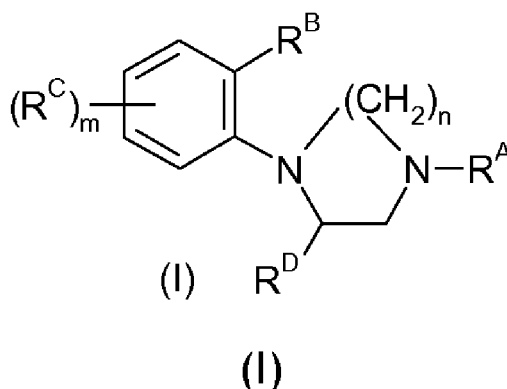




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(54) **Title:** GLUCOSE TRANSPORT INHIBITORS

(57) **Abstract:** The present invention relates to chemical compounds of general formula (I): in which R^A , R^B , R^C , R^D , m , and n are as given in the description and in the claims, and which effectively and selectively inhibit glucose transporter 1 (GLUT1), to methods of preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds, to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, as well as to intermediate compounds useful in the preparation of said compounds.



GLUCOSE TRANSPORT INHIBITORS

The present invention relates to chemical compounds that selectively inhibit glucose transporter 1 (GLUT1), to methods of preparing said compounds, to pharmaceutical compositions and combinations comprising said compounds, to the use of said compounds for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease, as well as to intermediate compounds useful in the preparation of said compounds.

10 BACKGROUND OF THE INVENTION

Glucose is an essential substrate for metabolism in most cells. Because glucose is a polar molecule, transport through biological membranes requires specific transport proteins. Transport of glucose through the apical membrane of intestinal and kidney epithelial cells depends on the presence of secondary active Na⁺/glucose symporters, SGLT-1 and SGLT-2, which concentrate glucose inside the cells, using the energy provided by co-transport of Na⁺ ions down their electrochemical gradient. Facilitated diffusion of glucose through the cellular membrane is otherwise catalyzed by glucose carriers (protein symbol GLUT, gene symbol SLC2 for Solute Carrier Family 2) that belong to a superfamily of transport facilitators (major facilitator superfamily) including organic anion and cation transporters, yeast hexose transporter, plant hexose/proton symporters, and bacterial sugar/proton symporters.

Basal glucose transporters (GLUTs) function as glucose channels and are required for maintaining the basic glucose needs of cells. These GLUTs are constitutively expressed and functional in cells and are not regulated by (or sensitive to) insulin. All cells use both glycolysis and oxidative phosphorylation in mitochondria but rely overwhelmingly on oxidative phosphorylation when oxygen is abundant, switching to glycolysis at times of oxygen deprivation (hypoxia), as it occurs in cancer. In glycolysis, glucose is converted to pyruvate

- and two ATP molecules are generated in the process. Cancer cells, because of their faster proliferation rates, are predominantly in a hypoxic (low oxygen) state. Therefore, cancer cells use glycolysis (lactate formation) as their predominant glucose metabolism pathway. Such a glycolytic switch not only gives cancer higher potentials for metastasis and invasiveness, but also increases cancer's vulnerability to external interference in glycolysis. The reduction of basal glucose transport is likely to restrict glucose supply to cancer cells, leading to glucose deprivation that forces cancer cells to slow down growth or to starve.
- 10 All known GLUT proteins contain 12 transmembrane domains and transport glucose by facilitating diffusion, an energy-independent process. GLUT1 transports glucose into cells probably by alternating its conformation. According to this model, GLUT1 exposes a single substrate-binding site toward either the outside or the inside of the cell. Binding of glucose to one site
- 15 triggers a conformational change, releasing glucose to the other side of the membrane. Results of transgenic and knockout animal studies support an important role for these transporters in the control of glucose utilization, glucose storage and glucose sensing. The GLUT proteins differ in their kinetics and are tailored to the needs of the cell types they serve. Although more than
- 20 one GLUT protein may be expressed by a particular cell type, cancers frequently overexpress GLUT1, which is a high affinity glucose transporter, and its expression level is correlated with invasiveness and metastasis potentials of cancers, indicating the importance of upregulation of glucose transport in cancer cell growth and in the severity of cancer malignancy. GLUT1 expression
- 25 was also found to be significantly higher than that of any other glucose transporters.

Evidence indicates that cancer cells are more sensitive to glucose deprivation than normal cells. Numerous studies strongly suggest that basal glucose

30 transport inhibition induces apoptosis and blocks cancer cell growth. Anti-

angiogenesis has been shown to be a very effective way to restrict cancer growth and cause cancer ablation.

Reduced GLUT1 expression following transfection of GLUT1 antisense cDNA
5 into cancer cell lines has been shown to suppress cell growth in vitro and tumor growth in vivo, and to reduce in vitro invasiveness of cells (Noguchi Y. et al. Cancer Lett 154(2), 2000, 175-182; Ito S. et al. J Natl Cancer Inst 94(14), 2002, 1080-1091).

10 It has been demonstrated that GLUT1 is the most highly expressed hexose transporter in ErbB2- and PyVMT-induced mouse mammary carcinoma models, and that reducing the level of GLUT1 using shRNA or Cre/lox results in reduced glucose usage, reduced growth on plastic and in soft agar, and impaired tumor growth in nude mice (Christian D. Young et al., PLoS ONE, August 2011,
15 Volume 6, Issue 8, e23205, 1-12).

Therefore, inhibition of GLUT1 represents a promising approach for the treatment of proliferative disorders including solid tumours such as carcinomas and sarcomas and leukaemias and lymphoid malignancies or other disorders
20 associated with uncontrolled cellular proliferation.

Different compounds have been disclosed in prior art which show an inhibitory effect on GLUT1. For example, WO2011/119866(A1) discloses composition and methods for glucose transport inhibition; WO2012/051117(A2) discloses
25 substituted benzamides as GLUT1 inhibitors. However, pyrazolopyrimidine compounds have not been reported in the context of GLUT1 inhibition.

WO2005/117909(A2) discloses, *inter alia*, substituted pyrazolopyrimidine compounds which inhibit p70S6 and/or Akt kinases.

30

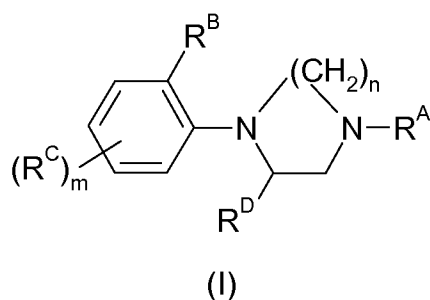
US2004/0204400A1 discloses substituted pyrazolopyrimidine compounds for the treatment of infections by enteroviruses.

- 5 However, the state of the art described above does not specifically disclose the compounds of general formula (I) of the present invention, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same, as described and defined herein, and as hereinafter referred to as “compounds of the present invention”, or their pharmacological activity.

10

SUMMARY of the INVENTION

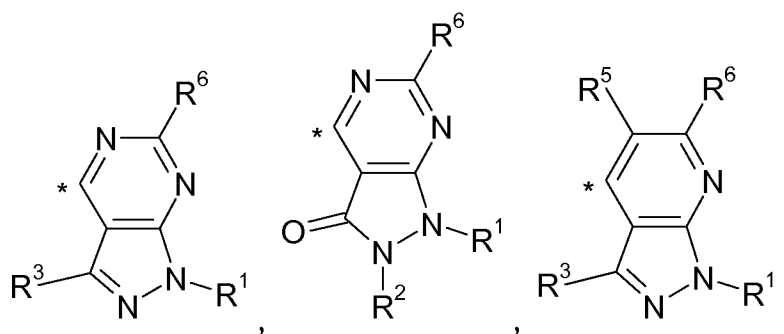
The present invention covers compounds of general formula (I) :

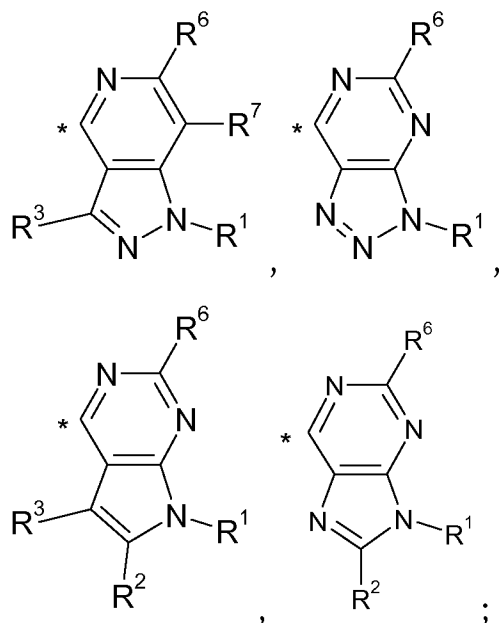


15

in which :

R^A is selected from the group consisting of:





wherein * indicates the point of attachment of said groups with the rest of the molecule;

5

R^B represents a hydrogen atom or a -OH, -SH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, -S-(C₁-C₃-alkyl), -S-(halo-C₁-C₃-alkyl), -N(H)(C₁-C₃-alkyl),
-N(C₁-C₃-alkyl)(C₁-C₃-alkyl) or a H₂N-C₁-C₃-alkyl- group;

10

each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-,
C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
aryl-, heteroaryl-, 3- to 10-membered heterocycloalkyl-,
4- to 10-membered heterocycloalkenyl-, C₃-C₇-cycloalkyl-,
-C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂,
-N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
-N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b},

20

-N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)₂R⁸,
 -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;

or

5 when two R^C groups are present ortho to each other on the phenyl-
 group, said two R^C groups together form a bridge :

O(CH₂)₂O, *O(CH₂)O*, *O(CF₂)O*, *CH₂C(R^{8a})(R^{8b})O*, *C(=O)N(R^{8a})CH₂*,
 N(R^{8a})C(=O)CH₂O, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents
 the point of attachment to said phenyl- group;

10

R^D represents a hydrogen atom or a methyl- group;

R¹ represents a hydrogen atom or a C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 C₂-C₆-alkynyl-, C₁-C₆-alkoxy-, C₁-C₆-alkoxy-C₁-C₆-alkyl-,

15

C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
 C₄-C₈-cycloalkenyl-, -(CH₂)_p-C₄-C₈-cycloalkenyl,
 3- to 10-membered heterocycloalkyl-,
 -(CH₂)_p-(3- to 10-membered heterocycloalkyl),
 4- to 10-membered heterocycloalkenyl-,

20

-(CH₂)_p-(4- to 10-membered heterocycloalkenyl),
 aryl-, -(CH₂)_p-aryl, heteroaryl- or -(CH₂)_p-heteroaryl group,
 wherein said group is optionally substituted, identically or differently,
 with 1, 2, 3, 4 or 5 R⁹ groups ;

25

R² represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group ;

R³ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,

30

-C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,

-N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸ or -O(C=O)N(R^{8a})R^{8b} group ;

wherein said C₁-C₃-alkyl- group is optionally substituted with a group
 5 selected from: -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸,
 -OR⁸, -O(C=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} and
 -S(=O)(=NR^{8c})R⁸ ;

10 R⁵ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group;

R⁶ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,
 15 -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,
 -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸ or
 -O(C=O)R⁸ group ;
 wherein said C₁-C₃-alkyl- group is optionally substituted with a group
 20 selected from: -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸,
 -OR⁸, -O(C=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} and
 -S(=O)(=NR^{8c})R⁸ ;

25 R⁷ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group;

R⁸, R^{8a}, R^{8b}, R^{8c}

represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-, (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, heteroaryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-C₁-C₆-alkyl- or (aryl)-(3- to 10-membered heterocycloalkyl)- group; said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 3- to 10-membered heterocycloalkyl-, (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-, heteroaryl-C₁-C₆-alkyl- or (aryl)-(3- to 10-membered heterocycloalkyl)- group being optionally substituted one or more times, identically or differently, with R¹⁰;

or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with a C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group, the phenyl- group being optionally substituted 1, 2 or 3 times, identically or differently, with halogen, C₁-C₃-alkyl- or C₁-C₃-alkoxy;

20

R⁹ represents a halogen atom, or a -CN, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₆-alkyl)-, HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-,

25

3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b}, -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸, -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;

30

wherein the aryl-, heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C ;

R^{10} represents a halogen atom, or a C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkyl-, -CN,
 5 -C(=O) R^{11} , -C(=O)N(H) R^{11} , -C(=O)N(R^{11a}) R^{11b} , -C(=O)O- R^{11} , -N(R^{11a}) R^{11b} ,
 -NO₂, -N(H)C(=O) R^{11} , -N(R^{11a})C(=O) R^{11b} , -N(H)C(=O)N(R^{11a}) R^{11b} ,
 -N(R^{11a})C(=O)N(R^{11b}) R^{11c} , -N(H)C(=O)OR¹¹, -N(R^{11a})C(=O)OR^{11b},
 -N(H)S(=O)₂ R^{11} , -N(R^{11a})S(=O)₂ R^{11b} , -OR¹¹, -O(C=O) R^{11} , -O(C=O)N(R^{11a}) R^{11b} ,
 -O(C=O)OR¹¹, -SR¹¹, -S(=O) R^{11} , -S(=O)₂ R^{11} , -S(=O)₂N(H) R^{11} ,
 10 -S(=O)₂N(R^{11a}) R^{11b} or -S(=O)(=NR^{11a}) R^{11b} group;

R^{11} , R^{11a} , R^{11b} , R^{11c}

represent, independently from each other, a hydrogen atom or a C_1 - C_6 -alkyl- group;

15

m is an integer of 0, 1, 2 or 3 ;

n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

t is an integer of 3, 4 or 5 ;

20

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same ;

for use in the treatment or prophylaxis of a disease.

25

The present invention further relates to a pharmaceutical composition comprising a compound of formula (I), *supra*.

The present invention further relates to the use of a compound of formula (I),
 30 *supra*, for the prophylaxis or treatment of a disease.

The present invention further relates to the use of a compound of formula (I), *supra*, for the preparation of a medicament for the prophylaxis or treatment of a disease.

5

The present invention further relates to the compounds of formula (I), *supra*, *per se*, wherein the following compounds are excluded:

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-

10 1H-pyrazolo[3,4-d]pyrimidine,

4-[4-(2-fluorophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine.

The present invention further relates to methods of preparing compounds of general formula (I), *supra*.

15

DETAILED DESCRIPTION of the INVENTION

The terms as mentioned in the present text have preferably the following meanings :

20

The term “halogen atom” or “halo-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

25 The term “C₁-C₆-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms, e.g. a methyl, ethyl, propyl, butyl, pentyl, hexyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *iso*-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, *neo*-pentyl, 1,1-dimethylpropyl, 4-
30 methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl,

1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C₁-C₄-alkyl"), e.g. a methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms ("C₁-C₃-alkyl"), e.g. a methyl, ethyl, *n*-propyl- or *iso*-propyl group.

The term "halo-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C₁-C₆-alkyl" is defined *supra*, and in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkyl group is, for example, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, or -CH₂CF₃.

The term "C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent group of formula -O-(C₁-C₆-alkyl), in which the term "C₁-C₆-alkyl" is defined *supra*, e.g. a methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *tert*-butoxy, *sec*-butoxy, pentoxy, *iso*-pentoxy, or *n*-hexoxy group, or an isomer thereof.

The term "halo-C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkoxy group is, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCF₂CF₃, or -OCH₂CF₃.

The term "C₁-C₆-alkoxy-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically

or differently, by a C₁-C₆-alkoxy group, as defined *supra*, e.g. methoxyalkyl, ethoxyalkyl, propyloxyalkyl, *iso*-propoxyalkyl, butoxyalkyl, *iso*-butoxyalkyl, *tert*-butoxyalkyl, *sec*-butoxyalkyl, pentyloxyalkyl, *iso*-pentyloxyalkyl, hexyloxyalkyl group, or an isomer thereof.

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The term "halo-C₁-C₆-alkoxy-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy-C₁-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said
 10 halogen atom is F. Said halo-C₁-C₆-alkoxy-C₁-C₆-alkyl group is, for example, -CH₂CH₂OCF₃, -CH₂CH₂OCHF₂, -CH₂CH₂OCH₂F, -CH₂CH₂OCF₂CF₃, or -CH₂CH₂OCH₂CF₃.

15 The term "C₂-C₆-alkenyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C₂-C₃-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds
 20 may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (*E*)-2-methylvinyl, (*Z*)-2-methylvinyl, homoallyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, (*E*)-but-1-enyl, (*Z*)-but-1-enyl, pent-4-enyl, (*E*)-pent-3-enyl, (*Z*)-pent-3-enyl, (*E*)-pent-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-pent-1-enyl, hex-5-enyl, (*E*)-hex-4-enyl, (*Z*)-hex-4-enyl,
 25 (*E*)-hex-3-enyl, (*Z*)-hex-3-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-1-enyl, (*Z*)-hex-1-enyl, *iso*-propenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (*E*)-1-methylprop-1-enyl, (*Z*)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (*E*)-2-methylbut-2-enyl, (*Z*)-2-methylbut-2-enyl,
 30 (*E*)-1-methylbut-2-enyl, (*Z*)-1-methylbut-2-enyl, (*E*)-3-methylbut-1-enyl,

(Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl,
 (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl,
 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl,
 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl,
 5 4-methylpent-3-enyl, (E)-3-methylpent-3-enyl, (Z)-3-methylpent-3-enyl,
 (E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl,
 (Z)-1-methylpent-3-enyl, (E)-4-methylpent-2-enyl, (Z)-4-methylpent-2-enyl,
 (E)-3-methylpent-2-enyl, (Z)-3-methylpent-2-enyl, (E)-2-methylpent-2-enyl,
 (Z)-2-methylpent-2-enyl, (E)-1-methylpent-2-enyl, (Z)-1-methylpent-2-enyl,
 10 (E)-4-methylpent-1-enyl, (Z)-4-methylpent-1-enyl, (E)-3-methylpent-1-enyl,
 (Z)-3-methylpent-1-enyl, (E)-2-methylpent-1-enyl, (Z)-2-methylpent-1-enyl,
 (E)-1-methylpent-1-enyl, (Z)-1-methylpent-1-enyl, 3-ethylbut-3-enyl,
 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-ethylbut-2-enyl,
 (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-enyl,
 15 (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl,
 (Z)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl,
 (Z)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl,
 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (E)-2-propylprop-1-enyl,
 (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl, (Z)-1-propylprop-1-enyl,
 20 (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl,
 (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl,
 (E)-3,3-dimethylprop-1-enyl, (Z)-3,3-dimethylprop-1-enyl,
 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl,
 hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or
 25 allyl.

The term "C₂-C₆-alkynyl" is to be understood as preferably meaning a linear or
 branched, monovalent hydrocarbon group which contains one or more triple
 bonds, and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3
 30 carbon atoms ("C₂-C₃-alkynyl"). Said C₂-C₆-alkynyl group is, for example,

ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 5 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 10 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-ynyl.

The term “C₃-C₇-cycloalkyl” is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5, 6 or 7 carbon 15 atoms. Said C₃-C₇-cycloalkyl group is for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring. Particularly, said ring contains 3, 4, 5 or 6 carbon atoms (“C₃-C₆-cycloalkyl”).

The term “C₄-C₈-cycloalkenyl” is to be understood as preferably meaning a 20 monovalent, monocyclic hydrocarbon ring which contains 4, 5, 6, 7 or 8 carbon atoms and one or two double bonds, in conjugation or not, as the size of said cycloalkenyl ring allows. Particularly, said ring contains 4, 5 or 6 carbon atoms (“C₄-C₆-cycloalkenyl”). Said C₄-C₈-cycloalkenyl group is for example a cyclobutenyl, cyclopentenyl, or cyclohexenyl group.

25

The term “3- to 10-membered heterocycloalkyl”, is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NR^a, in 30 which R^a represents a hydrogen atom, or a C₁-C₆-alkyl- group ; it being possible

for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom.

Particularly, said 3- to 10-membered heterocycloalkyl can contain 2, 3, 4, 5 or 6 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a “3- to 7-membered heterocycloalkyl”), more particularly said heterocycloalkyl can contain 4, 5 or 6 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a “4- to 6-membered heterocycloalkyl”).

10

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidiny, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxoliny, pyrrolidiny, imidazolidiny, pyrazolidiny, or a 6-membered ring, such as tetrahydropyranyl, piperidiny, morpholiny, dithianyl, thiomorpholiny, piperazinyl, or trithianyl, or a 7-membered ring, such as a diazepanyl ring, for example.

The term “4- to 10-membered heterocycloalkenyl”, is to be understood as meaning an unsaturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NR^a, in which R^a represents a hydrogen atom or a C₁-C₆-alkyl- group ; it being possible for said heterocycloalkenyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom. Examples of said heterocycloalkenyl may contain one or more double bonds, e.g. 4H-pyranyl, 2H-pyranyl, 3H-diaziriny, 2,5-dihydro-1H-pyrrolyl, [1,3]dioxolyl, 4H-[1,3,4]thiadiaziny, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiaziny group.

30

The term “aryl” is to be understood as preferably meaning a monovalent, aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a “C₆-C₁₄-aryl” group), particularly a ring having 6 carbon atoms (a “C₆-aryl” group), e.g. a phenyl group; or a ring having 9 carbon atoms (a “C₉-aryl” group), e.g. an indanyl or indenyl group, or a ring having 10 carbon atoms (a “C₁₀-aryl” group), e.g. a tetralinyl, dihydronaphthyl, or naphthyl group, or a biphenyl group (a “C₁₂-aryl” group), or a ring having 13 carbon atoms, (a “C₁₃-aryl” group), e.g. a fluorenyl group, or a ring having 14 carbon atoms, (a “C₁₄-aryl” group), e.g. an anthracenyl group. Preferably, the aryl group is a phenyl group.

The term “heteroaryl” is understood as preferably meaning a monovalent, monocyclic-, bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and in addition in each case can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indolizinyl, purinyl, *etc.*, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.*.

In general, and unless otherwise mentioned, the heteroaryl or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridyl includes pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl; or the term thienyl includes thien-2-yl and thien-3-yl. Preferably, the heteroaryl group is a pyridinyl group.

The term "C₁-C₆", as used throughout this text, e.g. in the context of the definition of "C₁-C₆-alkyl", "C₁-C₆-haloalkyl", "C₁-C₆-alkoxy", or "C₁-C₆-haloalkoxy" is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 6, i.e. 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as any sub-range comprised therein, e.g. C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more particularly C₁-C₄; in the case of "C₁-C₆-haloalkyl" or "C₁-C₆-haloalkoxy" even more particularly C₁-C₂.

Similarly, as used herein, the term "C₂-C₆", as used throughout this text, e.g. in the context of the definitions of "C₂-C₆-alkenyl" and "C₂-C₆-alkynyl", is to be understood as meaning an alkenyl group or an alkynyl group having a finite number of carbon atoms of 2 to 6, i.e. 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₂-C₆" is to be interpreted as any sub-range comprised therein, e.g. C₂-C₆, C₃-C₅, C₃-C₄, C₂-C₃, C₂-C₄, C₂-C₅; particularly C₂-C₃.

Further, as used herein, the term "C₃-C₇", as used throughout this text, e.g. in the context of the definition of "C₃-C₇-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 7, i.e. 3, 4, 5, 6 or 7 carbon atoms. It is to be understood further that said term "C₃-C₇" is to be interpreted as any sub-range comprised therein, e.g. C₃-C₆, C₄-C₅, C₃-C₅, C₃-C₄, C₄-C₆, C₅-C₇; particularly C₃-C₆.

As used herein, the term “leaving group” refers to an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. The leaving group as used herein is suitable for nucleophilic aliphatic and/or aromatic substitution, e.g. a halogen atom, in particular chloro, bromo or iodo, or a group selected from methanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonyloxy, nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-*tert*-butyl-benzene)sulfonyloxy, benzenesulfonyloxy, and (4-methoxy-benzene)sulfonyloxy.

As used herein, the term “protective group” is a protective group attached to a nitrogen in intermediates used for the preparation of compounds of the general formula (I). Such groups are introduced e.g. by chemical modification of the respective amino group in order to obtain chemoselectivity in a subsequent chemical reaction. Protective groups for amino groups are described for example in T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999; more specifically, said groups can be selected from substituted sulfonyl groups, such as mesyl-, tosyl- or phenylsulfonyl-, acyl groups such as benzoyl, acetyl or tetrahydropyranyloxy-, or carbamate based groups, such as *tert*.-butoxycarbonyl (Boc), or can include silicon, as in e.g. 2-(trimethylsilyl)ethoxymethyl (SEM).

As used herein, the term “one or more times”, e.g. in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning “one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times”.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

5

The compounds of this invention contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration. In certain instances, asymmetry may also be present due to restricted rotation
10 about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations are included within the scope of the present invention.

15 Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques
20 known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric,
25 diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated

diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

10

In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of

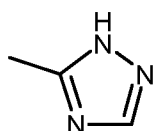
the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

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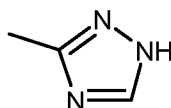
The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention
10 may be achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, the compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole
15 moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, *viz.* :

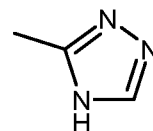
20



1H-tautomer



2H-tautomer



4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in
25 any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

- 5 The present invention also relates to useful forms of the compounds as disclosed herein, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar
10 solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or
15 hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a
20 salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic,
25 inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present
30 invention may be, for example, an acid-addition salt of a compound of the

present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as

5 formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic,

10 trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic,

15 sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base

20 which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiazine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butanetriol. Additionally, basic nitrogen containing groups may be

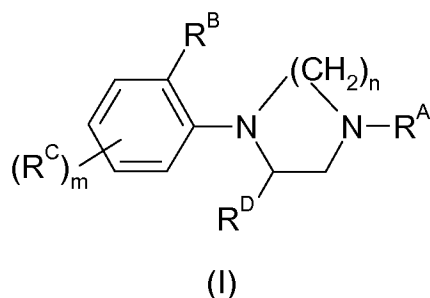
25 quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

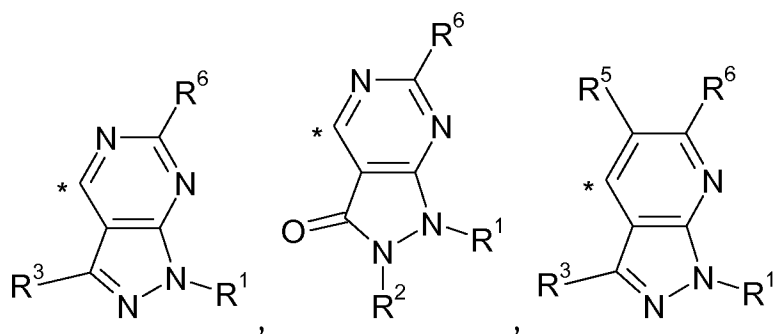
Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

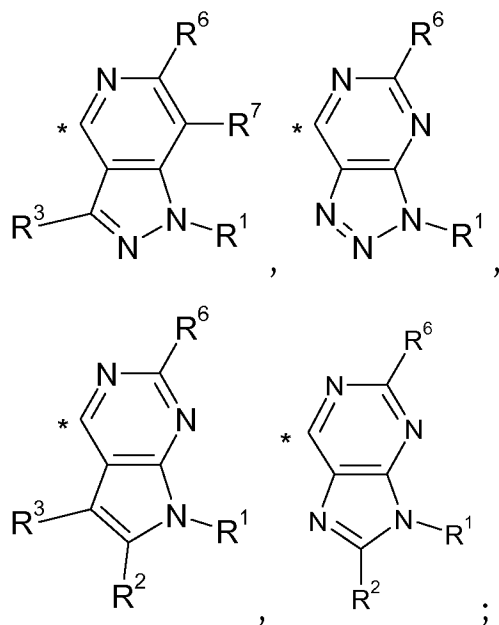
In accordance with a first aspect, the present invention relates to compounds of general formula (I) :



in which :

R^A is selected from the group consisting of:





wherein * indicates the point of attachment of said groups with the rest
of the molecule;

5

R^B represents a hydrogen atom or a -OH, -SH, -NH₂, C₁-C₃-alkoxy-,
HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, -
S-(C₁-C₃-alkyl), -S-(halo-C₁-C₃-alkyl), -N(H)(C₁-C₃-alkyl),
-N(C₁-C₃-alkyl)(C₁-C₃-alkyl) or a H₂N-C₁-C₃-alkyl- group;

10

each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-,
C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-,
C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
aryl-, heteroaryl-, 3- to 10-membered heterocycloalkyl-,
4- to 10-membered heterocycloalkenyl-, C₃-C₇-cycloalkyl-,
-C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂,
-N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
-N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b},

20

-N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)₂R⁸,
 -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;

or

5 when two R^C groups are present ortho- to each other on the phenyl-
 group, said two R^C groups together form a bridge :

O(CH₂)₂O, *O(CH₂)O*, *O(CF₂)O*, *CH₂C(R^{8a})(R^{8b})O*, *C(=O)N(R^{8a})CH₂*,
 N(R^{8a})C(=O)CH₂O, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents
 the point of attachment to said phenyl- group;

10

R^D represents a hydrogen atom or a methyl- group;

R¹ represents a hydrogen atom or a C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 C₂-C₆-alkynyl-, C₁-C₆-alkoxy-, C₁-C₆-alkoxy-C₁-C₆-alkyl-,

15

C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
 C₄-C₈-cycloalkenyl-, -(CH₂)_p-C₄-C₈-cycloalkenyl,
 3- to 10-membered heterocycloalkyl-,
 -(CH₂)_p-(3- to 10-membered heterocycloalkyl),
 4- to 10-membered heterocycloalkenyl-,

20

-(CH₂)_p-(4- to 10-membered heterocycloalkenyl),
 aryl-, -(CH₂)_p-aryl, heteroaryl- or -(CH₂)_p-heteroaryl group,
 wherein said group is optionally substituted, identically or differently,
 with 1, 2, 3, 4 or 5 R⁹ groups ;

25

R² represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group ;

R³ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,

30

-C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,

-N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸ or -O(C=O)N(R^{8a})R^{8b} group ;

wherein said C₁-C₃-alkyl- group is optionally substituted with a group
 5 selected from: -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸,
 -OR⁸, -O(C=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} and
 -S(=O)(=NR^{8c})R⁸ ;

10 R⁵ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group;

R⁶ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,
 15 -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,
 -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸ or
 -O(C=O)R⁸ group ;
 wherein said C₁-C₃-alkyl- group is optionally substituted with a group
 20 selected from: -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸,
 -OR⁸, -O(C=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} and
 -S(=O)(=NR^{8c})R⁸ ;

25 R⁷ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group;

R⁸, R^{8a}, R^{8b}, R^{8c}

represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-, (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, heteroaryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-C₁-C₆-alkyl- or (aryl)-(3- to 10-membered heterocycloalkyl)- group; said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 3- to 10-membered heterocycloalkyl-, (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-, heteroaryl-C₁-C₆-alkyl-, (aryl)-(3- to 10-membered heterocycloalkyl)- group being optionally substituted one or more times, identically or differently, with R¹⁰; or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group, the phenyl- group being optionally substituted 1, 2 or 3 times, identically or differently, with halogen, C₁-C₃-alkyl- or C₁-C₃-alkoxy;

20

R⁹ represents a halogen atom, or a -CN, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₆-alkyl)-, HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b}, -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸, -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;

30

wherein the aryl-, heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C ;

R^{10} represents a halogen atom, or a C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkyl-, -CN,
 5 -C(=O) R^{11} , -C(=O)N(H) R^{11} , -C(=O)N(R^{11a}) R^{11b} , -C(=O)O- R^{11} , -N(R^{11a}) R^{11b} ,
 -NO₂, -N(H)C(=O) R^{11} , -N(R^{11a})C(=O) R^{11b} , -N(H)C(=O)N(R^{11a}) R^{11b} ,
 -N(R^{11a})C(=O)N(R^{11b}) R^{11c} , -N(H)C(=O)OR¹¹, -N(R^{11a})C(=O)OR^{11b},
 -N(H)S(=O)₂ R^{11} , -N(R^{11a})S(=O)₂ R^{11b} , -OR¹¹, -O(C=O) R^{11} , -O(C=O)N(R^{11a}) R^{11b} ,
 -O(C=O)OR¹¹, -SR¹¹, -S(=O) R^{11} , -S(=O)₂ R^{11} , -S(=O)₂N(H) R^{11} ,
 10 -S(=O)₂N(R^{11a}) R^{11b} or -S(=O)(=NR^{11a}) R^{11b} group;

R^{11} , R^{11a} , R^{11b} , R^{11c}

represent, independently from each other, a hydrogen atom or a C_1 - C_6 -alkyl- group;

15

m is an integer of 0, 1, 2 or 3 ;

n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

t is an integer of 3, 4 or 5 ;

20

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same ;

25 wherein the following compounds are excluded:

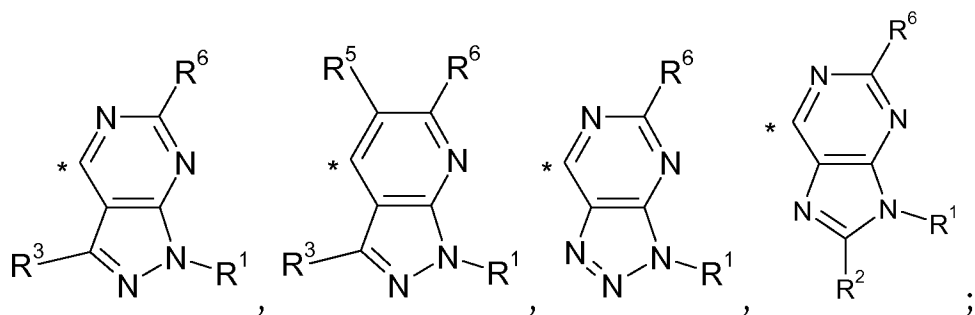
4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
 1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-
 1H-pyrazolo[3,4-d]pyrimidine,
 4-[4-(2-fluorophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine.

30

In another preferred embodiment, the present invention relates to compounds of general formula (I), *supra*, wherein the following compounds are excluded:

- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 5 1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-
1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2-fluorophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- methyl 3-fluoro-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-
[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}benzoate,
- 10 3-fluoro-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-
d]pyrimidin-3-yl}benzoic acid,
- methyl trans-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-
d]pyrimidin-3-yl}cyclohexanecarboxylate,
- trans-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-
15 d]pyrimidin-3-yl}cyclohexanecarboxylic acid,
- 3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-
yl}methyl)benzoic acid,
- methyl 4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-
1-yl}methyl)benzoate, and
- 20 4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-
yl}methyl)benzoic acid.

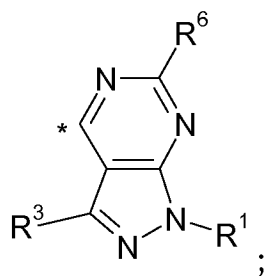
In another preferred embodiment, R^A is selected from the group consisting of:



wherein * indicates the point of attachment of said groups with the rest of the molecule.

5

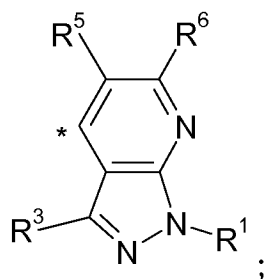
In a particularly preferred embodiment, R^A represents:



wherein * indicates the point of attachment of said group with the rest of the molecule.

10

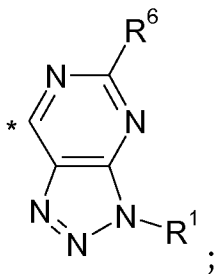
In another particularly preferred embodiment, R^A represents:



wherein * indicates the point of attachment of said group with the rest of the molecule.

