%) of the title compound. The mono tosylate is elucidated by NMR spectroscopy.

M.p.: sinter from 160 °C on, melting 170-175 °C (decomposition).

MS: m/z (MH^+) = 519.9, 522.0.

9. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride

{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester (5.00 g, 8.2 mmol) is treated with HCl/diethylether (4N, 100 mL), stirred for 1h at ambient temperature, the solvents are evaporated and the residue is washed with diethylether. 3.90 g (87 %) of the title compuond are obtained as colorless solid with m.p. 201–203 °C.

MS: m/z (MH^+) = 506.0, 508.1.

Separation of enantiomers:

N-(3-Amino-propyl)-N-[(R)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride and

N-(3-Amino-propyl)-N-[(S)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride

The separation of the enantiomers of racemic N-(3-amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride is performed by preparative chromatography: 250 x 20 mm CHIRALPAK AD-H 5µM, 0.7 ml/min of ethanol + 0.1% diethylamine at 40 °C:

The enantiomers elute at 6.59 and 15.38 min. Both enantiomers are isolated by mixing with 1N HCl in diethylether and stirring in this mixture. The mixture is evaporated and the residue is dissolved in a mixture of water and acetonitrile and lyophilized.

The first eluting enantiomer (6.59 min, example 9a) has a MH^+ of 506.1 (ee = 97.9%) and at Na 589nm at 20°C in $CHCl_3$ (0.4535 g/100ml) $[\alpha]_D^{20}$ = + 226 °. Thus, enantiomerically pure (+)-N-(3-Amino-propyl)-N-[1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide hydrochloride has $[\alpha]_D^{20}$ = + 231 ° (c=0.4535, $CHCl_3$).

The second eluting enantiomer (15.38 min, example 9b) has a MH^+ of 506.0 (ee = 99.7%).

The absolute stereochemistry of the (+)-isomer (9a) is tentatively assigned to the enantiomer with the R-configuration. Consequently, the S-configuration is assigned to the (-)-enantiomer (9b).

10. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-trifluoromethyl-benzamide trifluoroacetate

81 mg of (3-{[(RS)-1-6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-trifluoromethyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound A10) are dissolved in 4 mL dichloromethane and 1.5 mL trifluoroacetic acid. After stirring this mixture for 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 64 mg (78%) of the title compound are obtained as colorless solid.

M.p.: 218 °C.

MS: m/z (MH^+) = 574.0, 575.9.

Using similar procedures to those described herein above but with suitable choice of the starting materials, which are mentioned below, the following compounds of formula I (especially in form of their hydrochloride salts) may be prepared:

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-3-methyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-fluoro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methoxy-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-bromo-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-chloro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-trifluoromethyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-3-methyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-fluoro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methoxy-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-bromo-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-chloro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-trifluoromethyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-3-methyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-fluoro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methoxy-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-bromo-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-chloro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-trifluoromethyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3-methyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-fluoro-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methoxy-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-bromo-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-chloro-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-trifluoromethyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3-methyl-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-fluoro-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methoxy-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-bromo-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-chloro-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-trifluoromethyl-benzamide

N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-methyl-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-3-methyl-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-fluoro-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-methoxy-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-bromo-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-chloro-benzamide
N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-trifluoromethyl-benzamide

11. N-[(RS)-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide

A solution of 89 mg (1.0 eq) 6-Benzyl-3-chloro-5-[(RS)-1-(3-dimethylamino-propylamino)-2-methyl-propyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound A11), 87 μL (3.0 eq) triethylamine and 33 μL (1.2 eq) 4-methylbenzoyl chloride in 2 mL dichloromethane is stirred for 16 hours at ambient temperature. The product is extracted between dichloromethane and a saturated $NaHCO_3$-solution, the organic phase is dried over magnesium sulfate and the crude product is purified by preparative HPLC. 20 mg (17%) of the title compound is isolated by means of lyophilization.

M.p.: sinter at 71-72 °C and melting at 88-91 °C.

MS: m/z (MH^+) = 548.1, 550.2.

Using similar procedures to those described for Example 11 but with suitable choice of the starting materials, which are mentioned below, and the appropriate benzoic acid derivatives the following compounds of formula I may be prepared:

N-[(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-3-methyl-benzamide

N-[(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-fluoro-benzamide

N-[(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-methoxy-benzamide

N-[(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-bromo-benzamide

N-[(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-chloro-benzamide

N-[(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-trifluoromethyl-benzamide

12. N-(4-Amino-butyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide trifluoroacetate

126 mg of {4-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-butyl}-carbamic acid tert-butyl ester (compound A12) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 85 mg (66%) of the title compound are obtained as colorless foam.

M.p.: 179-182 °C.

MS: m/z (MH^+) = 534.1, 536.1.

13. N-(2-Amino-ethyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide

164 mg of {2-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-ethyl}-carbamic acid tert-butyl ester (compound A13) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 1 hour at ambient temperature the solvent is removed. Addition of dichloromethane and basification with saturated aqueous $NaHCO_3$-solution followed by extraction of the aqueous phase with dichloromethane results after drying over magnesium sulfate and evaporation of the solvent in 145 mg (quant.) of the title compound.

M.p.: 119-120 °C.

MS: m/z (MH^+) = 506.1, 507.9.

14. N-(2-Amino-ethyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide trifluoroacetate

125 mg of {2-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-ethyl}-carbamic acid tert-butyl ester (compound A13) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 70 mg (55%) of the title compound are obtained as colorless solid.

M.p.: 173-174 °C.

MS: m/z (MH^+) = 506.0, 508.0.

15. N-[(RS)-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(2-dimethylamino-ethyl)-4-methyl-benzamide

A mixture of 70 mg N-(2-Amino-ethyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide (compound 13), 33 µL formalin and 52 µL formic acid is heated for 8 hours at 100 °C. After cooling, the crude product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 100:0 to 90:10. This yielded 35 mg (46%) of the title compound as colorless solid.

M.p.: 94-95 °C.

MS: m/z (MH^+) = 534.0, 536.0.

16. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo [1,5-c]pyrimidin-5-yl)-1-cyclobutyl-methyl]-4-methyl-benzamide trifluoroacetate

159 mg of {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclobutyl-methyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (compound A14) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 1 hour at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry

that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 140 mg (87%) of the title compound are obtained as colorless solid.

M.p.: sinter at 158-179 °C and melting at 180-185 °C.

MS: m/z (MH^+) = 532.0, 534.1.

17. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-methyl-benzamide trifluoroacetate

60 mg of {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (compound A15) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 1.5 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 43 mg (70%) of the title compound are obtained as colorless solid.

M.p.: 179-182 °C.

MS: m/z (MH^+) = 534.0, 535.8.

18. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-4-methyl-benzamide hydrochloride

80 mg of {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (compound A16) dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 2 hours at ambient temperature the solvent is removed. The residue is dissolved in dichloromethane and treated with saturated aqueous $NaHCO_3$-solution. Extraction of the aqueous layer followed by drying over MgSO4 results in the free base of the title compound. The solvent is evaporated and the residue is treated with 1M HCl in diethylether. The precipitate is filtered, washed with diethylether and dried in vacuo. This afforded 18 mg (26%) of the title compound as colorless solid.

M.p.: 156-158 °C.

MS: m/z (MH^+) = 518.0, 520.1.

19. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-4-bromo-benzamide trifluoroacetate

34 mg of (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound A17) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 21 mg (60%) of the title compound are obtained as colorless solid.

M.p.: 178-180 °C (decomposition).

MS: m/z (MH^+) = 581.9, and also MH^++2 and MH^++4.

20. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide trifluoroacetate

104 mg of (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(3-fluoro-4-methyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound A18) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 1.5 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 61 mg (57%) of the title compound are obtained as pale yellow solid.

M.p.: 140-158 °C (decomposition).

MS: m/z (MH^+) = 537.9, 540.0.

21. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-2-fluoro-4-methyl-benzamide trifluoroacetate

83 mg of (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(2-fluoro-4-methyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound A19) are dissolved in 4 mL dichloromethane and 1 mL trifluoroacetic acid. After stirring this mixture for 2 hours at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 39 mg (46%) of the title compound are obtained as colorless powder.

M.p.: sinter 178-181 °C and melting at 182-192 °C.

MS: m/z (MH^+) = 538.0, 539.9.

22. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3,4-dichloro-benzamide trifluoroacetate

88 mg of (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(3,4-dichloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound A20) are dissolved in 2 mL dichloromethane and 0.5 mL trifluoroacetic acid. After stirring this mixture for 1 hour at ambient temperature the solvent is removed. Addition of diethylether results in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 37 mg (41%) of the title compound are obtained as colorless solid.

M.p.: 184-185 °C.

MS: m/z (MH^+) = 573.8, 575.9, 577.8.

23. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-2,3-dichloro-benzamide trifluoroacetate

67 mg of (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(2,3-dichloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound A21) are dissolved in 2 mL dichloromethane and 0.5 mL trifluoroacetic acid. After stirring this mixture for 1 hour at ambient temperature the solvent is removed. Addition of diethylether results

in a white slurry that is filtered. The precipitate is washed with diethylether and dried in vacuo. By this method 31 mg (46%) of the title compound are obtained as colorless solid.

M.p.: 187-188 °C.

MS: m/z (MH^+) = 573.9, 576.0, 577.8.

24. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride

87 mg of {3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(4-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester (compound A22) are dissolved in 4 M HCl in dioxane. After stirring this mixture for 3 hour at ambient temperature the solvent is removed. By this method 78 mg (quant.) of the title compound are obtained as colorless solid.

MS: m/z (MH^+) = 563.9, 566.0.

25. N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide hydrochloride

155 mg of {3-[[(RS)-1-(6-Benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (compound A24) are dissolved in 2 mL dioxane and treated with 4 M HCl in dioxane (3 mL). After stirring this mixture for 3 hour at ambient temperature the solvent is removed. By this method 80 mg (57%) of the title compound are obtained as colorless solid.

MS: m/z (MH^+) = 504.0.

Starting materials:

Some of the compounds in this section have an optionally substituted benzoyl group, which may be designated in the systematic name as phenyl-carbonyl group or alternatively, as a phenyl-methanoyl group. A special substituted phenyl group in this connection is the m-tolyl group (3-methyl-phenyl) or the p-tolyl group (4-methyl-phenyl).

A1. {3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

393 mg {3-[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propylamino]-propyl}-carbamic acid tert-butyl ester (0.87 mmol) (compound B1) are solved in 5 ml dichlormethane, afterwards 0.37 ml triethylamine (2.61 mmol) and 161 mg 4-Methyl-benzoyl chloride (1.04 mmol) are added and the reaction mixture is stirred 4 h at ambient temperature. The product is extracted between CH_2Cl_2 and saturated $NaHCO_3$-solution, the organic phase is dried over sodium sulphate and the crude product is purified by silica gel flash chromatography. By this method 377 mg (77%) of a colorless solid are obtained.

A2. {3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

220 mg {3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester (0.38 mmol) (compound A1) are solved in 2ml dichloromethane. 70 mg N-Bromo-succinimide (0.39 mmol) are added and the reaction mixture is stirred 4 h at ambient temperature. The product is extracted between CH_2Cl_2 and saturated $NaHCO_3$-solution. The organic layer is dried over sodium sulfate. The solvents are evaporated and the crude product is purified by silica gel flash chromatography. By this method 170 mg (69 %) of a colorless solid are obtained.

M.p.: 95–97 °C.

A3. {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-m-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester

0.300 g (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 0.095 mL (1.2 eq) m-toluoyl chloride and 0.248 mL (3.0 eq) triethylamine are dissolved in 3 mL dichloromethane and stirred for 48 hours at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous sodium hydrogen carbonate solution the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using n-hexane and ethyl acetate in a mixture of 3:2 povides a mixture of starting material and the title compound. A second silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and

acetic acid from 39:59:2 to 0:100:0 yields 0.151 g (41%) of the title compound as a white solid. Furthermore 0.105 g (35%) of the starting material is recovered.

M.p. 83.9 °C.

MS: m/z (MH^+) = 619.9, 621.9.

A4. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-fluoro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

0.300 g (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 0.085 mL (1.2 eq) 4-fluorobenzoyl chloride and 0.248 mL (3.0 eq) triethylamine are dissolved in 3 mL dichloromethane and stirred for 48 hours at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous sodium hydrogen carbonate solution the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using gradient of n-hexane, ethyl acetate and acetic acid from 59:39:2 to 0:100:0 provides the title compound with some impurities and the pure starting material (0.190 g, 63%). A second silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yields 0.096 g (26%) of the title compound as a white solid.

M.p. 143.0 °C (foam).

MS: m/z (MH^+) = 623.9, 625.9.

A5. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-methoxy-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

0.300 g (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 0.122 g (1.2 eq) p-anisoyl chloride and 0.248 mL (3.0 eq) triethylamine are dissolved in 3 mL dichloromethane and stirred for 48 hours at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous sodium hydrogen carbonate solution the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using of n-hexane, ethyl acetate and acetic acid in a mixture of 39:59:2 yields 0.018 g (5%) of the title compound as a white solid.

M.p. 115.7 °C (decomposition).

MS: m/z (MH^+) = 635.9, 637.9.

A6. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

0.300 g (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 0.158 mg (1.2 eq) p-bromobenzoyl chloride and 0.248 mL (3.0 eq) triethylamine are dissolved in 3 mL dichloromethane

and stirred for 48 hours at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous sodium hydrogen carbonate solution the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using n-hexane and ethyl acetate in a mixture of 3:2 povides a mixture of starting material and the title compound. A second silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yields 0.159 g (39%) of the title compound as a white solid. Furthermore 0.180 g (60%) of the starting material are recovered.