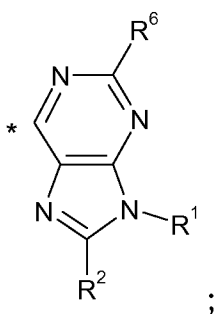
15

In another particularly preferred embodiment, R^A represents:



wherein * indicates the point of attachment of said group with the rest of the molecule.

- 5 In another particularly preferred embodiment, R^A represents:



wherein * indicates the point of attachment of said group with the rest of the molecule.

- 10 In a preferred embodiment, R^B represents a hydrogen atom or a -OH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, fluoro-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy-, -S-(C₁-C₃-alkyl), -S-(fluoro-C₁-C₃-alkyl), -N(H)(C₁-C₃-alkyl), or a -N(C₁-C₃-alkyl)(C₁-C₃-alkyl) group.
- 15 In a more preferred embodiment, R^B represents a hydrogen atom or a -OH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, or a -S-(C₁-C₃-alkyl)-group.

In another more preferred embodiment, R^B represents a hydroxymethyl- group.

20

In a particularly preferred embodiment, R^B represents a -OH, -NH₂, C₁-C₂-alkoxy- or a -S-(C₁-C₂-alkyl)- group.

In another particularly preferred embodiment, R^B represents a -OH group.

- 5 In another particularly preferred embodiment, R^B represents a -NH₂ group.

In another particularly preferred embodiment, R^B represents a methoxy- group.

10

In another particularly preferred embodiment, R^B represents an ethoxy- group.

- 15 In another particularly preferred embodiment, R^B represents a -SCH₃ group.

In another preferred embodiment, each R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-,
 20 fluoro-C₁-C₃-alkoxy-C₁-C₃-alkyl-, aryl-, heteroaryl-, 4- to 7-membered heterocycloalkyl-, C₃-C₇-cycloalkyl-, -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} , -NO₂, -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(H)C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)C(=O)N(R^{8a}) R^{8b} , -N(H)S(=O)₂ R^8 , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 or -S(=O)₂N(R^{8a}) R^{8b} group;

- 25 or when two R^C groups are present ortho to each other on the phenyl- group, said two R^C groups together form a bridge :
 O(CH₂)O, *O(CF₂)O*, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents the point of attachment to said phenyl- group.

In a particularly preferred embodiment, each R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, phenyl-, 5- or 6-membered heteroaryl-, -C(=O)R⁸,
 -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,
 5 -N(R^{8c})C(=O)R⁸, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}, -N(H)S(=O)₂R⁸, -S(=O)₂R⁸,
 -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group;

or when two R^C groups are present ortho to each other on the phenyl- group, said two R^C groups together form a bridge :

O(CH₂)O or *(CH₂)_t*; wherein each * represents the point of attachment to
 10 said phenyl- group.

In another particularly preferred embodiment, each R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, phenyl-, 5- or 6-membered heteroaryl-,
 15 -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,
 -N(R^{8c})C(=O)R⁸, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}, -N(H)S(=O)₂R⁸, -S(=O)₂R⁸,
 -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group.

In another particularly preferred embodiment, two R^C groups in ortho- position
 20 to each other on the phenyl- group together form a bridge :
 O(CH₂)O or *(CH₂)_t*; wherein each * represents the point of attachment to
 said phenyl- group.

In another particularly preferred embodiment, each R^C independently
 25 represents a halogen atom, or a -CN, -OH, pyridyl-, C₁-C₃-alkoxy-, C₁-C₃-alkyl-,
 HO-C₁-C₃-alkyl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}, -N(H)S(=O)₂R⁸, -S(=O)₂R⁸
 or -S(=O)₂N(H)R⁸ group.

- In another particularly preferred embodiment, each R^C independently represents a fluoro, chloro, bromo atom, or a -CN, -OH, pyrid-3-yl-, methoxy-, ethoxy-, C_1 - C_3 -alkyl-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-NH_2$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}$,
 5 $-N(H)S(=O)_2R^8$, $-S(=O)_2R^8$ or $-S(=O)_2N(H)R^8$ group.

In another particularly preferred embodiment, each R^C independently represents a $-C(=O)N(H)R^{8a}$ group.

- 10 In another particularly preferred embodiment, each R^C independently represents a fluoro atom, a chloro atom, or a -CN, $-C(=O)OCH_3$, $-C(=O)NH_2$ or $-C(=O)N(H)-CH_2-CH_2-OH$ group.

- In another particularly preferred embodiment, each R^C independently
 15 represents a chloro atom, or a $-C(=O)OCH_3$, $-C(=O)NH_2$ or $-C(=O)N(H)-CH_2-CH_2-OH$ group.

- In another particularly preferred embodiment, each R^C independently represents a chloro atom or a -CN group group.
 20

In another particularly preferred embodiment, each R^C independently represents a chloro atom.

- In another particularly preferred embodiment, each R^C independently
 25 represents a fluoro atom.

In another particularly preferred embodiment, each R^C independently represents a -CN group group.

In another particularly preferred embodiment, each R^C independently represents a $-C(=O)OCH_3$ group.

In another particularly preferred embodiment, each R^C independently
5 represents a $-C(=O)NH_2$ group.

In another particularly preferred embodiment, each R^C independently represents a $-C(=O)N(H)-CH_2-CH_2-OH$ group.

10 In another preferred embodiment, R^D represents a hydrogen atom or a methyl-group.

In another preferred embodiment, R^D represents a methyl- group.

15 In a more preferred embodiment, R^D represents a hydrogen.

In another preferred embodiment, R^1 represents a hydrogen atom or a C_1 - C_6 -alkyl-, C_1 - C_6 -alkoxy-, C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl-, C_3 - C_7 -cycloalkyl-,
-(CH_2)_p- C_3 - C_7 -cycloalkyl, 4- to 7-membered heterocycloalkyl-,
20 -(CH_2)_p-(4- to 7-membered heterocycloalkyl), phenyl-, naphthyl-,
-(CH_2)_p-phenyl, 5- or 6-membered heteroaryl- or -(CH_2)_p-(5- or 6-membered heteroaryl) group, wherein said group is optionally substituted, identically or differently, with 1, 2, or 3 R^9 groups.

25 In a particularly preferred embodiment, R^1 represents a C_1 - C_6 -alkyl-, C_3 - C_7 -cycloalkyl-, -(CH_2)_p- C_3 - C_7 -cycloalkyl,
4- to 7-membered heterocycloalkyl-,
-(CH_2)_p-(4- to 7-membered heterocycloalkyl), phenyl-, -(CH_2)_p-phenyl or
5- or 6-membered heteroaryl- group, wherein said group is optionally
30 substituted, identically or differently, with 1 or 2 R^9 groups.

In another particularly preferred embodiment, R¹ represents a C₅-C₆-cycloalkyl-, -(CH₂)_p-C₅-C₆-cycloalkyl, 5- or 6-membered heterocycloalkyl-, -(CH₂)_p-(5- or 6-membered heterocycloalkyl), phenyl-, thien-2-yl- or
5 -(CH₂)_p-phenyl group, wherein said group is optionally substituted, identically or differently, with 1 or 2 R⁹ groups .

In another particularly preferred embodiment, R¹ represents a cyclopentyl-, cyclohexyl-, cyclopentylmethyl-, cyclohexylmethyl-, tetrahydropyran-4-yl,
10 tetrahydropyran-4-ylmethyl-, phenyl-, thien-2-yl- or benzyl- group, wherein said phenyl- or benzyl- group is optionally substituted, identically or differently, with 1 or 2 R⁹ groups ;

In another particularly preferred embodiment, R¹ represents a phenyl- group,
15 wherein said group is optionally substituted, identically or differently, with 1 or 2 R⁹ groups .

In another particularly preferred embodiment, R¹ represents a phenyl- group, wherein said group is optionally substituted, once with fluoro, chloro, bromo,
20 methoxy- or methyl-.

In another particularly preferred embodiment, R¹ represents a phenyl- group, wherein said group is optionally substituted, once with fluoro or methyl-.

25 In another particularly preferred embodiment, R¹ represents a phenyl- group.

In another particularly preferred embodiment, R¹ represents a cyclopentyl-, cyclohexyl-, cyclopentylmethyl-, cyclohexylmethyl-, tetrahydropyran-4-yl or tetrahydropyran-4-ylmethyl- group.

30

In another particularly preferred embodiment, R¹ represents a cyclopentyl-group.

5 In another particularly preferred embodiment, R¹ represents a cyclopentylmethyl- group.

In another particularly preferred embodiment, R¹ represents a cyclohexyl-group.

10 In another particularly preferred embodiment, R¹ represents a cyclohexylmethyl- group.

In another particularly preferred embodiment, R¹ represents a tetrahydropyran-4-yl- group.

15 In another particularly preferred embodiment, R¹ represents a tetrahydropyran-4-ylmethyl- group.

In another preferred embodiment, R² represents a hydrogen atom or a
20 C₁-C₆-alkyl-, trifluoromethyl- or C₃-C₇-cycloalkyl- group.

In a more preferred embodiment, R² represents a hydrogen atom or a C₁-C₃-alkyl- group.

25 In a particularly preferred embodiment, R² represents a hydrogen atom or a methyl- group.

In another particularly preferred embodiment, R² represents a hydrogen atom.

30 In another particularly preferred embodiment, R² represents a methyl- group.

In another preferred embodiment, R^3 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, fluoro- C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkoxy- or HO- C_1 - C_3 -alkyl- group.

5

In a particularly preferred embodiment, R^3 represents a hydrogen atom or a C_1 - C_3 -alkyl-, trifluoromethyl- or HO- C_1 - C_2 -alkyl- group.

10 In another particularly preferred embodiment, R^3 represents a hydrogen atom or a methyl- group.

In another particularly preferred embodiment, R^3 represents a hydrogen atom.

15 In another preferred embodiment, R^5 represents a hydrogen atom or a C_1 - C_6 -alkyl-, trifluoromethyl- or C_3 - C_7 -cycloalkyl- group.

In another preferred embodiment, R^5 represents a hydrogen atom or a methyl-group.

20 In a particularly preferred embodiment, R^5 represents a hydrogen atom.

In another preferred embodiment, R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, fluoro- C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkoxy- or HO- C_1 - C_3 -alkyl- group.

25

In a particularly preferred embodiment, R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl-, trifluoromethyl- or HO- C_1 - C_2 -alkyl- group.

30 In another particularly preferred embodiment, R^6 represents a hydrogen atom or a methyl- group.

In another particularly preferred embodiment, R⁶ represents a hydrogen atom.

In a preferred embodiment, R⁸ and R^{8a} represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-,
5 (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-,
(4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, heteroaryl-,
aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-C₁-C₆-alkyl- group;
said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,
10 4- to 7-membered heterocycloalkyl-,
(4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, aryl-C₁-C₆-alkyl-,
(aryl)-O-(C₁-C₆-alkyl)-, heteroaryl- or heteroaryl-C₁-C₆-alkyl- group being
optionally substituted one or more times, identically or differently, with R¹⁰.

15 In another preferred embodiment, R^{8b} and R^{8c} represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-,
C₃-C₇-cycloalkyl- or aryl-C₁-C₆-alkyl- group.

In another preferred embodiment, R^{8a} and R^{8b}, together with the nitrogen atom
20 they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which
is optionally substituted once with a C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl-
group, the phenyl- group being optionally substituted 1, 2 or 3 times,
identically or differently, with halogen, C₁-C₃-alkyl- or C₁-C₃-alkoxy-.

25 In a more preferred embodiment, R⁸ and R^{8a} represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-,
(C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-,
(4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,

- 5- or 6-membered heteroaryl-, phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)- or (5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group; said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-,
- 5 (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-, phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)-, 5- or 6-membered heteroaryl-, (5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group being optionally substituted one or more times, identically or differently, with R¹⁰.
- 10 In another more preferred embodiment, R^{8b} and R^{8c} represent, independently from each other, a hydrogen atom, or a C₁-C₄-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, C₃-C₆-cycloalkyl- or a benzyl- group.

- In another more preferred embodiment, R^{8a} and R^{8b}, together with the nitrogen
- 15 atom they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with a C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group, the phenyl- group being optionally substituted 1 or 2 times, identically or differently, with fluoro, chloro, methyl- or methoxy-.

20

- In a particularly preferred embodiment, R⁸ and R^{8a} represent, independently from each other, a hydrogen atom or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-, (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
- 25 5- or 6-membered heteroaryl-, phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)- or (5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group; said C₁-C₆-alkyl-, phenyl-, naphthyl-, phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)-, 5- or 6-membered heteroaryl-, (5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group being optionally substituted
- 30 one or more times, identically or differently, with R¹⁰.

In another particularly preferred embodiment, R^{8b} and R^{8c} represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- or a methoxy- C_1 - C_3 -alkyl- group.

5

In another particularly preferred embodiment, R^{8a} and R^{8b} , together with the nitrogen atom they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with a C_1 - C_3 -alkyl- or a phenyl- group, the phenyl- group being optionally substituted once
10 with fluoro, chloro, methyl or methoxy-.

In another particularly preferred embodiment, R^8 and R^{8a} represent, independently from each other, a hydrogen atom, or a C_1 - C_6 -alkyl-, C_3 - C_7 -cycloalkyl-, (C_3 - C_7 -cycloalkyl)-(C_1 - C_6 -alkyl)-, 5- or 6-membered
15 heterocycloalkyl-, (5- or 6-membered heterocycloalkyl)-(C_1 - C_4 -alkyl)-, phenyl-, naphthyl-, 5- or 6-membered heteroaryl-, phenyl- C_1 - C_4 -alkyl-, (phenyl)-O- (C_1 - C_4 -alkyl)- or (5- or 6-membered heteroaryl)- C_1 - C_4 -alkyl- group;
said C_1 - C_6 -alkyl-, phenyl-, naphthyl-, phenyl- C_1 - C_4 -alkyl-,
(phenyl)-O- (C_1 - C_4 -alkyl)-, heteroaryl-, heteroaryl- C_1 - C_4 -alkyl- group being
20 optionally substituted one or more times, identically or differently, with R^{10} .

In another particularly preferred embodiment, R^{8a} and R^{8b} , together with the nitrogen atom they are attached to, form a 4- to 6-membered heterocycloalkyl- group, which is optionally substituted once with a
25 C_1 - C_3 -alkyl- or a phenyl- group, the phenyl- group being optionally substituted once with methoxy-.

In another particularly preferred embodiment, R^8 represents
30 a hydrogen atom,

or a C₁-C₆-alkyl- group, which is optionally substituted with up to three fluoro atoms,

5 or a C₁-C₄-alkyl- group, which is substituted by a -OH, -OCH₃, phenoxy-, -NH₂, -N(H)-CH₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(H)(C=O)CH₃, -C(=O)OH, -C(=O)OCH₃ or -C(=O)NH₂ group,

10 or a C₁-C₄-alkyl- group, which is substituted by a phenyl- group, wherein said phenyl- group is optionally substituted once with fluoro, trifluoromethyl-, or methoxy-,

15 or a C₁-C₄-alkyl- group, which is substituted by a 5- or 6-membered heterocycloalkyl- group, which is selected from morpholinyl-, pyrrolidinyl-, piperidinyl-, *N*-methyl-piprazinyl-, or 2-oxoimidazolidin-1-yl-,

20 or a C₁-C₄-alkyl- group, which is substituted by a 5- or 6-membered heteroaryl- group selected from pyridyl-, pyrazolyl-, thienyl-, pyrazinyl-, imidazolyl-, wherein said 5- or 6-membered heteroaryl- group is optionally substituted once by methyl-,

or a C₃-C₅-cycloalkyl- or cyclopropylmethyl- group,

25 or a tetrahydrofur-2-yl- group,

or a phenyl- or naphthyl- group, wherein the phenyl- group is optionally substituted once by fluoro, methoxy-, -C(=O)NH₂, or -S(=O)₂NH₂.

30 In another particularly preferred embodiment, R^{8a} represents

- a hydrogen atom,
- 5 or a C₁-C₆-alkyl- group, which is optionally substituted with up to three fluoro atoms,
- or a C₁-C₄-alkyl- group, which is substituted by a -OH, -OCH₃, phenoxy-, -NH₂, -N(H)-CH₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(H)(C=O)CH₃, -C(=O)OH, -C(=O)OCH₃ or -C(=O)NH₂ group,
- 10 or a C₁-C₄-alkyl- group, which is substituted by a phenyl- group, wherein said phenyl- group is optionally substituted once with fluoro, trifluoromethyl-, -S(=O)₂NH₂ or methoxy-,
- 15 or a C₁-C₄-alkyl- group, which is substituted by a 5- or 6-membered heterocycloalkyl- group, which is selected from morpholinyl-, pyrrolidinyl-, piperidinyl-, *N*-methyl-piprazinyl-, or 2-oxoimidazolidin-1-yl-,
- 20 or a C₁-C₄-alkyl- group, which is substituted by a 5- or 6-membered heteroaryl- group selected from pyridyl-, pyrazolyl-, thienyl-, pyrazinyl-, imidazolyl-, wherein said 5- or 6-membered heteroaryl- group is optionally substituted once by methyl-,
- 25 or a C₃-C₅-cycloalkyl- or cyclopropylmethyl- group,
- or a tetrahydrofuran-2-yl- group,
- or a phenyl- or naphthyl- group, wherein the phenyl- group is optionally
- 30 substituted once by fluoro, methoxy-, -C(=O)NH₂ or -S(=O)₂NH₂.

In another particularly preferred embodiment, R^{8a} represents a hydrogen atom.

- 5 In another particularly preferred embodiment, R^{8a} represents a 2-hydroxyethyl- group.

In another particularly preferred embodiment, R^{8a} represents a (4-aminosulfonyl)-phenylmethyl- group.

10

In another particularly preferred embodiment, R^{8a} represents a 2-(2-oxoimidazolidin-1-yl)ethyl- group.

- 15 In another particularly preferred embodiment, R^{8b} represents a hydrogen atom or a C_1 - C_3 -alkyl- or a 2-methoxyethyl- group.

In another particularly preferred embodiment, R^{8b} represents a hydrogen atom.

- 20 In another particularly preferred embodiment, R^{8b} represents a methyl- group.

In another particularly preferred embodiment, R^{8c} represents a hydrogen atom or a C_1 - C_3 -alkyl- or a 2-methoxyethyl- group.

- 25 In another particularly preferred embodiment, R^{8c} represents a hydrogen atom.

In another particularly preferred embodiment, R^{8c} represents a methyl- group.

- 30 In another particularly preferred embodiment, R^{8a} and R^{8b} , together with the nitrogen atom they are attached to, form an azetidino, morpholino or

N-phenylpiperazine ring, wherein said phenyl- group attached to the piperazine ring is optionally substituted once by methoxy-.

In another preferred embodiment, R^9 represents a halogen atom, or a -CN,
 5 C_1 - C_6 -alkoxy-, C_1 - C_6 -alkyl-, fluoro- C_1 - C_6 -alkyl-, $R^{8a}(R^{8b})N$ - C_1 - C_6 -alkyl-,
 $R^{8a}(R^{8b})N$ -C(=O)(C_1 - C_6 -alkyl)-, HO- C_1 - C_6 -alkyl-, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl-,
 fluoro- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl-, 4- to 7-membered heterocycloalkyl-, aryl-,
 heteroaryl-, -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -N(R^{8a}) R^{8b} , -NO₂,
 -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(H)C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)N(R^{8a}) R^{8b} ,
 10 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂ R^8 , -N(R^{8c})S(=O)₂ R^8 , -OR⁸,
 -O(C=O) R^8 , -O(C=O)N(R^{8a}) R^{8b} , -SR⁸, -S(=O) R^8 , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 ,
 -S(=O)₂N(R^{8a}) R^{8b} or -S(=O)(=NR^{8c}) R^8 group;

wherein the aryl- and heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C .

15

In another preferred embodiment, R^9 represents a halogen atom, or a -CN,
 C_1 - C_6 -alkoxy-, C_1 - C_6 -alkyl-, fluoro- C_1 - C_6 -alkyl-, $R^{8a}(R^{8b})N$ - C_1 - C_6 -alkyl-,
 $R^{8a}(R^{8b})N$ -C(=O)(C_1 - C_6 -alkyl)-, HO- C_1 - C_6 -alkyl-, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl-,
 fluoro- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl-, 4- to 7-membered heterocycloalkyl-, aryl-,
 20 heteroaryl-, -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} ,
 -NO₂, -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(H)C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)N(R^{8a}) R^{8b} ,
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂ R^8 , -N(R^{8c})S(=O)₂ R^8 , -OR⁸,
 -O(C=O) R^8 , -O(C=O)N(R^{8a}) R^{8b} , -SR⁸, -S(=O) R^8 , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 ,
 -S(=O)₂N(R^{8a}) R^{8b} or -S(=O)(=NR^{8c}) R^8 group;

25 wherein the aryl- and heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C .

In a more preferred embodiment, R^9 represents a halogen atom, or a -CN,
 C_1 - C_3 -alkoxy-, C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkyl-, $R^{8a}(R^{8b})N$ - C_1 - C_6 -alkyl-,

$R^{8a}(R^{8b})N-C(=O)(C_1-C_3\text{-alkyl})-$, $HO-C_1-C_3\text{-alkyl}-$, $C_1-C_3\text{-alkoxy}-C_1-C_3\text{-alkyl}-$,
 fluoro- $C_1-C_3\text{-alkoxy}-C_1-C_3\text{-alkyl}-$, 4- to 7-membered heterocycloalkyl-, aryl-,
 5- or 6-membered heteroaryl-, $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$,
 $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-NO_2$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)S(=O)_2R^8$,
 5 $-N(R^{8c})S(=O)_2R^8$, $-OR^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$ or $-S(=O)_2N(R^{8a})R^{8b}$ group;
 wherein the aryl- and the 5- or 6-membered heteroaryl- group is optionally
 substituted, one or more times, identically or differently, with R^C .

In a particularly preferred embodiment, R^9 represents a halogen atom, or a
 10 $-CN$, $C_1-C_3\text{-alkoxy}-$, $C_1-C_3\text{-alkyl}-$, trifluoromethyl-, $R^{8a}(R^{8b})N-C(=O)(C_1-C_3\text{-alkyl})-$,
 aryl-, 5- or 6-membered heteroaryl-, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-N(R^{8a})R^{8b}$,
 $-NO_2$, $-N(H)C(=O)R^8$, $-N(H)S(=O)_2R^8$, $-OR^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$ or
 $-S(=O)_2N(R^{8a})R^{8b}$ group;
 wherein the aryl- an 5- or 6-membered heteroaryl- group is substituted, one or
 15 more times, identically or differently, with R^C .

In another particularly preferred embodiment, R^9 represents a fluoro, chloro,
 or bromo atom, or a $-CN$, $C_1-C_3\text{-alkoxy}-$, methyl-, ethyl-, phenyl-,
 pyrazol-5-yl-, thien-3-yl-, $H_2N-C(=O)\text{-ethyl-}$, $-C(=O)NH_2$, $-C(=O)N(R^{8a})R^{8b}$, $-NH_2$,
 20 $-N(CH_3)_2$, $-NO_2$, $-S(=O)_2CH_3$, $-S(=O)_2N(H)R^8$ or $-S(=O)_2N(R^{8a})R^{8b}$ group, wherein
 said phenyl- group is optionally substituted once by a $-C(=O)NH_2$ group.

In another particularly preferred embodiment, R^9 represents a fluoro atom.

25 In another particularly preferred embodiment, R^9 represents a chloro atom.

In another particularly preferred embodiment, R^9 represents a bromo atom.

In another particularly preferred embodiment, R^9 represents a $-CN$ group.

In another particularly preferred embodiment, R⁹ represents a methyl- group.

In another particularly preferred embodiment, R⁹ represents a methoxy-group.

5

In another preferred embodiment, R¹⁰ represents a halogen atom, or a

C₁-C₃-alkyl-, fluoro-C₁-C₃-alkyl-, -CN, -C(=O)R¹¹, -C(=O)N(H)R¹¹,
 -C(=O)N(R^{11a})R^{11b}, -C(=O)O-R¹¹, -N(R^{11a})R^{11b}, -NO₂, -N(H)C(=O)R¹¹,
 -N(R^{11a})C(=O)R^{11b}, -N(H)C(=O)N(R^{11a})R^{11b}, -N(R^{11a})C(=O)N(R^{11b})R^{11c},
 10 -N(H)C(=O)OR¹¹, -N(R^{11a})C(=O)OR^{11b}, -N(H)S(=O)₂R¹¹, -N(R^{11a})S(=O)₂R^{11b}, -OR¹¹,
 -O(C=O)R¹¹, -O(C=O)N(R^{11a})R^{11b}, -SR¹¹, -S(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(H)R¹¹,
 -S(=O)₂N(R^{11a})R^{11b} or -S(=O)(=NR^{11a})R^{11b} group.

In a more preferred embodiment, R¹⁰ represents a halogen atom, or a

15 C₁-C₃-alkyl-, fluoro-C₁-C₃-alkyl-, -CN, -C(=O)R¹¹, -C(=O)N(H)R¹¹,
 -C(=O)N(R^{11a})R^{11b}, -C(=O)O-R¹¹, -N(R^{11a})R^{11b}, -NO₂, -N(H)C(=O)R¹¹,
 -N(R^{11a})C(=O)R^{11b}, -N(H)C(=O)N(R^{11a})R^{11b}, -N(R^{11a})C(=O)N(R^{11b})R^{11c},
 -N(H)S(=O)₂R¹¹, -N(R^{11a})S(=O)₂R^{11b}, -OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(H)R¹¹ or
 -S(=O)₂N(R^{11a})R^{11b} group

20

In a particularly preferred embodiment, R¹⁰ represents a halogen atom, or a
 C₁-C₃-alkyl-, trifluoromethyl-, -CN, -C(=O)R¹¹, -C(=O)N(H)R¹¹, -C(=O)O-R¹¹,
 -N(R^{11a})R^{11b}, -N(H)C(=O)R¹¹, -N(H)S(=O)₂R¹¹, -OR¹¹, -S(=O)₂R¹¹ or -S(=O)₂N(H)R¹¹
 group.

25

In another particularly preferred embodiment, R¹⁰ represents a halogen atom,
 or a C₁-C₃-alkyl-, trifluoromethyl-, -C(=O)N(H)R¹¹, -C(=O)O-R¹¹, -N(R^{11a})R^{11b},
 -N(H)C(=O)R¹¹, -N(H)S(=O)₂R¹¹, -OR¹¹, -S(=O)₂R¹¹ or -S(=O)₂N(H)R¹¹ group.

In another preferred embodiment, R^{11} , R^{11a} , R^{11b} , R^{11c} represent, independently from each other, a hydrogen atom or a C_1 - C_6 -alkyl- group.

In a more preferred embodiment, R^{11} , R^{11a} , R^{11b} , R^{11c} represent, independently
5 from each other, a hydrogen atom or a C_1 - C_3 -alkyl- group.

In a particularly preferred embodiment, R^{11} , R^{11a} , R^{11b} , R^{11c} represent, independently from each other, a hydrogen atom or a C_1 - C_2 -alkyl- group.

10 In another particularly preferred embodiment, R^{11} , R^{11a} , R^{11b} , R^{11c} represent, independently from each other, a hydrogen atom or a methyl- group.

In another preferred embodiment, m is an integer of 0, 1, 2 or 3.

15 In a particularly preferred embodiment, m is an integer of 0, 1 or 2.

In another particularly preferred embodiment, m is an integer of 0 or 1.

In another particularly preferred embodiment, m is an integer of 0.

20

In another particularly preferred embodiment, m is an integer of 1.

In another preferred embodiment, n is an integer of 2 or 3.

25 In another preferred embodiment, n is an integer of 2.

In another preferred embodiment, n is an integer of 3.

In a particularly preferred embodiment, p is an integer of 1 or 2.

30

In another particularly preferred embodiment, p is an integer of 1.

In another particularly preferred embodiment, p is an integer of 2.

5 In another preferred embodiment, t is an integer of 3, 4 or 5.

In a more preferred embodiment, t is an integer of 3 or 4.

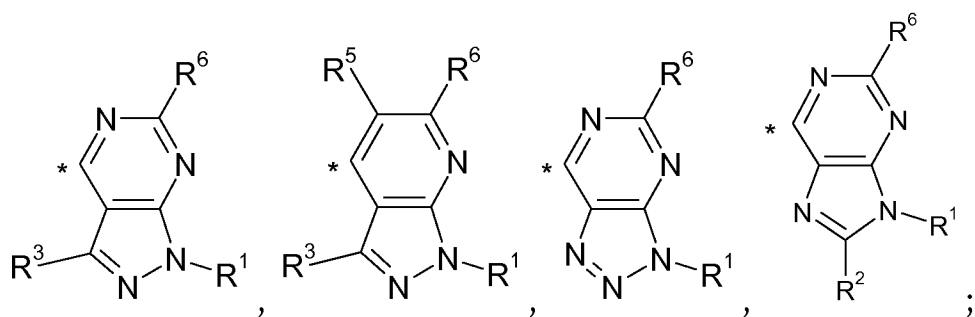
It is to be understood that the present invention relates to any sub-
10 combination within any embodiment of compounds of general formula (I),
supra.

Some examples of combinations are given hereinafter. However, the invention
is not limited to these combinations.

15

In a preferred embodiment,

R^A is selected from the group consisting of:



20

wherein * indicates the point of attachment of said groups with the rest
of the molecule;

R^B represents a hydrogen atom or a -OH, -NH₂, C₁-C₃-alkoxy-,
25 HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, fluoro-C₁-C₃-alkyl-,
fluoro-C₁-C₃-alkoxy-, -S-(C₁-C₃-alkyl), -S-(fluoro-C₁-C₃-alkyl),

-N(H)(C₁-C₃-alkyl) or a -N(C₁-C₃-alkyl)(C₁-C₃-alkyl) group;

each

5 R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₆-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-C₁-C₆-alkyl-, aryl-, heteroaryl-, 4- to 7-membered heterocycloalkyl-, C₃-C₇-cycloalkyl-,
 10 -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} , -NO₂, -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(H)C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)N(R^{8a}) R^{8b} ,
 15 -N(R^{8c})C(=O)C(=O)N(R^{8a}) R^{8b} , -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂ R^8 , -N(R^{8c})S(=O)₂ R^8 , -OR⁸, -O(C=O) R^8 , -O(C=O)N(R^{8a}) R^{8b} , -SR⁸, -S(=O) R^8 , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 , -S(=O)₂N(R^{8a}) R^{8b} or -S(=O)(=NR^{8c}) R^8 group;

or

15 when two R^C groups are present ortho to each other on the phenyl-group, said two R^C groups together form a bridge :
 O(CH₂)₂O, *O(CH₂)O*, *O(CF₂)O*, *CH₂C(R^{8a})(R^{8b})O*, *C(=O)N(R^{8a})CH₂*,
 N(R^{8a})C(=O)CH₂O, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents the point of attachment to said phenyl- group;

20

R^D represents a hydrogen atom or a methyl- group;

R^1 represents a hydrogen atom or a C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
 25 4- to 7-membered heterocycloalkyl-, -(CH₂)_p-(4- to 7-membered heterocycloalkyl), aryl-, -(CH₂)_p-aryl, heteroaryl- or -(CH₂)_p-heteroaryl group,
 wherein said group is optionally substituted, identically or differently, with 1, 2, 3, or 4 R^9 groups ;

30

- R^2 represents a hydrogen atom or a C_1 - C_3 -alkyl- group;
- R^3 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, fluoro- C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkoxy-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$,
 5 $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$,
 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-OR^8$,
 $-O(C=O)R^8$ or $-O(C=O)N(R^{8a})R^{8b}$ group ;
 wherein said C_1 - C_3 -alkyl- group is optionally substituted with a group
 10 selected from: $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$,
 $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$,
 $-OR^8$, $-O(C=O)R^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ and
 $-S(=O)(=NR^{8c})R^8$;
- 15 R^5 represents a hydrogen atom ;
- R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, fluoro- C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkoxy-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$,
 $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$,
 20 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-OR^8$ or
 $-O(C=O)R^8$ group ;
 wherein said C_1 - C_3 -alkyl- group is optionally substituted with a group
 selected from: $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$,
 25 $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$,
 $-OR^8$, $-O(C=O)R^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ and
 $-S(=O)(=NR^{8c})R^8$;

R^8 and R^{8a}

represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-, (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, heteroaryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)- or heteroaryl-C₁-C₆-alkyl- group ; said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-, (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-, heteroaryl-C₁-C₆-alkyl- group being optionally substituted one or more times, identically or differently, with R¹⁰;

R^{8b} and R^{8c}

represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or aryl-C₁-C₆-alkyl- group ;

or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group, the phenyl- group being optionally substituted 1, 2 or 3 times, identically or differently, with halogen, C₁-C₃-alkyl- or C₁-C₃-alkoxy;

25

R⁹ represents a halogen atom or a -CN, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₆-alkyl)-, HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, fluoro-C₁-C₆-alkoxy-C₁-C₆-alkyl-, 4- to 7-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,

30

-N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b},
 -N(R^{8c})C(=O)N(R^{8a})R^{8b}, -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸,
 -N(R^{8c})S(=O)₂R⁸, -OR⁸, -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -SR⁸, -S(=O)R⁸,
 -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;

5 wherein the aryl-, heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C ;

R¹⁰ represents a halogen atom, or a C₁-C₃-alkyl-, fluoro-C₁-C₃-alkyl-, -CN,
 -C(=O)R¹¹, -C(=O)N(H)R¹¹, -C(=O)N(R^{11a})R^{11b}, -C(=O)O-R¹¹, -N(R^{11a})R^{11b},
 10 -NO₂, -N(H)C(=O)R¹¹, -N(R^{11a})C(=O)R^{11b}, -N(H)C(=O)N(R^{11a})R^{11b},
 -N(R^{11a})C(=O)N(R^{11b})R^{11c}, -N(H)C(=O)OR¹¹, -N(R^{11a})C(=O)OR^{11b},
 -N(H)S(=O)₂R¹¹, -N(R^{11a})S(=O)₂R^{11b}, -OR¹¹, -O(C=O)R¹¹, -O(C=O)N(R^{11a})R^{11b},
 -SR¹¹, -S(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(H)R¹¹, -S(=O)₂N(R^{11a})R^{11b} or
 -S(=O)(=NR^{11a})R^{11b} group;

15

R¹¹, R^{11a}, R^{11b}, R^{11c}

represent, independently from each other, a hydrogen atom or a
 C₁-C₆-alkyl- group;

20 m is an integer of 0, 1, 2 or 3 ;

n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

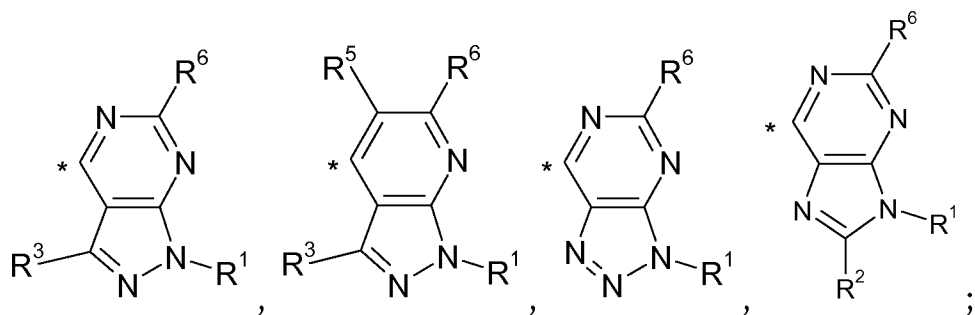
t is an integer of 3, 4 or 5 ;

25 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In a more preferred embodiment,

30

R^A is selected from the group consisting of:



wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a hydrogen atom or a -OH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy- or a -S-(C₁-C₃-alkyl)- group;

each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy-C₁-C₃-alkyl-, aryl-, heteroaryl-, 4- to 7-membered heterocycloalkyl-, C₃-C₇-cycloalkyl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}, -N(H)S(=O)₂R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group;

or

when two R^C groups are present ortho to each other on the phenyl-group, said two R^C groups together form a bridge :
O(CH₂)O, *O(CF₂)O*, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents the point of attachment to said phenyl- group ;

R^D represents a hydrogen atom or a methyl- group;

- R¹ represents a hydrogen atom or a C₁-C₆-alkyl-, C₁-C₆-alkoxy-,
C₁-C₃-alkoxy-C₁-C₃-alkyl-, C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
4- to 7-membered heterocycloalkyl-,
-(CH₂)_p-(4- to 7-membered heterocycloalkyl), phenyl-, naphthyl-,
5 -(CH₂)_p-phenyl, 5- or 6-membered heteroaryl- or
-(CH₂)_p-(5- or 6-membered heteroaryl) group,
wherein said group is optionally substituted, identically or differently,
with 1, 2, or 3 R⁹ groups ;
- 10 R² represents a hydrogen atom or a C₁-C₃-alkyl- group ;
- R³ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
fluoro-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy- or HO-C₁-C₃-alkyl- group ;
- 15 R⁵ represents a hydrogen atom ;
- R⁶ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
fluoro-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy- or HO-C₁-C₃-alkyl- group ;
- 20 R⁸ and R^{8a}
represent, independently from each other, a hydrogen atom or a
C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,
4- to 7-membered heterocycloalkyl-,
(4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
25 5- or 6-membered heteroaryl-, phenyl-C₁-C₆-alkyl-,
(phenyl)-O-(C₁-C₆-alkyl)- or (5- or 6-membered heteroaryl)-C₁-C₆-alkyl-
group; said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-
(C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-,
(4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
30 phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)-,

5- or 6-membered heteroaryl-,

(5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group being optionally substituted one or more times, identically or differently, with R¹⁰,

5 R^{8b} and R^{8c}

represent, independently from each other, a hydrogen atom, or a C₁-C₄-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, C₃-C₆-cycloalkyl- or a benzyl-group ;

or

10 R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a

4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group, the phenyl- group being optionally substituted 1 or 2 times, identically or differently, with fluoro, chloro, methyl- or methoxy-;

15

R⁹ represents a halogen atom or a -CN, C₁-C₃-alkoxy-, C₁-C₃-alkyl-, fluoro-C₁-C₃-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₃-alkyl)-, HO-C₁-C₃-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy-C₁-C₃-alkyl-, 4- to 7-membered heterocycloalkyl-, aryl-, 5- or 6-membered heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group;

20

wherein the aryl- and 5- or 6-membered heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C;

25

R¹⁰ represents a halogen atom, or a C₁-C₃-alkyl-, fluoro-C₁-C₃-alkyl-, -CN, -C(=O)R¹¹, -C(=O)N(H)R¹¹, -C(=O)N(R^{11a})R^{11b}, -C(=O)O-R¹¹, -N(R^{11a})R^{11b}, -NO₂, -N(H)C(=O)R¹¹, -N(R^{11a})C(=O)R^{11b}, -N(H)C(=O)N(R^{11a})R^{11b},

-N(R^{11a})C(=O)N(R^{11b})R^{11c}, -N(H)S(=O)₂R¹¹, -N(R^{11a})S(=O)₂R^{11b}, -OR¹¹,
 -S(=O)₂R¹¹, -S(=O)₂N(H)R¹¹ or -S(=O)₂N(R^{11a})R^{11b} group;

R¹¹, R^{11a}, R^{11b}, R^{11c}

5 represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- group;

m is an integer of 0, 1 or 2;

n is an integer of 2 or 3;

10 p is an integer of 1 or 2;

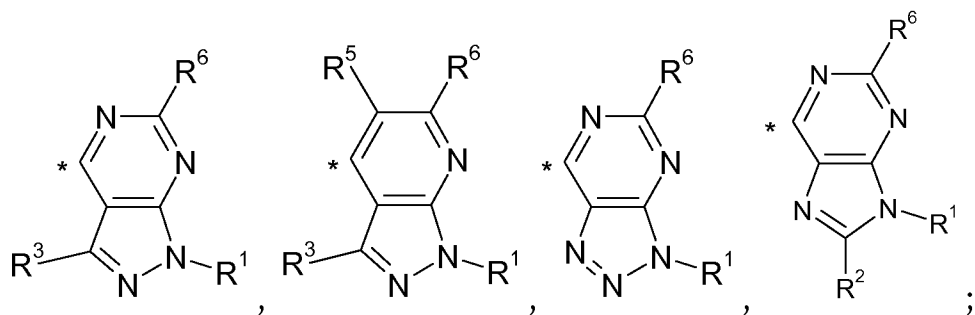
t is an integer of 3 or 4;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

15

In another preferred embodiment,

R^A is selected from the group consisting of:



20

wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a hydrogen atom or a -OH, -NH₂, C₁-C₃-alkoxy-,

25 HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy- or a -S-(C₁-C₃-alkyl)- group;

each

- 5 R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy-C₁-C₃-alkyl-, aryl-, heteroaryl-, 4- to 7-membered heterocycloalkyl-, C₃-C₇-cycloalkyl-, -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} , -NO₂, -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(H)C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)C(=O)N(R^{8a}) R^{8b} , -N(H)S(=O)₂ R^8 , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 or -S(=O)₂N(R^{8a}) R^{8b} group;
- 10 or
- when two R^C groups are present ortho to each other on the phenyl-group, said two R^C groups together form a bridge :
 $*O(CH_2)O*$, $*O(CF_2)O*$, $*NHC(=O)NH*$ or $*(CH_2)_t*$; wherein each * represents the point of attachment to said phenyl- group ;
- 15 R^D represents a hydrogen atom or a methyl- group;
- R^1 represents a hydrogen atom or a C₁-C₆-alkyl-, C₁-C₆-alkoxy-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
- 20 4- to 7-membered heterocycloalkyl-, -(CH₂)_p-(4- to 7-membered heterocycloalkyl), phenyl-, naphthyl-, -(CH₂)_p-phenyl, 5- or 6-membered heteroaryl- or -(CH₂)_p-(5- or 6-membered heteroaryl) group, wherein said group is optionally substituted, identically or differently,
- 25 with 1, 2, or 3 R^9 groups ;
- R^2 represents a hydrogen atom or a C₁-C₃-alkyl- group ;
- R^3 represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
- 30 fluoro-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy- or HO-C₁-C₃-alkyl- group ;

R⁵ represents a hydrogen atom ;

R⁶ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 5 fluoro-C₁-C₃-alkyl-, fluoro-C₁-C₃-alkoxy- or HO-C₁-C₃-alkyl- group ;

R⁸ and R^{8a}

represent, independently from each other, a hydrogen atom or a
 C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,
 10 4- to 7-membered heterocycloalkyl-,
 (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
 5- or 6-membered heteroaryl-, phenyl-C₁-C₆-alkyl-,
 (phenyl)-O-(C₁-C₆-alkyl)- or (5- or 6-membered heteroaryl)-C₁-C₆-alkyl-
 group; said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-
 15 (C₁-C₆-alkyl)-, 4- to 7-membered heterocycloalkyl-,
 (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
 phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)-,
 5- or 6-membered heteroaryl-,
 (5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group being optionally
 20 substituted one or more times, identically or differently, with R¹⁰,

R^{8b} and R^{8c}

represent, independently from each other, a hydrogen atom, or a
 C₁-C₄-alkyl-, C₁-C₃-alkoxy-C₁-C₃-alkyl-, C₃-C₆-cycloalkyl- or a benzyl-
 25 group ;

or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a
 4- to 7-membered heterocycloalkyl- group, which is optionally
 substituted once with C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group,

the phenyl- group being optionally substituted 1 or 2 times, identically or differently, with fluoro, chloro, methyl- or methoxy-;

- 5 R^9 represents a halogen atom or a -CN, C_1 - C_3 -alkoxy-, C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkyl-, $R^{8a}(R^{8b})N$ - C_1 - C_6 -alkyl-, $R^{8a}(R^{8b})N$ -C(=O)(C_1 - C_3 -alkyl)-, HO- C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkoxy- C_1 - C_3 -alkyl-, 4- to 7-membered heterocycloalkyl-, aryl-, 5- or 6-membered heteroaryl-, -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} , -NO₂, -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , 10 -N(H)S(=O)₂ R^8 , -N(R^{8c})S(=O)₂ R^8 , -OR⁸, -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 or -S(=O)₂N(R^{8a}) R^{8b} group;

wherein the aryl- and 5- or 6-membered heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^c ;

- 15 R^{10} represents a halogen atom, or a C_1 - C_3 -alkyl-, fluoro- C_1 - C_3 -alkyl-, -CN, -C(=O) R^{11} , -C(=O)N(H) R^{11} , -C(=O)N(R^{11a}) R^{11b} , -C(=O)O- R^{11} , -N(R^{11a}) R^{11b} , -NO₂, -N(H)C(=O) R^{11} , -N(R^{11a})C(=O) R^{11b} , -N(H)C(=O)N(R^{11a}) R^{11b} , -N(R^{11a})C(=O)N(R^{11b}) R^{11c} , -N(H)S(=O)₂ R^{11} , -N(R^{11a})S(=O)₂ R^{11b} , -OR¹¹, -S(=O)₂ R^{11} , -S(=O)₂N(H) R^{11} or -S(=O)₂N(R^{11a}) R^{11b} group;

20

R^{11} , R^{11a} , R^{11b} , R^{11c}

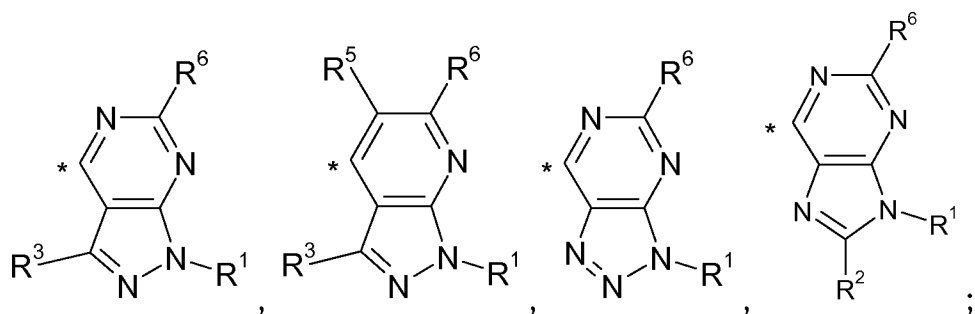
represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- group;

- 25 m is an integer of 0, 1 or 2;
n is an integer of 2 or 3;
p is an integer of 1 or 2;
t is an integer of 3 or 4;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5 In a particularly preferred embodiment,

R^A is selected from the group consisting of:



10 wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a -OH, -NH₂, C₁-C₂-alkoxy- or a -S-(C₁-C₂-alkyl)- group;

15 each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, phenyl-, 5- or 6-membered heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}, -N(H)S(=O)₂R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group;

or

when two R^C groups are present ortho to each other on the phenyl-group, said two R^C groups together form a bridge :

25 *O(CH₂)O* or *(CH₂)_t*; wherein each * represents the point of attachment to said phenyl- group ;

- R^D represents a hydrogen atom or a methyl- group;
- 5 R¹ represents a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl-,
4- to 7-membered heterocycloalkyl-,
-(CH₂)_p-(4- to 7-membered heterocycloalkyl), phenyl, -(CH₂)_p-phenyl or
5- or 6-membered heteroaryl- group,
wherein said group is optionally substituted, identically or differently,
with 1 or 2 R⁹ groups ;
- 10 R² represents a hydrogen atom or a methyl- group ;
- R³ represents a hydrogen atom or a C₁-C₃-alkyl-, trifluoromethyl- or
HO-C₁-C₂-alkyl- group;
- 15 R⁵ represents a hydrogen atom;
- R⁶ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
trifluoromethyl-, trifluoromethoxy- or HO-C₁-C₂-alkyl- group;
- 20 R⁸ and R^{8a}
represent, independently from each other, a hydrogen atom, or a
C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,
4- to 7-membered heterocycloalkyl-,
25 (4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
5- or 6-membered heteroaryl-, phenyl-C₁-C₆-alkyl-,
(phenyl)-O-(C₁-C₆-alkyl)- or (5- or 6-membered heteroaryl)-C₁-C₆-alkyl-
group; said C₁-C₆-alkyl-, phenyl-, naphthyl-, phenyl-C₁-C₆-alkyl-,
(phenyl)-O-(C₁-C₆-alkyl)-, 5- or 6-membered heteroaryl-,

(5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group being optionally substituted one or more times, identically or differently, with R¹⁰,

R^{8b} and R^{8c}

5 represent, independently from each other, a hydrogen atom or a C₁-C₃-alkyl- or a methoxy-C₁-C₃-alkyl- group ;

or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with a C₁-C₃-alkyl- or a phenyl- group, the phenyl- group being optionally substituted once with fluoro, chloro, methyl- or methoxy-;

R⁹ represents a halogen atom, or a -CN, C₁-C₃-alkoxy-, C₁-C₃-alkyl-, trifluoromethyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₃-alkyl)-, aryl-, 5- or 6-membered heteroaryl-, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(H)S(=O)₂R⁸, -OR⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group; wherein the aryl- and 5- or 6-membered heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C;

R¹⁰ represents a halogen atom, or a C₁-C₃-alkyl-, trifluoromethyl-, -CN, -C(=O)R¹¹, -C(=O)N(H)R¹¹, -C(=O)O-R¹¹, -N(R^{11a})R^{11b}, -N(H)C(=O)R¹¹, -N(H)S(=O)₂R¹¹, -OR¹¹, -S(=O)₂R¹¹ or -S(=O)₂N(H)R¹¹ group;

25

R¹¹, R^{11a}, R^{11b}, R^{11c}

represent, independently from each other, a hydrogen atom or a C₁-C₂-alkyl- group;

30 m is an integer of 0, 1 or 2;

n is an integer of 2 or 3;

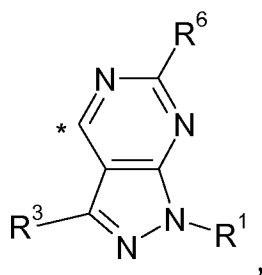
p is an integer of 1 or 2;

t is an integer of 3 or 4;

5 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another particularly preferred embodiment,

10 R^A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule;

15

R^B represents a -OH, methoxy- or a -SCH₃ group;

R^C represents a halogen atom, or a -CN, -OH, pyridyl-, C₁-C₃-alkoxy-, C₁-C₃-alkyl-, HO-C₁-C₃-alkyl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b},
 20 -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b},
 -N(H)S(=O)₂R⁸, -S(=O)₂R⁸ or -S(=O)₂N(H)R⁸ group;

R^D represents a hydrogen atom or a methyl- group;

25 R^1 represents a C₅-C₆-cycloalkyl-, -(CH₂)_p-C₅-C₆-cycloalkyl,

5- or 6-membered heterocycloalkyl-, $-(CH_2)_p$ -(5- or 6-membered heterocycloalkyl), phenyl-, thien-2-yl or $-(CH_2)_p$ -phenyl group, wherein said group is optionally substituted, identically or differently, with 1 or 2 R^9 groups ;

5

R^3 represents a hydrogen atom;

R^6 represents a hydrogen atom;

10 R^8 and R^{8a}

represent, independently from each other, a hydrogen atom, or a C_1 - C_6 -alkyl-, C_3 - C_7 -cycloalkyl-, $(C_3$ - C_7 -cycloalkyl)-(C_1 - C_6 -alkyl)-, 5- or 6-membered heterocycloalkyl-, (5- or 6-membered heterocycloalkyl)-(C_1 - C_4 -alkyl)-, phenyl-, naphthyl-, 15 5- or 6-membered heteroaryl-, phenyl- C_1 - C_4 -alkyl-, (phenyl)-O-(C_1 - C_4 -alkyl)- or (5- or 6-membered heteroaryl)- C_1 - C_4 -alkyl-group; said C_1 - C_6 -alkyl-, phenyl-, naphthyl-, phenyl- C_1 - C_4 -alkyl-, (phenyl)-O-(C_1 - C_4 -alkyl)-, 5- or 6-membered heteroaryl-, (5- or 6-membered heteroaryl)- C_1 - C_4 -alkyl- group being optionally 20 substituted one or more times, identically or differently, with R^{10} ;

 R^{8b} and R^{8c}

represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- or a methoxy- C_1 - C_3 -alkyl- group ;

25 or

R^{8a} and R^{8b} , together with the nitrogen atom they are attached to, form a 4- to 6-membered heterocycloalkyl- group, which is optionally substituted once with a C_1 - C_3 -alkyl- or a phenyl- group, the phenyl-group being optionally substituted once with methoxy-;

30

R⁹ represents a halogen atom or a -CN, C₁-C₃-alkoxy-, C₁-C₃-alkyl-,
 trifluoromethyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₃-alkyl)-, aryl-,
 5- or 6-membered heteroaryl-, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b},
 -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(H)S(=O)₂R⁸, -OR⁸, -S(=O)₂R⁸,
 5 -S(=O)₂N(H)R⁸ or -S(=O)₂N(R^{8a})R^{8b} group;
 wherein the aryl- and 5- or 6-membered heteroaryl- group is
 substituted, one or more times, identically or differently, with R^C;

R¹⁰ represents a halogen atom or a C₁-C₃-alkyl-, trifluoromethyl-,
 10 -C(=O)N(H)R¹¹, -C(=O)O-R¹¹, -N(R^{11a})R^{11b}, -N(H)C(=O)R¹¹, -N(H)S(=O)₂R¹¹,
 -OR¹¹, -S(=O)₂R¹¹ or -S(=O)₂N(H)R¹¹ group;

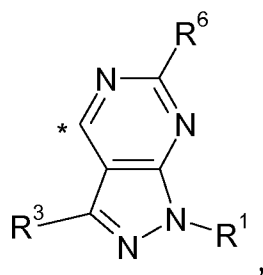
R¹¹, R^{11a}, R^{11b}, R^{11c}
 represent, independently from each other, a hydrogen atom or a
 15 C₁-C₂-alkyl- group;

m is an integer of 0 or 1;
 n is an integer of 2 or 3;
 p is an integer of 1;

20 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
 of same.

In another particularly preferred embodiment,

25 R^A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule;

5

R^B represents a -OH, methoxy- or a -SCH₃ group;

R^C represents a fluoro, chloro, bromo atom, or a -CN, -OH, pyrid-3-yl-, methoxy-, ethoxy-, C₁-C₃-alkyl-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,

10

-C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -NH₂, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b}, -N(H)S(=O)₂R⁸, -S(=O)₂R⁸ or -S(=O)₂N(H)R⁸ group;

R^D represents a hydrogen atom or a methyl- group;

15

R^1 represents a cyclopentyl-, cyclohexyl-, cyclopentylmethyl-, cyclohexylmethyl-, tetrahydropyran-4-yl, tetrahydropyran-4-ylmethyl-, phenyl-, thien-2-yl- or benzyl- group,

wherein said phenyl- and benzyl- group is optionally substituted,

20

identically or differently, with 1 or 2 R⁹ groups ;

R^3 represents a hydrogen atom;

R^6 represents a hydrogen atom;

25

R⁸ and R^{8a}

represent, independently from each other,

a hydrogen atom,

5 or a C₁-C₆-alkyl- group, which is optionally substituted with up to three fluoro atoms,

or a C₁-C₄-alkyl- group, which is substituted by a -OH, -OCH₃, phenoxy-,
-NH₂, -N(H)-CH₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(H)(C=O)CH₃, -C(=O)OH,
10 -C(=O)OCH₃ or -C(=O)NH₂ group,

or a C₁-C₄-alkyl- group, which is substituted by a phenyl- group, wherein
said phenyl- group is optionally substituted once with fluoro,
trifluoromethyl-, -S(=O)₂NH₂ or methoxy-,
15

or a C₁-C₄-alkyl- group, which is substituted by a 5- or 6-membered
heterocycloalkyl- group, which is selected from morpholinyl-,
pyrrolidinyl-, piperidinyl-, *N*-methyl-piprazinyl- or
2-oxoimidazolidin-1-yl-,
20

or a C₁-C₄-alkyl- group, which is substituted by a 5- or 6-membered
heteroaryl- group selected from pyridyl-, pyrazolyl-, thienyl-,
pyrazinyl-, imidazolyl-, wherein said 5- or 6-membered heteroaryl-
group is optionally substituted once by methyl-,
25

or a C₃-C₅-cycloalkyl- or cyclopropylmethyl- group,

or a tetrahydrofur-2-yl- group,

or a phenyl- or naphthyl- group, wherein the phenyl- group is optionally substituted once by fluoro, methoxy-, $-C(=O)NH_2$ or $-S(=O)_2NH_2$;

R^{8b} and R^{8c}

5 represent, independently from each other, a hydrogen atom or a C_1 - C_3 -alkyl- or a 2-methoxyethyl- group ;

or

R^{8a} and R^{8b} , together with the nitrogen atom they are attached to, form an azetidino, morpholino or N-phenylpiperazine ring, wherein said phenyl-
10 group attached to the piperazine ring is optionally substituted once by methoxy-;

R^9 represents a fluoro, chloro, or bromo atom, or a $-CN$, C_1 - C_3 -alkoxy-, methyl-, ethyl-, phenyl-, pyrazol-5-yl-, thien-3-yl-, $H_2N-C(=O)$ -ethyl-,
15 $-C(=O)NH_2$, $-C(=O)N(R^{8a})R^{8b}$, $-NH_2$, $-N(CH_3)_2$, $-NO_2$, $-S(=O)_2CH_3$, $-S(=O)_2N(H)R^8$ or $-S(=O)_2N(R^{8a})R^{8b}$ group, wherein said phenyl- group is optionally substituted once by a $-C(=O)NH_2$ group;

m is an integer of 0 or 1;

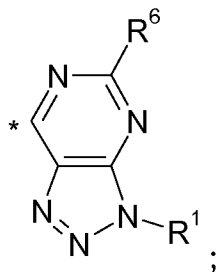
20 n is an integer of 2 or 3;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

25

In another particularly preferred embodiment,

R^A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule;

5

R^B represents a -OH or a methoxy- group;

R^C represents a fluoro atom, a chloro atom, or a -CN, -C(=O)NH₂ or -C(=O)N(H)-CH₂-CH₂-OH group;

10

R^D represents a hydrogen atom;

R^1 represents a cyclohexyl- or phenyl- group, wherein said group is optionally substituted, identically or differently, with 1 or 2 R^9 groups;

15

R^6 represents a hydrogen atom;

R^9 represents a fluoro atom, or a methyl- or -C(=O)NH₂ group;

20

m is an integer of 0 or 1;

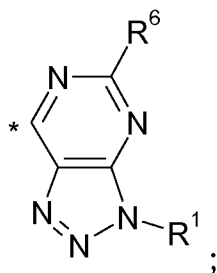
n is an integer of 2 or 3;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

25

In another particularly preferred embodiment,

R^A represents



5

wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a -OH or a methoxy- group;

10

R^C represents a -CN group;

R^D represents a hydrogen atom;

15 R¹ represents a cyclohexyl- or phenyl- group,
wherein said group is optionally substituted, identically or differently,
with 1 or 2 R⁹ groups;

R⁶ represents a hydrogen atom;

20

R⁹ represents a fluoro atom, or a methyl- or -C(=O)NH₂ group;

m is an integer of 0 or 1;

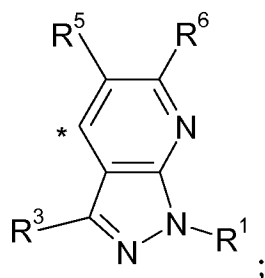
n is an integer of 2 or 3;

25

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5 In another particularly preferred embodiment,

R^A represents



10 wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a methoxy- group;

15 R^C represents a fluoro atom, a chloro atom, or a -CN, -C(=O)NH₂, or -C(=O)N(H)-CH₂-CH₂-OH group;

R^D represents a hydrogen atom;

20 R¹ represents a phenyl- group which is optionally substituted once by fluoro;

R³ represents a hydrogen atom;

25 R⁵ represents a hydrogen atom;

R^6 represents a hydrogen atom;

m is an integer of 0 or 1;

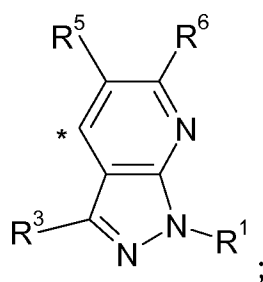
n is an integer of 2 or 3;

5

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

10 In another particularly preferred embodiment,

R^A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule;

15

R^B represents a methoxy- group;

R^C represents a chloro atom, or a $-C(=O)OCH_3$, $-C(=O)NH_2$ or

20 $-C(=O)N(H)-CH_2-CH_2-OH$ group;

R^D represents a hydrogen atom;

R^1 represents a phenyl- group which is optionally substituted once by
25 fluoro;

R^3 represents a hydrogen atom;

R^5 represents a hydrogen atom;

5 R^6 represents a hydrogen atom;

m is an integer of 0 or 1;

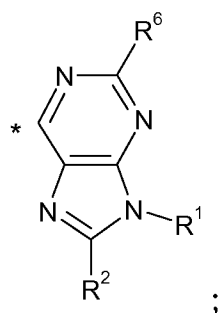
n is an integer of 2 or 3;

10 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another particularly preferred embodiment,

15

R^A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule;

20

R^B represents a methoxy- group;

R^C represents a fluoro atom, a chloro atom, or a -CN, -C(=O)NH₂ or

25 -C(=O)N(H)-CH₂-CH₂-OH group;

R^D represents a hydrogen atom;

R^1 represents a phenyl- group;

5 R^2 represents a hydrogen atom or a methyl- group;

R^6 represents a hydrogen atom;

m is an integer of 0 or 1;

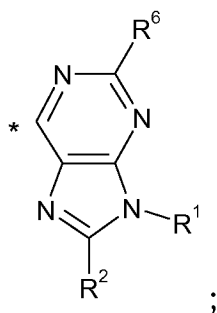
10 n is an integer of 2 or 3;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

15

In another particularly preferred embodiment,

R^A represents



20

wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a methoxy- group;

25

R^D represents a hydrogen atom;

R¹ represents a phenyl- group;

R² represents a hydrogen atom or a methyl- group;

5

R⁶ represents a hydrogen atom;

m is an integer of 0;

n is an integer of 2 or 3;

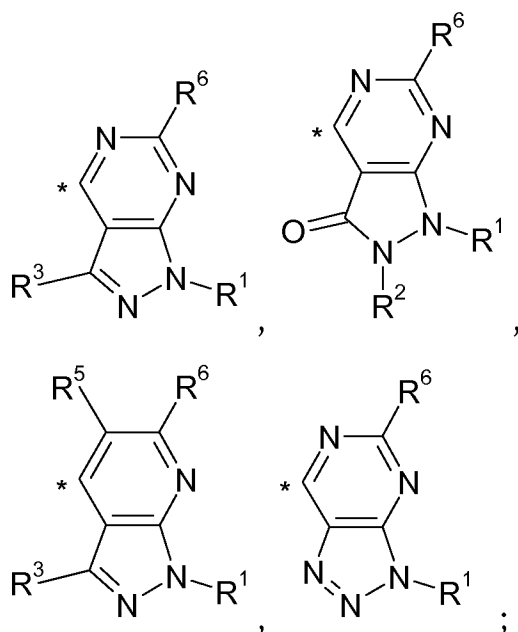
10

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another preferred embodiment

15

R^A is selected from the group consisting of:



20

wherein * indicates the point of attachment of said groups with the rest of the molecule.

R^B represents a hydrogen atom or a -OH, -SH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, HO-C₁-C₃-alkoxy-, halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, -S-(C₁-C₃-alkyl), -S-(halo-C₁-C₃-alkyl), -N(H)(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)(C₁-C₃-alkyl) or a H₂N-C₁-C₃-alkyl- group;

5

each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 10 -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} , -NO₂,
 -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(H)C(=O)N(R^{8a}) R^{8b} , -N(R^{8c})C(=O)N(R^{8a}) R^{8b} ,
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O) R^8 , -N(R^{8c})S(=O) R^8 ,
 -N(H)S(=O)₂ R^8 , -N(R^{8c})S(=O)₂ R^8 , -N=S(=O)(R^{8a}) R^{8b} , -OR⁸, -O(C=O) R^8 ,
 -O(C=O)N(R^{8a}) R^{8b} , -O(C=O)OR⁸, -SR⁸, -S(=O) R^8 , -S(=O)N(H) R^8 ,
 15 -S(=O)N(R^{8a}) R^{8b} , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 , -S(=O)₂N(R^{8a}) R^{8b} or
 -S(=O)(=NR^{8c}) R^8 group;

or

when two R^C groups are present ortho to each other on the phenyl-group, said two R^C groups together form a bridge :

20 *O(CH₂)₂O*, *O(CH₂)O*, *O(CF₂)O*, *CH₂C(R^{8a})(R^{8b})O*, *C(=O)N(R^{8a})CH₂*,
 N(R^{8a})C(=O)CH₂O, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents the point of attachment to said phenyl- group ;

R^D represents a hydrogen atom;

25 R^1 represents a C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl, C₁-C₆-alkoxy-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl, C₄-C₈-cycloalkenyl-, -(CH₂)_p-C₄-C₈-cycloalkenyl,
 3- to 10-membered heterocycloalkyl-,
 -(CH₂)_p-(3- to 10-membered heterocycloalkyl),
 30 4- to 10-membered heterocycloalkenyl-,

-(CH₂)_p-(4- to 10-membered heterocycloalkenyl),
 aryl-, -(CH₂)_p-aryl, heteroaryl- or -(CH₂)_p-heteroaryl group,
 wherein said group is optionally substituted, identically or differently,
 with 1, 2 or 3 R⁹ groups ;

5

R² represents a hydrogen atom ;

R³ represents a hydrogen atom ;

10

R⁵ represents a hydrogen atom ;

R⁶ represents a hydrogen atom ;

R⁷ represents a hydrogen atom ;

15

R⁸, R^{8a}, R^{8b}, R^{8c}

represent, independently from each other, a hydrogen atom, or a
 C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, C₂-C₆-alkenyl-,
 3- to 10-membered heterocycloalkyl-, aryl-,
 heteroaryl-, aryl-C₁-C₆-alkyl- or heteroaryl-C₁-C₆-alkyl- group ;

20

R⁹ represents a halogen atom, or a -CN, C₁-C₆-alkoxy-, C₁-C₆-alkyl-,
 halo-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-,
 C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 3- to 10-membered heterocycloalkyl-, -C(=O)R⁸, -C(=O)N(H)R^{8a},
 -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸,
 -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)R⁸, -N(R^{8c})S(=O)R⁸,
 -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -N=S(=O)(R^{8a})R^{8b}, -OR⁸, -O(C=O)R⁸,
 -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)N(H)R⁸,

25

30

-S(=O)N(R^{8a})R^{8b}, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or
-S(=O)(=NR^{8c})R⁸ group;

m is an integer of 0, 1, 2 or 3 ;

5 n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

q is an integer of 0 or 1 ;

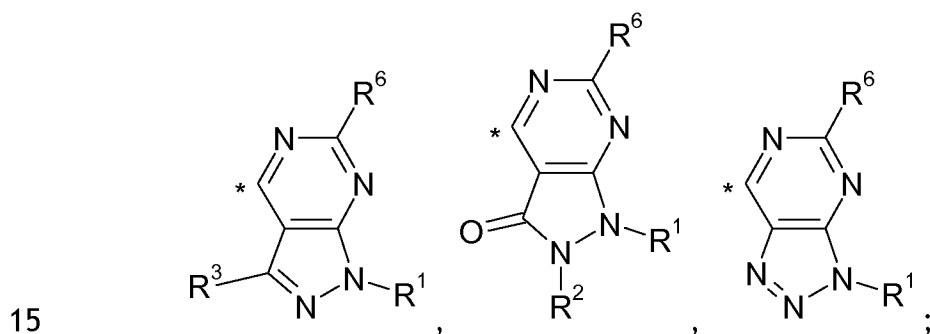
t is an integer of 3, 4 or 5 ;

and

10 x is an integer of 0, 1 or 2.

In another preferred embodiment

R^A is selected from the group consisting of:



wherein * indicates the point of attachment of said groups with the rest of the molecule.

20 R^B represents a hydrogen atom or a -OH, -SH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, (C₁-C₃-alkyl)-S- or a (halo-C₁-C₃-alkyl)-S- group;

each

25 R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl- or halo-C₁-C₆-alkyl- group;

- R^D represents a hydrogen atom;
- R^1 represents a C_3 - C_7 -cycloalkyl-, $-(CH_2)_p$ - C_3 - C_7 -cycloalkyl-,
 5 3- to 10-membered heterocycloalkyl-,
 $-(CH_2)_p$ -(3- to 10-membered heterocycloalkyl),
 aryl-, $-(CH_2)_p$ -aryl, heteroaryl- or $-(CH_2)_p$ -heteroaryl group,
 wherein said group is optionally substituted, identically or differently,
 with 1, 2 or 3 R^9 groups ;
- R^2 represents a hydrogen atom or a C_1 - C_6 -alkyl- or C_3 - C_7 -cycloalkyl- group ;
- R^3 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-,
 halo- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$,
 15 $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$,
 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)R^8$, $-N(R^{8c})S(=O)R^8$,
 $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-N=S(=O)(R^{8a})R^{8b}$, $-OR^8$, $-O(C=O)R^8$,
 $-O(C=O)N(R^{8a})R^{8b}$, $-O(C=O)OR^8$, $-SR^8$, $-S(=O)R^8$, $-S(=O)N(H)R^8$,
 20 $-S(=O)N(R^{8a})R^{8b}$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ or
 $-S(=O)(=NR^{8c})R^8$ group ;
 wherein said C_1 - C_3 -alkyl- group is optionally substituted with a group
 selected from: $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$,
 $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$,
 25 $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$, $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)R^8$,
 $-N(R^{8c})S(=O)R^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-N=S(=O)(R^{8a})R^{8b}$, $-OR^8$,
 $-O(C=O)R^8$, $-O(C=O)N(R^{8a})R^{8b}$, $-O(C=O)OR^8$, $-SR^8$, $-S(=O)R^8$, $-S(=O)N(H)R^8$,
 $-S(=O)N(R^{8a})R^{8b}$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$,
 $-S(=O)(=NR^{8c})R^8$;

30

R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-, halo- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$,
 $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$,
 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
5 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-OR^8$ or
 $-O(C=O)R^8$ group ;
 wherein said C_1 - C_3 -alkyl- group is optionally substituted with a group
 selected from: $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$,
 $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$,
 10 $-OR^8$, $-O(C=O)R^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ and
 $-S(=O)(=NR^{8c})R^8$;

R^8 , R^{8a} , R^{8b} , R^{8c}
 represent, independently from each other, a hydrogen atom or a
 15 C_1 - C_6 -alkyl- group ;

R^9 represents a halogen atom, or a $-CN$, C_1 - C_6 -alkoxy-, C_1 - C_6 -alkyl-,
 halo- C_1 - C_6 -alkyl-, $R^{8a}(R^{8b})N$ - C_1 - C_6 -alkyl-, HO- C_1 - C_6 -alkyl-,
 C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl-, halo- C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl-, C_2 - C_6 -alkenyl-,
 20 3- to 10-membered heterocycloalkyl-, $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$,
 $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-NO_2$, $-N(H)C(=O)R^8$,
 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)R^8$, $-N(R^{8c})S(=O)R^8$,
 $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-N=S(=O)(R^{8a})R^{8b}$, $-OR^8$, $-O(C=O)R^8$,
 25 $-O(C=O)N(R^{8a})R^{8b}$, $-O(C=O)OR^8$, $-SR^8$, $-S(=O)R^8$, $-S(=O)N(H)R^8$,
 $-S(=O)N(R^{8a})R^{8b}$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ or
 $-S(=O)(=NR^{8c})R^8$ group;

m is an integer of 0, 1, 2 or 3 ;

30 n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

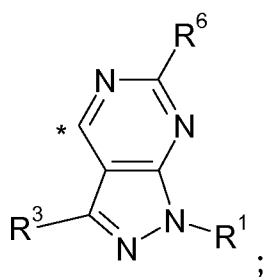
and

q is an integer of 0 or 1.