M.p. 96 °C (foam).

MS: m/z (MH^+) = 683.8, 685.8, 687.8.

A7. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-chloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

0.300 g (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 0.092 mL (1.2 eq) 4-chlorobenzoyl chloride and 0.248 mL (3.0 eq) triethylamine are dissolved in 3 mL dichloromethane and stirred for 48 hours at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous sodium hydrogen carbonate solution the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using n-hexane and ethyl acetate in a mixture of 3:2 povides a mixture of starting material and the title compound. A second silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yields 0.160 g (42%) of the title compound as a white solid. Furthermore 0.170 g (57%) of the starting material is recovered.

M.p. 93 °C (foam).

MS: m/z (MH^+) = 639.9, 641.8, MH^++4.

A8. {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester

0.405 g (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 0.336 mL (1.2 eq) 4-methylbenzoyl chloride and 0.128 mL (3.0 eq) triethylamine are dissolved in 4 mL dichloromethane and stirred for 16 hours at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous sodium hydrogen carbonate solution the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yield 0.145 g (29%) of the title compound as a white solid. Furthermore 0.259 g (64%) of the starting material are recovered.

M.p. 92-94 °C, sinter 82 °C.

MS: m/z (MH^+) = 619.9, MH^++2.

A9. {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

{3-[1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propylamino]-propyl}-carbamic acid *tert*-butyl ester (4.00 g, 8.2 mmol) (compound B2) is dissolved in dichlormethane (40 mL), treated with triethylamine (3.6 mL, 24.6 mmol) and 4-methylbenzoyl chloride (1.30 mL, 9.8 mmol) and stirred 15 h at ambient temperature. It is diluted with dichlormethane, washed with aqueous $NaHCO_3$-solution and the organic phase is dried. After evaporation, the residue is purified by chromatography. 4.5 g (90 %) of a colorless solid of m.p. 80–82 °C is obtained.

A10. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-trifluoromethyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A solution of 200 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 88 µL (1.5 eq) 4-(trifluoromethyl)-benzoyl chloride with catalytic amount of DMAP in 10 mL pyridine is heated for 16 hours at 70 °C. Evaporation of the pyridine followed by two times coevaporation with toluene results in the crude product. This material is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. By this method 102 mg (38%) of the title compound are obtained as a colorless solid.

M.p.: 106-108 °C.

MS: m/z (MH^+) = 673.9, 675.8.

The following compounds may be prepared by benzoylation reaction of compound B1 with the appropriate benzoic acid derivative analogously or similarly as described for compounds A1 and A3 to A9:

{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(3-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-fluoro-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methoxy-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-bromo-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-chloro-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-trifluoromethyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

The following compounds may be prepared by bromination of the appropriate compounds mentioned afore analogously or similarly as described for compound A2:
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(3-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-fluoro-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methoxy-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-bromo-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-chloro-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-trifluoromethyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

The following compounds may be prepared by benzoylation reaction of compound B2 with the appropriate benzoic acid derivative analogously or similarly as described for compounds A1 and A3 to A9:
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(3-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-fluoro-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-methoxy-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-bromo-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-chloro-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-(4-trifluoromethyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

The following compounds may be prepared by benzoylation reaction of compound B4 with the appropriate benzoic acid derivative analogously or similarly as described for compounds A1 and A3 to A9:
{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-m-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-fluoro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

(3-{[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-methoxy-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-chloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-trifluoromethyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

The following compounds may be prepared by bromination of the appropriate compounds mentioned afore analogously or similarly as described for compound A2:
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-m-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-fluoro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-methoxy-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-chloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(4-trifluoromethyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

The following compounds may be prepared by benzoylation reaction of compound B5 with the appropriate benzoic acid derivative analogously or similarly as described for compounds A1 and A3 to A9:
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester
{3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-(1-m-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-[1-(4-fluoro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-[1-(4-methoxy-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

(3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-[1-(4-chloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester
(3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-[1-(4-trifluoromethyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A11. 6-Benzyl-3-chloro-5-[(RS)-1-(3-dimethylamino-propylamino)-2-methyl-propyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

A suspension of 544 mg (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C3) and 742 µL N^1,N^1-dimethylpropane-1,3-diamine (2.5 eq) in 1.5 mL $Ti(O^iPr)_4$ is heated for 16 hours at 50 °C. This crude mixture with the imine as main product is dissolved in 5 mL glacial acetic acid and treated with 400 mg (6.6 eq) $NaBH_4$. This mixture is stirred for 16 hours at ambient temperature to give the crude mixture containing the title compound. The solution is treated with 2 M aqueous NaOH-solution to an pH of 12 and extracted with 1-butanol. Purification by silica gel flash chromatography using a gradient of dichloromethane, methanol and triethylamine from 89:9:2 to 79:19:2 resulted in 105 mg (15%) of the title compound as a colorless oil. MS: m/z (MH^+) = 430.1, 432.2.

The following compounds may be prepared by reductive amination reaction of the appropriate compound C1 to C6 with N^1,N^1-dimethyl-propane-1,3-diamine (Me_2N-$(CH_2)_3$-NH_2) analogously or similarly as described for compounds B1 to B3.
6-Benzyl-5-[(RS)-1-(3-dimethylamino-propylamino)-propyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one
6-Benzyl-3-chloro-5-[(RS)-1-(3-dimethylamino-propylamino)-propyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one
6-Benzyl-5-[(RS)-1-(3-dimethylamino-propylamino)-2-methyl-propyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one
6-Benzyl-5-[(RS)-1-(3-dimethylamino-propylamino)-2-methyl-butyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one
6-Benzyl-3-chloro-5-[(RS)-1-(3-dimethylamino-propylamino)-2-methyl-butyl]-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

A12. {4-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-butyl}-carbamic acid tert-butyl ester

A solution of 180 mg (1.0 eq) {4-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-butyl}-carbamic acid tert-butyl ester (compound B6), 175 µL (1.5 eq) 4-methyl benzoyl chloride and 145 µL (3.7 eq) triethylamine in 3.5 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 10 mL dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution, the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography

using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 127 mg (71%) of the title compound as a colorless solid.

M.p.: 82-84 °C.

MS: m/z (MNa^+) = 656.2, and also MNa^++2.

A13. {2-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-ethyl}-carbamic acid tert-butyl ester

A solution of 200 mg (1.0 eq) {2-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-ethyl}-carbamic acid tert-butyl ester (compound B7), 205 µL (3.8 eq) 4-methyl benzoyl chloride and 171 µL (3.0 eq) triethylamine in 4 mL dichloromethane is stirred for 62 hours at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yielded 125 mg (50%) of the title compound as a colorless solid.

M.p.: 119-120 °C.

MS: m/z (MH^+) = 605.9, 608.0.

A14. {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclobutyl-methyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester

A solution of 300 mg (1.0 eq) (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclobutyl-methyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound B8), 115 µL (1.5 eq) 4-methyl benzoyl chloride and 241 µL (3.0 eq) triethylamine in 6 mL dichloromethane is stirred for 2 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 194 mg (53%) of the title compound as a colorless foam. Furthermore 76 mg (25%) of the starting material is recovered.

M.p.: 108-111 °C.

MS: m/z (MH^+) = 631.8, 633.8.

A15. {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester

A solution of 260 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5c]pyrimidin-5-yl)-2-methyl-butylamino]-propyl}-carbamic acid tert-butyl ester (compound B5), 100 µL (1.5 eq) 4-methyl benzoyl chloride and 208 µL (3.0 eq) triethylamine in 5 mL dichloromethane is stirred for 16 hours at ambient temperature. After addition of 10 mL of

dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yielded 81 mg (26%) of the title compound as a pale yellow foam. Furthermore 147 mg (57%) of the starting material is recovered.

M.p.: 67-68 °C.

MS: m/z (MH^+) = 633.9, 635.8.

A16. {3-[[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester

A solution of 257 mg (1.0 eq) (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound B9), 135 µL (2.0 eq) 4-methyl benzoyl chloride and 212 µL (3.0 eq) triethylamine in 5 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yielded 90 mg (29%) of the title compound as a colorless foam. Furthermore 73 mg (29%) of the starting material is recovered.

M.p.: 85-87 °C.

MS: m/z (MH^+) = 617.9, 619.9.

A17. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-[1-(4-bromo-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A solution of 196 mg (1.0 eq) (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-amino}-propyl)-carbamic acid tert-butyl ester (compound B9), 105 mg (1.2 eq) 4-bromo benzoyl chloride and 166 µL (3.0 eq) triethylamine in 4 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 50 mg (18%) of the title compound as a colorless foam.

M.p.: 120-122 °C.

MS: m/z (MH^+) = 681.8, 683.6, 685.4.

A18. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(3-fluoro-4-methyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A solution of 330 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 171 mg (1.5 eq) 3-fluoro-4-methyl benzoyl chloride and 274 µL (3.0 eq) triethylamine in 8 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 59:39:2 to 0:100:0 yielded 115 mg (27%) of the title compound as a pale yellow foam. Furthermore 122 mg (37%) of the starting material is recovered.

M.p.: 88-91 °C.

MS: m/z (MH^+) = 637.8, 639.8.

A19. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(2-fluoro-4-methyl-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A solution of 277 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 142 mg (1.5 eq) 2-fluoro-4-methyl benzoyl chloride and 229 µL (3.0 eq) triethylamine in 7 mL dichloromethane is stirred for 2 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 59:39:2 to 0:100:0 yielded 100 mg (28%) of the title compound as a colorless foam. Furthermore 100 mg (36%) of the starting material is recovered.

M.p.: sinter at 100 °C and melting at 110-112 °C.

MS: m/z (MH^+) = 637.9, 639.9.

A20. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(3,4-dichloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A solution of 259 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 129 mg (1.2 eq) 3,4-dichloro benzoyl chloride and 214 µL (3.0 eq) triethylamine in 6 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL

saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 88 mg (22%) of the title compound as a colorless foam.

M.p.: 104-107 °C.

MS: m/z (MH^+) = 673.6, 675.7, 677.8.

A21. {3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-[1-(2,3-dichloro-phenyl)-carbonyl]-amino}-propyl)-carbamic acid tert-butyl ester

A solution of 300 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B3), 143 mg (1.2 eq) 2,3-dichloro benzoyl chloride and 249 µL (3.0 eq) triethylamine in 7 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a gradient of n-hexane, ethyl acetate and acetic acid from 39:59:2 to 0:100:0 yielded 67 mg (17%) of the title compound as a colorless solid. Furthermore 164 mg (55%) of the starting material is recovered.

M.p.: 109-110 °C.

MS: m/z (MH^+) = 673.8, 676.0, 677.9.

A22. {3-[[(RS)-1-(6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(4-methyl-benzoyl)-amino]-propyl}-carbamic acid tert-butyl ester

0.10 g of {3-[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound A23) are dissolved in 3 mL DMF. After adding 36.3 mg (1.2 eq) NBS at 0 °C the mixture is stirred for 16 hours at ambient temperature. Addition of water followed by extraction of the aqueous phase with dichloromethane yielded after drying over magnesium sulfate and evaporation of the solvent the crude product. The residue is purified by flash chromatography using n-hexane / ethylacetate in a ratio of 2:1 and yielded 90 mg (80%) of the title compound as colorless oil.

A23. {3-[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester

A solution of 151 mg {3-[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl)-carbamic acid tert butyl ester (1.0 eq) (compound B4), 55 mg (1.5 eq) p-methyl benzoyl chloride and 132 µL (3.0 eq) triethylamine in 5 mL dichloromethane is stirred for 1

days at ambient temperature and for 1 day at 40 °C. After addition of 10 mL of dichloromethane and 10 mL saturated aqueous $NaHCO_3$-solution the phases are separated and the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a ratio of n-hexane, ethyl acetate and acetic acid 66:32:2 yielded 105 mg (80%) of the title compound with impurities of acetic acid.

A24. {3-[[(RS)-1-(6-Benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-(1-p-tolyl-carbonyl)-amino]-propyl}-carbamic acid tert-butyl ester

A solution of 155 mg (1.0 eq) {3-[(RS)-1-(6-Benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester (compound B10), 62 µL (1.5 eq) p-tolyl benzoyl chloride and 137 µL (3.0 eq) triethylamine in 6 mL tetrahydrofurane is stirred for 3 days at ambient temperature. The solvent is evaporated in vacuo. Purification of the crude product by silica gel flash chromatography using a ratio of n-hexane, ethyl acetate and acetic acid 66:32:2 yielded 150 mg (78%) of the title compound with impurities of acetic acid.

B1. {3-[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propylamino]-propyl}-carbamic acid *tert*-butyl ester

437 mg 6-Benzyl-2-methyl-5-propionyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (1.48 mmol) (compound C1) and 516 mg (3-Amino-propyl)-carbamic acid tert-butyl ester (2.96 mmol) are dissolved in 4 ml THF. 1.9 ml $Ti(O^iPr)_4$ (4.44 mmol) are added and the reaction mixture is stirred 14 h at ambient temperature. Afterwards 4 ml ethanol and 412 mg $NaCNBH_3$ (5.92 mmol) are added and the mixture is stirred 2 h at ambient temperature. After adding water the inorganic salts are filtrated, washed with ethanole and the filtrate is evaporated. The residue is suspended in dichloromethane, dried over sodium sulphate and filtrated. After removing the solvents the crude product is purified by silica gel flash chromatography. By this method 540 mg (80 %) of a colorless solid is obtained.
M.p.: 72-74 °C.

B2. {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propylamino]-propyl}-carbamic acid *tert*-butyl ester

6-Benzyl-3-chloro-2-methyl-5-propionyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one (3.70 g, 11.2 mmol) (compound C2) and *N*-Boc-1,3-diaminopropane (2.60 g, 14.6 mmol) are dissolved in THF (28 mL), treated with $Ti(O^iPr)_4$ (6.40 g, 22.4 mmol) and stirred for 14h at ambient temperature. Then ethanol (28 mL) and $NaCNBH_3$ (1.40 g, 22.4 mmol) are added and it is stirred for 2 h at ambient temperature. After adding of water it is filtered and the filtrate is evaporated. The residue is purified by silica gel flash chromatography. A colorless solid of m.p. 73–75 °C is obtained.

B3. {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester

1.10 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C3) are dissolved in 15 ml tetrahydrofurane. 1.39 g (2.5 eq) tert-butyl-N-(3-aminopropyl)carbamate and 2.86 mL (3.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred for 72 hours at reflux. After cooling the mixture is treated with an aqueous citric acid solution and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yield a two-phase system. The two phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yields the crude mixture of the corresponding imine.

This mixture of the crude imine is dissolved in 20 mL acetic acid. 0.61 g (5.0 eq) sodium borohydride are added. The reaction mixture is stirred for 1 hour at ambient temperature. After addition of water the mixture is extracted with etyhl acetate. The combined organic phase is once washed with saturated aqueous sodium hydrogencarbonate solution. The organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. This yields 0.62 g (39%) of the title compound as a white foam.

M.p. 51-53 °C (foam).

MS: m/z (MH^+) = 501.9, 504.0.

B4. {3-[(RS)-1-(6-Benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester

The title compound may be prepared by reductive amination reaction of compound C4 with *N*-Boc-1,3-diaminopropane analogously or similarly as described for compounds B1 to B3.

B5. {3-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butylamino]-propyl}-carbamic acid tert-butyl ester

0.70 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-butanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C5) are dissolved in 40 mL tetrahydrofurane. 1.36 g (4.0 eq) tert-butyl-N-(3-aminopropyl)carbamate and 3.50 mL (6.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred in a sealed tube for 72 hours at reflux. After cooling, the mixture is treated with an aqueous solution of citric acid and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yielded a two-phase system. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yielded the crude mixture of the corresponding imine.

The mixture of the crude imine is dissolved in 12 mL acetic acid. 0.37 g (5.0 eq) sodium borohydride are added and the mixture is stirred for 16 hours at ambient temperature. The solvent is evaporated and the residue is partitioned between saturated aqueous $NaHCO_3$-solution and dichloromethane. After phase separation, the aqueous phase is extracted three times with dichloromethane. The

combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. This yielded 0.34 g (34%) of the title compound as colorless foam.
M.p.: 64-65 °C.
MS: m/z (MH^+) = 516.0, 518.0.

B6. {4-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-butyl}-carbamic acid tert-butyl ester

1.87 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C3) are dissolved in 23 mL tetrahydrofurane. 2.56 g (2.5 eq) tert-butyl-N-(3-aminobutyl)carbamate and 4.86 mL (3.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred in a sealed tube for 72 hours at 80 °C. After cooling, the mixture is treated with an aqueous solution of citric acid and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yielded a two-phase system. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yielded the crude mixture of the corresponding imine.
The mixture of the crude imine is dissolved in 35 mL acetic acid. 1.05 g (5.0 eq) sodium borohydride are added and the mixture is stirred for 1 hour at ambient temperature. The solvent is evaporated and the residue is partitioned between saturated aqueous $NaHCO_3$-solution and dichloromethane. After phase separation the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. This yielded 0.44 g (16%) of the title compound as colorless foam.
M.p.: 63-65 °C.
MS: m/z (MH^+) = 516.0, 518.0.

B7. {2-[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-ethyl}-carbamic acid tert-butyl ester

0.61 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C3) are dissolved in 8 mL tetrahydrofurane. 0.71 g (2.5 eq) tert-butyl-N-(3-aminoethyl)carbamate and 1.58 mL (3.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred in a sealed tube for 72 hours at 80 °C. After cooling, the mixture is treated with an aqueous solution of citric acid and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yielded a two-phase system. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yielded the crude mixture of the corresponding imine.
The mixture of the crude imine is dissolved in 11 mL acetic acid. 0.33 g (5.0 eq) sodium borohydride are added and the mixture is stirred for 1 hour at ambient temperature. The solvent is evaporated and

the residue is partitioned between saturated aqueous $NaHCO_3$-solution and dichloromethane. After phase separation, the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. This yielded 0.21 g (25%) of the title compound as colorless foam.

M.p.: 73-75 °C.

MS: m/z (MH^+) = 487.9, 490.0.

B8. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclobutyl-methyl]-amino}-propyl)-carbamic acid tert-butyl ester

0.63 g (1.0 eq) of 6-Benzyl-3-chloro-5-(1-cyclobutyl-carbonyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C6) are dissolved in 4 mL tetrahydrofurane. 0.54 g (2.5 eq) tert-butyl-N-(3-aminopropyl)carbamate and 1.10 mL (3.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred in a sealed tube for 72 hours at 80 °C. After cooling, the mixture is treated with an aqueous solution of citric acid and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yielded a two-phase system. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yielded the crude mixture of the corresponding imine.

This mixture of the crude imine is dissolved in 8 mL acetic acid. 0.23 g (5.0 eq) sodium borohydride is added and the mixture is stirred for 1 hour at ambient temperature. The solvent is evaporated and the residue is partitioned between saturated aqueous $NaHCO_3$-solution and dichloromethane. After phase separation, the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. This yielded 0.50 g (79%) of the title compound as colorless foam.

M.p.: 73-75 °C.

MS: m/z (MH^+) = 514.0, 516.0.

B9. (3-{[(RS)-1-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-amino}-propyl)-carbamic acid tert-butyl ester

1.81 g (1.0 eq) of 6-Benzyl-3-chloro-5-(1-cyclopropyl-carbonyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C7) are dissolved in 20 mL tetrahydrofurane. 2.31 g (2.5 eq) tert-butyl-N-(3-aminopropyl)carbamate and 4.70 mL (3.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred in a sealed tube for 5 days at 80 °C. After cooling, the mixture is treated with an aqueous solution of citric acid and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yielded a two-phase system. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yielded the crude mixture of the corresponding imine.

This mixture of the crude imine is dissolved in 30 mL acetic acid. 1.0 g (5.0 eq) sodium borohydride are added and the mixture is stirred for 2 hours at ambient temperature. The sovent is evaporated and the residue is partitioned between saturated aqueous $NaHCO_3$-solution and dichloromethane. After phase separation, the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50. This yielded 0.26 g of a mixture containing the title compound. This mixture was used for the further synthetic pathway.

M.p.: 74-76 °C.

MS: m/z (MH^+) = 500.0, 502.0 (analytical data measured with recovered pure starting material from A16).

B10. {3-[(RS)-1-(6-Benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propylamino]-propyl}-carbamic acid tert-butyl ester

0.55 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound C8) are dissolved in 7 mL tetrahydrofurane. 0.74 g (2.5 eq) tert-butyl-N-(3-aminoetyl)carbamate and 1.51 mL (3.0 eq) titanium(IV)isopropoxide are added and this mixture is stirred in a sealed tube for 72 hours at 80 °C. After cooling, the mixture is treated with an aqueous solution of citric acid and stirred for another 15 min at ambient temperature. Addition of dichloromethane and filtration of the mixture yielded a two-phase system. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is removed in vacuo. This yielded the crude mixture of the corresponding imine.

The mixture of the crude imine is dissolved in 12 mL acetic acid. 0.33 g (5.0 eq) sodium borohydride are added and the mixture is stirred for 90 minutes at ambient temperature. The solvent is evaporated and the residue is partitioned between saturated aqueous $NaHCO_3$-solution and dichloromethane. After phase separation, the aqueous phase is extracted three times with dichloromethane. The combined organic phase is dried over magnesium sulfate and the solvent is evaporated in vacuo. The crude product is purified by silica gel flash chromatography using a cyclohexane ethyl acetate in a 2:1 mixture. This yielded 0.16 g (19%) of the title compound as colorless solid.

C1. 6-Benzyl-2-methyl-5-propionyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

770 mg 6-Benzyl-5-((RS)-1-hydroxy-propyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (2.59 mmol) (compound D1) are dissolved in 15 ml dichloromethane, 1.5 g molecular sieve (4 Å, 500 mg/mmol Substrat) and 1060 mg NMO (7.8 mmol) are added and the reaction mixture is stirred 2 h at ambient temperature. Afterwards TPAP (100 mg, 0.26 mmol) are added and the mixture is stirred 14 h at ambient temperature. The reaction mixture is filtrated over silica gel, washed with etylacetate and evaporated. The residue is purified by silica gel flash chromatography. By this method 452 mg (59 %) of a yellow solid are obtained. M.p.: 128–130 °C.

C2. 6-Benzyl-3-chloro-2-methyl-5-propionyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

6-Benzyl-3-chloro-5-((RS)-1-hydroxy-propyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (6.00 g, 18.0 mmol) (compound D2) is dissolved in CH_2Cl_2 (90 mL) and treated with molecular sieve (4Å, 9.00 g) and NMO (7.30 g, 54.0 mmol) and stirred for 2h at ambient temperature. To the mixture is added TPAP (633 mg, 1.8 mmol) and it is stirred for 14 h at ambient temperature. The mixture is filtered and evaporated. The residue is purified by silica gel flash chromatography. The title compound is obtained as 3.80 g of a yellow solid with m.p. 128 °C.

C3. 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one

1.61 g (1.0 eq) of 6-Benzyl-3-chloro-5-((RS)-1-hydroxy-2-methyl-propyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound D3) are dissolved in 60 mL of dichloromethane at room temperature. To this mixture are added 7 g (1,5 g/mmol) of mol sieves 4 Å and 2.53 g (4.0 eq) N-methylmorpholine-N-oxide. After 30 min stirring at ambient temperature 0.33 g (0.2 eq) tetrapropylammonium perruthenate is added. After 16 hours the reaction mixture is filtered through silica gel and washed out with ethyl acetate. The solvent is removed in vacuo. Flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yields 1.09 g (68%) of the title compound as a white solid.

M.p. 146.7 °C.

MS: m/z (MH^+) = 344.1, 346.1.

C4. 6-Benzyl-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one

The title compound may be prepared by oxidation of compound D4 analogously or similarly as described for compounds C1 to C3.

C5. 6-Benzyl-3-chloro-2-methyl-5-(2-methyl-butanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one

1.12 g (1.0 eq) of 6-Benzyl-3-chloro-5-((RS)-1-hydroxy-2-methyl-butyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound D5) are dissolved in 50 mL of dichloromethane at ambient temperature. 4.6 g (1.5 g/mmol) of mol sieves 4 Å and 1.68 g (4.0 eq) N-methylmorpholine-N-oxide are added to this mixture. After 30 min stirring at ambient temperature 0.22 g (0.2 eq) tetrapropylammonium perruthenate are added. After 16 hours the reaction mixture is filtered through silica gel using ethyl acetate as eluent. The solvent is removed in vacuo. Flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 0.78 g (70%) of the title compound as a colorless solid.

M.p.: 122-123 °C.

MS: m/z (MH^+) = 358.1, 360.1.

C6. 6-Benzyl-3-chloro-5-(1-cyclobutyl-carbonyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

A suspension of 0.63 g (1.0 eq) of 6-Benzyl-3-chloro-5-((RS)-1-cyclobutyl-1-hydroxy-methyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound D6), 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and 1.29 g iodobenzene diacetate in 4 mL dichloromethane is stirred for 2 days at ambient temperature.

This mixture is treated with aqueous $Na_2S_2O_3$-solution (1M) and dichloromethane. Phase separation and extraction of the aqueous layer with dichloromethane resulted after drying over magnesium sulfate and evaporation of the solvent in vacuo in the crude product. Silica gel flash chromatography with a ratio of n-hexane and ethyl acetate 3:7 yielded 0.63 g (quant.) of the title compound as a colorless solid.

M.p.: 96-97 °C.

MS: m/z (MH^+) = 356.1, 358.1.

C7. 6-Benzyl-3-chloro-5-(1-cyclopropyl-carbonyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

0.33 g (1.0 eq) of 6-Benzyl-3-chloro-5-(1-cyclopropyl-(RS)-1-hydroxy-methyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound D7) are dissolved in 15 mL of dichloromethane at ambient temperature. 1.43 g (1.5 g/mmol) of mol sieves 4 Å and 0.51 g (4.0 eq) N-methylmorpholine-N-oxide are added to this mixture. After 30 min stirring at ambient temperature 67 mg (0.2 eq) tetrapropylammonium perruthenate are added. After 16 hours the reaction mixture is filtered through silica gel with ethyl acetate as eluent. The solvent is removed in vacuo. Flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 30:70 yielded 0.23 g (68%) of the title compound as a colorless solid.

M.p.: 151-152 °C.

MS: m/z (MH^+) = 342.2, 344.2.

C8. 6-Benzyl-3-fluoro-2-methyl-5-(2-methyl-propanoyl)-6H-pyrazolo[1,5-c]pyrimidin-7-one

A suspension of 0.55 g (1.0 eq) of 6-Benzyl-3-fluoro-5-(1-hydroxy-2-methyl-propyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound D8), 55 mg (0.22 eq) 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and 1.21 g (2.2 eq) iodobenzene diacetate in 10 mL dichloromethane is stirred for 3 days at ambient temperature. After addition of 25 mg (0.1 eq) TEMPO the mixture is stirred for another 2 days at ambient temperature. This mixture is treated with aqueous $Na_2S_2O_3$-solution (1M) and dichloromethane. Phase separation and extraction of the aqueous layer with dichloromethane resulted after drying over sodium sulfate and evaporation of the solvent in vacuo in the crude product. Silica gel flash chromatography with a ratio of cyclohexane and ethyl acetate of 3:2 yielded 0.55 g (quant.) of the title compound as a yellow solid.