5

In another preferred embodiment

R^A represents



10

wherein * indicates the point of attachment of said groups with the rest of the molecule.

R^B represents a hydrogen atom or a -OH, -NH₂, C₁-C₃-alkoxy-,

HO-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, (C₁-C₃-alkyl)-S- or a

15

(halo-C₁-C₃-alkyl)-S- group;

each

R^C independently represents a halogen atom, or a -OH or a C₁-C₆-alkyl-

group;

20

R^D represents a hydrogen atom;

R¹ represents a C₃-C₇-cycloalkyl-, 3- to 10-membered heterocycloalkyl-, aryl-, -(CH₂)_p-aryl or heteroaryl- group,

25

wherein said group is optionally substituted, identically or differently, with 1, 2 or 3 R⁹ groups ;

R² represents a hydrogen atom ;

R³ represents a hydrogen atom ;

5

R⁵ represents a hydrogen atom ;

R⁶ represents a hydrogen atom ;

10 R⁸, R^{8a}, R^{8b}, R^{8c}

represent, independently from each other, a hydrogen atom or a C₁-C₆-alkyl- group ;

15 R⁹ represents a halogen atom, or a -CN, C₁-C₆-alkyl-, aryl-, heteroaryl-,
-C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸ or -S(=O)₂R⁸ group;
wherein the aryl- or heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^C ;

m is an integer of 0 or 1 ;

20 n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

and

q is an integer of 0 or 1 .

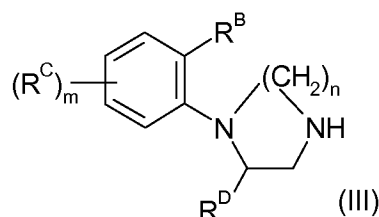
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Methods of preparation

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

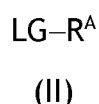
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In a preferred embodiment, the present invention relates to a method of preparing compounds of general formula (I), *supra*, in which method an intermediate of general formula (III) :



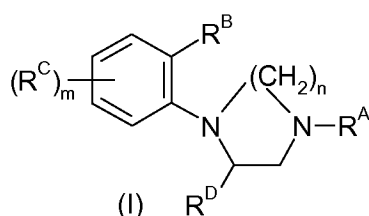
in which R^B , R^C , R^D , m , and n are as defined for the compounds of general formula (I), *supra*;

is allowed to react with a compound of general formula (II) :



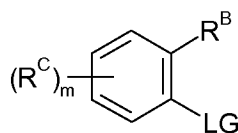
in which R^A is as defined for the compounds of general formula (I), *supra*, and LG is a leaving group;

thus providing a compound of general formula (I) :



in which R^A , R^B , R^C , R^D , m , and n are as defined *supra*.

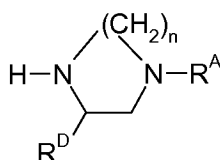
In another preferred embodiment, the present invention relates to a method of preparing compounds of general formula (I), *supra*, in which method an intermediate of general formula (VI) :



(VI)

in which R^B , R^C and m are as defined for the compounds of general formula (I),
 5 *supra*, and LG is a leaving group;

is allowed to react with a compound of general formula (V) :

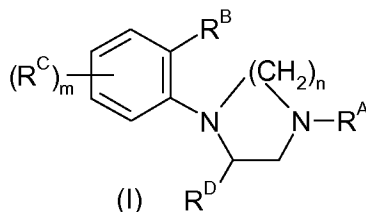


(V)

10

in which R^A , R^D and n are as defined for the compounds of general formula (I),
supra;

thus providing a compound of general formula (I) :

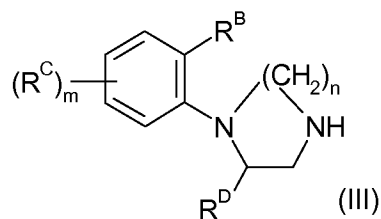


(I)

15

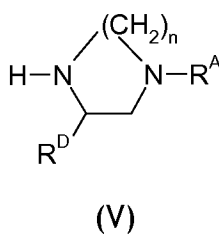
in which R^A , R^B , R^C , R^D , m , and n are as defined *supra*.

In accordance with a further aspect, the present invention covers intermediate
 20 compounds which are useful in the preparation of compounds of the present
 invention of general formula (I), particularly in the method described herein.
 In particular, the present invention covers compounds of general formula (III):



in which R^B , R^C , R^D , m , and n are as defined for the compounds of general formula (I), *supra*;

5 and of general formula (V):

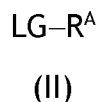


in which R^A , R^D and n are as defined for the compounds of general formula (I), *supra*;

10

In accordance with yet another aspect, the present invention covers the use of the intermediate compounds :

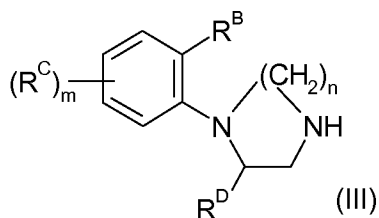
15 (i) of general formula (II):



in which R^A is as defined for the compounds of general formula (I), *supra*, and LG is a leaving group;

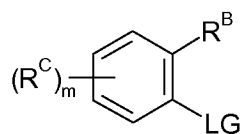
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(ii) of general formula (III):



in which R^B , R^C , R^D , m , and n are as defined for the compounds of general formula (I), *supra*; and/or

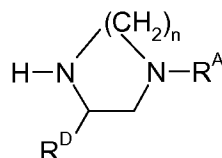
(iii) of general formula (VI)



(VI)

in which R^B , R^C and m are as defined for the compounds of general formula (I), *supra*, and LG is a leaving group; and/or

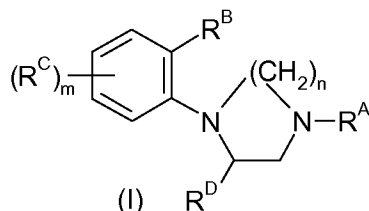
(iv) of general formula (V)



(V)

in which R^A , R^D and n are as defined for the compounds of general formula (I), *supra*;

15 for the preparation of compounds of general formula (I):



(I)

in which R^A , R^B , R^C , R^D , m , and n are as defined *supra*.

As one of ordinary skill in the art is aware of, the methods described above may comprise further steps like e.g. the introduction of a protective group and the cleavage of the protective group.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally

occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may
5 also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl
10 alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate ; one or more coloring agents ; one or more flavoring agents ; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for
15 example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially,
20 intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or
25 polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers,

methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable
5 detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-
10 oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives
20 and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can
25 be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and

the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known
5 methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an
10 alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an
15 ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution,
20 isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

25 A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will

therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches
5 may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous,
10 pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition
15 to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such
20 implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to
25 as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et*

al., "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

10 **acidifying agents** (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid) ;

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine) ;

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal) ;

aerosol propellants (examples include but are not limited to carbon dioxide, CCl₂F₂, F₂ClC-CClF₂ and CClF₃)

20 **air displacement agents** (examples include but are not limited to nitrogen and argon) ;

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate) ;

25 **antimicrobial preservatives** (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol,

cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal) ;

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene,
5 hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite) ;

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers) ;

10 **buffering agents** (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup,
15 syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red
20 No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red) ;

clarifying agents (examples include but are not limited to bentonite) ;

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan
25 monooleate, polyoxyethylene 50 monostearate) ;

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin) ;

- 5 **humectants** (examples include but are not limited to glycerol, propylene glycol and sorbitol) ;

levigating agents (examples include but are not limited to mineral oil and glycerin) ;

- 10 **oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil) ;

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment) ;

- 15 **penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

- 20 **plasticizers** (examples include but are not limited to diethyl phthalate and glycerol) ;

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation) ;

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax) ;

suppository bases (examples include but are not limited to cocoa butter and
5 polyethylene glycols (mixtures)) ;

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate) ;

suspending agents (examples include but are not limited to agar, bentonite,
10 carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum) ;

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and
15 sucrose) ;

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc) ;

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin,
20 liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch) ;

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate,
25 sodium phosphate, sorbitol and starch) ;

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac) ;

- 5 **tablet direct compression excipients** (examples include but are not limited to dibasic calcium phosphate) ;

- tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch
10 glycollate and starch) ;

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc) ;

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate) ;

- 15 **tablet/capsule opaquants** (examples include but are not limited to titanium dioxide) ;

tablet polishing agents (examples include but are not limited to carnuba wax and white wax) ;

- thickening agents** (examples include but are not limited to beeswax, cetyl
20 alcohol and paraffin) ;

tonicity agents (examples include but are not limited to dextrose and sodium chloride) ;

- viscosity increasing agents** (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose,
25 polyvinyl pyrrolidone, sodium alginate and tragacanth) ; and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be
5 illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 - 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60
10 minutes.

Lyophilised powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lyophilised powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 - 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or
15 dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 - 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 - 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

20 50 mg/mL of the desired, water-insoluble compound of this invention

5 mg/mL sodium carboxymethylcellulose

4 mg/mL TWEEN 80

9 mg/mL sodium chloride

9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

- 5 Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene
10 glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

- Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and
15 non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

- Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active
20 ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for
25 immediate release, without the need of water.

Combination therapies

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other

- pharmaceutical agents where the combination causes no unacceptable adverse effects. The present invention relates also to such combinations. For example, the compounds of this invention can be combined with known anti-hyperproliferative or other indication agents, and the like, as well as with
- 5 admixtures and combinations thereof. Other indication agents include, but are not limited to, anti-angiogenic agents, mitotic inhibitors, alkylating agents, anti-metabolites, DNA-intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, or anti-hormones.
- 10 Preferred additional pharmaceutical agents are: 131I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, BAY 80-6946, BAY 1000394, BAY 86-9766 (RDEA 119), belotecan, bendamustine, bevacizumab, bexarotene,
- 15 bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, crisantaspase, cyclophosphamide, cyproterone, cytarabine,
- 20 dacarbazine, dactinomycin, darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, epirubicin, epitiostanol, epoetin alfa, epoetin beta,
- 25 eptaplatin, eribulin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab
- 30 tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, interferon

alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiostane, 5 mercaptopurine, methotrexate, methoxsalen, Methyl aminolevulinate, methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, 10 paclitaxel, palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polysaccharide-K, porfimer sodium, 15 pralatrexate, prednimustine, procarbazine, quinagolide, raloxifene, raltitrexed, ranimustine, razoxane, regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil 20 + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, valrubicin, vandetanib, vaporeotide, vemurafenib, vinblastine, vincristine, 25 vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), 30 which is hereby incorporated by reference, such as asparaginase, bleomycin,

carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, 5 lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of 10 the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5- 15 azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, 20 melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as 25 epothilone and its derivatives, irinotecan, raloxifen and topotecan.

The compounds of the invention may also be administered in combination with protein therapeutics. Such protein therapeutics suitable for the treatment of cancer or other angiogenic disorders and for use with the compositions of the invention include, but are not limited to, an interferon (e.g., interferon

.alpha., .beta., or .gamma.) supraagonistic monoclonal antibodies, Tuebingen, TRP-1 protein vaccine, Colostrinin, anti-FAP antibody, YH-16, gemtuzumab, infliximab, cetuximab, trastuzumab, denileukin diftitox, rituximab, thymosin alpha 1, bevacizumab, mecasermin, mecasermin rinfabate, oprelvekin, 5 natalizumab, rhMBL, MFE-CP1 + ZD-2767-P, ABT-828, ErbB2-specific immunotoxin, SGN-35, MT-103, rinfabate, AS-1402, B43-genistein, L-19 based radioimmunotherapeutics, AC-9301, NY-ESO-1 vaccine, IMC-1C11, CT-322, rhCC10, r(m)CRP, MORAb-009, aviscumine, MDX-1307, Her-2 vaccine, APC-8024, NGR-hTNF, rhH1.3, IGN-311, Endostatin, volociximab, PRO-1762, 10 lexatumumab, SGN-40, pertuzumab, EMD-273063, L19-IL-2 fusion protein, PRX-321, CNTO-328, MDX-214, tigapotide, CAT-3888, labetuzumab, alpha-particle-emitting radioisotope-linked lintuzumab, EM-1421, HyperAcute vaccine, tucotuzumab celmoleukin, galiximab, HPV-16-E7, Javelin - prostate cancer, Javelin - melanoma, NY-ESO-1 vaccine, EGF vaccine, CYT-004-MelQbG10, WT1 15 peptide, oregovomab, ofatumumab, zalutumumab, cintredekin besudotox, WX-G250, Albuferon, aflibercept, denosumab, vaccine, CTP-37, efungumab, or 131I-chTNT-1/B. Monoclonal antibodies useful as the protein therapeutic include, but are not limited to, muromonab-CD3, abciximab, edrecolomab, daclizumab, gentuzumab, alemtuzumab, ibritumomab, cetuximab, 20 bevicizumab, efalizumab, adalimumab, omalizumab, muromomab-CD3, rituximab, daclizumab, trastuzumab, palivizumab, basiliximab, and infliximab.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

- (1) yield better efficacy in reducing the growth of a tumor or even 25 eliminate the tumor as compared to administration of either agent alone,
- (2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

- (3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
- 5 (4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,
- (5) provide for a higher response rate among treated patients,
- (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
- 10 (7) provide a longer time for tumor progression, and/or
- (8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

Methods of treatment and/or prophylaxis

- 15 The compounds of formula (I), *supra*, as described and defined herein have surprisingly been found to effectively and selectively inhibit GLUT1 and may therefore be used for the treatment and/or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or
- 20 diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours
- 25 including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine

tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

- 5 In accordance with another aspect therefore, the present invention covers a compound of general formula (I), or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned
10 *supra*.

Another particular aspect of the present invention is the use of a compound of general formula (I), described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically
15 acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

Another particular aspect of the present invention is the use of a compound of general formula (I) described *supra* for manufacturing a pharmaceutical
20 composition for the treatment or prophylaxis of a disease.

The compounds of the present invention can be used in particular in therapy and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of
25 the tumour growth.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs

include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-
5 intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

10 Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's
15 sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-
20 related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and
25 rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a

patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day.

- 5 The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen
- 10 will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from
- 15 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of

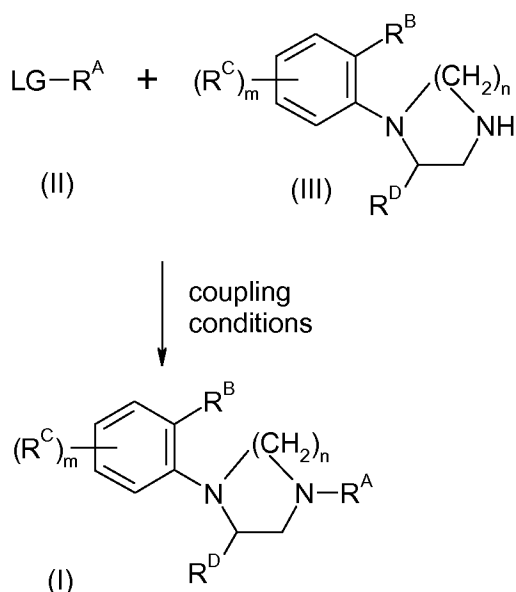
20 administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

General synthesis of compounds of general formula (I) of the present invention

The following paragraphs outline a variety of synthetic approaches suitable to
5 prepare compounds of formula (I), and intermediates useful for their synthesis.
In addition to the routes described below, also other routes may be used to
synthesise the target compounds, in accordance with common general
knowledge of a person skilled in the art of organic synthesis. The order of
transformations exemplified in the following schemes is therefore not intended
10 to be limiting, and suitable synthesis steps from various schemes can be
combined to form additional synthesis sequences. In addition, interconversion
of any of the substituents, in particular R^B , R^C , R^1 , R^2 , R^3 , R^5 or R^6 , can be
achieved before and/or after the exemplified transformations. These
modifications can be such as the introduction of protective groups, cleavage of
15 protective groups, reduction or oxidation of functional groups, halogenation,
metallation, metal catalysed coupling reactions, exemplified by but not
limited to Suzuki, Sonogashira and Ullmann coupling, ester saponifications,
amide coupling reactions, and/or substitution or other reactions known to a
person skilled in the art. These transformations include those which introduce
20 a functionality allowing for further interconversion of substituents.
Appropriate protective groups and their introduction and cleavage are well-
known to a person skilled in the art (see for example T.W. Greene and P.G.M.
Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999).
Specific examples are described in the subsequent paragraphs. Further, it is
25 possible that two or more successive steps may be performed without work-up
being performed between said steps, e.g. a “one-pot” reaction, as it is well-
known to a person skilled in the art.

A general strategy to assemble the molecules of the invention consists in a
30 coupling reaction to form the carbon-nitrogen bond linking the heteroaromatic

moiety R^A and the heteroalicyclic head group of an intermediate of general formula (III) as outlined in Scheme 1:



5

Scheme 1: Preparation of compounds of the formula (I) from intermediates (II) and (III).

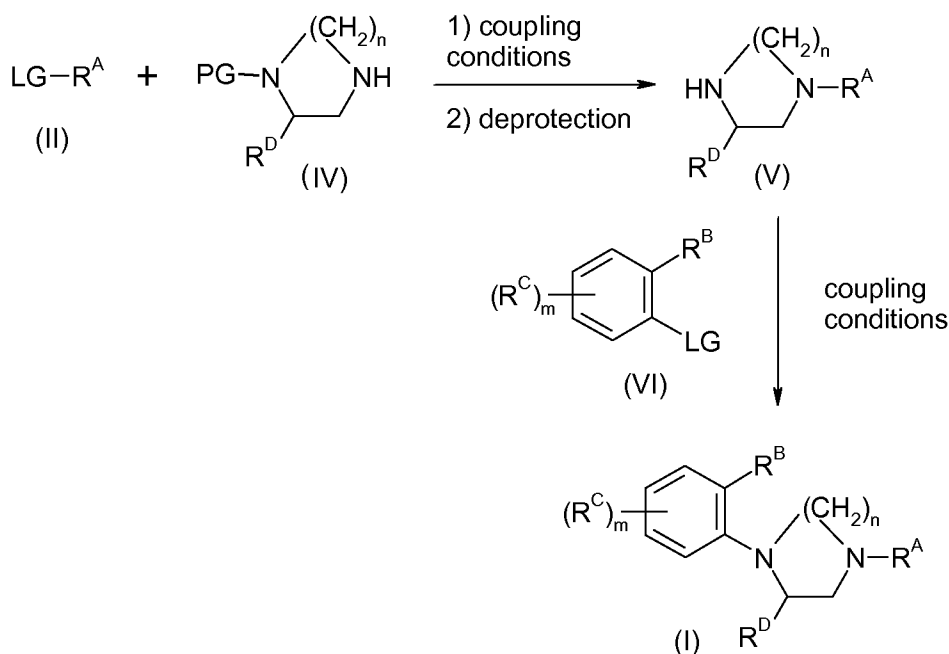
This step employs a heterocyclic precursor (II), in which R^A is as defined for the compounds of general formula (I), *supra*, and in which LG is a leaving group suitable for nucleophilic aromatic substitution, such as fluoro, chloro, bromo, or a triflate group, or a moiety suitable for metal catalysed amination reactions, e.g. bromo or iodo, which is coupled with an intermediate (III), in which R^B , R^C , R^D , m and n are as defined for the compounds of general formula (I). Synthetic approaches to various chemotypes of compounds (II) are outlined below; intermediates (III), if not commercially available, can be prepared e.g. by amination of cyclic diamines (IV) with arenes (VI) and subsequent deprotection, for the structures of (IV) and (VI) see Scheme 2.

The coupling reaction may be carried out as an aromatic nucleophilic substitution reaction using a dipolar solvent, e.g. DMF, DMSO, HMPA, or

acetonitrile at elevated temperatures with or without applying microwave irradiation. Addition of a base, for example triethylamine, DIPEA, DBU, sodium carbonate, potassium carbonate, cesium carbonate or the like, may be advantageous. Alternatively, the coupling can be carried out using a metal
5 catalysed coupling reaction known to the person skilled in the art (for a general overview see: D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, 2, 27-50.).

Alternatively, and as outlined in Scheme 2, compounds of the formula (II), in which R^A is as defined for the compounds of general formula (I), *supra*, and in
10 which LG is a leaving group suitable for nucleophilic aromatic substitution, such as fluoro, chloro, bromo, or a triflate group, or a moiety suitable for metal catalysed amination reactions, e.g. bromo or iodo, can be elaborated into compounds of the general formula (I) by reaction with a monoprotected cyclic diamine of the formula (IV), in which R^D is as defined for
15 the compounds of general formula (I), and in which PG represents a protective group. Said reaction can be accomplished *inter alia* by a Buchwald amination reaction well known to the person skilled in the art. Subsequent removal of the protective group yields intermediates of the formula (V), being subjected subsequently to another coupling or substitution reaction with intermediates
20 of formula (VI), in which R^B , R^C and m are as defined for the compounds of general formula (I), and in which LG stands for a leaving group, giving rise to compounds of the general formula (I). Intermediate arenes of the formula (VI) and monoprotected cyclic diamines of formula (IV) both are well known to the person skilled in the art and are commercially available in many cases.

25



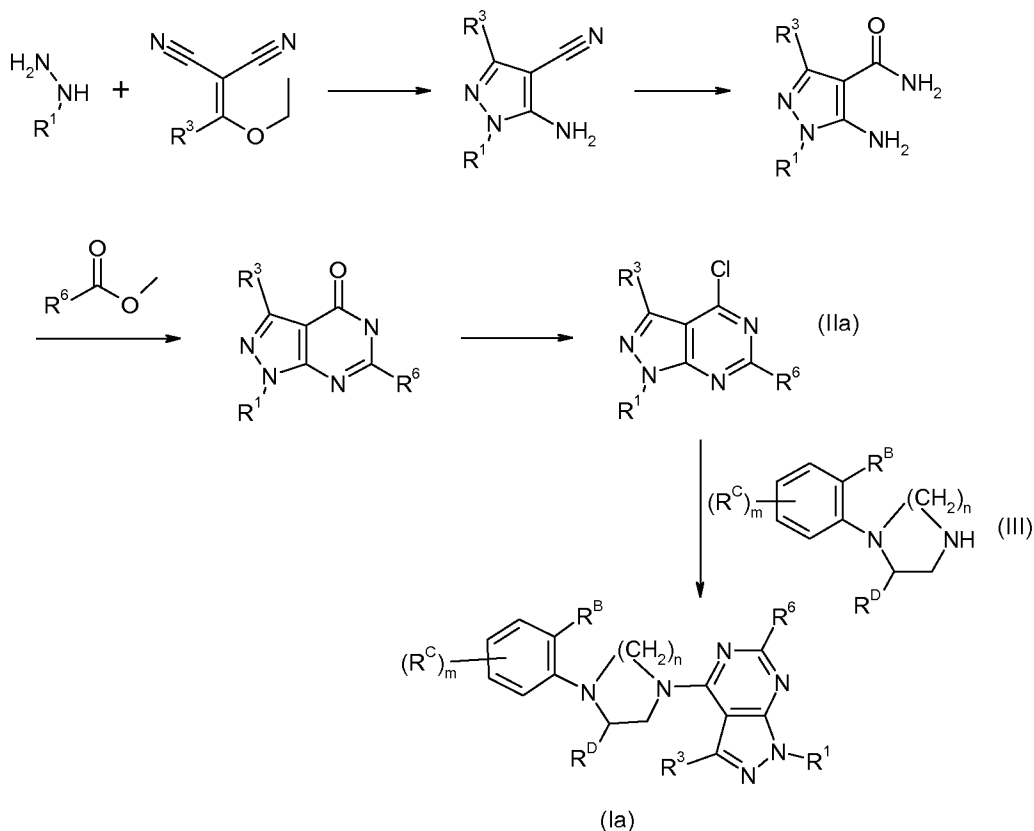
Scheme 2: Preparation of compounds of the formula (I) from intermediates of the formula (II) and (IV).

5

Various heterocyclic precursors of the general formula (II), including those discussed below based on a pyrazolopyrimidine core (IIa), triazolopyrimidine core (IIb), purine core (IIc), triazolopyridine core (IId) or pyrazolopyridine core (IIe), II f), II g), and II h) can be prepared by methods known from the literature. For illustrative purposes, the synthesis of several heterocyclic systems preferred within this invention is shown here in detail. A more general overview on fused bicyclic hetarenes can be found in the chemical literature, for instance in “Y. Yamamoto (editor), Science of Synthesis - Hetarenes and related Ring Systems Volume 16, Thieme, Stuttgart, New York **2004**”; D. StC. Black (editor) Science of Synthesis - Hetarenes and related Ring Systems Volume 15, Thieme, Stuttgart, New York **2005**”.

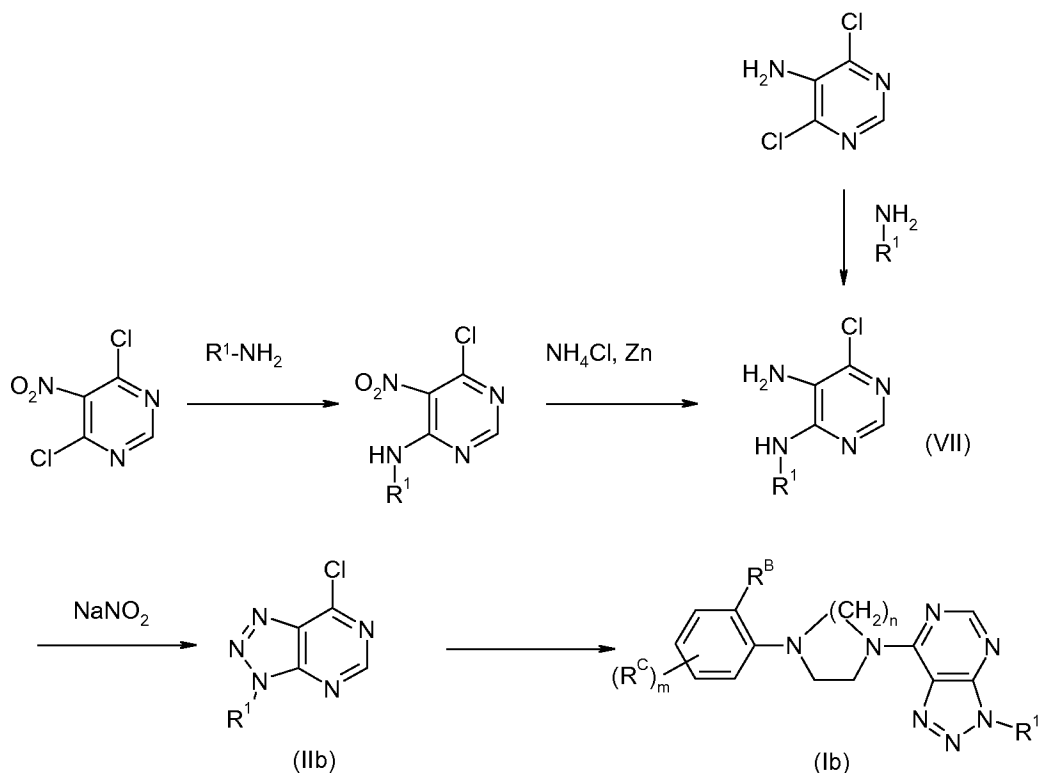
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Scheme 3: Synthesis of pyrazolopyrimidine derivatives (Ia) *via* precursors of formula (IIa)

5 Pyrazolopyrimidine precursors of the formula (IIa), in which R¹, R³ and R⁶ are
as defined for the compounds of general formula (I), *supra*, can be prepared as
shown in Scheme 3 according to the method published in the literature (C. C.
Cheng, R. K. Robins, *J. Org. Chem.* **1956**, 21, 1240-1256). They are readily
converted into compounds of the formula (Ia), which constitute a subgroup of
10 the compounds of the compounds of the general formula (I) in which R^A
represents a pyrazolopyrimidine core, by amination with intermediates (III), in
which R^B, R^C, R^D, m and n are as defined for the compounds of general formula
(I). A similar procedure for an analogous pyrrolopyrimidine series starting from
a 2-aminopyrrole-3-carboxamide derivative has been described by Hiyashita et
15 al, *Heterocycles* **1994**, 39, 345-356.

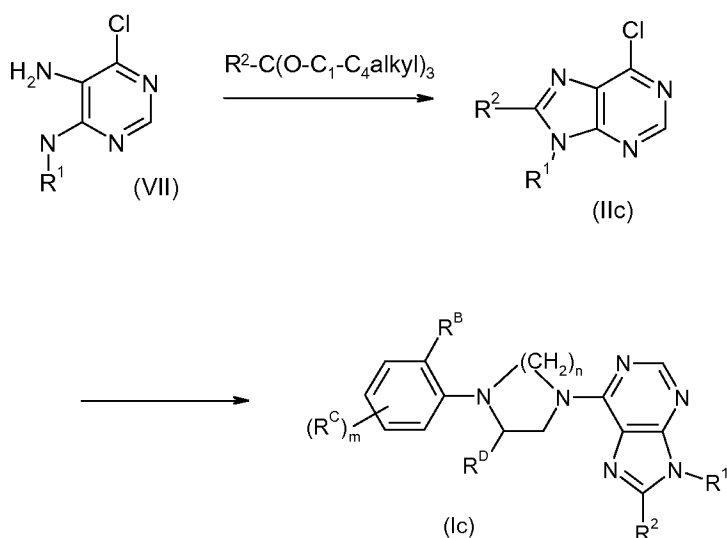


Scheme 4: Preparation of triazolopyrimidine derivatives of the formula (Ib)

- 5 Triazolopyrimidine derivatives of the formula (Ib), in which R^B , R^C , R^D , R^1 , n and m are as defined for the compounds of general formula (I), *supra*, constitute a different subgroup of the compounds of the general formula (I) in which R^A represents a triazolopyrimidine core. Said triazolopyrimidine derivatives of the formula (Ib) can be approached via diaminopyrimidine intermediates of the formula (VII), in which R^1 is as defined for the compounds of general formula (I). Diaminopyrimidines of formula (VII) are available by initial introduction of the R^1 -containing moiety by aromatic nucleophilic substitution followed by reduction of the nitro group, starting from commercial 2,4-dichloro-5-nitropyrimidine, as outlined in Scheme 4.
- 10 Alternatively 2,4-dichloro-5-aminopyrimidine may be used. Diaminopyrimidines of the formula (VII) are then reacted with sodium nitrite (method described in WO 2008/137436 and by Semple et al, *Bioorganic Med. Chem. Lett.* **2011**, *21*, 3134-3141) in the presence of a suitable acid, such as glacial acetic acid or

hydrochloric acid, to give triazolopyrimidines of the formula (IIb), which can be elaborated into the compounds of the formula (Ib) e.g. by the methods described in Schemes 1 and 2.

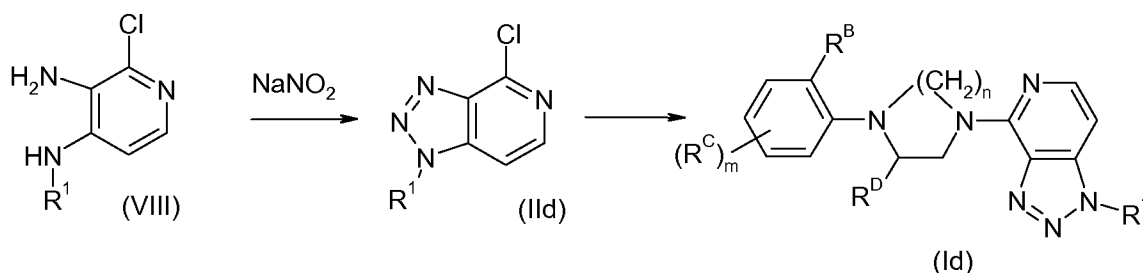
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Scheme 5: Synthesis of purine derivatives of the formula (Ic)

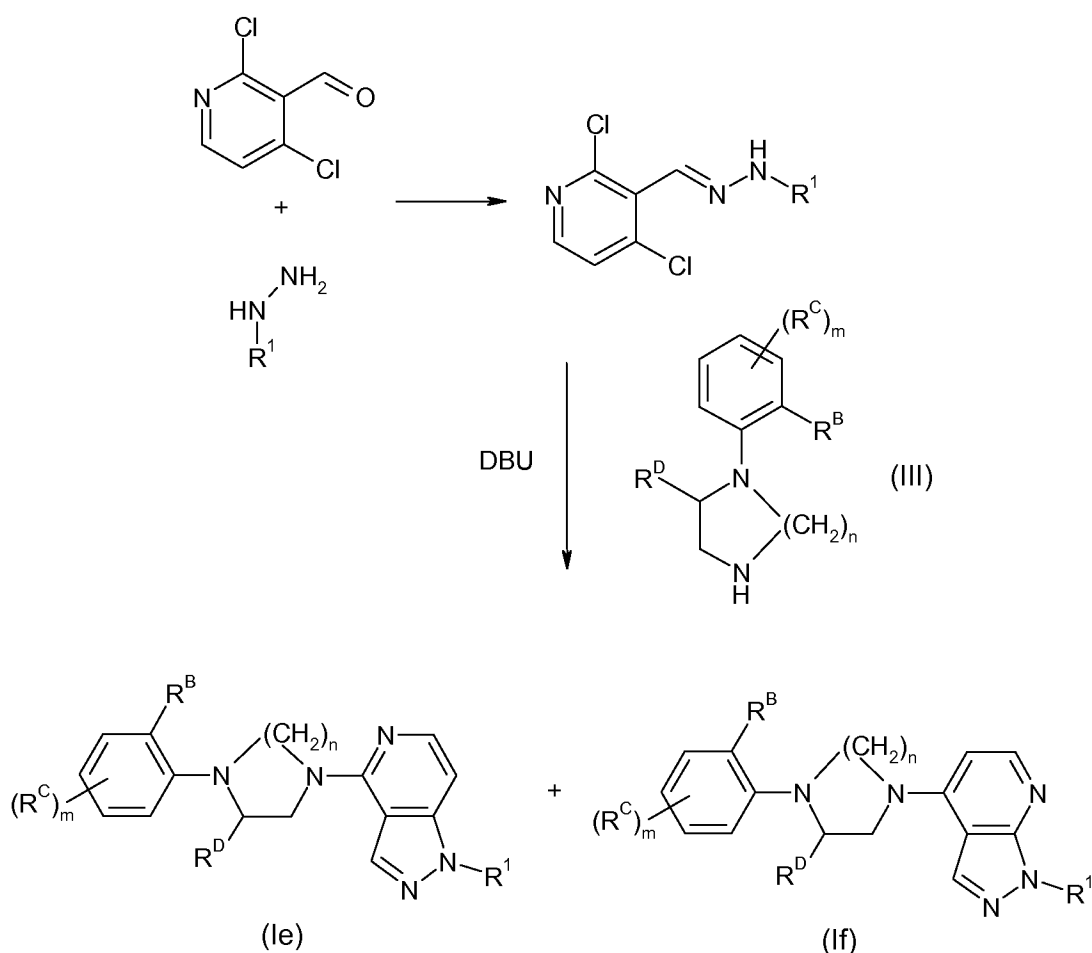
The method described in Scheme 4 can be adapted for the synthesis of purine derivatives of the formula (Ic), in which R^B , R^C , R^D , R^1 , R^2 , m and n are as defined for the compounds of general formula (I) and which constitute another different subgroup of the compounds of the general formula (I), by using an orthoester $R^2-C-(O-C_1-C_4\text{-alkyl})_3$, in which R^2 is as defined for the compounds of general formula (I) instead of sodium nitrite for the transformation of diaminopyrimidines of the formula (VII). Said reaction gives rise to chloropurine intermediates of the formula (IIc), which are converted into compounds of the formula (Ic) as described above.