D1. 6-Benzyl-5-((RS)-1-hydroxy-propyl)-2-methyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

To a solution of 7.2 ml MeLi (11.5 mmol, 1.6 M in Et_2O) in THF (20 ml), 2.3 ml EtMgBr (6.9 mmol, 3 M in Et_2O) are added at – 78 °C. The solution is stirred 1 h at – 78°C.

1 g 6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (2.89 mmol) (compound E1) diluted in 4 ml DMPU and 10 ml THF are added dropwise under argon atmosphere. Afterwards the reaction mixture is stirred 2 h at – 78°C and 3 h at –30 °C. The reaction mixture is quenched with aqueous NH_4Cl-solution and then warmed up to ambient temperature. The product is extracted between ethylacetate and water. The organic phase is dried over sodium

sulphate. After evaporating the solvents the crude product is purified by silica gel flash chromatography. By this method 352 mg (42%) of the title compound are obtained. M.p.: 190–191 °C.

D2. 6-Benzyl-3-chloro-5-((RS)-1-hydroxy-propyl)-2-methyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

To a mixture of THF (4 mL) and MeLi (1.25 mL, 2.0 mmol, 1.6 M in Et_2O) are added at -78 °C EtMgBr (0.48 mL, 1.2 mmol, 3.0 M in Et_2O), the solution is stirred 1 h at this temperature and 6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (compound E2) is added. The mixture is stirred for 6h at - 70 °C and then the mixture is hydrolyzed with aqueous NH_4Cl solution and stirred at ambient temperature. After adding water the mixture is extracted with ethylacetate, the organic phase is dried and evaporated. The residue is purified by silica gel flash chromatography. 201 mg are obtained with a melting point of 80–82 °C.

D3. 6-Benzyl-3-chloro-5-((RS)-1-hydroxy-2-methyl-propyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

25 mL of methyllithium (2.0 eq, 1.6 M solution in diethylether) and 24 mL of isopropylmagnesium bromide (1.2 eq, ~1M solution in tetrahydrofurane) are added to 200 mL dry tetrahydrofurane at –78°C. After one hour at –78°C 6g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (compound E2) is added. After stirring this mixture for an additional 2 hours, a saturated aqueous solution of ammonium chloride is added. At ambient temperature the mixture is extracted with ethyl acetate and the combined organic phase is dried over magnesium sulfate. After filtration the solvent is evaporated under vacuo. The crude product is crystallized from ethyl acetate. This yields 2.83 g of the title compound. Flash chromatography of the mother liquor using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yields another 1.15 g of the title compound (together 58% yield) as a white solid.

M.p. 72.9 °C.

MS: m/z (MH^+) = 345.9, 347.9.

D4. 6-Benzyl-5-((RS)-1-hydroxy-2-methyl-propyl)-2-methyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

The title compound may be prepared from compound E1 analogously or similarly as described for compound D1.

D5. 6-Benzyl-3-chloro-5-((RS)-1-hydroxy-2-methyl-butyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

12.5 mL of methyllithium (2.0 eq, 1.6 M solution in diethylether) and 12 mL of sec-butylmagnesium bromide (1.2 eq, ~1M solution in tetrahydrofurane) are added to 100 mL dry tetrahydrofurane at –78°C. After one hour at –78°C 3.0 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (compound E2) are added. After stirring this mixture for an additional 2.5 hours, a saturated aqueous solution of ammonium chloride is added. The mixture is extracted with ethyl acetate and the combined organic phase is dried over magnesium sulfate. After

filtration, the solvent is evaporated in vacuo. Silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 1.2 g (33%) of the title compound as colorless foam.

M.p.: 72-73 °C.

MS: m/z (MH^+) = 360.2, 362.2.

D6. 6-Benzyl-3-chloro-5-((RS)-1-cyclobutyl-1-hydroxy-methyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

1.0 mL (3.0 eq) Cyclobutylbromide and 0.24 g (3.0 eq) magnesium (Grignard) are dissolved in 20 mL diethylether. The grignard reaction is started with iodine and heating of the suspension to reflux. After 90 minutes at reflux a solution of 1.0 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (compound E2) in 15 mL THF is added dropwise. After stirring for 16 hours at ambient temperature the reaction is stopped with ammonium chloride. Extraction of the aqueous phase with ethyl acetate resulted after drying over magnesium sulfate and evaporation of the solvent in vacuo in the crude product. Silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 0.20 g (17%) of the title compound as a colorless solid.

M.p.: 188-193 °C (decomposition).

MS: m/z (MH^+) = 358.1, 360.0.

D7. 6-Benzyl-3-chloro-5-(1-cyclopropyl-(RS)-1-hydroxy-methyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

1.0 g (1.0 eq) of 6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (compound E2) are dissolved in 30 mL THF and at 0 °C 16.5 mL (2.5 eq, 0.5 M in THF) cyclopropylmagnesiumbromide are added dropwise. After stirring for 3 days at ambient temperature the mixture is treated with a saturated aqueous solution of ammonium chloride. Extraction of the water phase with dichloromethane resulted after drying over magnesium sulfate and evaporation of the solvent in vacuo the crude product. Silica gel flash chromatography using a gradient of n-hexane and ethyl acetate from 100:0 to 50:50 yielded 0.56 g (49%) of the title compound as a colorless solid.

M.p.: 119-120 °C.

MS: m/z (MH^+) = 344.1, 346.1.

D8. 6-Benzyl-3-fluoro-5-(1-hydroxy-2-methyl-propyl)-2-methyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

3.2 mL of methyllithium (2.0 eq, 1.6 M solution in diethylether) and 3 mL of isopropylmagnesium bromide (1.2 eq, ~1M solution in tetrahydrofurane) are added to 25 mL dry tetrahydrofurane at –78°C. After one hour at –78°C 0.6 g (1.0 eq) of 6-Benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde (compound E3) are added. After stirring this mixture for an additional 3 hours the reaction is quenched by treatment with a 10% aqueous ammonium chloride solution. The mixture is extracted with diethylether and the combined organic phase is dried over magnesium

sulfate. After filtration, the solvent is evaporated in vacuo. Silica gel flash chromatography using a ratio of n-hexane and ethyl acetate of 1:1 yielded 0.23 g (27%) of the title compound as slightly yellow solid.

E1. 6-Benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde

6-Benzyl-3-bromo-2,5-dimethyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (24.0 g, 72.2 mmol) (compound F1) are dissolved in 350 ml dioxane. 24 g selendioxide are added and the reaction mixture is heated to reflux for 12 h. Afterwards the reaction mixture is filtered, the residue is washed with diethylether and the filtrate is evaporated. By this method 22.7 g (90 %) of the title compound are obtained. M.p.: 187-189 °C.

E2. 6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde

2.29 g (1.0 eq) of 6-Benzyl-3-chloro-2,5-dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one (compound F2) are dissolved in 40 mL dioxane and treated with 2.64 g (3.0 eq) selenium dioxide. This mixture is heated at reflux for 5 hours. After filtration off the inorganic salts, the filtrate is evaporated in vacuo. This residue is purified by silica gel flash chromatography using cyclohexane and ethyl acetate in a mixture of 2:1 to yield 2.10 g (88%) of the title compound. M.p. 187-188 °C.

E3. 6-Benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidine-5-carbaldehyde

A solution of 6.75 g (1.0 eq) of 6-Benzyl-3(4)-fluoro-2,5-dimethyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound F3) in 125 mL dioxane is treated with 10.55 g (3.0 eq) selenium dioxide. The mixture is heated for 7 days at reflux. This mixture is filtered, the solution is concentrated and washed three times with diethylether. The mother liquor is purified using flash chromatography (ethylacetate as eluent). This resulted in 0.60 g (8%) of the title compound.

F1. 6-Benzyl-3-bromo-2,5-dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

32 g (126 mmol) of the 6-Benzyl-2,5-dimethyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (compound G1) are dissolved in 300 ml CCl_4. 22.5 g (126 mmol) NBS and 2.1 g (12.6 mmol) AIBN are added to the solution, it is stirred at ambient temperature for 18 h. Afterwards the solution is diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$ solution. The organic phase is dried over sodium sulphate and the solvents are evaporated. The crude product is purified by silica gel flash chromatography. By this method 24.1 g (58 %) of the title compound are obtained.

F2. 6-Benzyl-3-chloro-2,5-dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

2.83 g (1.0 eq) 6-Benzyl-2,5-dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one (compound G1) are dissolved in 35 mL tetrachloromethane and treated with 1.50 g (1.0 eq) N-chlorosuccinimide for 5 hours at reflux. The reaction mixture is diluted with dichloromethane and washed with saturated aqueous sodium hydrogen carbonate solution. Drying of the organic phase over sodium sulfate and evaporation of the solvent yields the crude product. The residue is purified by silica gel flash chromatography using cyclohexane and ethyl acetate in a mixture of 2:1 to yield 2.70 g (84%) of the title compound.
M.p. 140-142 °C.

F3. 6-Benzyl-3(4)-fluoro-2,5-dimethyl-6H-pyrazolo[1,5-c]pyrimidin-7-one

14.7 g of 6-Benzyl-2,5-dimethyl-6H-pyrazolo[1,5-c]pyrimidin-7-one (1.0 eq, compound G1) are dissolved in 300 mL acetonitrile and treated at 0 °C with 22.6 g Selectfluor (1.1 eq). After stirring for 1 hour at this temperature, the solvent is removed in vacuo, the residue is dissolved in dichloromethane and neutralized with a saturated aqueous hydrogen carbonate solution. The aqueous phase is extracted with dichloromethane and the combined organic layer is dried over magnesium sulfate. After evaporation of the solvent, the oily residue is crystallized from diethylether. The crystals are further purified using flash chromatography (cyclohexane / ethylacetate = 1.5:1). This yielded 2.67 g (17%) of the title compound as a colorless solid.

G1. 6-Benzyl-2,5-dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

2.30 g (1.0 eq) 2,5-dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one (compound H1) are dissolved in 35 mL N,N-dimethylformamide (DMF). 2.20 g (1.1 eq) potassium carbonate and 1.9 mL benzyl bromide are added. The mixture is stirred at ambient temperature for 14 hours. After addition of water the aqueous phase is extracted with dichloromethane. The combined organic phase is dried over sodium sulfate and the solvent is evaporated in vacuo. The residue is washed with diethylether and yield 3.35 g (94%) of the title compound.

H1. 2,5-Dimethyl-6*H*-pyrazolo[1,5-c]pyrimidin-7-one

2.30 g (1.0 eq) semicarbazide hydrochloride are dissolved in 40 mL water. After addition of 1.10 g (0.5 eq) of a saturated aqueous solution of sodium carbonate and 2.90 g (1.0 eq) of heptane-2,4,6-trione (compound I1), the mixture is heated for 1 hour at 100°C. Extraction of the mixture with dichloromethane yields after evaporation of the solvent in vacuo 2.6 g (79%) of the title compound.
M.p. 205-208 °C.

I1. Heptane-2,4,6-trione

50.0 g 2,6-Dimethyl-γ-pyrone are dissolved in 250 mL ethanol and treated with 50 mL of a 16 M aqueous solution of sodium hydroxide. This mixture is heated for 5 hours at 60°C and for another 1 hour at 100°C. The residue is filtered off and washed with diethylether. This residue is now dissolved in water and put in 500 mL of a 3 M aqueous solution of hydrochloric acid. The aqueous phase is

extracted with diethylether. The combined organic phase is dried over sodium sulfate and the solvent is evaporated in vacuo. This yields 31.6 g (55%) of the title compound. M.p. 43-45 °C.

Commercial utility

The compounds of formula I, I* and I**, and their pharmacologically and/or pharmaceutically acceptable salts (= the compounds according to the present invention) have valuable pharmacological and/or pharmaceutical properties which can make them commercially applicable. Thus, for example, the compounds according to this invention can act as inhibitors of the mitotic kinesin Eg5 and these compounds are expected to be commercially applicable in the therapy of diseases responsive to the inhibition of this kinesin, such as e.g. those diseases mentioned below. Also, for example, the compounds according to this invention can display cell-cycle dependent, anti-proliferative and/or apoptosis inducing activity.

The mitotic kinesin Eg5 is an enzyme essential for the assembly and function of the bipolar mitotic spindle. Eg5 plays essential roles during all phases of mitosis. Drugs that perturb mitosis have proven clinically effective in the treatment of many cancers. Despite the diverse array of essential spindle proteins that could be exploited as targets for the discovery of novel cancer therapies, all spindle-targeted therapeutics in clinical use today act on only one protein, tubulin. Surprisingly, kinesin Eg5 expression is most abundant in proliferating human tissues, whereas it is absent from most postmitotic cells, such as e.g. human central nervous system neurons, consistent with an exclusive or almost confined role for Eg5 in cell proliferation. In contrary to drugs that directly interfere with microtubule dynamic instability, Eg5 kinesin inhibitors are expected not to disrupt microtubule-based cellular processes, e.g. neuronal transport, that are unrelated to proliferation. During mitosis, Eg5 is essentially involved in organizing microtubules into a bipolar structure that forms the mitotic spindle. Experimental perturbation of Eg5 function causes a characteristic malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death.

The compounds according to this invention can be used to modulate mitotic spindle formation, thus causing prolonged cell cycle arrest in mitosis, which is frequently followed by apoptosis. By "modulate" herein is meant altering mitotic spindle formation, including increasing and decreasing spindle formation. By "mitotic spindle formation" herein is meant organization of microtubules into bipolar structures by mitotic kinesins. By "dysfunction of the mitotic spindle" herein is meant mitotic arrest and monopolar spindle formation. “Malformation of the mitotic spindle” encompasses the splaying of mitotic spindle poles, or otherwise causing morphological perturbation of the mitotic spindle.