In a fashion analogous to the procedure shown in Scheme 4, triazolopyridine derivatives of the formula (Id), constituting a further different subgroup of the compounds of the general formula (I), can be approached starting from diaminopyridine derivatives of the formula (VIII) as outlined in Scheme 6.



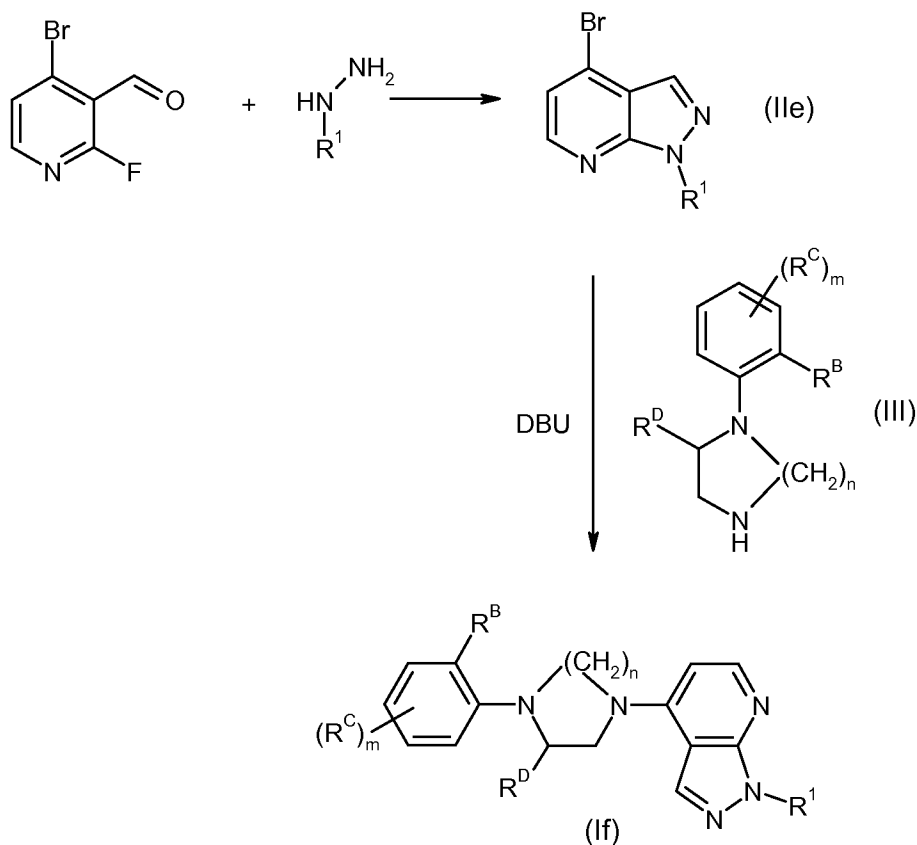
5 **Scheme 6:** Preparation of triazolopyridine derivatives of the formula (Id)

Pyrazolo-5-pyridines of the formula (Ie), alongside the regioisomeric pyrazolo-7-pyridines of the formula (If), also both forming subgroups of the compounds of the general formula (I), and in which R^B, R^C, R^D, R¹, m and n are as defined for the compounds of general formula (I), *supra*, can be synthesized according to Scheme 7. The bicyclic heterocycle is built from 2,4-dichloronicotinaldehyde (method described in WO 2010/106333) and hydrazines R¹-NH-NH₂, in which R₁ is as defined for the compounds of general formula (I), *via* intermediate hydrazone formation and subsequent cyclisation and addition of N-nucleophile of the formula (III), in which R^B, R^C, R^D, m and n are as defined for the compounds of general formula (I), in one step using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, to give compounds of the formulae (Ie) and (If), respectively.



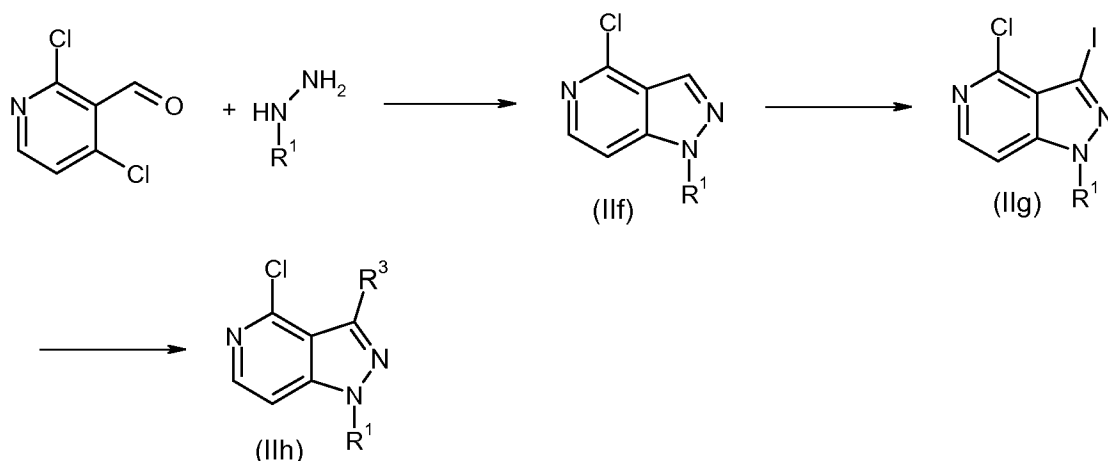
Scheme 7: Preparation of pyrazolopyridines of the formulae (Ie) and (If)

- 5 In order to selectively prepare the pyrazolo-7-pyridines of the formula (If) without concomitant regioisomer formation, 4-bromo-2-fluoronicotinaldehyde can be used instead of 2,4-dichloronicotinaldehyde as shown in Scheme 8. This alternative method allows for the isolation of the intermediate bromo-pyrazolopyridines of the formula (Ile), in which R¹ is as defined for the
- 10 compounds of general formula (I). Intermediate (Ile) is then reacted with intermediates of the formula (III), in which R^B, R^C, R^D, m and n are as defined for the compounds of general formula (I), in the presence of DBU as outlined in Scheme 6, to give compounds of the formula (If).



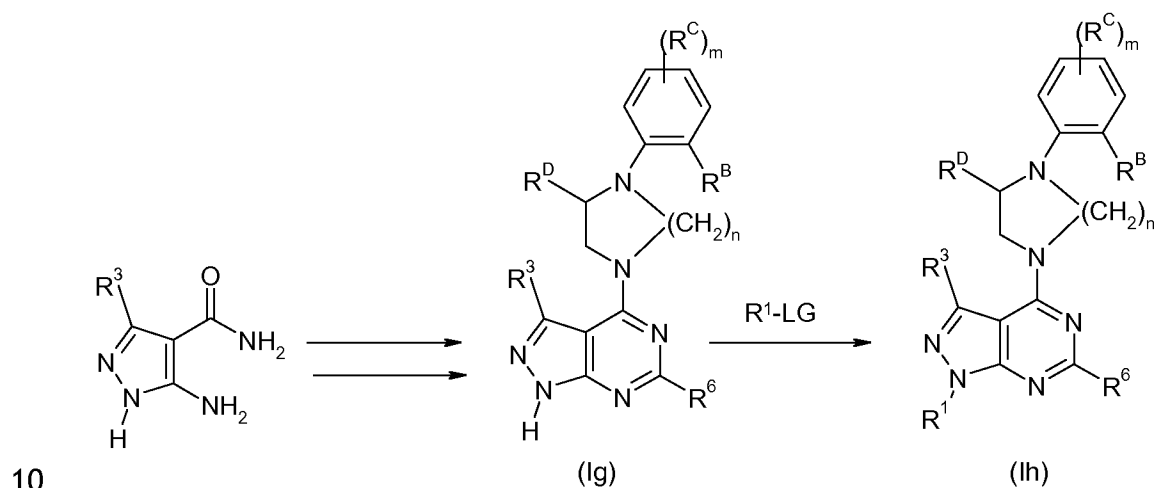
Scheme 8: Alternative approach to pyrazolopyridines of the formula (If)

A method for the introduction of various R^3 substituents is exemplarily shown in Scheme 9 for the pyrazolopyridine derivatives of the formula (IIh), in which R^1 and R^3 are as defined for the compounds of general formula (I), R^3 however being different from hydrogen, and can be accomplished for instance *via* a iodination reaction as described in WO 2012/38743 employing readily available intermediates (IIf) and giving rise to iodo compounds of the formula (IIg). Iodine can then be used for metal catalysed carbon-carbon bond forming reactions such as the Suzuki or the Sonogashira coupling, optionally followed by further modification, in order to introduce various R^3 groups.



Scheme 9: Preparation of pyrazolopyridine intermediates of the formula (IIh)

- 5 As an alternative synthetic strategy, allowing for late-stage diversification of R^1 , coupling of a readily assembled precursor containing both the heteroalicyclic moiety and the heterocyclic moiety with a suitably substituted R^1 . This strategy is briefly outlined in scheme 10.



Scheme 10: Route to pyrazolopyridine derivatives of formula (Ih) suitable for late-stage R^1 diversification

- 15 Using the strategy described above, pyrazolopyrimidines of the formula (Ih), in which R^B , R^C , R^D , R^1 , R^3 , R^6 , m and n are as defined for the compounds of

general formula (I), R¹ however being different from hydrogen, can be synthesized starting from 2-aminopyrazole-carboxamide derivatives which are elaborated to the pyrazolopyrimidine core and then coupled to an intermediate of general formula (III) as described in Scheme 3, to give
 5 pyrazolopyrimidine derivatives of the formula (Ig), featuring a hydrogen attached to N-1. The introduction of R¹ different from hydrogen is then carried out by a metal catalyzed coupling with a compound of the formula R¹-LG, in which R¹ is as defined for the compounds of general formula (I) but different from hydrogen, and in which LG stands for a leaving group suitable for
 10 nucleophilic substitution, such as fluoro, chloro, bromo, or a triflate group, or a moiety suitable for metal catalysed amination reactions, e.g. bromo or iodo. The coupling reagent may involve palladium (for a general overview see: D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, 2, 27-50.), or copper (for a general overview see: J.X. Qiao, P.Y.S. Lam, *Synthesis* **2011**, 829-856).

15

EXPERIMENTAL SECTION

Chemical compound names were generated using the software ACD Name batch, Version 12.01, by Advanced Chemical Development, Inc.; in doubt, the
 20 chemical identity of intermediates and example compounds is primarily to be defined by their chemical structure as shown in the experimental section.

Abbreviations

DMF	<i>N,N</i> -dimethylformamide
HPLC	high performance liquid chromatography
UPLC	ultra performance liquid chromatography
DAD	diode array detector
ELSD	evaporative light scattering detector
ESI	electrospray ionization
DLD1	colorectal adenocarcinoma cells isolated by D.L. Dexter

CHO-K1	chinese hamster ovary K1 cells
H460	lung carcinoma cells
RCC	renal cell carcinoma cells
VHL	von Hippel-Lindau
DMEM	Dulbecco's modified eagle medium
FCS	fetal calf serum
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HMPA	Hexamethylphosphoramide
KRP	Krbes-Ringer phosphate
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
Xphos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Examples were analyzed and characterized by the following analytical methods to determine characteristic retention time and mass spectrum:

5

<i>System:</i>	Waters Acquity UPLC-MS: Binary Solvent Manager, Sample Manager/Organizer, Column Manager, PDA, ELSD, SQD 3001
<i>Column:</i>	Acquity UPLC BEH C18 1.7 50x2.1mm
<i>Solvent:</i>	A1 = H ₂ O + 0.1% HCOOH A2 = H ₂ O + 0.2% NH ₃
	B1 = Acetonitrile
<i>Gradient:</i>	0-1.6 min 1-99% B, 1.6-2.0 min 99% B
<i>Flow:</i>	0.8 mL/min
<i>Temperature:</i>	60 °C
<i>Injection:</i>	2.0 µL
<i>Detection:</i>	DAD scan range 210-400 nm -> Peak table
	ELSD
<i>Method:</i>	MS ESI+, ESI- Switch -> diverse scan ranges possible

Method 1: UPLC (ACN-HCOOH)

Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7
50x2.1mm; eluent A: water + 0.1% formic acid, eluent B: acetonitril; gradient: 0-1.6
min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60 °C; injection: 2
5 µL; DAD scan: 210-400 nm; ELSD

Method 2: UPLC-MS (MCW-SQ-HSST3)

Instrument: Waters ACQUITY SQD UPLC system; column: Waters Acquity UPLC HSS T3
1.8 µ 50 x 1 mm; eluent A: 1 L water + 0.25 mL 99% formic acid , eluent B: 1 L
10 acetonitrile + 0.25 mL 99% formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A →
2.0 min 5% A temperature: 50°C; flow: 0.40 mL/min; UV-detection: 208 - 400 nm.

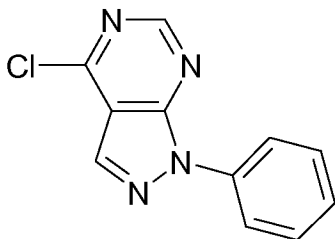
Method3:

Instrument: Waters Acquity UPLCMS SQD 3001; Column: Acquity UPLC BEH C18 1.7
15 µm, 50x2.1mm; eluent A: water + 0.1vol% formic acid, eluent B: acetonitrile,
gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60
°C; injection: 2 µL; DAD scan: 210-400 nm; ELSD

NMR peak forms are stated as they appear in the spectra, possible higher order
20 effects have not been considered.

Intermediates**Intermediate 1A**

25 **4-Chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine**



6.0 g (28.3 mmol) 1-Phenyl-1,5-dihydro-4H-pyrazolo(3,4-d)pyrimidin-4-one
(commercially available) was suspended in 13.0 mL (141 mmol) phosphoric

trichloride and the mixture was heated to reflux for 48 h. The solvent was removed under reduced pressure, the residue solidified upon trituration with dichloromethane to get 3.65 g (15.82 mmol, 54% of theory, 96% pure) of 4-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine. The material was used in subsequent steps without further purification.

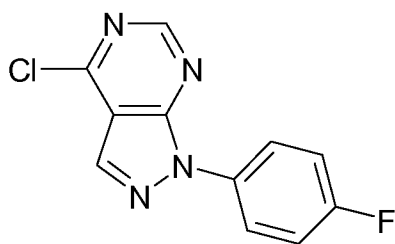
LC-MS (analytical method 2): $R_t = 1.08$ min, MS (ESIpos): $m/z = 231$ (M+H)⁺.

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 7.46 (t, 1H), 7.64 (t, 2H), 8.17 (d, 2H), 8.78 (s, 1H), 9.00 (s, 1H).

The following intermediates were prepared in analogy to intermediate 1A:

Intermediate 2A

4-Chloro-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine

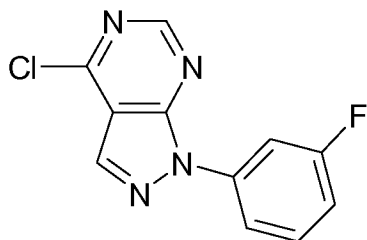


UPLC-MS: $R_t = 1.27$ min, MS (ESIpos): $m/z = 249$ (M+H)⁺.

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 7.40-7.51 (m, 2H), 8.09-8.19 (m, 2H), 8.74 (s, 1H), 8.98 (s, 1H).

Intermediate 3A

4-Chloro-1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine

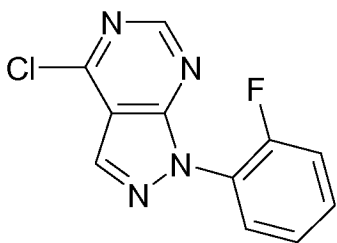


UPLC-MS: $R_t = 1.29$ min, MS (ESIpos): $m/z = 249$ (M+H)⁺.

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 7.20-7.32 (m, 1H), 7.59-7.72 (m, 1H), 7.99-8.12 (m, 2H), 8.80 (s, 1H), 9.01 (s, 1H).

5 Intermediate 4A

4-Chloro-1-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine

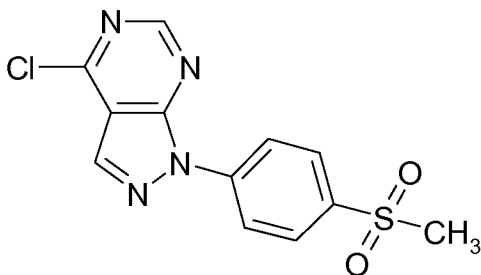


UPLC-MS: R_t = 1.11 min, MS (ESIpos): m/z = 249 ($M+H$) $^+$.

10

Intermediate 5A

4-Chloro-1-[4-(methylsulfonyl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine

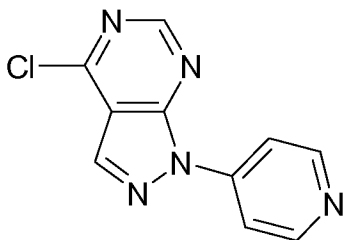


15 LC-MS (analytical method 1): R_t = 1.01 min, MS (ESIpos): m/z = 310 ($M+H$) $^+$.

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.29 (s, 3 H) 8.16 - 8.21 (m, 2 H) 8.50 - 8.56 (m, 2 H) 8.89 (s, 1 H) 9.08 (s, 1 H).

Intermediate 6A

20 4-Chloro-1-(pyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidine

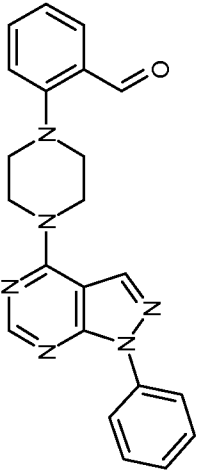


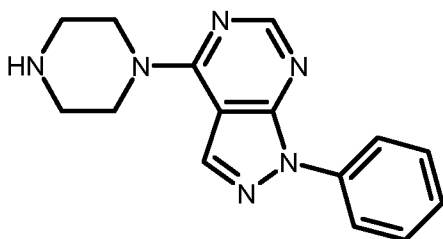
LC-MS (analytical method 1): Rt = 0.68 min, MS (ESIpos): m/z = 232 (M+H)+.

¹H-NMR (300 MHz, DMSO d₆) δ (ppm) = 8.77 - 8.82 (m, 2 H) 8.98 - 9.04 (m, 2 H)
9.06 (s, 1 H) 9.20 (s, 1 H).

Intermediate 7A

2-[4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzaldehyde was prepared in analogy to examples 2 and 3 by reacting intermediate 1A with the appropriately substituted piperazine derivatives. The reaction times were adapted.

Intermediate	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
7A	 2-[4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzaldehyde	1A	(300 MHz, DMSO- <i>d</i> ₆) δ (ppm) = 2.99 - 3.08 (m, 4 H) 4.06 - 4.18 (m, 4 H) 4.65 (d, 2 H) 5.15 (t, 1 H) 7.05 - 7.15 (m, 2 H) 7.23 (d, 1 H) 7.38 (d, 1 H) 7.49 (d, 1 H) 7.57 (t, 2 H) 8.15 - 8.23 (m, 2 H) 8.42 (s, 1 H) 8.64 (s, 1 H) ppm.	(method 1): R _t = 1.35 min, MS (ESIpos): m/z = 384 (M+H) ⁺ .

Intermediate 8A**1-phenyl-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine**

5

Step 1:

To a solution of 4.0 g (17.3 mmol) of intermediate 1A) in 73 mL DMF 3.23 g (17.3 mmol) Mono-Boc-piperazine and 7.77 mL (52.0 mmol) DBU were added and the reaction mixture was heated at 125°C for 3 hours. After cooling at rt the resulted mixture was concentrated in vacuo and the residue was purified via Biotage chromatography (100 g snap column: hexane / 10 - 70% ethyl acetate). Using this procedure tert-butyl 4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate was obtained: 5.53 g (84% yield).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 1.41 (s, 9H), 3.48 - 3.56 (m, 4H), 3.93 - 4.00 (m, 4H), 7.29 - 7.36 (m, 1H), 7.49 - 7.56 (m, 2H), 8.13 (s, 1H), 8.14 - 8.17 (m, 1H), 8.37 (s, 1H), 8.56 (s, 1H).

15

Step 2:

To a solution of 5.53 g (14.5 mmol) of tert-butyl 4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate prepared in step 1) in 52.4 mL 4M HCl-solution in dioxane was stirred for 1 hour at rt. Concentration in vacuo gave 4.6 g (99% yield) of raw 1-phenyl-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride salt which was used without any further purification.

25

Step 3:

To a solution of 4.6 g (14.5 mmol) of raw 1-phenyl-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride salt prepared in step 2) in 95 mL of dioxane and 10 mL of water was added 46.0 g (333 mmol) potassium carbonate. The mixture

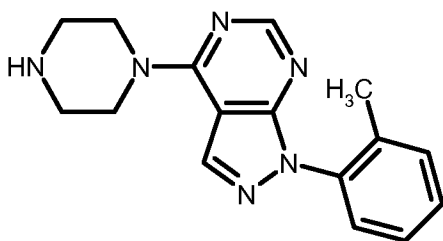
was stirred for 2 hour at rt. After filtration and washing with ethyl acetate the filtrate was concentrated in vacuo. The raw material was mixed again in dioxane / water plus potassium carbonate as explained before. Using the same procedure the desired material was obtained as solid: 4.1 g (100% yield).

- 5 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 2.76 - 2.85 (m, 4H), 3.82 - 3.89 (m, 4H), 7.30 - 7.35 (m, 1H), 7.49 - 7.55 (m, 2H), 8.11 - 8.16 (m, 2H), 8.33 (s, 1H), 8.53 (s, 1H).

Intermediate 9A

1-(2-methylphenyl)-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine

10



Step 1:

In analogy to the synthesis of intermediate 8A) step 1) 350 mg (1.43 mmol) of 4-chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (preparation known:

- 15 Bioorganic & Medicinal Chemistry Letters, 2004, vol.14, p.2121 - 2126 or WO2005/47288) and 266 mg (1.43 mmol) Mono-Boc-piperazine gave tert-butyl 4-[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate: 531 mg (91% yield).

- 20 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.44 (s, 9H), 2.04 (s, 3H), 3.50 - 3.58 (m, 4H), 3.96 - 4.02 (m, 4H), 7.30 - 7.40 (m, 2H), 7.41 - 7.46 (m, 2H), 8.25 (s, 1H), 8.55 (s, 1H).

Step 2:

- 25 In analogy to the synthesis of intermediate 8A) step 2) 531 mg (1.35 mmol) of tert-butyl 4-[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazine-1-carboxylate gave 1-(2-methylphenyl)-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride which was used without any further purification.

Step 3:

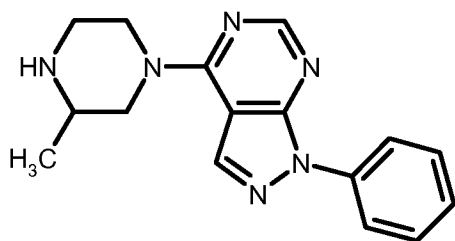
In analogy to the synthesis of intermediate 8A) step 3) 445 mg (1.35 mmol) 1-(2-methylphenyl)-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine hydrochloride gave the desired material: 312 mg (75% yield).

- 5 ¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.04 (s, 3H), 2.80 - 2.87 (m, 4H), 3.85 - 3.92 (m, 4H), 7.30 - 7.39 (m, 2H), 7.40 - 7.46 (m, 2H), 8.21 (s, 1H), 8.52 (s, 1H).

Intermediate 10A

(+/-)-4-(3-methylpiperazin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

10



Step 1:

In analogy to the synthesis of intermediate 8A) step 1) 288 mg (1.25 mmol) of intermediate 1A) and 300 mg (1.50 mmol) (+/-)-1-Boc-2-methyl-piperazine gave tert-butyl (+/-)-tert-butyl 2-methyl-4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate: 338 mg (65% yield).

15

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 1.08 (d, 3H), 1.40 (s, 9H), 3.31 - 3.54 (m, 2H), 3.67 (dd, 1H), 3.77 - 3.90 (m, 1H), 4.21 (br. s., 1H), 4.39 (d, 2H), 7.28 - 7.36 (m, 1H), 7.48 - 7.56 (m, 2H), 8.12 (s, 1H), 8.15 (d, 1H), 8.35 (s, 1H), 8.57 (s, 1H).

20

Step 2:

In analogy to the synthesis of intermediate 8A) step 2) 338 mg (0.86 mmol) (+/-)-tert-butyl 2-methyl-4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-1-carboxylate gave (+/-)-4-(3-methylpiperazin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine hydrochloride which was used without any further purification.

25

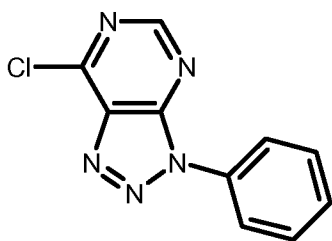
Step 3:

In analogy to the synthesis of intermediate 8A) step 3) 283 mg (0.86 mmol) (+/-)-4-(3-methylpiperazin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine hydrochloride gave the desired material: 224 mg (84% yield).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 1.04 (d, 3H), 2.61 - 2.76 (m, 3H), 2.98 (d, 1H),
5 3.11 (br. s., 1H), 3.30 (br. s., 2H), 7.28 - 7.36 (m, 1H), 7.47 - 7.55 (m, 2H), 8.08 - 8.13 (m, 1H), 8.14 (d, 1H), 8.32 (s, 1H), 8.55 (s, 1H).

Intermediate 11A

7-chloro-3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine



10

Step 1:

To a suspension of 10.0 g (61.0 mmol) 4,6-dichloropyrimidine-5-amine and 5.68 g (61.0 mmol) aniline in 20 mL ethanol and 130 mL water was added 2.0 mL 37% aq HCl. This mixture was heated at 85°C for 16 hours. The mixture was cooled in an ice
15 bad and the formed solid was filtered off. The solid was washed with 50 mL water, 50 mL hexane and dried in vacuo. Using this procedure 6-chloro-N⁴-phenylpyrimidine-4,5-diamine was obtained without any further purification: 11.8 g (85% yield).

20 ¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 6.16 (br. s., 2H), 6.96 - 7.04 (m, 1H), 7.25 - 7.33 (m, 2H), 7.65 - 7.71 (m, 2H), 7.83 (s, 1H), 8.73 (s, 1H).

Step 2:

25 To a solution of 420 mg (1.9 mmol) of intermediate 11A) step 1) in 12.2 mL water and 3.4 mL acetic acid a solution of 158 mg (2.28 mmol) sodium nitrite in 4.2 mL water at 0°C was given. The mixture was stirred for 2 hours at rt and then diluted with 200 mL ethyl acetate. The organic layer was washed threetimes with 30 mL saturated sodium hydrogencarbonate and brine. The organic phase was dried over sodium sulfate and

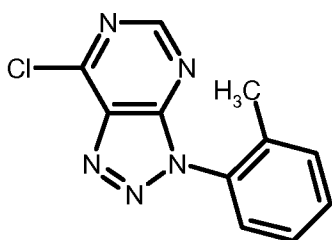
after filtration concentrated under reduced pressure to dryness. The raw material was purified with a Biotage chromatography system (25 g snap column, hexane / 10 - 60% ethyl acetate). Using this procedure the desired material was obtained: 440 mg (99% yield).

5

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO } d_6$) δ (ppm) = 7.62 - 7.67 (m, 1H), 7.71 - 7.78 (m, 2H), 8.11 - 8.17 (m, 2H), 9.20 (s, 1H).

Intermediate 12A

10 7-chloro-3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine



Step 1:

To a solution of 4.5 g (23.2 mmol) 4,6-dichloro-5-nitropyrimidine in 74.7 mL THF and 6.5 mL triethylamine was slowly added a solution of 2.11 g (19.7 mmol) o-toluidine in 10 mL THF at 0°C. The mixture was stirred for 1 hour at rt and then diluted with 250 mL ethyl acetate. The organic layer was washed with 50 mL water and brine, dried over sodium sulfate and after filtration concentrated in vacuo. The raw material was purified via a Biotage chromatography system (100 g snap column, hexane / 0 - 100% ethyl acetate). Using this procedure 4.35 g of a 7:3-mixture of 6-chloro-N-(2-methylphenyl)-5-nitropyrimidin-4-amine and N,N'-bis(2-methylphenyl)-5-nitropyrimidine-4,6-diamine was obtained.

To a solution of this mixture in 350 mL acetic acid 9.18 g (164 mmol) Fe was added and stirred for 1 hour at rt. After filtration the mixture was concentrated in vacuo and resolved in 250 mL ethyl acetate. This organic phase was washed twice with 50 mL aq. saturated sodium hydrogencarbonate, brine and dried over sodium sulfate. Filtration and concentration in vacuo gave a raw material which was purified via twice chromatography using silicagel (hexane / 0- 50% diethylether). Using this procedure the desired 6-chloro-N⁴-(2-methylphenyl)pyrimidine-4,5-diamine was obtained: 1.69 g (42% yield).

$^1\text{H-NMR}$ (300 MHz, DMSO d_6) δ (ppm) = 2.12 (s, 3H), 5.26 (s, 2H), 7.05 - 7.30 (m, 4H), 7.65 (s, 1H), 8.16 (s, 1H).

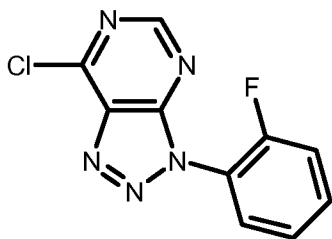
5 Step 2:

In analogy to intermediate 11A) step2) 1.69 g (7.20 mmol) 6-chloro- N^4 -(2-methylphenyl)pyrimidine-4,5-diamine of step1) gave the desired material: 1.54 g (84% yield).

10 $^1\text{H-NMR}$ (300 MHz, DMSO d_6) δ (ppm) = 2.09 (s, 3H), 7.43 - 7.62 (m, 4H), 9.07 (s, 1H).

Intermediate 13A

7-chloro-3-(2-fluorophenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine



15 Step 1:

In analogy to intermediate 12A) step 1) 4.5 g (23.2 mmol) 4,6-dichloro-5-nitropyrimidine and 2.07 g (18.6 mmol) 2-fluoroaniline gave the desired 6-chloro- N^4 -(2-fluorophenyl)pyrimidine-4,5-diamine: 587 mg (24% yield).

20 $^1\text{H-NMR}$ (300 MHz, DMSO d_6) δ (ppm) = 4.58 (s, 2H), 6.97 - 7.23 (m, 3H), 7.71 - 7.80 (m, 2H), 7.85 (s, 1H).

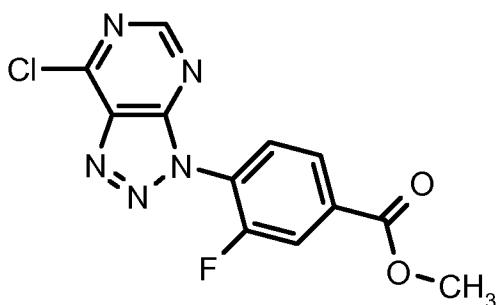
Step 2:

25 In analogy to intermediate 11A) step2) 1.65 g (6.91 mmol) 6-chloro- N^4 -(2-fluorophenyl)pyrimidine-4,5-diamine of step1) gave the desired material: 1.50 g (78% yield).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 7.53 (dt, 1H), 7.65 (ddd, 1H), 7.71 - 7.80 (m, 1H), 7.84 (td, 1H), 9.12 (s, 1H).

Intermediate 14A

5 methyl 4-(7-chloro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-3-fluorobenzoate



Step 1:

In analogy to intermediate 11A) step 1) 2.91 g (17.7 mmol) 4,6-dichloropyrimidine-5-amine and 3.00 g (17.7 mmol) methyl 4-amino-3-fluorobenzoate gave the desired
 10 methyl 4-[(5-amino-6-chloropyrimidin-4-yl)amino]-3-fluorobenzoate: 1.46 g (28% yield).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = $^1\text{H-NMR}$ (300MHz, $\text{DMSO-}d_6$): Shift [ppm]= 3.81 (s, 3H), 5.40 (s, 1H), 5.61 (s, 2H), 7.43 - 7.54 (m, 1H), 7.55 - 7.63 (m, 1H), 7.67 -
 15 7.77 (m, 3H), 7.82 (s, 1H), 7.86 - 7.94 (m, 1H), 8.49 (br. s., 1H), 8.94 (br. s., 1H).

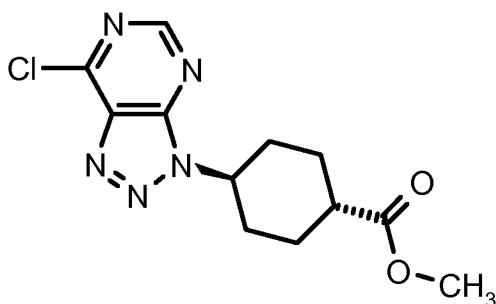
Step 2:

In analogy to intermediate 11A) step2) 1.78 g (6.0 mmol) methyl 4-[(5-amino-6-chloropyrimidin-4-yl)amino]-3-fluorobenzoate and in change additional 6.05 mL 37%
 20 aq. hydrochloric acid gave the desired material: 1.67 g (86% yield).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.89 - 3.94 (m, 3H), 7.99 - 8.07 (m, 1H), 8.07 - 8.15 (m, 2H), 9.15 (s, 1H).

25 Intermediate 15A

methyl trans-4-(7-chloro-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclohexanecarboxylate



Step 1:

In analogy to intermediate 12A) step 1) 5.56 g (28.6 mmol) 4,6-dichloropyrimidine-5-amine and 4.50 g (23.2 mmol) methyl trans-4-aminocyclohexanecarboxylate hydrochloride gave the desired methyl trans-4-[(5-amino-6-chloropyrimidin-4-yl)amino]cyclohexanecarboxylate: 3.35 g (39% yield).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 1.16 - 1.31 (m, 2H), 1.31 - 1.50 (m, 2H), 1.88 - 2.03 (m, 4H), 2.22 - 2.36 (m, 1H), 3.56 (s, 3H), 3.73 - 3.89 (m, 1H), 5.02 (s, 2H), 6.53 (d, 1H), 7.68 (s, 1H).

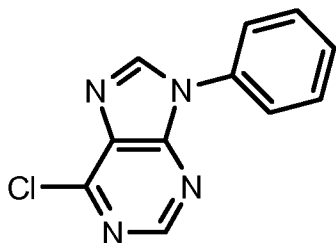
Step 2:

In analogy to intermediate 11A) step2) 3.35 g (11.8 mmol) methyl trans-4-[(5-amino-6-chloropyrimidin-4-yl)amino]cyclohexanecarboxylate and in change additional 5.0 mL 37% aq. hydrochloric acid gave the desired material: 2.92 g (81% yield).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 1.55 - 1.73 (m, 2H), 2.03 - 2.25 (m, 6H), 2.49 - 2.58 (m, 1H), 3.60 (s, 3H), 4.94 (tt, 1H), 9.04 (s, 1H).

20 Intermediate 16A

6-chloro-9-phenyl-9H-purine



A suspension of 300 mg of procedure 6-chloro-N⁴-phenylpyrimidine-4,5-diamine from example 11a) step 1) in 4.0 mL ethyl orthoformate and 4 mL acetic anhydride was

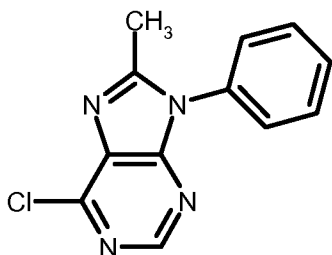
heated at 120°C for 1 hour in a microwave reactor. After cooling to rt the mixture was concentrated in vacuo and resolved in ethyl acetate. This organic phase was washed with aq. saturated sodium hydrogencarbonate and brine, dried over sodium sulfate and concentrated after filtration in vacuo. The raw material was purified
5 twice via a Biotage chromatography system (25 g snap column, hexane / 0 - 100% ethyl acetate). This procedure gave the desired material: 139 mg (40% yield).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 7.51 (d, 1H), 7.56 - 7.66 (m, 2H), 7.83 - 7.92 (m, 2H), 8.82 (s, 1H), 9.08 (s, 1H).

10

Intermediate 17A

6-chloro-8-methyl-9-phenyl-9H-purine



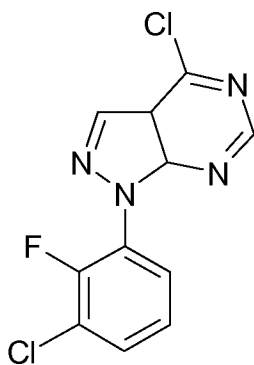
15 A suspension of 300 mg of procedure 6-chloro-N⁴-phenylpyrimidine-4,5-diamine from example 11a) step 1) in 4.0 mL 1,1,1-triethoxyethane and 4 mL acetic anhydride was heated at 120°C for 1 hour in a microwave reactor. After cooling to rt the mixture was concentrated in vacuo and resolved in ethyl acetate. This organic phase was washed with aq. saturated sodium hydrogencarbonate and brine, dried over sodium
20 sulfate and concentrated after filtration in vacuo. The raw material was purified via a Biotage chromatography system (25 g snap column, hexane / 0 - 100% ethyl acetate). This procedure gave the desired material: 218 mg (64% yield).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.49 (s, 3H), 7.54 - 7.66 (m, 5H), 8.62 (s, 1H).

25

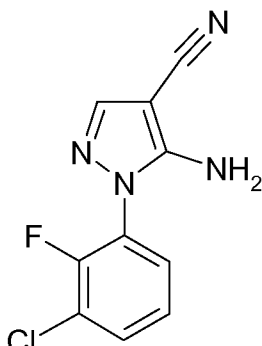
Intermediate 18A

4-chloro-1-(3-chloro-2-fluorophenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-*d*]pyrimidine



Step1:

5-amino-1-(3-chloro-2-fluorophenyl)-1H-pyrazole-4-carbonitrile



5

3.9 g (19.8 mmol) 3-chloro-2-fluorophenylhydrazine hydrochloride, 2.42 g (19.8 mmol) (ethoxymethylene)malononitrile and 8.28 mL (29.4 mmol) *N,N*-diethylethanamine in 48 mL ethanol were stirred under reflux for 3 h. The reaction mixture was allowed to reach rt and was poured into ice water. A 100 mg reaction mixture (reacted in the same way) was added. The solid was filtered off and dried under vacuum at 45°C giving 3.3 g (69%) product.

10

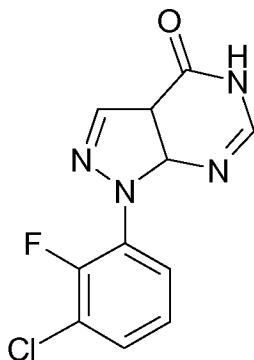
LC-MS (analytical method 3): $R_t = 0.93$ min, MS (ESIpos): $m/z = 237$ ($M+H$)⁺.

¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 6.85 (s, 2H), 7.30 - 7.38 (m, 1H), 7.42 - 7.51 (m, 1H), 7.67 - 7.76 (m, 1H), 7.78 (s, 1H).

15

Step2:

1-(3-chloro-2-fluorophenyl)-1,3a,5,7a-tetrahydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one



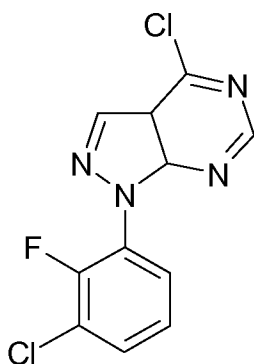
3.2 g (13.5 mmol) 5-amino-1-(3-chloro-2-fluorophenyl)-1*H*-pyrazole-4-carbonitrile in 25 mL of formic acid were stirred 8 h at 110°C bath temperature. The reaction mixture was allowed to reach rt. 120 mL ethanol were added to the reaction mixture
 5 (including a 100 mg reaction prepared in the same way). The solid was filtered off under suction, washed twice with ethanol and dried under vacuum at 45°C affording 1.6 g (43%) product.

LC-MS (analytical method 3): R_t = 0.87 min, MS (ESIpos): m/z = 265 ($M+H$)⁺.

¹H-NMR (300MHz, DMSO- d_6): δ [ppm] = 7.42 (td, 1H), 7.64 (td, 1H), 7.78 (td, 1H), 8.12
 10 (s, 1H), 8.37 (s, 1H), 12.33 - 12.58 (m, 1H).

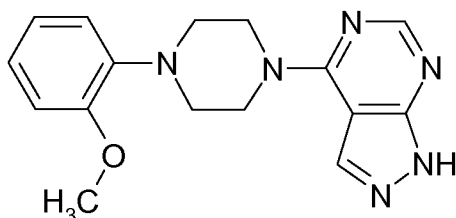
Step 3:

4-chloro-1-(3-chloro-2-fluorophenyl)-3a,7a-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine

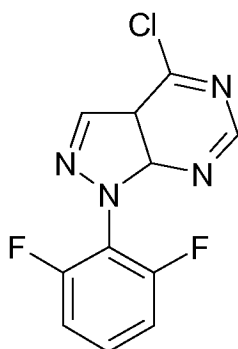


15 200 mg (0.76 mmol) 1-(3-chloro-2-fluorophenyl)-1,3a,5,7a-tetrahydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one in 2 mL of phosphoric trichloride were stirred 4 h at 130°C bath temperature. The reaction mixture was allowed to reach rt. The volatile compounds were removed on a rotavap. Toluene was added and removed on a rotavap. The residue was dried under vacuum yielding 210 mg (74%) product.

20 LC-MS (analytical method 3): R_t = 1.20 min, MS (ESIpos): m/z = 283 ($M+H$)⁺.

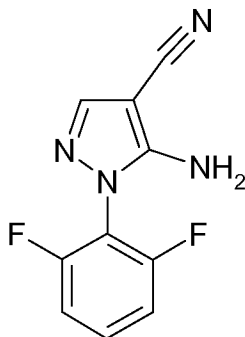
Intermediate 19A**4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine**

- 6.0 g (38.8 mmol) 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine, 7.464 g (38.8 mmol) 1-(2-methoxyphenyl)piperazine and 17.38 mL (116.5 mmol) DBU in 54 mL anhydrous DMF were stirred three h at 120°C. The reaction was allowed to reach rt and was concentrated on a rotavap. Water was added to the residue and the reaction mixture was poured into diluted aqueous sodium hydrogencarbonate solution. It was stirred 30 minutes and the solid was filtered off under suction. The solid was washed five times with water and dried 48 h at 45°C under vacuum yielding 11 g (91%) product.
- LC-MS (analytical method 3): R_t = 0.82 min, MS (ESIpos): m/z = 311 ($M+H$)⁺.
- ¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 3.02 - 3.11 (m, 4H), 3.79 (s, 3H), 3.98 - 4.09 (m, 4H), 6.81 - 7.01 (m, 5H), 8.22 (s, 1H), 8.30 (s, 1H).

15 Intermediate 20A**4-chloro-1-(2,6-difluorophenyl)-3a,7a-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine**

Step1:

5-amino-1-(2,6-difluorophenyl)-1*H*-pyrazole-4-carbonitrile



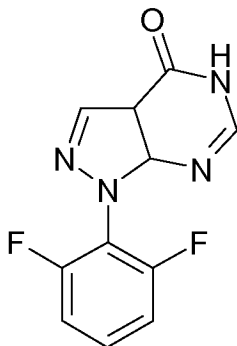
1 g (5.54 mmol) 2,6-difluorophenylhydrazine hydrochloride, 0.676 g (5.54 mmol) (ethoxymethylene)malononitrile and 2.3 mL (16.6 mmol) *N,N*-diethylethanamine in 9 mL ethanol were stirred 3 h at 80°C bath temperature. The reaction was allowed to reach rt and was poured with the reaction mixture of a 170 mg batch into ice water. The solid was filtered off, washed with water and dried under vacuum at 45°C to afford 673 mg (47%) product.

LC-MS (analytical method 5): R_t = 0.75 min, MS (ESIpos): m/z = 221 ($M+H$)⁺.

¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm] = 6.90 (br. s., 2H), 7.31 (t, 2H), 7.56 - 7.69 (m, 1H), 7.79 (s, 1H).

Step 2:

1-(2,6-difluorophenyl)-1,3a,5,7a-tetrahydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



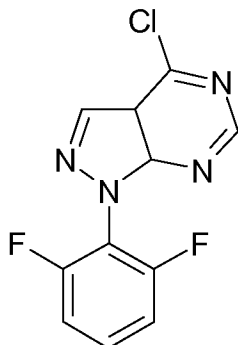
670 mg (3.04 mmol) 5-amino-1-(2,6-difluorophenyl)-1*H*-pyrazole-4-carbonitrile in 2.07 mL of formic acid were stirred 4 h at 110°C bath temperature. The reaction mixture was allowed to reach rt. The reaction mixture was diluted with ethanol and stirred for 5 minutes. The solid was filtered off under suction, washed with ethanol and dried under vacuum at 45°C to give 448 mg (59%) product.

LC-MS (analytical method 5): R_t = 0.46 min, MS (ESIpos): m/z = 249 ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm] = 7.40 (t, 2H), 7.64 - 7.75 (m, 1H), 8.09 (s, 1H), 8.39 (s, 1H), 11.72 - 13.28 (m, 1H).

Step 3:

4-chloro-1-(2,6-difluorophenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidine



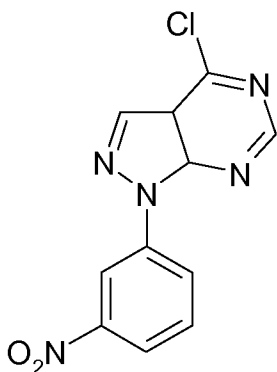
- 5 350 mg (1.41 mmol) 1-(2,6-difluorophenyl)-1,3a,5,7a-tetrahydro-4H-pyrazolo[3,4-d]pyrimidin-4-one in 1.78 mL of phosphoric trichloride were stirred 4 h at 100°C bath temperature. The reaction mixture was allowed to reach rt. The reaction mixture was poured into ice water and extracted three times with dichloromethane. The combines organic layers were washed with water, dried over magnesium sulfate and
- 10 concentrated. 77 mg (20%) product were isolated.

LC-MS (analytical method 3): $R_t = 1.12$ min, MS (ESIpos): $m/z = 267$ ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 7.44 - 7.51 (m, 2H), 7.72 - 7.82 (m, 1H), 8.87 (s, 1H), 8.90 - 8.94 (m, 1H).

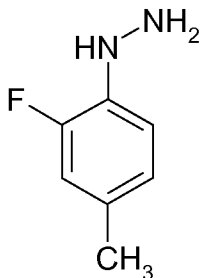
15 Intermediate 21A

4-chloro-1-(3-nitrophenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidine



Step1:

- 20 (2-fluoro-4-methylphenyl)hydrazine

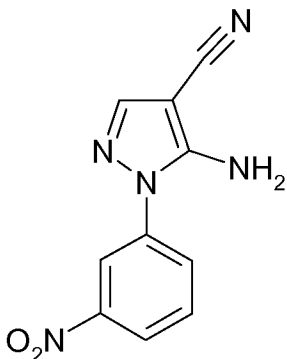


1.0 g (7.99 mmol) 2-fluoro-4-methylaniline was suspended in 7 mL 37% aqueous hydrochloric acid. At 0 to -4°C 717 mg (10.39 mmol) sodium nitrite in 2.5 mL water were added. It was stirred 0.5 h at this temperature. At 0°C 3.03 g (15.98 mmol) tin(II) chloride in 2.5 mL 37% aqueous hydrochloric acid were added. It was stirred 2 h at 0°C. The reaction mixture was poured into ice water and extracted with dichloromethane. The aqueous layer was made alkaline with 32% aqueous sodium hydroxide and extracted three times with dichloromethane. These combined organic phases were washed with water, dried over magnesium sulfate and concentrated. 700 mg (59%) product was obtained.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 2.14 (s, 3H), 3.90 (s, 2H), 6.29 (s, 1H), 6.73 - 6.81 (m, 2H), 6.96 - 7.03 (m, 1H).

Step2:

15 5-amino-1-(3-nitrophenyl)-1H-pyrazole-4-carbonitrile



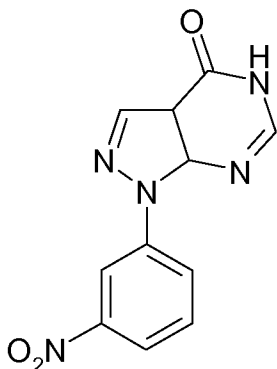
19.4 g (102.3 mmol) (3-nitrophenyl)hydrazine hydrochloride, 12.496 g (102.3 mmol) (ethoxymethylene)malononitrile and 42.78 mL (307.0 mmol) *N,N*-diethylethanamine were heated 3 h under reflux in 250 mL ethanol. The reaction was allowed to reach rt and poured into 1.5 L ice water. The precipitate was filtered off with suction and dried at 45°C under vacuum to give 22.7 g (92%) product.

LC-MS (analytical method 3): *R*_t = 0.85 min, MS (ESIpos): *m/z* = 230 (*M*+H)⁺.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm]= 6.95 (s, 2H), 7.74 - 7.87 (m, 2H), 7.92 - 8.00 (m, 1H), 8.19 - 8.29 (m, 2H).

Step3:

5 **1-(3-nitrophenyl)-1,3a,5,7a-tetrahydro-4H-pyrazolo[3,4-d]pyrimidin-4-one**



11.0 g (47.99 mmol) 5-amino-1-(3-nitrophenyl)-1H-pyrazole-4-carbonitrile in 90 mL of formic acid were stirred 8 h at 110°C bath temperature. The reaction mixture was allowed to reach rt. The reaction mixture was diluted with 250 mL ethanol. The solid
10 was filtered off under suction, washed twice with ethanol and dried under vacuum at 45°C affording 11.18 g (91%) product.

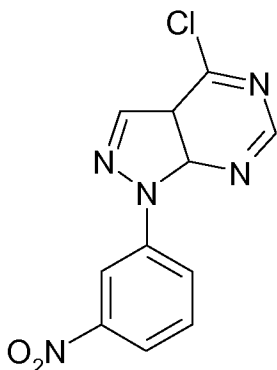
LC-MS (analytical method 3): R_t = 0.83 min, MS (ESIpos): m/z = 258 ($M+H$)⁺.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm]= 7.84 (t, 1H), 8.21 (ddd, 1H), 8.29 (s, 1H), 8.40 (s, 1H), 8.54 (ddd, 1H), 9.00 (t, 1H), 12.45 - 12.75 (m, 1H).

15

Step4:

4-chloro-1-(3-nitrophenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidine



6.0 g (23.33 mmol) 1-(3-nitrophenyl)-1,3a,5,7a-tetrahydro-4H-pyrazolo[3,4-
20 d]pyrimidin-4-one in 20.0 mL of phosphoric trichloride were stirred 15 h at 130°C bath temperature. The reaction mixture was allowed to reach rt. The residue was

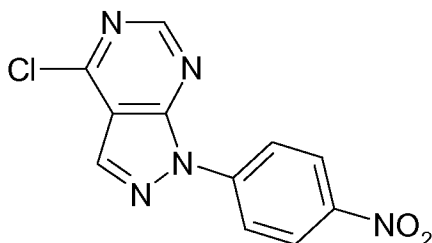
treated with toluene, concentrated again and tert-butyl methyl ether was added. The solid was filtered off with suction and dried at rt affording 6.2 g (95%) product.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 7.89 (t, 1H), 8.24 (ddd, 1H), 8.63 (ddd, 1H), 8.83 (s, 1H), 9.04 - 9.09 (m, 2H).

5

Intermediate 22A

4-chloro-1-(4-nitrophenyl)-3a,7a-dihydro-1H-pyrazolo[3,4-d]pyrimidine



10 Step 1:

To 5.0 g (32.65 mmol) (4-nitrophenyl)hydrazine and 9.10 mL (65.3 mmol) *N,N*-diethylethanamine in 90 mL ethanol were added 3.987 g (32.65 mmol) (ethoxymethylene)malononitrile. The reaction was stirred under reflux over night and cooled to rt. It was concentrated. The residue was dissolved in dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated. The solid was treated with hexane, filtered off and dried under vacuum affording 7.024 g (91%) product which was used in the next step without further purification.

15

Step 2:

7.024 g (30.65 mmol) 5-amino-1-(4-nitrophenyl)-1*H*-pyrazole-4-carbonitrile in 5.78 mL (153.2 mmol) formic acid were stirred 0.5 h under reflux. The reaction mixture was allowed to reach rt and concentrated to give 7.882 g (71%) product which was used in the next step without further purification.

20

LC-MS (analytical method 6): *R*_t = 0.83 min, MS (ESIpos): *m/z* = 258 (*M*+*H*)⁺.

25

Step 3:

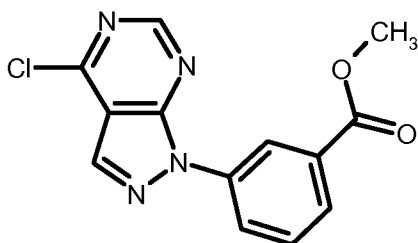
6.6 g (25.66 mmol) 1-(4-nitrophenyl)-1,3a,5,7a-tetrahydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one in 11.96 mL of phosphoric trichloride were stirred over night at 130°C in a microwave tube. The reaction mixture was treated several times with

dichloromethane and concentrated on a rotavap to yield 9.879 g (>100%) crude product which was used in the next step without further purification.

LC-MS (analytical method 6): $R_t = 1.26$ min, MS (ESIpos): $m/z = 276$ ($M+H$)⁺.

5 Intermediate 23A

methyl 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate



Step 1:

- 3.17 g (25.96 mmol) (Ethoxymethylene)malononitrile and 5.26 g (25.96 mmol) methyl 3-hydrazinobenzoate hydrochloride were suspended in 42 mL ethanol. After addition of 10.85 mL (77.87 mmol) triethylamine (clear solution) the reaction mixture was heated for 5 hours at 80 °C. After cooling, the reaction mixture was poured on ice water (100 mL) and stirred for 45 minutes. The precipitate was filtered off and dried in vacuo yielding 6.84 g (> 100%) of methyl 3-(5-amino-4-cyano-1H-pyrazol-1-yl)benzoate which was used without further purification in the next step.
- UPLC-MS: $RT = 0.86$ min; $m/z = 243$ (ES⁺, $M+1$)

Step 2:

- 6.84 g (28.3 mmol) Methyl 3-(5-amino-4-cyano-1H-pyrazol-1-yl)benzoate and 19.2 mL formic acid were heated over night at 110 °C. After cooling the reaction mixture was diluted with ethanol and stirred for five minutes at room temperature. The precipitate was filtered off yielding 3.39 g of methyl 3-(4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate. The crude material which was only 50% pure was used without further purification in step 3.
- UPLC-MS: $RT = 0.98$ min; $m/z = 271$ (ES⁺, $M+1$)

Step 3:

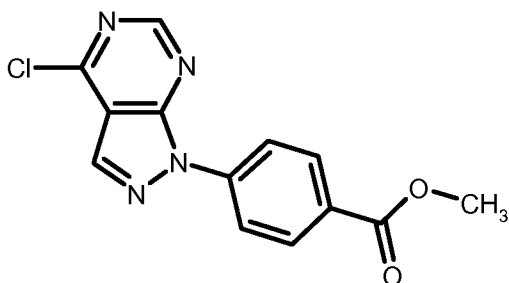
1.60 g (50% pure) Methyl 3-(4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate and 4.14 mL (44.40 mmol) phosphoric trichloride were heated for two

hours at 100 °C. After evaporation of the phosphoric trichloride the black oily residue was treated with methyl-tert. butylether. No precipitate formed. The methyl tert. butylether was evaporated and the residue (2.7 g; yield much larger than 100 %) was used without further purification.

- 5 UPLC-MS: RT = 1.23 min; m/z = 289/91 (ES+, M+1)

Intermediate 24A

methyl 4-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate



- 10 Step 1:

3.69 g (30.2 mmol) (Ethoxymethylene)malononitrile and 6.12 g (30.2 mmol) methyl 4-hydrazinobenzoate hydrochloride were suspended in 49 mL ethanol. After addition of 12.63 mL (90.6 mmol) triethylamine the reaction mixture was heated for 2 hours at 80 °C. After cooling, the reaction mixture was poured on ice water and stirred for 30 minutes. The precipitate was filtered off and dried in vacuo yielding 6.61 g (85.8%) of methyl 4-(5-amino-4-cyano-1H-pyrazol-1-yl)benzoate.
UPLC-MS: RT = 0.90 min; m/z = 243 (ES+, M+1)

Step 2:

- 20 6.61 g (27.3 mmol) Methyl 4-(5-amino-4-cyano-1H-pyrazol-1-yl)benzoate and 18.5 mL formic acid were heated four hours at 110 °C. After cooling the reaction mixture was diluted with ethanol and stirred for five minutes at room temperature. The precipitate was filtered off, washed with ethanol yielding 3.26 g (42%) of pure methyl 4-(4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate.
25 UPLC-MS: RT = 0.85 min; m/z = 271 (ES+, M+1)

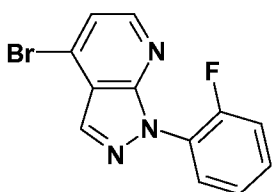
Step 3:

2.20 g (8.14 mmol) Methyl 4-(4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate and 10.3 mL (110.5 mmol) phosphoric trichloride were heated for 24 hours at 100 °C. After evaporation of the phosphoric trichloride the residue was suspended in methyl-tert. butylether. The precipitate was filtered off yielding 2.19 g (93.2 %) of the title compound.

UPLC-MS: RT = 1.27 min; m/z = 289/ 91 (ES+, M+1)

Intermediate 25A

4-bromo-1-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine

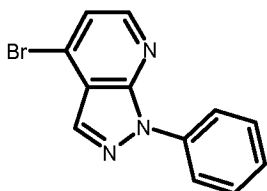


3.70 g (18.14 mmol) 4-Bromo-2-fluoronicotinaldehyde and 2.29 g (18.14 mmol) (2-fluorophenyl)hydrazine were dissolved in 82.6 mL 2-methylpropanenitrile. After addition of 17.74 g (54.44 mmol) cesium carbonate the reaction mixture was stirred for 4 hours at room temperature to allow complete reaction to the intermediate hydrazone (safety reasons). Stirring was now continued over night at 120 °C. Due to an incomplete reaction stirring was continued for 65 hours at 120 °C. The reaction mixture was diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed with brine and dried (sodium carbonate). After evaporation of the solvent the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 1.80 g (33.3%) of the title compound.

UPLC-MS: RT = 1.23 min; m/z = 292/ 4 (ES+, M+1)

Intermediate 26A

4-bromo-1-phenyl-1H-pyrazolo[3,4-b]pyridine

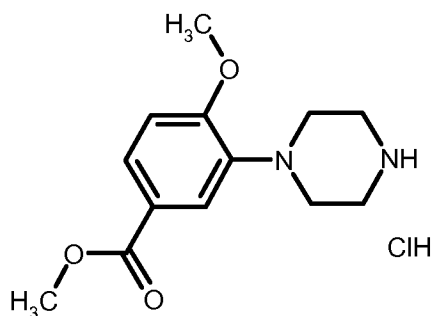


3.70 g (18.14 mmol) 4-Bromo-2-fluoronicotinaldehyde and 1.96 g (18.14 mmol) phenylhydrazine were dissolved in 82.6 mL 2-methylpropanenitrile. After addition of 17.74 g (54.44 mmol) cesium carbonate the reaction mixture was stirred for 4 hours at room temperature to allow complete reaction to the intermediate hydrazone (safety reasons). Stirring was now continued over night at 120 °C. Due to an incomplete reaction stirring was continued for 65 hours at 120 °C. The reaction mixture was diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed with brine and dried (sodium carbonate). After evaporation of the solvent the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 0.55 g (8.9%) of the title compound.

UPLC-MS: RT = 1.39 min; m/z = 274/ 6 (ES+, M+1)

Intermediate 1B

methyl 4-methoxy-3-(piperazin-1-yl)benzoate hydrochloride salt



Step 1:

To a solution of 17.2 g (90.0 mmol) of mono-Boc-piperazine and 20.0 g (81.6 mmol) methyl 3-bromo-4-methoxybenzoate in a mixture of 225 mL toluene and 225 mL tert.-butanol 1.83 g (8.16 mmol) palladium(II)acetate and 3.89 g (8.16 mmol) Xphos were added and the reaction mixture was heated to reflux under an N₂-atmosphere for 4 days at 90 °C. After cooling to rt the mixture was diluted with 100 mL of water and 250 mL of ethyl acetate. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The residue was purified with a Biotage Chromatography system (340 g snap column, hexane / 0 - 100% ethyl acetate and yielded tert-butyl 4-[2-methoxy-5-(methoxycarbonyl)phenyl]piperazine-1-carboxylate

: 18.0 g (60% yield).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.38 (s, 9H), 2.83 - 2.92 (m, 4H), 3.37 - 3.47 (m, 4H), 3.76 (s, 3H), 3.83 (s, 3H), 7.03 (d, 1H), 7.39 (d, 1H), 7.61 (dd, 1H).

5

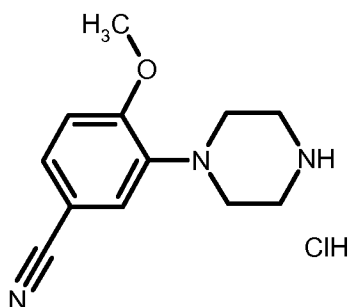
Step 2:

A solution of 10.0 g (28.5 mmol) of tert-butyl 4-[2-methoxy-5-(methoxycarbonyl)phenyl]piperazine-1-carboxylate prepared in step 1) in 91 mL 4M HCl-solution in dioxane was stirred for 1 hour at rt. Concentration in vacuo gave 9.3 g of desired compound as a raw product which was used without any further purification.

10

Intermediate 2B

15 **4-methoxy-3-(piperazin-1-yl)benzonitrile hydrochloride salt**



Step 1:

In analogy to intermediate 1B) step1) 996 mg (5.19 mmol) of mono-Boc-piperazine and 1.0 g (4.72 mmol) 3-bromo-4-methoxybenzonitrile gave tert-butyl 4-(5-cyano-2-methoxyphenyl)piperazine-1-carboxylate: 1.0 g (55% yield).

20

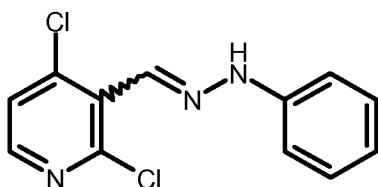
$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.38 (s, 9H), 2.86 - 2.93 (m, 4H), 3.37 - 3.43 (m, 4H), 3.83 (s, 3H), 7.07 (d, 1H), 7.21 (d, 1H), 7.44 (dd, 1H).

25

Step 2:

In analogy to intermediate 1B) step 2) 200 mg (0.63 mmol) of tert-butyl 4-(5-cyano-2-methoxyphenyl)piperazine-1-carboxylate of step 1) gave 161 mg of desired compound as a raw product which was used without any further purification.

5

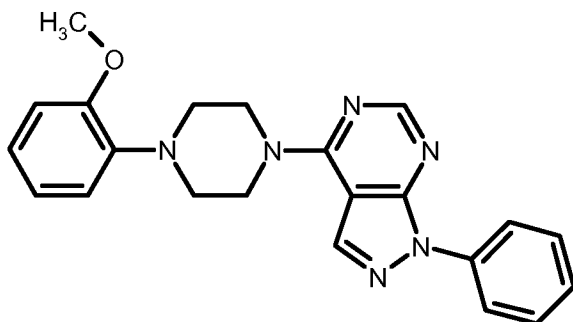
Intermediate 1C**2,4-dichloro-3-[(E/Z)-(phenylhydrazono)methyl]pyridine**

- 10 To a solution of 3.32 g (30.7 mmol) of phenylhydrazine in 25 mL dimethoxyethane was added a suspension of 2.7 g 2,4-dichloronicotinaldehyde in 15 mL dimethoxyethane and the resulting mixture was refluxed for 2 hours. After cooling to rt this mixture was concentrated in vacuo and purified via a Biotage Chromatography system (50 g snap column, hexane / 0 - 100% ethyl acetate then ethyl acetate / 0 -
- 15 50% methanol) This procedure gave the desired material: 4.7 g (90% yield).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 6.78 - 6.85 (m, 1H), 7.07 (dd, 2H), 7.24 (dd, 2H), 7.64 (d, 1H), 8.07 (s, 1H), 8.24 (d, 1H), 10.92 (s, 1H).

20

Examples**Example 1****4-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine**



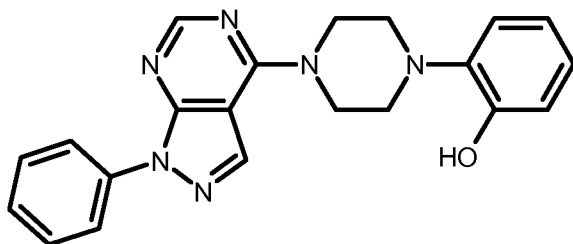
Intermediate **1A** (100 mg, 0.43 mmol) was dissolved in 2.5 mL DMF under an atmosphere of argon at room temperature. 194 μ L (1.30 mmol) DBU and 119 mg (0.52 mmol) 1-(2-methoxyphenyl)-piperazine hydrochloride were added and the mixture
 5 was stirred at 120 °C for 7 h. Two thirds of the solvent were removed by distillation in vacuo, the residue was charged onto a preparative HPLC device and the title compound was purified by chromatography (column: Kromasil C18 5 μ 100Å 20x250mm, solvent A: water with 0.05% TFA, solvent B: acetonitrile with 0.05% TFA; gradient: 0-8min 30% B; 8-18min. ramp to 60% B; 18-28min. ramp to 80% B, 28-40
 10 min. 80% B; flow: 12mL/min). The product was obtained as colourless solid (62 mg, 0.16 mmol, 37% of theory).

LC-MS (analytical method 2): R_t = 1.24 min, MS (ESIpos): m/z = 387 ($M+H$)⁺.

¹H-NMR (400 MHz, DMSO d_6) δ (ppm) = 3.11-3.18 (m, 4H), 3.84 (s, 3H), 4.10-4.16 (m, 4H), 6.89-7.03 (m, 4H), 7.37 (t, 1H), 7.56 (t, 2H), 8.17 (d, 2H), 8.42 (s, 1H), 8.65 (s,
 15 1H).

Example 2

2-[4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol



20 A solution of 4.70 g (20.37 mmol) 4-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (intermediate **1A**) in 22 mL DMF was placed in a sealable glass tube. 4.36 g 24.45 mmol 2-(piperazin-1-yl)phenol and 9.12 mL (61.12 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added and the glass tube was sealed with a teflon screw top. The reaction mixture was heated for 24 hours at 120°C and

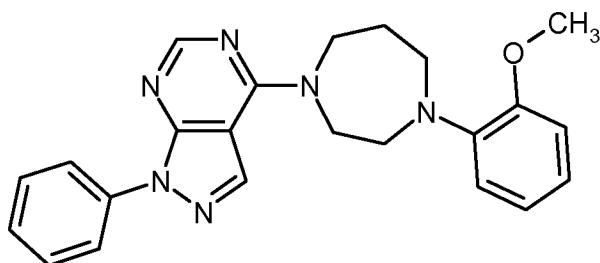
concentrated under reduced pressure. Chromatography over 340 g silica gel (hexane/ethyl acetate 7/3) gave 2.09 g (5.61 mmol, 28%) 2-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol.

LC-MS (analytical method 1): $R_t = 1.31$ min, MS (ESIpos): $m/z = 373$ ($M+H$)⁺.

- 5 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.98 - 3.20 (m, 4 H) 4.03 - 4.27 (m, 4 H) 6.69 - 6.98 (m, 4 H) 7.31 - 7.41 (m, 1 H) 7.56 (t, 2 H) 8.13 - 8.23 (m, 2 H) 8.41 (s, 1 H) 8.66 (s, 1 H) 9.14 (s, 1 H).

Example 3

- 10 4-[4-(2-Methoxyphenyl)-1,4-diazepan-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

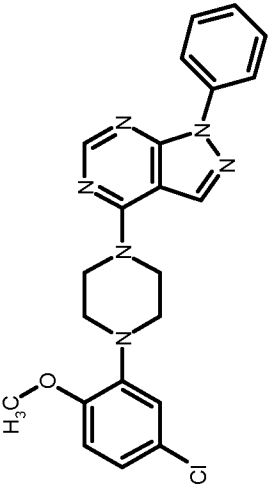
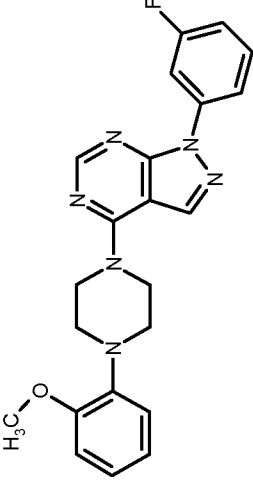


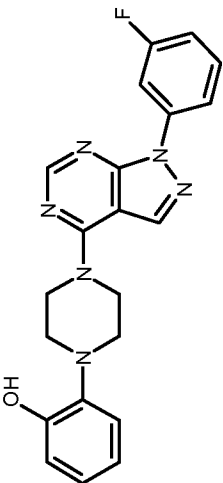
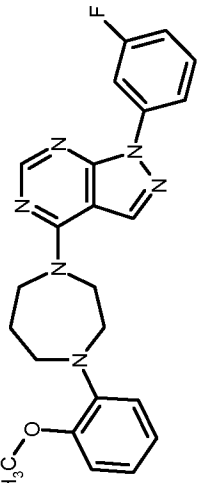
- 100 mg (0.43 mmol) 4-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine was dissolved in 2 mL DMF and given in a sealable glass tube. 107 mg (0.52 mmol) 1-(2-methoxyphenyl)-1,4-diazepane and 194 μ L (1.30 mmol) 1,8-diazabicyclo[5.4.0]undec-7-ene were added and the glass tube was sealed with a teflon screw top. The reaction mixture was heated for 3 hours at 120°C and concentrated under reduced pressure. Chromatography over 25 g silica gel (hexane/ethyl acetate 8/2) gave 102 mg (0.25 mmol, 59%) 4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine.