Further on, these compounds can be useful in the treatment of benign or malignant neoplasia.
A “neoplasia” is defined by cells displaying aberrant cell proliferation and/or survival and/or a block in differentiation. A “benign neoplasia” is described by hyperproliferation of cells, incapable of forming an aggressive, metastasizing tumor in-vivo. In contrast, a “malignant neoplasia” is described by cells with multiple cellular and biochemical abnormalities, capable of forming a systemic disease, for example forming tumor metastasis in distant organs.

Various diseases are caused aberrant cell proliferation ("hyperproliferation") as well as evasion from apoptosis. These diseases include e.g. benign hyperplasia like that of the prostate ("BPH") or colon epithelium, psoriasis, glomerulonephritis or osteoarthritis. Most importantly these diseases include malignant neoplasia commonly described as cancer and characterized by tumor cells finally metastasizing into distinct organs or tissues. Malignant neoplasia include solid and hematological tumors. Solid tumors are exemplified by tumors of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands (e.g. thyroid and adrenal cortex), esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, sarcoma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva. Malignant neoplasia include inherited cancers exemplified by retinoblastoma and Wilms tumor. In addition, malignant neoplasia include primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Hematological tumors are exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site as well as AIDS related malignancies.

The invention therefore relates to a use of the compounds according to the invention in the manufacture of pharmaceutical compositions, a method of treatment or a combination according to the invention, in which the cancer to be treated is selected from the group consisting of
cancer of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands, esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, sarcoma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva;
inherited cancers, retinomblastoma and Wilms tumor;
leukemia, lymphoma, non-Hodgkins disease, chronic and acute myeloid leukaemia, acute lymphoblastic leukemia, Hodgkins disease, multiple myeloma and T-cell lymphoma;
myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site and AIDS related malignancies.

It is to be noted that a cancer disease as well as a malignant neoplasia does not necessarily require the formation of metastases in distant organs. Certain tumors exert devastating effects on the primary organ itself through their aggressive growth properties. These can lead to the destruction of the tissue and organ structure finally resulting in failure of the assigned organ function.

Neoplastic cell proliferation might affect normal cell behaviour and organ function. For example the formation of new blood vessels, a process described as neovascularization, is induced by tumors or tumor metastases. Compounds according to this invention can be commercially applicable for the treatment of pathophysiological relevant processes caused by benign or neoplastic cell proliferation,

such as but not limited to neovascularization by unphysiological proliferation of vascular endothelial cells.

Drug resistance is of particular importance for the frequent failure of standard cancer therapeutics. This drug resistance is caused by various cellular and molelcular mechanisms like overexpression of drug efflux pumps or mutation within the cellular target protein. The commercial applicability of the compounds according to this invention is not limited to 1st line treatment of patients. Patients with resistance to defined cancer chemotherapeutics or target specific anti-cancer drugs (2nd or 3rd line treatment) can be also amenable for treatment with the compounds according to this invention.

Due to their cellular anti-proliferative properties, compounds according to the present invention may be also commercially usable for treatment of diseases associated with cell cycle and cell proliferation, such as, besides cancer discussed above, for example, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, atherosclerosis, hyperplasia, restenosis, cardiac hypertrophy, (auto)immune disorders, fungal disorders, bone diseases, or acute or chronic inflammation.
Thus, the invention relates to compounds according to the invention for use in the treatment of diseases.

Compounds according to the present invention can be commercially applicable for treatment, prevention or amelioration of the diseases of benign and malignant behavior as described before, such as e.g. benign or malignant neoplasia, particularly cancer (such as e.g. any of those cancer diseases described above), especially a cancer that is susceptible to Eg5 inhibition.

In the context of their properties, functions and usabilities mentioned herein, the compounds according to the present invention are expected to be distinguished by valuable and desirable effects related therewith, such as e.g. by low toxicity, superior bioavailability in general (such as e.g. good enteral absorption), superior therapeutic window, absence of significant side effects, and/or further beneficial effects related with their therapeutic and pharmaceutical suitability.

The invention further includes a method for treating (hyper)proliferative diseases and/or disorders responsive to the induction of apoptosis, particularly those diseases, disorders, conditions or illnesses mentioned above, in mammals, including humans, suffering therefrom comprising administering to said mammals in need thereof a pharmacologically and/or pharmaceutically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention.

The present invention further includes a method useful to modulate apoptosis and/or aberrant cell growth in the therapy of benign or malignant neoplastic diseases, such as e.g. cancer, comprising administering to a subject in need of such therapy a pharmacologically and/or pharmaceutically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention.

The invention further includes a method for modulating, particularly inhibiting, Eg5 activity in cells comprising administering a pharmacologically and/or pharmaceutically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention to a patient in need of such modulation, particularly inhibition.

The present invention further includes a method to modulate the mitotic spindle, i.e., for example, altering mitotic spindle formation, including decreasing spindle formation, or increasing or decreasing spindle pole separation causing malformation of the mitotic spindle poles, comprising administering a pharmacologically and/or pharmaceutically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention to a patient in need of such modulation.

The present invention further includes a method to inhibit mitosis in cells comprising administering a pharmacologically and/or pharmaceutically active and therapeutically effective and tolerable amount of one or more of the compounds according to this invention to a patient in need of such inhibition.

The present invention further includes a method for treating, preventing or ameliorating diseases and/or disorders associated with Eg5 kinesin activity, such as, for example, (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, for example, benign neoplasia or malignant neoplasia, e.g. cancer, in a mammal comprising administering a pharmacologically and/or pharmaceutically active and therapeutically effective and tolerable amount of one or more compounds according to the present invention to said mammal in need thereof.

The present invention further relates to the use of the compounds according to this invention for the production of pharmaceutical compositions which are employed for the treatment, prophylaxis and/or amelioration of one or more of the illnesses mentioned.

The present invention further relates to the use of the compounds according to this invention for the production of pharmaceutical compositions which can be used in the treatment, prevention or amelioration of (hyper)proliferative diseases of benign or malignant behaviour and/or disorders responsive to the induction of apoptosis in a mammal, such as, for example, benign or malignant neoplasia, e.g. cancer.

The present invention further relates to the use of the compounds according to this invention for the production of pharmaceutical compositions which can be used use in the treatment, prevention or amelioration of disorders responsive to arresting of aberrant cell growth and/or induction of apoptosis.

The present invention further relates to the use of the compounds according to this invention for the production of pharmaceutical compositions for treating, preventing or ameliorating benign or malignant neoplasia, particularly cancer, such as e.g. any of those cancer diseases described above.

The present invention further relates to pharmaceutical compositions comprising one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent.

The present invention further relates to pharmaceutical compositions made by combining one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent.

The present invention further relates to pharmaceutical compositions comprising one or more of the compounds according to this invention and pharmaceutically acceptable auxiliaries and/or excipients.

The present invention also relates to pharmaceutical compositions for treating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, which include benign neoplasia and malignant neoplasia, including cancer, comprising a compound according to this invention.

The present invention further relates to combinations comprising one or more of the compounds according to this invention and pharmaceutically acceptable auxiliaries, excipients and/or vehicles, e.g. for treating, preventing or ameliorating benign or malignant neoplasia, particularly cancer, such as e.g. any of those cancer diseases described above.

The present invention further relates to a combination comprising a compound according to this invention and a pharmaceutically acceptable excipient, carrier and/or diluent, e.g. for treating, preventing or ameliorating benign or malignant neoplasia, particularly cancer, such as e.g. any of those cancer diseases described above.

The present invention further relates to a composition consisting essentially of a therapeutically effective and tolerable amount of one or more compounds according to this invention together with the usual pharmaceutically acceptable vehicles, diluents and/or excipients for use in therapy, e.g. for treating, preventing or ameliorating hyperproliferative diseases, such as e.g. cancer, and/or disorders responsive to induction of apoptosis.

The present invention further relates to compounds according to this invention for use in therapy, such as, for example, in the treatment, prevention or amelioration of (hyper)proliferative diseases of benign or malignant behaviour and/or disorders responsive to the induction of apoptosis, such as e.g. those diseases mentioned herein, particularly cancer.

The present invention further relates to compounds according to this invention having anti-proliferative and/or apoptosis inducing activity.

The present invention further relates to compounds according to this invention having Eg5 inhibiting properties.

The present invention further relates to pharmaceutical compositions according to this invention having Eg5 inhibiting properties.

The present invention further relates to pharmaceutical compositions according to this invention having anti-proliferative activity.

The present invention further relates to pharmaceutical compositions according to this invention having apoptosis inducing activity.

The invention further relates to the use of a pharmaceutical composition comprising one or more of the compounds according to this invention as sole active ingredient(s) and a pharmaceutically acceptable carrier or diluent in the manufacture of pharmaceutical products for the treatment and/or prophylaxis of the illnesses mentioned above.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective inhibiting Eg5 and/or inhibiting cellular (hyper)proliferation and/or inducing apoptosis, ameliorating the symptoms of a Eg5 mediated disease and/or a (hyper)proliferative disease and/or a disorder responsive to the induction of apoptosis, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating a Eg5 mediated disease and/or a (hyper)proliferative disease and/or a disorder responsive to the induction of apoptosis, and wherein said pharmaceutical agent comprises one or more compounds according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions according to this invention are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds of the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, dragees, pills, cachets, granules, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions (such as e.g. micro-emulsions or lipid emulsions), suspensions (such as e.g. nano suspensions), gels, solubilisates or solutions (e.g. sterile solutions), or encapsuled in liposomes or as beta-cyclodextrine inclusion complexes or the like, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries, vehicles, excipients, diluents, carriers or adjuvants which are suitable for the desired pharmaceutical formulations, preparations or compositions on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers (such as e.g. polyoxyethylenglyceroltriricinoleat 35, PEG 400, Tween 80, Solutol HS15 or the like), colorants, complexing agents, permeation promoters, stabilizers, fillers, binders, thickeners, disintegrating agents, buffers, pH regulators (e.g. to obtain neutral, alkaline or acidic formulations), polymers, lubricants, coating agents, propellants, tonicity adjusting agents, surfactants, flavorings, sweeteners or dyes, can be used.
In particular, auxiliaries and/or excipients of a type appropriate to the desired formulation and the desired mode of administration are used.

The administration of the compounds, pharmaceutical compositions or combinations according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery are preferred.

For the treatment of dermatoses, the compounds of the invention can be in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds of the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, lotions, pastes, gels or solutions.

The pharmaceutical compositions according to the invention can be prepared by processes known per se. The dosage of the compounds of the invention (= active compounds) is carried out in the order of magnitude customary for Eg5 inhibitors, inhibitors for cellular (hyper)proliferation or apoptosis inducers. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The customary dose in the case of systemic therapy (p.o.) may be between 0.03 and 60 mg/kg per day, (i. v.) may be between 0.03 and 60 mg/kg/h. In another embodiment, the customary dose in the case of systemic therapy (p.o.) is between 0.3 and 30 mg/kg per day, (i. v.) is between 0.3 and 30 mg/kg/h.
The choice of the optimal dosage regime and duration of medication, particularly the optimal dose and manner of administration of the active compounds necessary in each case can be determined by a person skilled in the art on the basis of his/her expert knowledge.

Depending upon the particular disease, to be treated or prevented, additional therapeutic active agents, which are normally administered to treat or prevent that disease, may optionally be coadministered with the compounds according to this invention. As used herein, additional therapeutic

agents that are normally administered to treat or prevent a particular disease are known as appropriate for the disease being treated.

For example, compounds according to this invention may be combined with one or more standard therapeutic agents used for treatment of the diseases as mentioned before.
In one particular embodiment, compounds according to this invention may be combined with one or more art-known anti-cancer agents, such as e.g. with one or more chemotherapeutic and/or target specific anti-cancer agents as described below.

Examples of known chemotherapeutic anti-cancer agents frequently used in combination therapy include, but not are limited to (i) alkylating/carbamylating agents such as Cyclophosphamid (Endoxan®), Ifosfamid (Holoxan®), Thiotepa (Thiotepa Lederle®), Melphalan (Alkeran®), or chloroethylnitrosourea (BCNU); (ii) platinum derivatives like cis-platin (Platinex® BMS), oxaliplatin, satraplatin or carboplatin (Cabroplat® BMS); (iii) antimitotic agents / tubulin inhibitors such as vinca alkaloids (vincristine, vinblastine, vinorelbine), taxanes such as Paclitaxel (Taxol®), Docetaxel (Taxotere®) and analogs as well as new formulations and conjugates thereof, epothilones such as Epothilone B (Patupilone®), Azaepothilone (Ixabepilone®) or ZK-EPO, a fully synthetic epothilone B analog; (iv) topoisomerase inhibitors such as anthracyclines (exemplified by Doxorubicin / Adriblastin®), epipodophyllotoxines (examplified by Etoposide / Etopophos®) and camptothecin and camptothecin analogs (exemplified by Irinotecan / Camptosar® or Topotecan / Hycamtin®); (v) pyrimidine antagonists such as 5-fluorouracil (5-FU), Capecitabine (Xeloda®), Arabinosylcytosine / Cytarabin (Alexan®) or Gemcitabine (Gemzar®); (vi) purin antagonists such as 6-mercaptopurine (Puri-Nethol®), 6-thioguanine or fludarabine (Fludara®) and finally (vii) folic acid antagonists such as methotrexate (Farmitrexat®) or premetrexed (Alimta®).