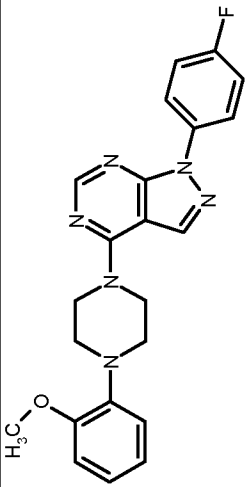
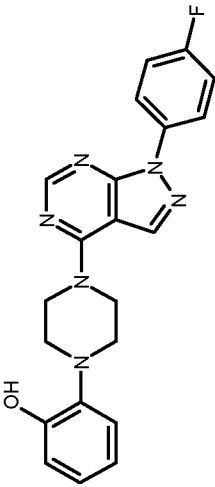
LC-MS (analytical method 1): $R_t = 1.35$ min, MS (ESIpos): $m/z = 401$ ($M+H$)⁺.

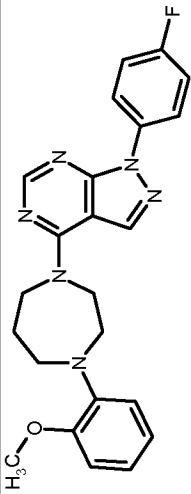
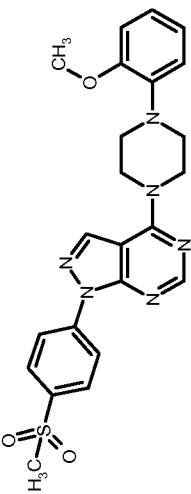
- ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 1.99 (s, 1 H) 2.15 (br. s., 1 H) 3.20 (br. s., 2 H) 3.31 (s, 3 H) 3.39 (br. s., 1 H) 3.50 (br. s., 1 H) 4.07 (br. s., 1 H) 4.13 (br. s., 2 H) 4.18 (br. s., 1 H) 6.74 - 6.95 (m, 4 H) 7.30 - 7.40 (m, 1 H) 7.52 - 7.60 (m, 2 H) 8.18 (d, 2 H) 8.37 (br. s., 1 H) 8.50 (s, 1 H).

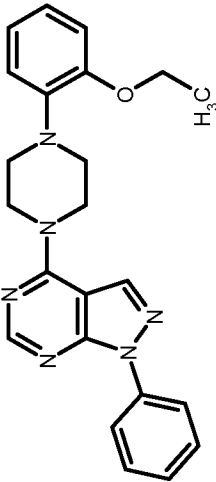
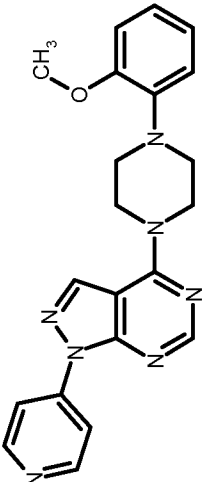
The following examples were prepared in analogy to examples 2 and 3 by reacting intermediates 1A, 2A, 3A, 4A, 5A and 6A, respectively with the appropriately substituted piperazine or diazepane derivatives. The reaction times were adapted.

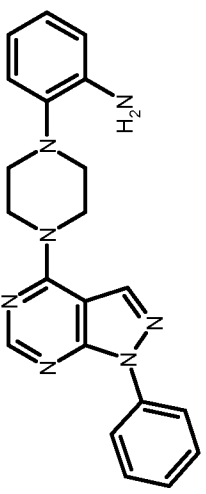
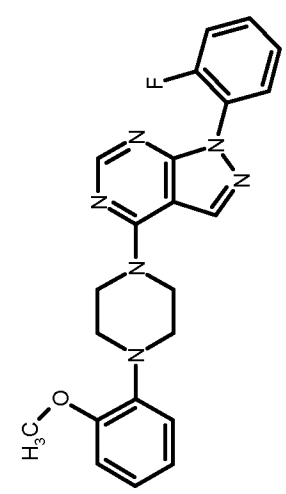
Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
4	 4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine	1A	(400 MHz, DMSO- <i>d</i> ₆) δ (ppm) = 3.16 - 3.19 (m, 4 H) 3.84 (s, 3 H) 4.10 - 4.16 (m, 4 H) 6.92 (d, 1 H) 6.97 - 7.08 (m, 2 H) 7.34 - 7.44 (m, 1 H) 7.56 (t, 2 H) 8.12 - 8.21 (m, 2 H) 8.42 (s, 1 H) 8.64 (s, 1 H)	(method 2): <i>R</i> _t = 1.26 min, MS (ESIpos): <i>m/z</i> = 421 (<i>M</i> +H) ⁺ .
5	 1-(3-Fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	3A	(300 MHz, DMSO <i>d</i> ₆) δ (ppm) = 3.02-3.20 (m, 4H), 3.81 (s, 3H), 4.01-4.18 (m, 4H), 6.80-7.03 (m, 4H), 7.10-7.22 (m, 1H), 7.50-7.63 (m, 1H), 8.03-8.18 (m, 2H), 8.42 (s, 1H), 8.67 (s, 1H).	(method 1): <i>R</i> _t = 1.47 min, MS (ESIpos): <i>m/z</i> = 405 (<i>M</i> +H) ⁺ .

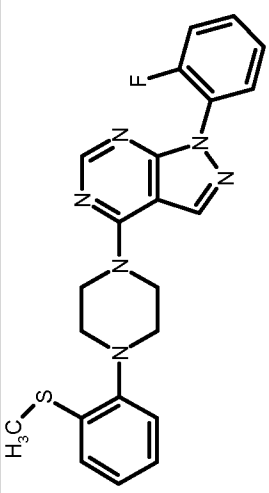
Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
	pyrazolo[3,4-d]pyrimidine			
6	 2-[4-(1-(3-Fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol	3A	(400 MHz, DMSO-d ₆): δ (ppm) = 3.01-3.16 (m, 4 H), 4.05-4.18 (m, 4H), 6.69 - 6.78 (m, 1H), 6.78-6.92 (m, 3H), 7.12-7.22 (m, 1H), 7.52-7.62 (m, 1H), 8.05-8.18 (m, 2 H), 8.41 (s, 1 H), 8.66 (s, 1 H), 9.10 (s, 1 H).	(method 1): R _t = 1.39 min, MS (ESIpos): m/z = 391 (M+H) ⁺ .
7	 1-(3-Fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	3A	(300 MHz, DMSO-d ₆): δ (ppm) = 1.83-2.20 (very br. m, 2H), 3.05-3.60 (very br. m, partly obscured by the signal of the water of the solvent, 4H), 3.72 (s, 3H), 3.98-4.25 (very br. m, 4H), 6.71 - 6.95 (m, 4H), 7.09-7.22 (m, 1H), 7.49-7.15 (m,	(method 1): R _t = 1.46 min, MS (ESIpos): m/z = 419 (M+H) ⁺ .

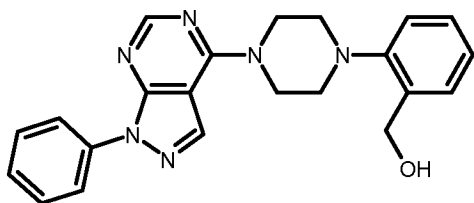
Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
8	 1-(4-Fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	2A	(400 MHz, DMSO- <i>d</i> ₆) δ (ppm) = 3.05-3.18 (m, 4H), 3.81 (s, 3H), 4.02-4.15 (m, 4H), 6.82-7.01 (m, 4H), 7.32- 7.42 (m, 2H), 8.12-8.22 (m, 2H), 8.39 (s, 1H), 8.62 (s, 1H).	(method 1): R _t = 1.43 min, MS (ESIpos): m/z = 405 (M+H) ⁺ .
9	 2-[4-(1-(4-Fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol	2A	(400 MHz, DMSO- <i>d</i> ₆): δ (ppm) = 3.01-3.16 (m, 4 H), 4.05-4.18 (m, 4H), 6.69 - 6.78 (m, 1H), 6.78-6.92 (m, 3H), 7.32-7.42 (m, 2H), 8.12- 8.22 (m, 2 H), 8.39 (s, 1 H), 8.62 (s, 1 H), 9.09 (s, 1 H).	(method 1): R _t = 1.33 min, MS (ESIpos): m/z = 391 (M+H) ⁺ .

Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
10	 1-(4-Fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	2A	(300 MHz, DMSO- <i>d</i> ₆): δ (ppm) = 1.88-2.19 (very br., 2H), 3.07-3.55 (very br., partly obscured by the signal of the water of the solvent, 4H), 3.71 (s, 3H), 3.95-4.23 (very br., 4H), 6.70- 6.95 (m, 4H), 7.30- 7.45 (m, 2H), 8.10-8.23 (m, 2H), 8.32 (s, 1H), 8.49 (s, 1H).	(method 1): R_t = 1.20 min, MS (ESIpos): m/z = 419 (M+H) ⁺ .
11	 4-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-[4-(methylsulfonyl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine	5A	(300 MHz, dichloromethane- <i>d</i> ₂): δ (ppm) = 3.08 (s, 3 H) 3.19 - 3.29 (m, 4 H) 3.89 (s, 3 H) 4.12 - 4.25 (m, 4 H) 6.88 - 6.98 (m, 3 H) 6.98 - 7.10 (m, 1 H) 8.05 (d, 2 H) 8.26 (s, 1 H) 8.47 (s, 1 H) 8.65 (d, 2 H).	(method 1): R_t = 1.24 min, MS (ESIpos): m/z = 465 (M+H) ⁺ .

Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
12	 4-[4-(2-Ethoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine	1A	(300 MHz, DMSO- <i>d</i> ₆) δ (ppm) 1.40 (t, 3 H) 3.11 - 3.21 (m, 4 H) 4.08 (q, 2 H) 4.09 - 4.18 (m, 4 H) 6.85 - 7.00 (m, 4 H) 7.32 - 7.41 (m, 1 H) 7.52 - 7.61 (m, 2 H) 8.18 (dd, 2 H) 8.42 (s, 1 H) 8.66 (s, 1 H)	(method 1): R _t = 1.49 min, MS (ESIpos): m/z = 401 (M+H) ⁺ .
13	 4-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-(pyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidine	6A	(300 MHz, DMSO- <i>d</i> ₆) δ (ppm) = 3.10 - 3.20 (m, 4 H) 3.84 (s, 3 H) 4.09 - 4.18 (m, 4 H) 6.86 - 6.97 (m, 2 H) 6.97 - 7.02 (m, 2 H) 8.33 - 8.40 (m, 2 H) 8.50 (s, 1 H) 8.67 - 8.74 (m, 2 H) 8.77 (s, 1 H) ppm	(method 1): R _t = 1.23 min, MS (ESIpos): m/z = 388 (M+H) ⁺ .

Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
14	 2-[4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]aniline	1A	(400 MHz, DMSO- <i>d</i> ₆) δ (ppm) = 2.52 (m, 4 H), 2.97 (m, 4 H) 4.90 (s br, 2 H) 6.55 (td, 1 H) 6.71 (dd, 1 H) 6.78 - 6.87 (m, 1 H) 6.88 - 6.94 (m, 1 H) 7.34 - 7.40 (m, 1 H) 7.54 - 7.59 (m, 2 H) 8.16 - 8.22 (m, 2 H) 8.41 (s, 1 H) 8.65 (s, 1 H)	(method 1): <i>R</i> _t = 1.28 min, MS (ESIpos): <i>m/z</i> = 372 (<i>M</i> + <i>H</i>) ⁺ .
15	 1-(2-Fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	4A	(400 MHz, DMSO <i>d</i> ₆) δ (ppm) = 3.08-3.20 (m, 4H), 3.83 (s, 3H), 4.06-4.20 (m, 4H), 6.86-7.06 (m, 4H), 7.38-7.47 (m, 1H), 7.47-7.55 (m, 1H), 7.55-7.69 (m, 2H), 8.31 (s, 1H), 8.68 (s, 1H).	(method 1): <i>R</i> _t = 1.38 min, MS (ESIpos): <i>m/z</i> = 405 (<i>M</i> + <i>H</i>) ⁺ .

Example	Structure/ Name	Synthesized from Intermediate	¹ H-NMR	LC-MS:
16	 1-(2-Fluorophenyl)- 4-{4-[2-(methylsulfanyl)phenyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine	4A	(400 MHz, DMSO <i>d</i> ₆) δ (ppm) = 2.43 (s, 3H), 3.00-3.18 (m, 4H), 4.03-4.22 (m, 4H), 7.08-7.25 (m, 4H), 7.39-7.48 (m, 1H), 7.48-7.55 (m, 1H), 7.55-7.70 (m, 2H), 8.31 (s, 1H), 8.69 (s, 1H).	(method 1): R_t = 1.66 min, MS (ESIpos): m/z = 421 (M+H) ⁺ .

Example 17**{2-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanol**

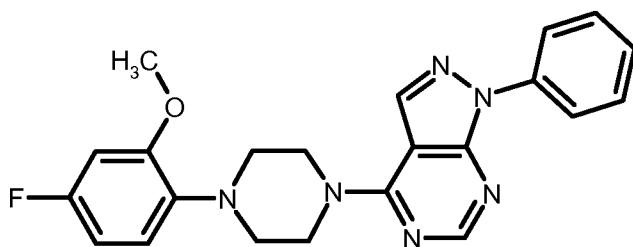
100 mg (0.26 mmol) 2-[4-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzaldehyde (intermediate 7A) was dissolved in 2 mL methanol and cooled to 0°C. 49 mg (1.30 mmol) Sodium borohydride was added and stirring was continued for 2 h at 25°C. The precipitated solid was filtered off, washed with cold methanol and dried *in vacuo* to obtain 30 mg (0.08 mmol, 30%) of the target compound.

LC-MS (analytical method 1): $R_t = 1.24$ min, MS (ESIpos): $m/z = 387$ ($M+H$)⁺.

10 ¹H-NMR (300 MHz, DMSO d_6) δ (ppm) = 2.99 - 3.08 (m, 4 H) 4.06 - 4.18 (m, 4 H) 4.65 (d, 2 H) 5.15 (t, 1 H) 7.05 - 7.15 (m, 2 H) 7.23 (d, 1 H) 7.38 (d, 1 H) 7.49 (d, 1 H) 7.57 (t, 2 H) 8.15 - 8.23 (m, 2 H) 8.42 (s, 1 H) 8.64 (s, 1 H).

Example 18

15 **4-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine**



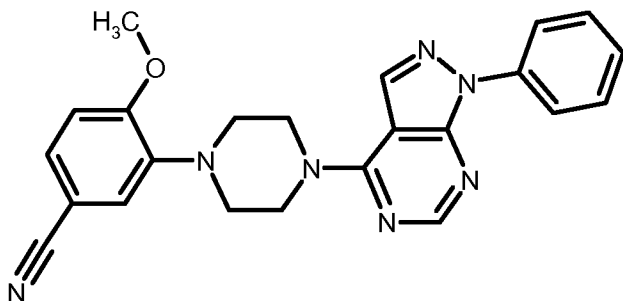
To a solution of 125 mg (0.54 mmol) of intermediate 1A) in 3 mL DMF 137 mg (0.65 mmol) 1-(4-fluoro-2-methoxyphenyl)piperazine and 0.24 mL (1.63 mmol) DBU were added and the reaction mixture was heated at 125°C for 2 hours. After cooling at rt the resulted solid was filtered off. The filtrate was concentrated in vacuo and stirred with methyl tert.-butylether. The remaning solid of this procedure together with the first part was stirred in ethyl acetate and the resulting solid was dried in vacuo and gave the desired material: 54mg (24% yield, 98% purity).

25

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.01 - 3.08 (m, 4H), 3.81 (s, 3H), 4.04 - 4.12 (m, 4H), 6.67 (td, 1H), 6.84 - 6.94 (m, 2H), 7.29 - 7.36 (m, 1H), 7.48 - 7.56 (m, 2H), 8.11 - 8.17 (m, 2H), 8.38 (s, 1H), 8.61 (s, 1H).

5 Example 19

4-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine



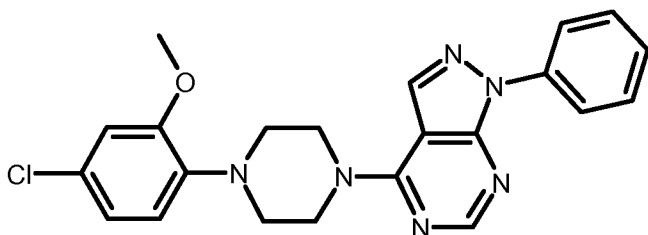
To a solution of 300 mg (1.07 mmol) of intermediate 8A) and 250 mg (1.18 mmol) 3-bromo-4-methoxybenzonitrile in a mixture of 6 mL toluene and 6 mL tert.-butanol
10 24.0 mg (0.11 mmol) Palladium(II)acetate and 51.0 mg (0.11 mmol) Xphos were added and the reaction mixture was heated to reflux under an N_2 -atmosphere for 7 hours and at 90°C for 16 hours. After cooling to rt the mixture was filtered and to the filtrate water and ethyl acetate were added. After separation of the phases the
15 water-phase was extracted again with ethyl acetate. The combined organic phases were washed with brine and dried with sodium sulfate. After filtration and evaporation in vacuo the resulting raw material was purified twice with a Biotage Chromatography system (10 g snap column, hexane plus 0 to 100% ethyl acetate, then ethyl acetate plus 0 to 100% methanol). The given material (94 mg) was stirred in
20 ether, then dried and gave the desired material: 50 mg (11% yield, 95% purity).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.16 (d, 4H), 3.89 (s, 3H), 4.06 - 4.13 (m, 4H), 7.13 (d, 1H), 7.28 (d, 1H), 7.30 - 7.36 (m, 1H), 7.45 - 7.57 (m, 3H), 8.11 - 8.17 (m, 2H), 8.39 (s, 1H), 8.62 (s, 1H).

25

Example 20

4-[4-(4-chloro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

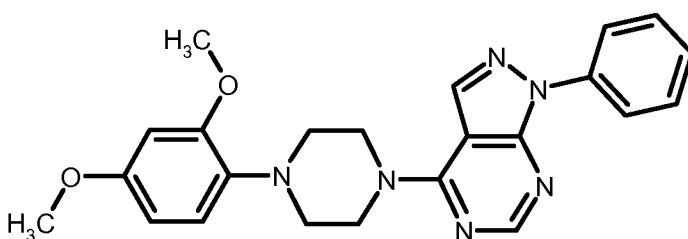


- 5 In analogy to example 19) 150 mg (0.54 mmol) of intermediate 8A) and 130 mg (0.59 mmol) 1-bromo-4-chloro-2-methoxybenzene gave after purification via HPLC the desired material: 36 mg (14% yield, 92% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.06 - 3.12 (m, 4H), 3.82 (s, 3H), 4.05 - 4.12 (m, 4H), 6.86 - 6.94 (m, 2H), 7.00 - 7.02 (m, 1H), 7.29 - 7.36 (m, 1H), 7.52 (t, 2H), 8.14 (d, 2H), 8.38 (s, 1H), 8.61 (s, 1H).

Example 21

15 4-[4-(2,4-dimethoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

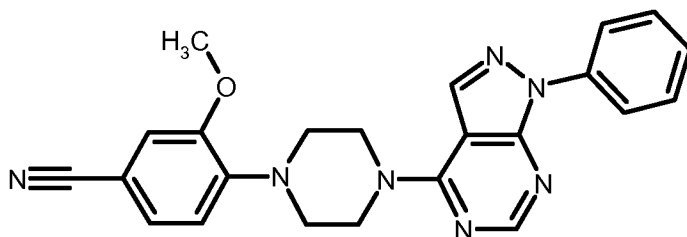


- In analogy to example 19) 150 mg (0.54 mmol) of intermediate 8A) and 128 mg (0.59 mmol) 1-bromo-2,4-dimethoxybenzene gave after purification via HPLC the desired material: 68 mg (30% yield, 97% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.96 - 3.06 (m, 4H), 3.68 (s, 3H), 3.78 (s, 3H), 4.03 - 4.11 (m, 4H), 6.42 (dd, 1H), 6.54 (d, 1H), 6.83 (d, 1H), 7.29 - 7.36 (m, 1H), 7.52 (t, 2H), 8.11 - 8.17 (m, 2H), 8.37 (s, 1H), 8.61 (s, 1H).

Example 22

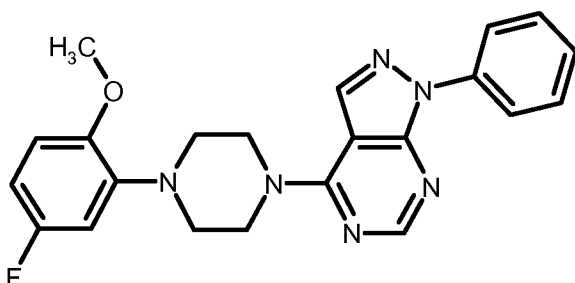
3-methoxy-4-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzonitrile



- 5 In analogy to example 19) 150 mg (0.54 mmol) of intermediate 8A) and 128 mg (0.59 mmol) 4-bromo-3-methoxybenzonitrile gave after twice purification via Biotage chromatography (25 g snap column hexane / 0 - 100% ethyl acetate) the desired material: 33 mg (7.5% yield, 95% purity).
- 10 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.23 - 3.29 (m, 4H), 3.86 (s, 3H), 4.07 - 4.13 (m, 4H), 7.00 (d, 1H), 7.29 - 7.39 (m, 4H), 7.52 (t, 3H), 8.11 - 8.17 (m, 2H), 8.38 (s, 1H), 8.61 (s, 1H).

Example 23

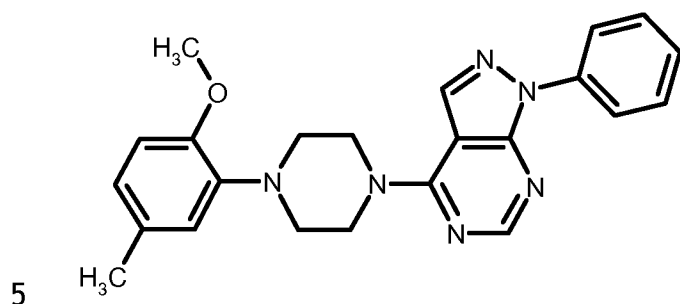
- 15 **4-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine**



- In analogy to example 19) 150 mg (0.54 mmol) of intermediate 8A) and 130 mg (0.59 mmol) 2-bromo-4-fluoro-1-methoxybenzene gave after purification via the desired material: 40 mg (18% yield, 95% purity).
- 20 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.10 - 3.16 (m, 4H), 3.79 (s, 3H), 4.06 - 4.13 (m, 4H), 6.71 - 6.79 (m, 2H), 6.94 (dd, 1H), 7.29 - 7.37 (m, 1H), 7.53 (t, 2H), 8.14 (d, 2H), 8.38 (s, 1H), 8.62 (s, 1H).

Example 24

4-[4-(2-methoxy-5-methylphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine



To a solution of 100 mg (0.43 mmol) of intermediate 1A) in 2.6 mL THF 126 mg (0.52 mmol) 1-(2-Methoxy-5-methylphenyl)piperazine hydrochloride salt and 0.18 mL (1.3 mmol) triethylamine were added and the reaction mixture was stirred at rt for 2 hours. The mixture was concentrated in vacuo, the residue was purified via HPLC and gave the desired material: 27 mg (16% yield, 97% purity).

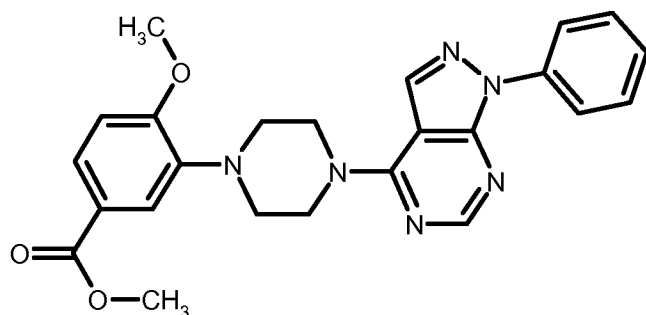
10

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.19 (s, 3H), 3.09 (br. s., 4H), 3.76 (s, 3H), 4.08 (br. s., 4H), 6.69 - 6.78 (m, 2H), 6.80 - 6.85 (m, 1H), 7.34 (d, 1H), 7.53 (t, 2H), 8.14 (d, 2H), 8.38 (s, 1H), 8.62 (s, 1H).

15

Example 25

methyl 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoate



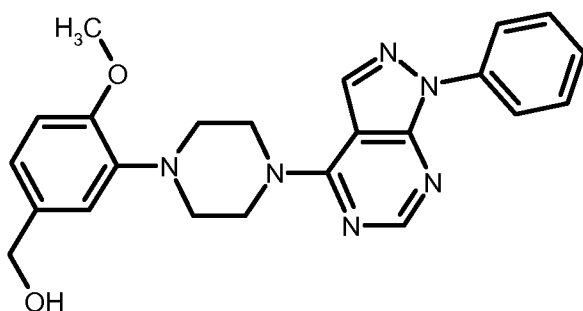
20 To a solution of 6.23 g (27.0 mmol) of intermediate 1A) in 300 mL THF 9.30 g (32.4 mmol) of intermediate 1B) and 11.3 mL (81.1 mmol) triethylamine were added and the reaction mixture was heated at 60°C for 1 hour. After cooling to rt the reaction

mixture was diluted with 500 mL ethyl acetate and a formed solid was obtained via filtration. This solid was the desired material and was used without any further purification: 9.0 g (67% yield, 90% purity).

- 5 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.11 - 3.18 (m, 4H), 3.77 (s, 3H), 3.89 (s, 3H), 4.07 - 4.14 (m, 4H), 7.09 (d, 1H), 7.29 - 7.37 (m, 1H), 7.45 (d, 1H), 7.53 (t, 2H), 7.64 (dd, 1H), 8.15 (d, 2H), 8.39 (s, 1H), 8.62 (s, 1H).

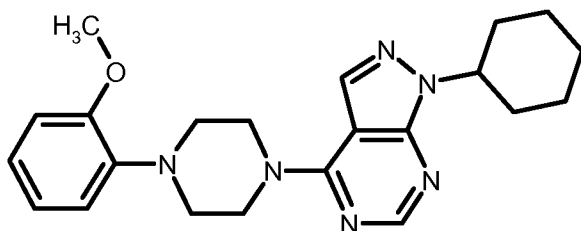
Example 26

- 10 {4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanol



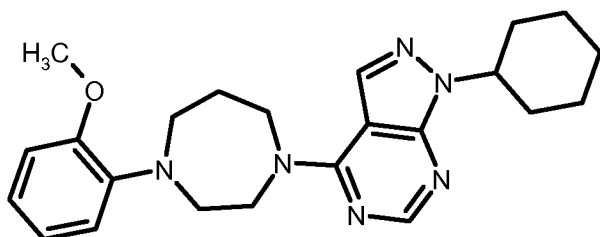
- To a suspension of 15.4 mg (0.41 mmol) lithium aluminiumhydride in 5 mL THF was added carefully a suspension of 150 mg (0.34 mmol) of the ester prepared in example 25) in 5 mL THF at 0°. The reaction mixture was stirred at rt for 30 minutes and then at 45°C. After cooling to rt 30 mL of water was carefully added to the reaction mixture. After the addition of 50 mL ethyl acetate the layers were separated and the organic phase was extracted twice with water. Then the organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified first with a Biotage Chromatography system (25 g snap column, hexane / 0 - 100% ethyl acetate) and finally via HPLC. Using this methodology the desired material was obtained: 22 mg (15% yield, 97% purity).

- ¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.09 - 3.14 (m, 4H), 3.79 (s, 3H), 4.07 - 4.13 (m, 4H), 4.37 (d, 2H), 4.98 (t, 1H), 6.86 - 6.92 (m, 3H), 7.30 - 7.36 (m, 1H), 7.53 (t, 2H), 8.15 (d, 2H), 8.38 (s, 1H), 8.62 (s, 1H).

Example 27**1-cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine**

- 5 To a solution of 250 mg (1.06 mmol) of 4-chloro-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Tetrahedron Letters, 2007, vol. 48, p. 3057 - 3059 or US3682918) in 3.13 mL THF 203 mg (1.06 mmol) 1-(2-methoxyphenyl)piperazine and 0.29 mL (2.12 mmol) triethylamine were added and the reaction mixture was stirred at rt for 20 hours. The reaction mixture was concentrated in vacuo. The residue was purified via a Biotage chromatography system (10 g snap column, hexane / 20 - 70% ethyl acetate) and gave the desired material: 320 mg (75% yield, 97% purity).

- ¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 1.22 (d, 1H), 1.35 - 1.49 (m, 2H), 1.67 (d, 1H), 1.77 - 1.93 (m, 6H), 3.03 - 3.10 (m, 4H), 3.79 (s, 3H), 4.00 - 4.07 (m, 4H), 4.57 - 4.68 (m, 1H), 6.81 - 6.92 (m, 2H), 6.93 - 6.99 (m, 2H), 8.24 (s, 1H), 8.29 (s, 1H).

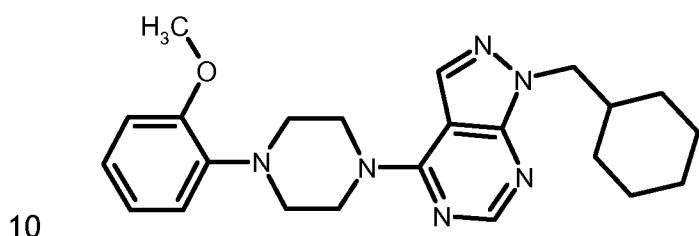
Example 28**1-cyclohexyl-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine**

- In analogy to example 27) 120 mg (0.51 mmol) of 4-chloro-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Tetrahedron Letters, 2007, vol. 48, p. 3057 - 3059 or US3682918) and 105 mg (0.51 mmol) 1-(2-Methoxyphenyl)-[1,4]diazepane gave the desired material: 64 mg (30% yield, 95% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 1.35 - 1.47 (m, 2H), 1.66 (d, 1H), 1.70- 1.75 (m, 1H), 1.77 - 1.94 (m, 7H), 2.05 (br. s., 1H), 3.14 (br. s., 2H), 3.41 (br. s., 2H), 3.70 (s, 3H), 3.93 - 4.14 (m, 4H), 4.55 - 4.65 (m, 1H), 6.72 - 6.89 (m, 4H), 8.14 (s, 1H), 8.19 (s, 1H).

Example 29

1-(cyclohexylmethyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



In analogy to example 27) 260 mg (1.04 mmol) of 4-chloro-1-(cyclohexylmethyl)-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Tetrahedron Letters, 2007, vol. 48, p. 3057 - 3059) and 199 mg (1.04 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 267 mg (61% yield, 97% purity).

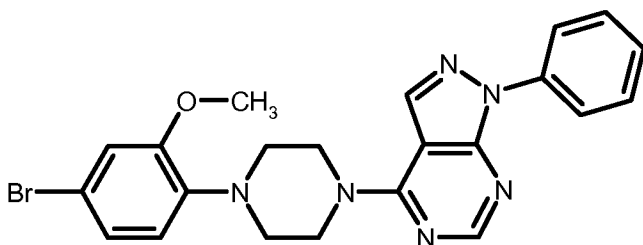
15

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 0.87 - 1.01 (m, 2H), 1.04 - 1.17 (m, 3H), 1.44 (d, 2H), 1.50 - 1.65 (m, 3H), 1.81 - 1.94 (m, 1H), 3.04 - 3.11 (m, 4H), 3.79 (s, 3H), 4.01 - 4.07 (m, 4H), 4.13 (d, 2H), 6.83 - 6.92 (m, 2H), 6.93 - 7.00 (m, 2H), 8.24 (s, 1H), 8.30 (s, 1H).

20

Example 30

4-[4-(4-bromo-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

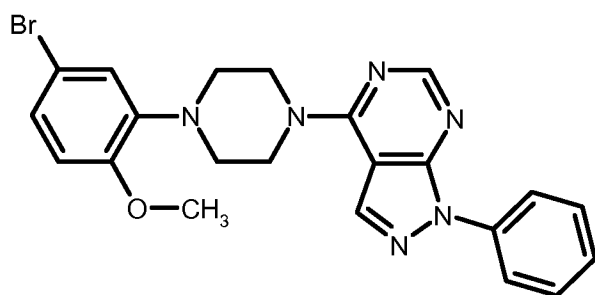


To a solution of 213 mg (0.92 mmol) of intermediate 1A) in 5.5 mL THF 300 mg (1.11 mmol) of commercially available 1-(4-bromo-2-methoxyphenyl)piperazine and 0.26 mL (1.84 mmol) triethylamine were added and the reaction mixture was stirred at 60°C for 20 hours. The reaction mixture was concentrated in vacuo. This residue was combined with the one of a second experiment using 3.18 g (13.8 mmol) of intermediate 1A) and 5.60 g (20.7 mmol) of 1-(4-bromo-2-methoxyphenyl)piperazine and purified via a Biotage chromatography system (100 g snap column, hexane / 20 - 100% ethyl acetate) and gave a raw product which was recrystallized twice (hexane / ethylacetate) yielding the desired material: 1.55 g (22% yield, 90% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.05 - 3.12 (m, 4H), 3.82 (s, 3H), 4.05 - 4.12 (m, 4H), 6.84 (d, 1H), 7.04 (dd, 1H), 7.11 (d, 1H), 7.30 - 7.37 (m, 1H), 7.52 (t, 2H), 8.13 (s, 1H), 8.15 (s, 1H), 8.38 (s, 1H), 8.61 (s, 1H).

Example 31

4-[4-(5-bromo-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

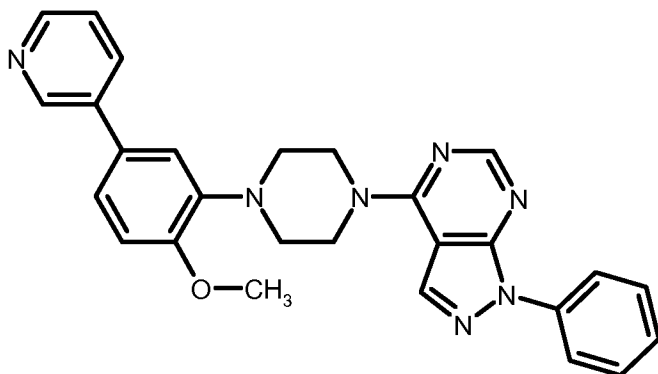


To a solution of 1.56 g (6.76 mmol) of intermediate 1A) in 35 mL THF 2.20 g (8.11 mmol) of commercially available 1-(5-bromo-2-methoxyphenyl)piperazine and 1.89 mL (13.5 mmol) triethylamine were added and the reaction mixture was stirred at 60°C for 4 hours. The reaction mixture was diluted with 50 mL of ethyl acetate and 50 mL of water. The formed solid was obtained via filtration yielding the desired material without any further purification: 2.1 g (63% yield, 95% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.12 - 3.19 (m, 4H), 3.83 (s, 3H), 4.08 - 4.15 (m, 4H), 6.95 (d, 1H), 7.01 (d, 1H), 7.15 (dd, 1H), 7.32 - 7.39 (m, 1H), 7.55 (t, 2H), 8.16 (s, 1H), 8.19 (d, 1H), 8.41 (s, 1H), 8.64 (s, 1H).