Examples of target specific anti-cancer drug classes used in experimental or standard cancer therapy include but are not limited to (i) kinase inhibitors such as e.g. Imatinib (Glivec®), ZD-1839 / Gefitinib (Iressa®), Bay43-9006 (Sorafenib), SU11248 / Sunitinib (Sutent®) or OSI-774 / Erlotinib (Tarceva®); (ii) proteasome inhibitors such as PS-341 / Bortezumib (Velcade®); (iii) histone deacetylase inhibitors like SAHA, PXD101, MS275, MGCD0103, Depsipeptide / FK228, NVP-LBH589, NVP-LAQ824, Valproic acid (VPA) and butyrates (iv) heat shock protein 90 inhibitors like 17-allylaminogeldanamycin (17-AAG); (v) vascular targeting agents (VTAs) like combretastin A4 phosphate or AVE8062 / AC7700 and anti-angiogenic drugs like the VEGF antibodies, such as Bevacizumab (Avastin®), or KDR tyrosine kinase inhibitors such as PTK787 / ZK222584 (Vatalanib); (vi) monoclonal antibodies such as Trastuzumab (Herceptin®) or Rituximab (MabThera / Rituxan®) or Alemtuzumab (Campath®) or Tositumab (Bexxar®) or C225/ Cetuximab (Erbitux®) or Avastin (see above) as well as mutants and conjugates of monoclonal antibodies, e.g. Gemtuzumab ozogamicin (Mylotarg®) or Ibritumomab tiuxetan (Zevalin®), and antibody fragments; (vii) oligonucleotide based therapeutics like G-3139 / Oblimersen (Genasense®); (viii) Toll-like receptor / TLR 9 agonists like Promune®, TLR 7 agonists

like Imiquimod (Aldara®) or Isatoribine and analogues thereof, or TLR 7/8 agonists like Resiquimod as well as immunostimulatory RNA as TLR 7/8 agonists; (ix) protease inhibitors (x) hormonal therapeutics such as anti-estrogens (e.g. Tamoxifen or Raloxifen), anti-androgens (e.g. Flutamide or Casodex), LHRH analogs (e.g. Leuprolide, Goserelin or Triptorelin) and aromatase inhibitors.

Other known target specific anti-cancer agents which may be used for combination therapy include bleomycin, retinoids such as all-trans retinoic acid (ATRA), DNA methyltransferase inhibitors such as the 2-deoxycytidine derivative Decitabine (Dacogen®) and 5-azacytidine, alanosine, cytokines such as interleukin-2, interferons such as interferon α2 or interferon-γ, death receptor agonists, such as TRAIL, DR4/5 agonistic antibodies, FasL and TNF-R agonists.

As exemplary anti-cancer agents, which may be useful in the combination therapy according to the present invention, any of the following drugs may be mentioned, without being restricted thereto, 5 FU, actinomycin D, ABARELIX, ABCIXIMAB, ACLARUBICIN, ADAPALENE, ALEMTUZUMAB, ALTRETAMINE, AMINOGLUTETHIMIDE, AMIPRILOSE, AMRUBICIN, ANASTROZOLE, ANCITABINE, ARTEMISININ, AZATHIOPRINE, BASILIXIMAB, BENDAMUSTINE, BEVACIZUMAB, BEXXAR, BICALUTAMIDE, BLEOMYCIN, BORTEZOMIB, BROXURIDINE, BUSULFAN, CAMPATH, CAPECITABINE, CARBOPLATIN, CARBOQUONE, CARMUSTINE, CETRORELIX, CHLORAMBUCIL, CHLORMETHINE, CISPLATIN, CLADRIBINE, CLOMIFENE, CYCLOPHOSPHAMIDE, DACARBAZINE, DACLIZUMAB, DACTINOMYCIN, DAUNORUBICIN, DECITABINE, DESLORELIN, DEXRAZOXANE, DOCETAXEL, DOXIFLURIDINE, DOXORUBICIN, DROLOXIFENE, DROSTANOLONE, EDELFOSINE, EFLORNITHINE, EMITEFUR, EPIRUBICIN, EPITIOSTANOL, EPTAPLATIN, ERBITUX, ERLOTINIB, ESTRAMUSTINE, ETOPOSIDE, EXEMESTANE, FADROZOLE, FINASTERIDE, FLOXURIDINE, FLUCYTOSINE, FLUDARABINE, FLUOROURACIL, FLUTAMIDE, FORMESTANE, FOSCARNET, FOSFESTROL, FOTEMUSTINE, FULVESTRANT, GEFITINIB, GENASENSE, GEMCITABINE, GLIVEC, GOSERELIN, GUSPERIMUS, HERCEPTIN, IDARUBICIN, IDOXURIDINE, IFOSFAMIDE, IMATINIB, IMPROSULFAN, INFLIXIMAB, IRINOTECAN, IXABEPILONE, LANREOTIDE, LETROZOLE, LEUPRORELIN, LOBAPLATIN, LOMUSTINE, LUPROLIDE, MELPHALAN, MERCAPTOPURINE, METHOTREXATE, METUREDEPA, MIBOPLATIN, MIFEPRISTONE, MILTEFOSINE, MIRIMOSTIM, MITOGUAZONE, MITOLACTOL, MITOMYCIN, MITOXANTRONE, MIZORIBINE, MOTEXAFIN, MYLOTARG, NARTOGRASTIM, NEBAZUMAB, NEDAPLATIN, NILUTAMIDE, NIMUSTINE, OCTREOTIDE, ORMELOXIFENE, OXALIPLATIN, PACLITAXEL, PALIVIZUMAB, PATUPILONE, PEGASPARGASE, PEGFILGRASTIM, PEMETREXED, PENTETREOTIDE, PENTOSTATIN, PERFOSFAMIDE, PIPOSULFAN, PIRARUBICIN, PLICAMYCIN, PREDNIMUSTINE, PROCARBAZINE, PROPAGERMANIUM, PROSPIDIUM CHLORIDE, RALOXIFEN, RALTITREXED, RANIMUSTINE, RANPIRNASE, RASBURICASE, RAZOXANE, RITUXIMAB, RIFAMPICIN, RITROSULFAN, ROMURTIDE, RUBOXISTAURIN, SARGRAMOSTIM, SATRAPLATIN, SIROLIMUS, SOBUZOXANE, SORAFENIB, SPIROMUSTINE, STREPTOZOCIN, SUNITINIB, TAMOXIFEN, TASONERMIN, TEGAFUR, TEMOPORFIN, TEMOZOLOMIDE, TENIPOSIDE, TESTOLACTONE, THIOTEPA, THYMALFASIN,

TIAMIPRINE, TOPOTECAN, TOREMIFENE, TRAIL, TRASTUZUMAB, TREOSULFAN, TRIAZIQUONE, TRIMETREXATE, TRIPTORELIN, TROFOSFAMIDE, UREDEPA, VALRUBICIN, VATALANIB, VERTEPORFIN, VINBLASTINE, VINCRISTINE, VINDESINE, VINORELBINE, VOROZOLE and ZEVALIN.

The anti-cancer agents mentioned herein above as combination partners of the compounds according to this invention are meant to include pharmaceutically acceptable derivatives thereof, such as e.g. their pharmaceutically acceptable salts.

The person skilled in the art is aware on the base of his/her expert knowledge of the kind, total daily dosage(s) and administration form(s) of the additional therapeutic agent(s) coadministered. Said total daily dosage(s) can vary within a wide range.

In practicing the present invention, the compounds according to this invention may be administered in combination therapy separately, sequentially, simultaneously, concurrently or chronologically staggered (such as e.g. as combined unit dosage forms, as separate unit dosage forms, as adjacent discrete unit dosage forms, as fixed or non-fixed combinations, as kit-of-parts or as admixtures) with one or more standard therapeutics (chemotherapeutic and/or target specific anti-cancer agents), in particular art-known anti-cancer agents, such as any of e.g. those mentioned above.

In this context, the present invention further relates to a combination comprising
a first active ingredient, which is at least one compound according to this invention, and
a second active ingredient, which is at least one art-known anti-cancer agent, such as e.g. one or more of those mentioned herein above,
for separate, sequential, simultaneous, concurrent or chronologically staggered use in therapy, such as e.g. in therapy of any of those diseases mentioned herein.

The term “combination” according to this invention may be present as a fixed combination, a non-fixed combination or a kit-of-parts.

A “fixed combination” is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a “fixed combination” is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A “kit-of-parts” is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a “kit-of-parts” is a combination

wherein the said first active ingredient and the said second active ingredient are present separately. The components of the may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The present invention further relates to a pharmaceutical composition comprising
a first active ingredient, which is at least one compound according to this invention, and
a second active ingredient, which is at least one art-known anti-cancer agent, such as e.g. one or more of those mentioned herein above, and, optionally,
a pharmaceutically acceptable carrier or diluent,
for separate, sequential, simultaneous, concurrent or chronologically staggered use in therapy.

The present invention further relates to a combination product comprising
a.) at least one compound according to this invention formulated with a pharmaceutically acceptable carrier or diluent, and
b.) at least one art-known anti-cancer agent, such as e.g. one or more of those mentioned herein above, formulated with a pharmaceutically acceptable carrier or diluent.

The present invention further relates to a kit-of-parts comprising a preparation of a first active ingredient, which is a compound according to this invention, and a pharmaceutically acceptable carrier or diluent; a preparation of a second active ingredient, which is an art-known anti-cancer agent, such as one of those mentioned above, and a pharmaceutically acceptable carrier or diluent; for simultaneous, concurrent, sequential, separate or chronologically staggered use in therapy. Optionally, said kit comprises instructions for its use in therapy, e.g. to treat (hyper)proliferative diseases and/or disorders responsive to the induction of apoptosis, such as e.g. cancer, more precisely, any of those cancer diseases described above.

The present invention further relates to a combined preparation comprising at least one compound according to this invention and at least one art-known anti-cancer agent for simultaneous, concurrent, sequential or separate administration.

The present invention further relates to combinations, compositions, formulations, preparations or kits according to the present invention having Eg5 inhibitory activity and/or anti-proliferative and/or apoptosis inducing properties.

In addition, the present invention further relates to a method for treating in combination therapy (hyper)proliferative diseases and/or disorders responsive to the induction of apoptosis, such as e.g. cancer, in a patient comprising administering a combination, composition, formulation, preparation or kit as described herein to said patient in need thereof.

In addition, the present invention further relates to a method for treating (hyper)proliferative diseases of benign or malignant behaviour and/or disorders responsive to the induction of apoptosis, such as e.g. cancer, in a patient comprising administering in combination therapy separately, simultaneously, concurrently, sequentially or chronologically staggered a pharmaceutically active and therapeutically effective and tolerable amount of a pharmaceutical composition, which comprises a compound according to this invention and a pharmaceutically acceptable carrier or diluent, and a pharmaceutically active and therapeutically effective and tolerable amount of one or more art-known anti-cancer agents, such as e.g. one or more of those mentioned herein, to said patient in need thereof.

In further addition, the present invention relates to a method for treating, preventing or ameliorating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer, particularly any of those cancer diseases mentioned herein, in a patient comprising administering separately, simultaneously, concurrently, sequentially or chronologically staggered to said patient in need thereof an amount of a first active compound, which is a compound according to the present invention, and an amount of at least one second active compound, said at least one second active compound being a standard therapeutic agent, particularly at least one art-known anti-cancer agent, such as e.g. one or more of those chemotherapeutic and target-specific anti-cancer agents mentioned herein, wherein the amounts of the first active compound and said second active compound result in a therapeutic effect.

In yet further addition, the present invention relates to a method for treating, preventing or ameliorating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as e.g. benign or malignant neoplasia, e.g. cancer, particularly any of those cancer diseases mentioned herein, in a patient comprising administering a combination according to the present invention.

In addition, the present invention further relates to the use of a composition, combination, formulation, preparation or kit according to this invention in the manufacture of a pharmaceutical product, such as e.g. a commercial package or a medicament, for treating, preventing or ameliorating (hyper)proliferative diseases, such as e.g. cancer, and/or disorders responsive to the induction of apoptosis, particularly those diseases mentioned herein, such as e.g. malignant or benign neoplasia.

The present invention further relates to a commercial package comprising one or more compounds of the present invention together with instructions for simultaneous, concurrent, sequential or separate use with one or more chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned herein.

The present invention further relates to a commercial package consisting essentially of one or more compounds of the present invention as sole active ingredient together with instructions for

simultaneous, concurrent, sequential or separate use with one or more chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned herein.

The present invention further relates to a commercial package comprising one or more chemotherapeutic and/or target specific anti-cancer agents, such as e.g. any of those mentioned herein, together with instructions for simultaneous, concurrent, sequential or separate use with one or more compounds according to the present invention.

The compositions, combinations, preparations, formulations, kits or packages mentioned in the context of the combination therapy according to this invention may also include more than one of the compounds according to this invention and/or more than one of the art-known anti-cancer agents mentioned.

The first and second active ingredient of a combination or kit-of-parts according to this invention may be provided as separate formulations (i.e. independently of one another), which are subsequently brought together for simultaneous, concurrent, sequential, separate or chronologically staggered use in combination therapy; or packaged and presented together as separate components of a combination pack for simultaneous, concurrent, sequential, separate or chronologically staggered use in combination therapy.

The type of pharmaceutical formulation of the first and second active ingredient of a combination or kit-of-parts according to this invention can be similar, i.e. both ingredients are formulated in separate tablets or capsules, or can be different, i.e. suited for different administration forms, such as e.g. one active ingredient is formulated as tablet or capsule and the other is formulated for e.g. intravenous administration.

The amounts of the first and second active ingredients of the combinations, compositions or kits according to this invention may together comprise a therapeutically effective amount for the treatment, prophylaxis or amelioration of a (hyper)proliferative diseases and/or a disorder responsive to the induction of apoptosis, particularly one of those diseases mentioned herein, such as e.g. malignant or benign neoplasia, especially cancer, like any of those cancer diseases mentioned herein.

In addition, compounds according to the present invention can be used in the pre- or post-surgical treatment of cancer.

In further addition, compounds of the present invention can be used in combination with radiation therapy.

A combination according to this invention can refer to a composition comprising both the compound(s) according to this invention and the other active anti-cancer agent(s) in a fixed combination (fixed unit

dosage form), or a medicament pack comprising the two or more active ingredients as discrete separate dosage forms (non-fixed combination). In case of a medicament pack comprising the two or more active ingredients, the active ingredients are preferably packed into blister cards which are suited for improving compliance.

Each blister card preferably contains the medicaments to be taken on one day of treatment. If the medicaments are to be taken at different times of day, the medicaments can be disposed in different sections on the blister card according to the different ranges of times of day at which the medicaments are to be taken (for example morning and evening or morning, midday and evening). The blister cavities for the medicaments to be taken together at a particular time of day are accommodated in the respective range of times of day. The various times of day are, of course, also put on the blister in a clearly visible way. It is also possible, of course, for example to indicate a period in which the medicaments are to be taken, for example stating the times.

The daily sections may represent one line of the blister card, and the times of day are then identified in chronological sequence in this column.

Medicaments which must be taken together at a particular time of day are placed together at the appropriate time on the blister card, preferably a narrow distance apart, allowing them to be pushed out of the blister easily, and having the effect that removal of the dosage form from the blister is not forgotten.

Biological Investigations

The ATPase activity of Eg5 kinesin motor domains (Cytoskeleton, cat. No. EG01) can be used to monitor the effects of modulating agents. The test compounds are dissolved as 10 mM solutions in dimethylsulfoxide (DMSO). 2 µl of appropriate DMSO dilutions of the test compounds are added to each well of a 96 well flat bottom plate. Each compound dilution is tested as triplicates. The reagents are added and the final reaction of the standard assay contains 15 mM Pipes, pH 6.8, 5.0 mM $MgCl_2$, 0.5 mM KCl, 1 mM EGTA, 0.1 mg/ml BSA, 1 µM Paclitaxel, 250 nM preformed microtubules (Cytoskeleton, cat. No. MT001), 300 µM ATP, and Eg5 protein (50 ng) in a reaction volume of 100 µl. The controls include buffer wells with ATP and 2% DMSO. Reactions are started by the addition of ATP, incubated at room temperature for 30 min., and terminated by removing 20 µl of the reaction volume and adding it to 80 µl of 1 M perchloric acid, followed by the addition of 80 µl Malachite green reagent. Malachite green reagent is prepared by mixing a solution of 4.2 g ammonium molybdate in 100 ml 4 N HCl with a solution of 0.135 g Malachite green in 300 ml H_2O. The reactions are incubated for a further 20 min. and then read at 615 nm.
The corresponding IC_{50} values of the compounds for Eg5 inhibition are determined from the concentration-effect curves.

Representative inhibitory values [measured as –log IC_{50} (mol/l)] determined in the aforementioned assay follow from the following table A, in which the numbers of the compounds correspond to the numbers of the examples.

Table A

Inhibition of Eg5 activity

Compound	-log IC_{50} [mol/l]
2 to 9, 9a, 10 and 11	The inhibitory values of these listed compounds are all ≥ 6.6

The anti-proliferative / cytotoxic activity of the compounds described herein can be tested on subclones of RKO human colon adenocarcinoma cells (Schmidt et al., Oncogene 19, 2423-2429; 2000) using the Alamar Blue cell viability assay (described in O´Brien et al. Eur J Biochem 267, 5421-5426, 2000). The compounds are dissolved as 10 mM solutions in DMSO and subsequently diluted in semi-logarithmic steps. DMSO dilutions are further diluted 1:100 into Dulbecco´s modified Eagle´s medium (DMEM) containing 10% fetal calf serum to a final concentration twice as much as the final concentration in the test. RKO subclones are seeded into 96 well flat bottom plates at a density of 4000 cells per well in a volume of 50 µl per well. 24 hours after seeding the 50 µl each of the compound dilutions in DMEM medium are added into each well of the 96 well plate. Each compound dilution is tested as triplicates. Wells containing untreated control cells are filled with 50 µl DMEM medium containing 1% DMSO. The cells are then incubated with the substances for 72 hours at 37°C

in a humidified atmosphere containing 5% carbon dioxide. To determine the viability of the cells, 10 µl of an Alamar Blue solution (Biosource) are added and the fluorescence is measured at an extinction of 544 nm and an emission of 590 nm. For the calculation of the cell viability the emission value from untreated cells is set as 100% viability and the emission rates of treated cells are set in relation to the values of untreated cells. Viabilities are expressed as % values. The Graphpad Prism program is used for the calculation of EC_{50} values for anti-proliferative / cytotoxic activity out of the obtained dose-response curves.

To determine the cell cycle specific mode of action, subclones of RKO colon adenocarcinoma cells (RKOp27 as described by Schmidt et al. in Oncogene 19, 2423-2429; 2000) are seeded into 96 well flat bottom plates at a density of 16000 cells per well in a volume of 50 µl per well in DMEM growth medium with 10% FCS containing 10 µM Ponasterone A. 24 hours after seeding the 50 µl each of the compound dilutions in DMEM medium are added into each well of the 96-well plate. Each compound dilution is tested as triplicates. Wells containing untreated control cells are filled with 50 µl DMEM medium containing 1% DMSO. The cells are then incubated with the substances for 72 hours at 37°C in a humidified atmosphere containing 5% carbon dioxide. To determine the viability of the cells, 10 µl of an Alamar Blue solution (Biosource) are added and the fluorescence is measured at an extinction of 544 nm and an emission of 590 nm. For the calculation of the cell viability the emission value from untreated cells is set as 100% viability and the emission rates of treated cells are set in relation to the values of untreated cells. Viabilities are expressed as % values. The Graphpad Prism program is used for the calculation of EC_{50} values out of the obtained dose-response curves. Viability is compared of proliferating cells grown in the absence of the inducer Ponasterone A, versus viability of cells arrested by the expression of ectopic p27Kip1 induced by Ponasterone A.

Representative values for anti-proliferation / cytotoxicity [measured as –log EC_{50} (mol/l)] determined in the aforementioned assays follow from the following table B, in which the numbers of the compounds correspond to the numbers of the examples.

Table B

Anti-proliferative / cytotoxic activity on RKO colon cancer cells

	Examples
-log EC_{50} [mol/l] RKO p27 uninduced (proliferating) ≥ 7.0	2, 3, 4, 5, 6, 7, 8, 8a, 9a, 13, 14, 17, 18, 19, 20, 21, 22, 24
-log EC_{50} [mol/l] RKO p27 uninduced (proliferating) < 7.0 but ≥ 6.0	1, 9, 10, 11, 12, 15, 16, 23

The value of -log EC_{50} [mol/l] RKO p27 induced (arrested) was below the minimum determined by the assay specification (≤ 5.0, ≤ 5.5 or ≤ 6.0).

The induction of apoptosis can be measured by using a Cell death detection ELISA (Roche Biochemicals, Mannheim, Germany). NCI-H460 non-small cell lung cancer cells are seeded into 96 well flat bottom plates at a density of 10000 cells per well in a volume of 50 µl RPMI medium (containing 10% fetal calf serum) per well. The compounds are dissolved as 10 mM solutions in DMSO and subsequently diluted in semi-logarithmic steps. DMSO dilutions are further diluted 1:100 into RPMI medium (containing 10% fetal calf serum) to a final concentration twice as much as the final concentration in the test. 24 hours after seeding the 50 µl each of the compound dilutions in RPMI medium are added into each well of the 96 Well plate. Each compound dilution is tested at least as duplicates. Wells containing untreated control cells are filled with 50 µl RPMI medium containing 1% DMSO. The cells are then incubated with the substances for 24 hours at 37°C in a humidified atmosphere containing 5% carbon dioxide. As a positive control for the induction of apoptosis, cells are treated with 50 µM Cisplatin (Gry Pharmaceuticals, Kirchzarten, Germany). Medium is then removed and the cells are lysed in 200 µl lysis buffer. After centrifugation as described by the manufacturer, 10 µl of cell lysate is processed as described in the protocol. The degree of apoptosis is calculated as follows: The absorbance at 405 nm obtained with lysates from cells treated with 50 µM cisplatin is set as 100 cpu (cisplatin units), while an absorbance at 405 nm of 0.0 is set as 0.0 cpu. The degree of apoptosis is expressed as cpu in relation to the value of 100 cpu reached with the lysates obtained from cells treated with 50 µM cisplatin.

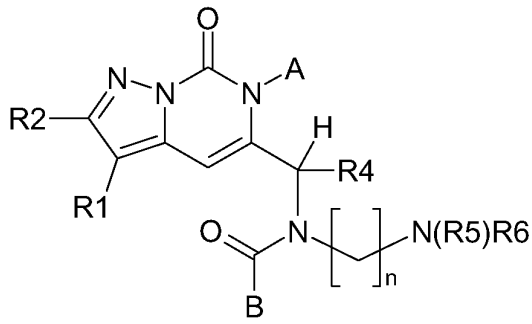
Experimental perturbation of Eg5 function causes a characteristic malformation of the mitotic spindle, which can be examined by confocal laser scanning microscopy. HeLa cervical cancer cells are grown overnight on glass cover slips (Nunc™ Lab-Tek™ Chamber Slides) in 1800 µl DMEM medium containing 10% fetal calf serum. The test compounds are dissolved as 10 mM solutions in DMSO. Appropriate DMSO dilutions of the test compounds are further diluted 1:20 into DMEM medium containing 10% fetal calf serum to a final concentration ten times as much as the final concentration in the test. 24 hours after seeding, 200 µl of the compound dilutions in DMEM medium are added into each well of the cover slip. As a control, 200 µl DMEM medium containing 5% DMSO are added. 24 hours after incubation with the test compounds, the cells are washed with PBS, and fixed with 3.7% formaldehyde in H_2O for 20 min. at 37°C. Subsequently, cells are washed with PBS and incubated with 0,1% Triton X-100 in a buffer containing 1.471 mM KH_2PO_4, 8.504 mM Na_2HPO_4, 137 mM NaCl, 1.325 mM $CaCl_2$, 2.685 mM KCl, 0.542 mM $MgCl_2$, pH 7.2 for 15 min. at room temperature. For saturation of non-specific binding, cells are incubated in 2% BSA/10% FCS in PBS (= blocking buffer) for 30 min. at room temperature prior to incubation with anti-alpha tubulin monoclonal antibodies (Sigma, #T5168; 1:1000), followed by Cy3-conjugated rabbit anti-mouse IgG (H+L) antibody (Jackson Immuno Research; 1:1000). All antibody incubations are performed for one hour at 37 °C in blocking buffer, and cells are washed three times in PBS between different incubations. DNA is counterstained with Hoechst 33342 (0.1 µg/ml). Coverslips are mounted in Vectashield (Vector Laboratories,

Burlingame, CA) and examined with a Leica TCS SP2 confocal laser scanning microscope fitted with appropriate filters (Leica Microsystems, Bensheim, Germany).

Some of the compounds according to this invention may be efficacious against p-glycoprotein mediated multidrug-resistent tumour cell lines (e.g. HCT-15), that can be measured as follows:
All cell lines used are cultured at standard conditions in a tissue culture incubator at 37°C, 5% CO_2 and 95% humidity. At day 1, cells are detached with Trypsin / EDTA and pelleted by centrifugation. Cells are resuspended at the appropriate density in culture medium, seeded into 96well microtiter plates and incubated over night in a tissue culture incubator at 37°C, 5% CO_2 and 95% humidity. Stock solution of all compounds to be tested are dissolved at 10mM in DMSO and at day 2 added to the microtiter plates in the desired dilutions. The final DMSO concentration in the microtiter plates is kept at 0.5 %. Control cells are treated with culture medium including a final concentration of 0.5% DMSO only. The microtiter plates are incubated with the compounds in a tissue culture incubator at 37°C, 5% CO_2 and 95% humidity for further 72 hours. To determine the viability of the cells at day 5, an Alamar Blue solution (Biosource) is added at 1/10 culture volume to the microtiter plates. The cells are incubated in a tissue culture incubator at 37°C, 5% CO_2 and 95% humidity for additional 1-6 hours and the fluorescence is measured at an extinction of 544 nm and an emission of 590 nm. For the calculation of the cell viability the emission value from untreated cells is set as 100% viability and the emission rates of treated cells are set in relation to the values of untreated cells. Viabilities are expressed as % values.
The Graphpad Prism program is used for the calculation of EC_{50} values out of the obtained dose-response curves.

Patent Claims

1. Compounds of formula I



(I)

in which

R1 is hydrogen or halogen,

R2 is 1-4C-alkyl,

A is Aryl-1-4C-alkyl, in which

Aryl is phenyl, or R3- and R31-substituted phenyl, in which

R3 is 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, hydroxyl, halogen, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R31 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R5 is hydrogen or 1-4C-alkyl,

R6 is hydrogen or 1-4C-alkyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is 1-4C-alkyl, trifluoromethyl, cyano, 1-4C-alkoxy, halogen, carboxyl, 1-4C-alkylcarbonyl, methylenedioxy, ethylenedioxy, 1-4C-alkoxy-1-4C-alkyl, hydroxy-1-4C-alkyl, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R71 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

n is 2, 3, 4, 5 or 6,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

2. Compounds of formula I according to claim 1, in which

R1 is hydrogen or halogen,

R2 is methyl or ethyl,

A is Arylmethyl, in which

Aryl is phenyl, or R3- and R31-substituted phenyl, in which

R3 is methyl, ethyl, trifluoromethyl, methoxy, ethoxy, hydroxyl, halogen, difluoromethoxy or trifluoromethoxy,

R31 is hydrogen, halogen, methyl, ethyl, methoxy or ethoxy,

R4 is methyl, ethyl, propyl, isopropyl, sec-butyl, cyclopropyl or cyclopropylmethyl,

R5 is hydrogen, methyl, ethyl, propyl or isopropyl,

R6 is hydrogen, methyl, ethyl, propyl or isopropyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, cyano, methoxy, ethoxy, halogen, carboxyl, acetyl, methylenedioxy, ethylenedioxy, methoxymethyl, hydroxymethyl, difluoromethoxy or trifluoromethoxy,

R71 is hydrogen, halogen, methyl, ethyl, methoxy or ethoxy,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

3. Compounds of formula I according to claim 1, in which

R1 is hydrogen, chlorine or bromine,

R2 is methyl or ethyl,

A is benzyl, halobenzyl (e.g. fluorobenzyl, chlorobenzyl or bromobenzyl), methylbenzyl, methoxybenzyl or hydroxybenzyl,

R4 is ethyl, propyl, isopropyl, sec-butyl or cyclopropyl,

either

R5 and R6 are both hydrogen,

or

R5 is methyl, and

R6 is hydrogen,

or

R5 is ethyl, and

R6 is hydrogen,

or

R5 is propyl, and

R6 is hydrogen,

or

R5 is isopropyl, and

R6 is hydrogen,

or

R5 and R6 are both methyl,

B is phenyl, or R7- and R71-substituted phenyl, in which

R7 is methyl, ethyl, trifluoromethyl, cyano, methoxy, ethoxy, halogen, carboxyl, methylenedioxy, ethylenedioxy, methoxymethyl or hydroxymethyl,

R71 is hydrogen, halogen, methyl or ethyl,

n is 2 or 3,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

4. Compounds of formula I according to any of the preceding claims comprising one or more of the following:

R1 is chlorine or bromine;

R2 is methyl;

A is benzyl;

R4 is ethyl or isopropyl;

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl;

B is 4-methylphenyl, 3-methylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl or 3-fluoro-4-methylphenyl; and

n is 3;

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

5. Compounds of formula I according to claim 1, in which

R1 is hydrogen, chlorine, bromine or fluorine,

R2 is methyl,

A is benzyl,

R4 is ethyl, isopropyl, sec-butyl, cyclopropyl or cyclobutyl,

either

R5 and R6 are both hydrogen,

or

R5 and R6 are both methyl,

B is 4-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 4-bromophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 3-fluoro-4-methylphenyl, 2-fluoro-4-methylphenyl, 3,4-dichlorophenyl or 2,3-dichlorophenyl,

n is 2, 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

6. Compounds of formula I according to claim 1, in which

R1 is chlorine, bromine or fluorine,

R2 is methyl,

A is benzyl,

R4 is ethyl, isopropyl, sec-butyl or cyclopropyl,

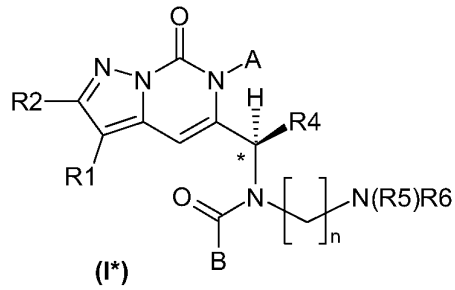
R5 and R6 are both hydrogen,

B is 4-methylphenyl, 3-methylphenyl, 4-fluorophenyl, 4-bromophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3-fluoro-4-methylphenyl, 2-fluoro-4-methylphenyl or 3,4-dichlorophenyl

n is 3 or 4,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

7. Compounds of formula I according to any of the preceding claims, wherein said compounds have the configuration as shown in formula I*



(I*)

and the salts thereof.

8. Compounds of formula I, selected from:

(1) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide,

(2) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide,

(3) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3-methyl-benzamide,

(4) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-fluoro-benzamide,

(5) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methoxy-benzamide,

(6) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-bromo-benzamide,

(7) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-chloro-benzamide,

(8) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide,

(9) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-propyl]-4-methyl-benzamide,

(10) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-trifluoromethyl-benzamide,

(11) N-[(RS)-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(3-dimethylamino-propyl)-4-methyl-benzamide,

(12) N-(4-Amino-butyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide,

(13) N-(2-Amino-ethyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide,

(14) N-(2-Amino-ethyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide,

(15) N-[(RS)-(6-Benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-methyl-propyl]-N-(2-dimethylamino-ethyl)-4-methyl-benzamide,

(16) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo [1,5-c]pyrimidin-5-yl)-1-cyclobutyl-methyl]-4-methyl-benzamide,

(17) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-butyl]-4-methyl-benzamide,

(18) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-4-methyl-benzamide,

(19) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-1-cyclopropyl-methyl]-4-bromo-benzamide,

(20) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3-fluoro-4-methyl-benzamide,

(21) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-2-fluoro-4-methyl-benzamide,

(22) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-3,4-dichloro-benzamide,

(23) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-chloro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-2,3-dichloro-benzamide,

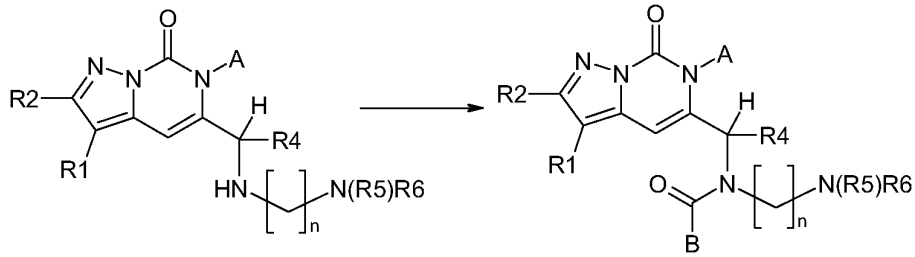
(24) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-bromo-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide,

(25) N-(3-Amino-propyl)-N-[(RS)-1-(6-benzyl-3-fluoro-2-methyl-7-oxo-6,7-dihydro-pyrazolo[1,5-c]pyrimidin-5-yl)-2-methyl-propyl]-4-methyl-benzamide,

and the salts, stereoisomers and the salts of the stereoisomers of these compounds.

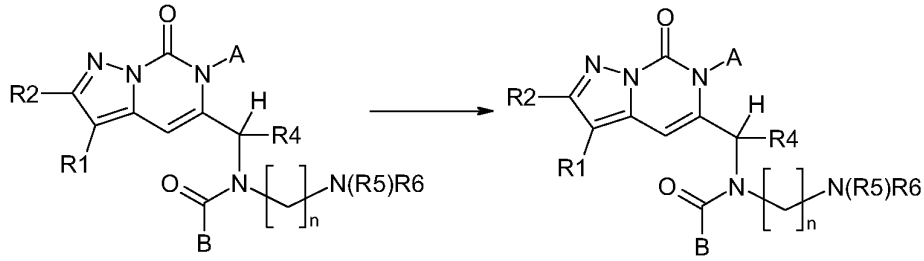
9. Process for preparing a compound according to any of claims 1 to 8, comprising at least one of the steps

(i) benzoylation of a compound of formula II, with the meanings of R1, R2, A, R4, R5 and R6 as indicated for the compounds according to any of claims 1 to 8, or with at least one of R5 and R6 being part of a protective group,



(II) **(I)**

(ii) halogenation of a compound of formula I wherein R1 = H to give a compound of formula I wherein R1 = halogen, or



(I) R1 = H (I) R1 = halogen

(iii) optionally the removal of protecting groups represented by at least one of R5 and R6 as indicated under (i).

10. Compounds according to any of the claims 1 to 8 for use in the treatment of diseases.

11. A pharmaceutical composition comprising one or more compounds according to any of the claims 1 to 8 together with customary pharmaceutical auxiliaries and/or excipients.

12. Use of the compounds according to any of the claims 1 to 8 in the manufacture of pharmaceutical compositions for treating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as, for example, benign and/or malignant neoplasia, e.g. cancer.

13. Pharmaceutical composition for treating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, which include benign neoplasia and malignant neoplasia, including cancer, comprising a compound according to any of claims 1 to 8.

14. A method for treating, preventing or ameliorating (hyper)proliferative diseases and/or disorders responsive to induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer, in a mammal comprising administering a therapeutically effective and tolerable amount of one or more compounds according to any of the claims 1 to 8 to said mammal in need thereof.

15. A method for modulating Eg5 kinesin activity comprising administering a therapeutically effective and tolerable amount of one or more compounds according to any of the claims 1 to 8 to a mammal in need of said modulation.

16. A combination comprising
a first active ingredient, which is at least one compound according to any of the claims 1 to 8, and
a second active ingredient, which is at least one anti-cancer agent selected from the group consisting of chemotherapeutic anti-cancer agents and target-specific anti-cancer agents,
for separate, sequential, simultaneous, concurrent or chronologically staggered use in therapy, such as e.g. therapy of (hyper)proliferative diseases of benign or malignant behaviour and/or disorders

responsive to the induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer.

17. A method for treating, preventing or ameliorating hyperproliferative diseases and/or disorders responsive to induction of apoptosis, such as, for example, benign or malignant neoplasia, e.g. cancer, in a patient comprising administering separately, simultaneously, concurrently, sequentially or chronologically staggered to said patient in need thereof
an amount of a first active compound, which is a compound according to any of the claims 1 to 8, and an amount of at least one second active compound, said second active compound being an anti-cancer agent selected from the group consisting of chemotherapeutic anti-cancer agents and target-specific anti-cancer agents,
wherein the amounts of the first active compound and said second active compound result in a therapeutic effect.

18. The combination or method according to claim 16 or 17, in which said chemotherapeutic anti-cancer agents are selected from (i) alkylating/carbamylating agents including Cyclophosphamid, Ifosfamid, Thiotepa, Melphalan and chloroethylnitrosourea; (ii) platinum derivatives including cis-platin, oxaliplatin, satraplatin and carboplatin; (iii) antimitotic agents / tubulin inhibitors including vinca alkaloids, such as e.g. vincristine, vinblastine or vinorelbine, taxanes, such as e.g. Paclitaxel, Docetaxel and analogs as well as formulations and conjugates thereof, and epothilones, such as e.g. Epothilone B, Azaepothilone or ZK-EPO; (iv) topoisomerase inhibitors including anthracyclines, such as e.g. Doxorubicin, epipodophyllotoxines, such as e.g. Etoposide, and camptothecin and camptothecin analogs, such as e.g. Irinotecan or Topotecan; (v) pyrimidine antagonists including 5-fluorouracil, Capecitabine, Arabinosylcytosine / Cytarabin and Gemcitabine; (vi) purin antagonists including 6-mercaptopurine, 6-thioguanine and fludarabine; and (vii) folic acid antagonists including methotrexate and pemetrexed.

19. The combination or method according to claim 16, 17 or 18, in which said target-specific anti-cancer agents are selected from (i) kinase inhibitors including Imatinib, ZD-1839 / Gefitinib, BAY43-9006 / Sorafenib, SU11248 / Sunitinib and OSI-774 / Erlotinib; (ii) proteasome inhibitors including PS-341 / Bortezomib; (iii) histone deacetylase inhibitors including SAHA, PXD101, MS275, MGCD0103, Depsipeptide / FK228, NVP-LBH589, NVP-LAQ824, Valproic acid (VPA) and butyrates; (iv) heat shock protein 90 inhibitors including 17-allylaminogeldanamycin (17-AAG); (v) vascular targeting agents (VAT) including combretastatin A4 phosphate and AVE8062 / AC7700, and anti-angiogenic drugs including VEGF antibodies, such as e.g. Bevacizumab, and KDR tyrosine kinase inhibitors, such as e.g. PTK787 / ZK222584 (Vatalanib); (vi) monoclonal antibodies including Trastuzumab, Rituximab, Alemtuzumab, Tositumab, Cetuximab and Bevacizumab as well as mutants and conjugates of monoclonal antibodies, such as e.g. Gemtuzumab ozogamicin or Ibritumomab tiuxetan, and antibody fragments; (vii) oligonucleotide based therapeutics including G-3139 / Oblimersen; (viii) Toll-like receptor / TLR 9 agonists including Promune®, TLR 7 agonists including Imiquimod and

Isatoribine and analogues thereof, or TLR 7/8 agonists including Resiquimod as well as immunostimulatory RNA as TLR 7/8 agonists; (ix) protease inhibitors; (x) hormonal therapeutics including anti-estrogens, such as e.g. Tamoxifen or Raloxifen, anti-androgens, such as e.g. Flutamide or Casodex, LHRH analogs, such as e.g. Luprolide, Goserelin or Triptorelin, and aromatase inhibitors; bleomycin; retinoids including all-trans retinoic acid (ATRA); DNA methyltransferase inhibitors including the 2-deoxycytidine derivative Decitabine and 5-azacytidine; alanosine; cytokines including interleukin-2; interferons including interferon α2 and interferon-γ; and death receptor agonists including TRAIL, DR4/5 agonistic antibodies, FasL and TNF-R agonists.

20. The use, method or combination according to any of the claims 12, 14, 16 and 17, in which said cancer is selected from the group consisting of
cancer of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands, esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, sarcoma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva;
inherited cancers, retinomblastoma and Wilms tumor;
leukemia, lymphoma, non-Hodgkins disease, chronic and acute myeloid leukaemia, acute lymphoblastic leukemia, Hodgkins disease, multiple myeloma and T-cell lymphoma;
myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site and AIDS related malignancies.