Example 32

4-{4-[2-methoxy-5-(pyridin-3-yl)phenyl]piperazin-1-yl}-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine



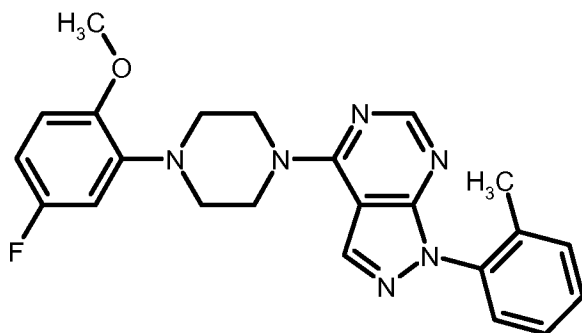
5

A mixture of 80 mg (0.17 mmol) of the compound prepared in example 31), 42 mg (0.34 mmol) 3-pyridylboronic acid, 126 mg (0.17 mmol) [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), 54.7 mg (0.52 mmol) sodium carbonate in a 0.23 mL water and 1.75 mL dioxane was heated for 90 minutes at 105°C in a microwave reactor. After cooling the mixture was purified via a Biotage chromatography system and HPLC yielding the desired material: 31 mg (37% yield, 95% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.23 - 3.27 (m, 4H), 3.89 (s, 3H), 4.13 - 4.19 (m, 4H), 7.11 (d, 1H), 7.24 (d, 1H), 7.36 (td, 2H), 7.43 (dd, 1H), 7.52 - 7.58 (m, 2H), 8.02 (dt, 1H), 8.15 - 8.18 (m, 1H), 8.18 - 8.20 (m, 1H), 8.42 (s, 1H), 8.50 (dd, 1H), 8.65 (s, 1H), 8.86 (d, 1H).

Example 33

4-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

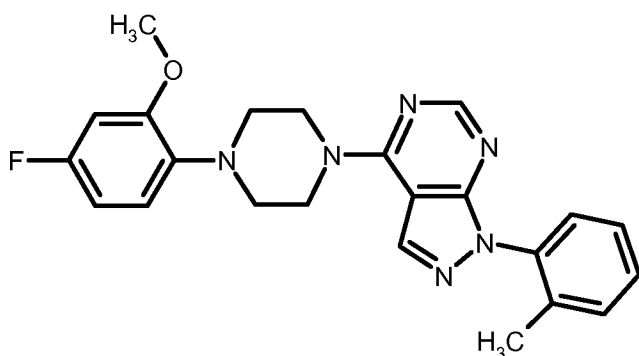


To a solution of 80 mg (0.33 mmol) of 4-chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Bioorganic & Medicinal Chemistry Letters, 2004, vol.14, p.2121 - 2126 or WO2005/47288) in 1.9 mL THF 66.7 mg (0.33 mmol) of 1-(5-fluoro-2-methoxyphenyl)piperazine (commercially available) and 0.14 mL (0.98 mmol) triethylamine were added and the reaction mixture was heated at 60°C for 1 hour. After cooling to rt the reaction mixture was diluted with 25 mL ethyl acetate and 25 mL water. The layers were separated and the organic phase was extracted with water and brine. Then the organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified with a Biotage Chromatography system (10 g snap column, hexane / 0 - 100% ethyl acetate). Using this methodology the desired material was obtained: 109 mg (75% yield, 95% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.05 (s, 3H), 3.13 - 3.20 (m, 4H), 3.82 (s, 3H), 4.09 - 4.16 (m, 4H), 6.73 - 6.81 (m, 2H), 6.96 (dd, 1H), 7.31 - 7.40 (m, 2H), 7.42 - 7.45 (m, 2H), 8.26 (s, 1H), 8.59 (s, 1H).

Example 34

4-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

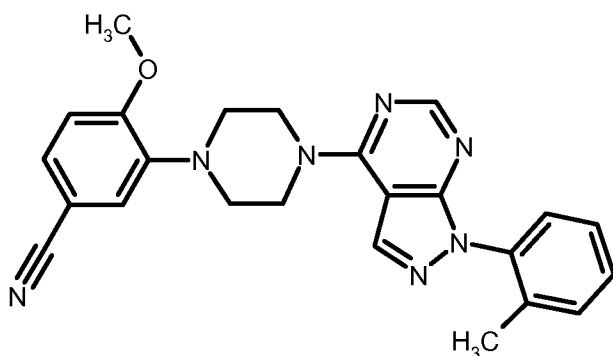


In analogy to example 19) 104 mg (0.35 mmol) of intermediate 9A) and 79 mg (0.39 mmol) 1-bromo-4-fluoro-2-methoxybenzene gave after purification via HPLC the desired material: 12 mg (7% yield, 90% purity).

- 5 ¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 2.18 (s, 3H), 3.19 - 3.27 (m, 4H), 3.94 (s, 3H), 4.22 - 4.29 (m, 4H), 6.63 - 6.74 (m, 2H), 6.92 (dd, 1H), 7.41 (br. s., 4H), 8.22 (s, 1H), 8.44 (s, 1H).

Example 35

- 10 4-methoxy-3-{4-[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}benzonitrile

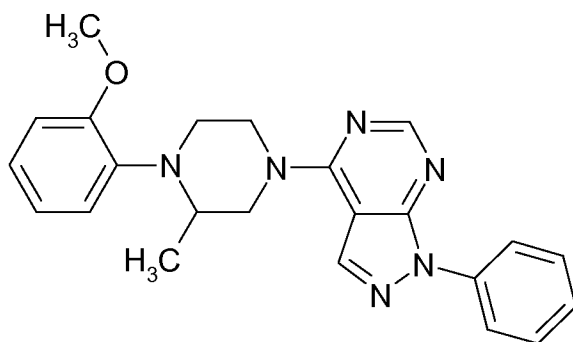


- In analogy to example 19) 104 mg (0.35 mmol) of intermediate 9A) and 82 mg (0.39 mmol) 3-bromo-4-methoxybenzonitrile gave after purification via a Biotage chromatography system (10g snap column, hexane / 50 - 100% ethyl acetate, then ethyl acetate / 0 - 100% methanol) the desired material: 23 mg (14% yield, 95% purity).
- 15

- ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.04 (s, 3H), 3.14 - 3.23 (m, 4H), 3.92 (s, 3H), 4.08 - 4.16 (m, 4H), 7.16 (d, 1H), 7.29 - 7.41 (m, 3H), 7.41 - 7.46 (m, 2H), 7.51 (dd, 1H), 8.27 (s, 1H), 8.60 (s, 1H).
- 20

Example 36

- (+/-)-4-[4-(2-methoxyphenyl)-3-methylpiperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine
- 25

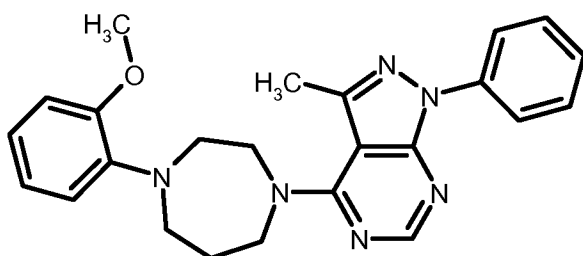


In analogy to example 19) 224 mg (0.76 mmol) of intermediate 10A) and 156 mg (0.84 mmol) 2-bromo-anisole gave after two purification via a Biotage chromatography system (25g snap column, hexane / 0 - 100% ethyl acetate, then ethyl acetate / 0 - 100% methanol) and a subsequent HPLC the desired material: 2.7 mg (0.8% yield, 95% purity).

¹H-NMR (500 MHz, CDCl₃) δ (ppm) = 1.01 (d, 3H), 3.03 - 3.11 (m, 1H), 3.39 - 3.46 (m, 1H), 3.77 - 3.86 (m, 2H), 3.89 (s, 3H), 4.15 - 4.24 (m, 2H), 4.31 - 4.40 (m, 1H), 6.89 - 6.96 (m, 2H), 7.02 (dd, 1H), 7.10 (ddd, 1H), 7.31 - 7.37 (m, 1H), 7.50 - 7.56 (m, 2H), 8.13 (s, 1H), 8.15 (d, 1H), 8.16 (s, 1H), 8.47 (s, 1H).

Example 37

4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine

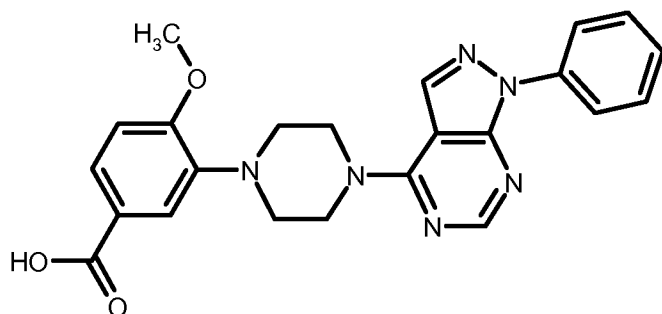


In analogy to example 33) 150 mg (0.61 mmol) of 4-chloro-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Chemical & Pharmaceutical Bulletin, 1998, vol.46, p.390 - 399 or Monatshefte fuer Chemie, 2008, vol.139, p.1405 - 1407) and 152 mg (0.74 mmol) 1-(2-methoxyphenyl)-1,4-diazepane gave the desired material: 125 mg (48% yield, 97% purity).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.99 - 2.09 (m, 2H), 2.65 (s, 3H), 3.16 (t, 2H), 3.37 - 3.44 (m, 2H), 3.69 (s, 3H), 3.95 - 4.05 (m, 4H), 6.70 - 6.89 (m, 5H), 7.24 - 7.33 (m, 1H), 7.44 - 7.53 (m, 2H), 8.09 (s, 1H), 8.12 (d, 1H), 8.28 (s, 1H).

5 **Example 38**

4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoic acid



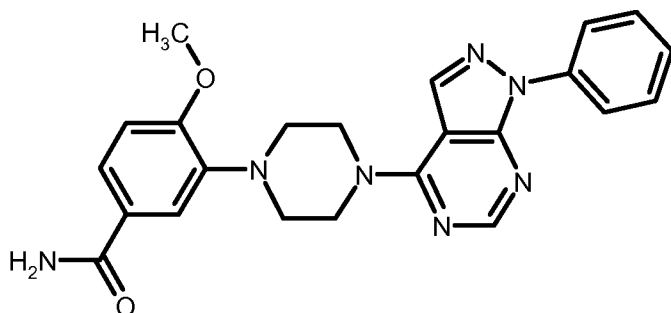
A mixture of 9.0 g (20 mmol) of example 25) in 150 mL THF, 45 mL methanol and a solution of 15 g sodium hydroxide in 300 mL water was heated for 20 hours at 45°C. Then the methanol was distilled off and the residue was diluted with water and acidified with 10% sulfuric acid up to pH = 2. The formed solid was filtered off and dried in vacuo. This procedure gave the desired material: 7.93 g (82% yield, 90% purity).

15

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.10 - 3.18 (m, 4H), 3.86 (s, 3H), 4.05 - 4.15 (m, 4H), 7.00 (d, 1H), 7.29 - 7.36 (m, 1H), 7.45 - 7.48 (m, 1H), 7.49 - 7.56 (m, 2H), 7.59 (dd, 1H), 8.13 - 8.15 (m, 1H), 8.16 (d, 1H), 8.37 - 8.40 (m, 1H), 8.61 (s, 1H).

20 **Example 39**

4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide



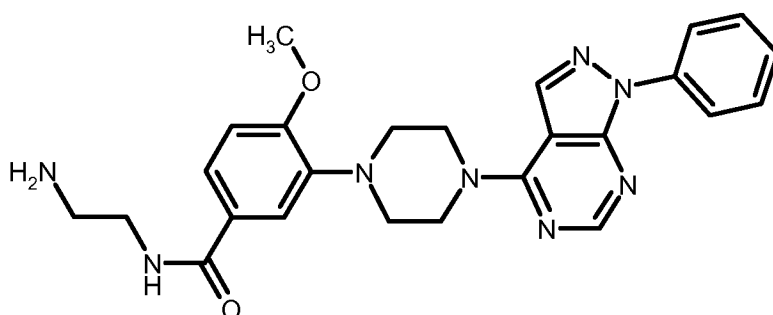
- To a solution of 150 mg (0.35 mmol) of example 38), 146 mg (0.38 mmol) HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), 121 μ l (0.70 mmol) diisopropylethylamine in 2.25 mL DMSO was added 0.70 mL 0.5M ammonia in dioxin. The mixture was stirred for 2 hours at rt and then diluted with ethyl acetate. The organic phase was washed with aq. sodium hydrogencarbonate, water and brine. Filtration (water repellent paper) and concentration gave a raw material which was purified via a Biotage chromatography system (10 g snap column, hexane / 0 - 100% ethyl acetate then ethyl acetate / 0 - 100% methanol) and HPLC.
- 10 This procedure gave the desired material: 60 mg (39% yield, 97% purity).

$^1\text{H-NMR}$ (300 MHz, DMSO d_6) δ (ppm) = 3.10 - 3.18 (m, 4H), 3.85 (s, 3H), 4.07 - 4.14 (m, 4H), 7.00 (d, 1H), 7.13 (br. s., 1H), 7.29 - 7.36 (m, 1H), 7.44 (d, 1H), 7.49 - 7.58 (m, 3H), 7.81 (br. s., 1H), 8.13 (s, 1H), 8.16 (d, 1H), 8.39 (s, 1H), 8.63 (s, 1H).

15

Example 40

N-(2-aminoethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide

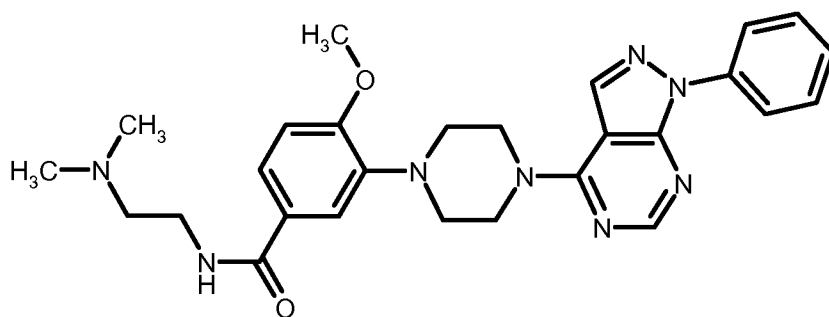


- 20 In analogy to example 39) 70 mg (0.16 mmol) of example 38) and 0.9 μ l (0.16 mmol) ethylene diamine gave after HPLC purification the desired material: 9.4 mg (11% yield, 90% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.62 - 2.67 (m, 2H), 3.12 - 3.17 (m, 4H), 3.18 - 3.26 (m, 4H), 3.86 (s, 3H), 4.08 - 4.14 (m, 4H), 7.01 (d, 1H), 7.31 - 7.37 (m, 1H), 7.41 (d, 1H), 7.50 - 7.56 (m, 3H), 8.14 (d, 1H), 8.15 - 8.17 (m, 1H), 8.24 (s, 1H), 8.39 (s, 1H), 8.63 (s, 1H).

Example 41

N-[2-(dimethylamino)ethyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide



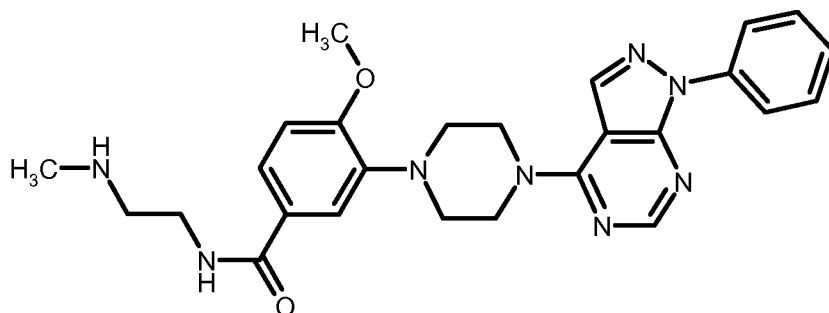
10

In analogy to example 39) 70 mg (0.16 mmol) of example 38) and 14.3 mg (0.16 mmol) N,N-dimethylethylenediamine gave after HPLC purification the desired material: 14 mg (17% yield, 97% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.13 (s, 6H), 2.34 (t, 2H), 3.11 - 3.17 (m, 4H), 3.30 (t, 2H), 3.86 (s, 3H), 4.08 - 4.15 (m, 4H), 7.02 (d, 1H), 7.31 - 7.36 (m, 1H), 7.40 (d, 1H), 7.49 - 7.56 (m, 3H), 8.14 (d, 1H), 8.16 (d, 1H), 8.19 (t, 1H), 8.39 (s, 1H), 8.63 (s, 1H).

Example 42

4-methoxy-N-[2-(methylamino)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide



In analogy to example 39) 100 mg (0.23 mmol) of example 38) and 17.2 mg (0.23 mmol) N-metylethylenediamine gave after HPLC purification the desired material: 2.4 mg (1.9% yield, 90% purity).

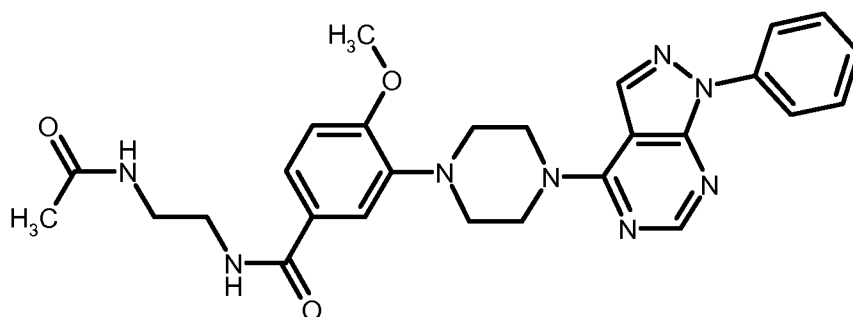
5

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 2.50 (s, 3H), 2.92 (t, 2H), 3.25 - 3.32 (m, 4H), 3.59 (q, 2H), 3.97 (s, 3H), 4.18 - 4.26 (m, 4H), 6.88 - 6.94 (m, 1H), 7.12 (br. s., 1H), 7.31 - 7.38 (m, 1H), 7.46 - 7.57 (m, 4H), 8.12 (s, 1H), 8.14 (s, 1H), 8.18 (s, 1H), 8.48 (s, 1H).

10

Example 43

N-[2-(acetamido)ethyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide

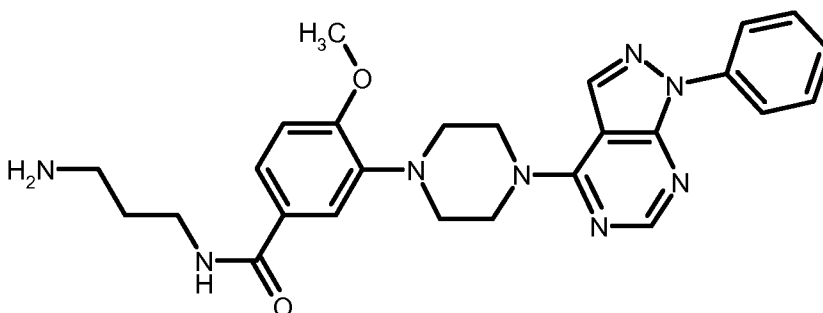


15 In analogy to example 39) 100 mg (0.23 mmol) of example 38) and 23.7 mg (0.23 mmol) N-acetythylenediamine gave after HPLC purification the desired material: 8.1 mg (6.4% yield, 95% purity).

20 ¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 2.00 (s, 3H), 3.26 - 3.34 (m, 4H), 3.46 - 3.63 (m, 4H), 3.97 (s, 3H), 4.17 - 4.26 (m, 4H), 6.17 (br. s., 1H), 6.93 (d, 1H), 7.16 (br. s., 1H), 7.30 - 7.38 (m, 1H), 7.45 - 7.57 (m, 4H), 8.12 (s, 1H), 8.15 (d, 1H), 8.18 (s, 1H), 8.49 (s, 1H).

Example 44

N-(3-aminopropyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide



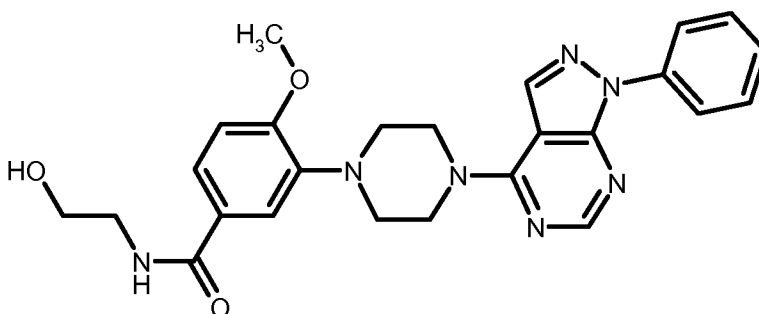
5

In analogy to example 39) 100 mg (0.23 mmol) of example 38) and 17.2 mg (0.23 mmol) propane-1,3-diamine gave after HPLC purification the desired material: 1.0 mg (0.8% yield, 85% purity).

- 10 ¹H-NMR (400 MHz, CDCl₃) δ (ppm) = 2.95 (t, 2H), 3.26 - 3.32 (m, 4H), 3.59 (q, 2H), 3.97 (s, 3H), 4.18 - 4.26 (m, 4H), 6.91 (d, 1H), 7.31 - 7.38 (m, 1H), 7.43 - 7.56 (m, 5H), 8.13 (s, 1H), 8.15 (s, 1H), 8.18 (s, 1H), 8.49 (s, 1H).

Example 45

- 15 **N-(2-hydroxyethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide**



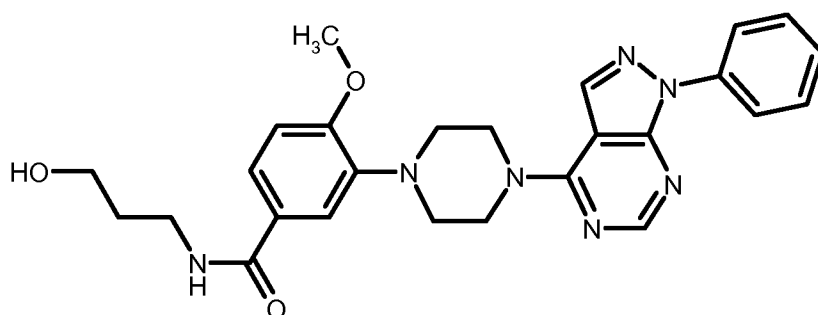
- 20 In analogy to example 39) 100 mg (0.23 mmol) of example 38) and 14.1 mg (0.23 mmol) 2-aminoethanol gave after HPLC purification the desired material: 7.5 mg (6.5% yield, 95% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.13 - 3.20 (m, 4H), 3.29 (q, 2H), 3.48 (q, 2H), 3.88 (s, 3H), 4.11 - 4.17 (m, 4H), 4.70 (t, 1H), 7.04 (d, 1H), 7.33 - 7.40 (m, 1H), 7.45 (d, 1H), 7.52 - 7.59 (m, 4H), 8.16 (s, 1H), 8.19 (d, 1H), 8.30 (t, 1H), 8.42 (s, 1H), 8.66 (s, 1H).

5

Example 46

N-(2-hydroxypropyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide

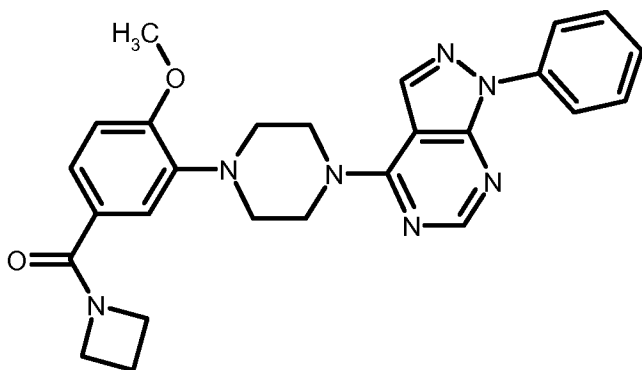


- 10 In analogy to example 39) 100 mg (0.23 mmol) of example 38) and 17.5 mg (0.23 mmol) 3-aminopropan-1-ol gave after HPLC purification the desired material: 9.0 mg (7.6% yield, 95% purity).

- 15 ¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 1.80 (tt, 2H), 3.08 (br. s., 1H), 3.25 - 3.33 (m, 4H), 3.63 (q, 2H), 3.72 (q, 2H), 3.97 (s, 3H), 4.16 - 4.27 (m, 4H), 6.51 (br. s., 1H), 6.92 (d, 1H), 7.31 - 7.38 (m, 1H), 7.39 - 7.58 (m, 4H), 8.13 (s, 1H), 8.15 (d, 1H), 8.17 (s, 1H), 8.49 (s, 1H).

Example 47

- 20 **azetidin-1-yl{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanone**



In analogy to example 39) 150 mg (0.35 mmol) of example 38) and 19.9 mg (0.35 mmol) azetidine gave after HPLC purification the desired material: 57 mg (31% yield, 90% purity).

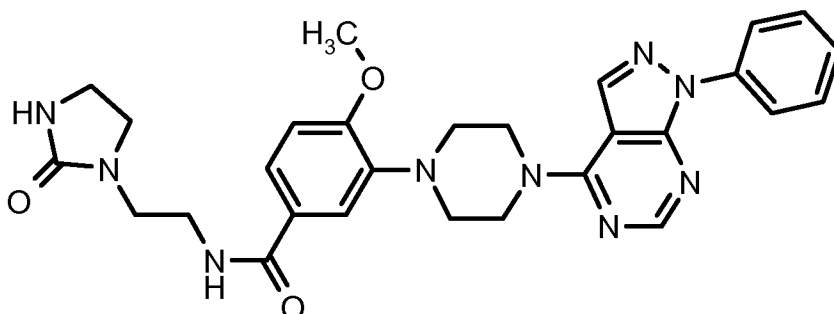
5

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.20 (quin, 2H), 3.08 - 3.17 (m, 4H), 3.85 (s, 3H), 3.98 (br. s., 2H), 4.05 - 4.16 (m, 5H), 4.28 (br. s., 2H), 7.00 (d, 1H), 7.08 - 7.24 (m, 2H), 7.26 (dd, 1H), 7.29 - 7.37 (m, 1H), 7.53 (t, 2H), 8.13 (s, 1H), 8.16 (d, 1H), 8.38 (s, 1H), 8.62 (s, 1H).

10

Example 48

4-methoxy-N-[2-(2-oxoimidazolidin-1-yl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide



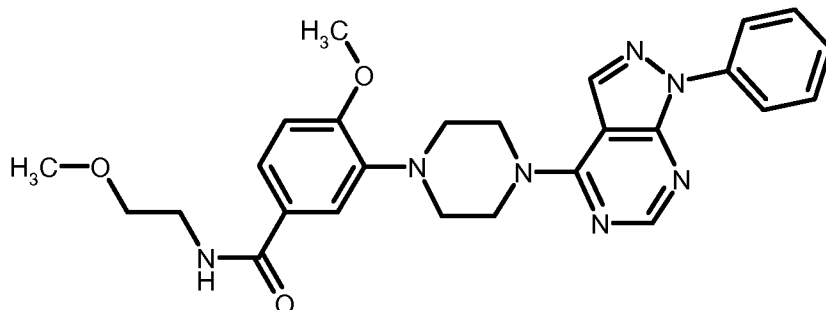
15 In analogy to example 39) 200 mg (0.47 mmol) of example 38) and 60.1 mg (0.47 mmol) 1-(2-aminoethyl)imidazolidin-2-one gave the desired material: 162 mg (62% yield, 97% purity).

20 ¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.14 - 3.23 (m, 8H), 3.30 - 3.42 (m, 4H), 3.88 (s, 3H), 4.10 - 4.17 (m, 4H), 6.26 (s, 1H), 7.04 (d, 1H), 7.33 - 7.39 (m, 1H), 7.42 (d,

1H), 7.49 - 7.59 (m, 3H), 8.16 (d, 1H), 8.19 (d, 1H), 8.35 (t, 1H), 8.42 (s, 1H), 8.65 (s, 1H).

Example 49

- 5 **4-methoxy-N-(2-methoxyethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide**

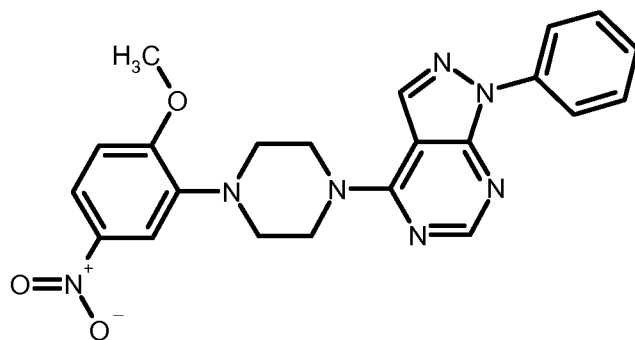


- In analogy to example 39) 100 mg (0.23 mmol) of example 38) and 17.5 mg (0.23 mmol) 2-methoxyethylamine gave after HPLC purification the desired material: 16 mg
10 (13% yield, 90% purity).

- ¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 3.26 - 3.33 (m, 4H), 3.39 (s, 3H), 3.56 (t, 2H), 3.65 (q, 2H), 3.97 (s, 3H), 4.18 - 4.26 (m, 4H), 6.41 (br. s., 1H), 6.91 (d, 1H), 7.30 - 7.38 (m, 1H), 7.43 (dd, 1H), 7.47 - 7.57 (m, 3H), 8.13 (s, 1H), 8.15 (d, 1H), 8.18 (s,
15 1H), 8.49 (s, 1H).

Example 50

- 4-[4-(2-methoxy-5-nitrophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine**



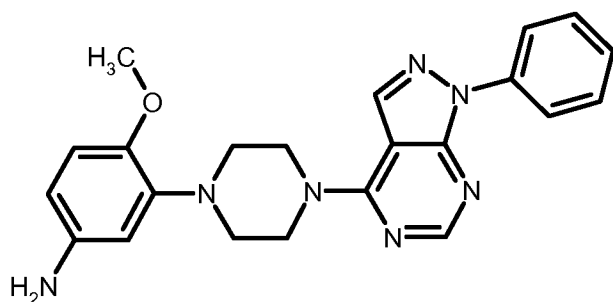
20

In analogy to example 31) 11.4 g (49.6 mmol) of intermediate 1A) and 16.3 g (59.5 mmol) 1-(2-methoxy-5-nitrophenyl)piperazine hydrochloride (commercially available) gave the desired material: 11.8 g (52% yield, 95% purity).

- 5 $^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.19 - 3.25 (m, 4H), 3.96 (s, 3H), 4.09 - 4.15 (m, 4H), 7.19 (d, 1H), 7.30 - 7.37 (m, 1H), 7.50 - 7.56 (m, 2H), 7.69 (d, 1H), 7.94 (dd, 1H), 8.14 (d, 1H), 8.15 - 8.18 (m, 1H), 8.40 (s, 1H), 8.62 (s, 1H).

Example 51

- 10 **4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]aniline**



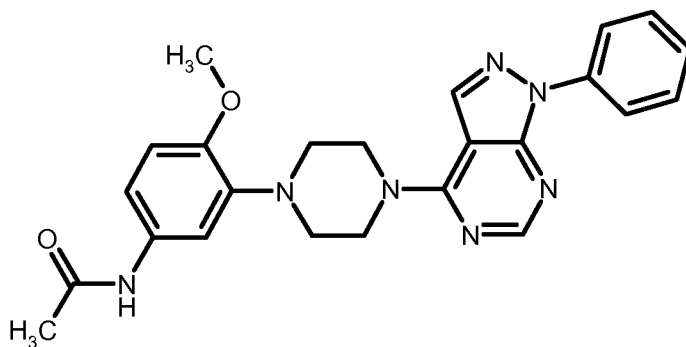
- To a mixture of 3.0 g (6.95 mmol) of example 50) in 86 mL ethanol and 4.3 mL water was added firstly 148 mg palladium on charcoal followed by 2.19 g (34.8 mmol) ammonium formate. This mixture was heated to reflux for 2 hours. After cooling to rt the catalyst is filtered off through a pad of celite and the filtrate is concentrated in vacuo. The residue was purified via a Biotage chromatography system (50g snap column, hexane / 0 - 100% ethyl acetate then ethyl acetate / 0 - 75 methanol). This procedure gave the desired material: 2.28 g (78% yield, 95% purity).

20

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.04 - 3.13 (m, 4H), 3.70 (s, 3H), 4.07 - 4.14 (m, 4H), 4.58 (br. s., 2H), 6.18 (dd, 1H), 6.24 (d, 1H), 6.67 (d, 1H), 7.36 (t, 1H), 7.55 (t, 2H), 8.16 (s, 1H), 8.18 (s, 1H), 8.40 (s, 1H), 8.64 (s, 1H).

25 Example 52

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide

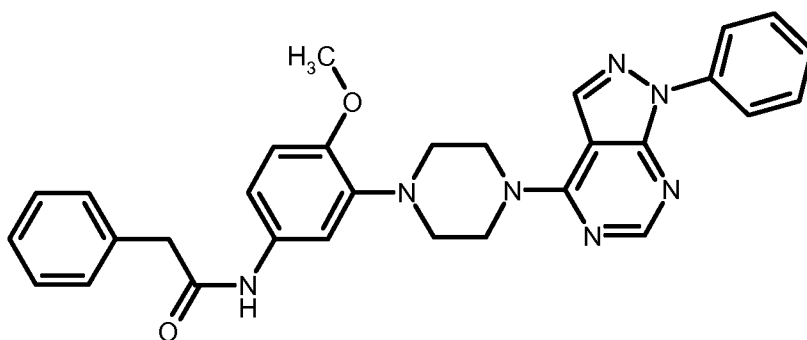


To a solution of 40 mg (0.1 mmol) of example 51) in 1.0 mL pyridine was added 11.3 μ l acetic anhydride and the mixture was stirred for 2 hours at rt. Then the mixture was diluted with 50 mL water and extracted twice with 50 mL ethyl acetate. The combined organic layers were extracted with saturated aq. sodium hydrogencarbonate, brine and dried over sodium sulfate. After a filtration the filtrate was concentrated in vacuo and the residue was purified via a Biotage chromatography system (10 g snap column, hexane / 0 - 100% ethyl acetate then ethyl acetate / 0 - 50% methanol). This procedure gave the desired material: 30 mg (66% yield, 97% purity).

$^1\text{H-NMR}$ (400 MHz, DMSO d_6) δ (ppm) = 1.96 (s, 3H), 3.05 - 3.12 (m, 4H), 3.77 (s, 3H), 4.06 - 4.14 (m, 4H), 6.87 (d, 1H), 7.15 - 7.21 (m, 2H), 7.30 - 7.36 (m, 1H), 7.49 - 7.56 (m, 2H), 8.14 (d, 1H), 8.15 - 8.18 (m, 1H), 8.38 (s, 1H), 8.63 (s, 1H), 9.70 (s, 1H).

Example 53

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}-2-phenylacetamide

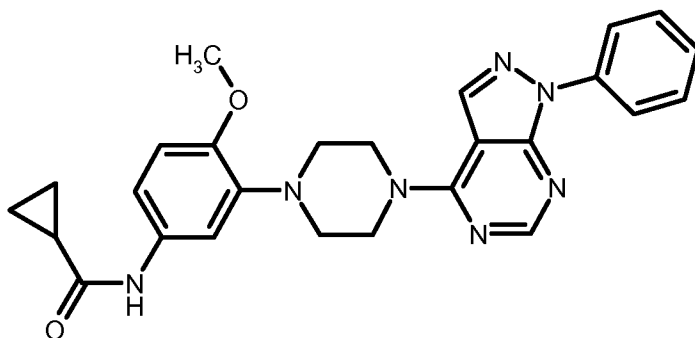


In analogy to example 37) 125 mg (0.31 mmol) of example 51) and 42.4 mg (0.31 mmol) phenyl acetic acid gave after HPLC purification the desired material: 67 mg (40% yield, 97% purity).

- 5 $^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.02 - 3.14 (m, 4H), 3.76 (s, 3H), 4.04 - 4.14 (m, 4H), 6.88 (d, 1H), 7.14 - 7.38 (m, 8H), 7.47 - 7.57 (m, 2H), 8.11 - 8.14 (m, 1H), 8.16 (d, 1H), 8.38 (s, 1H), 8.62 (s, 1H), 9.97 (s, 1H).

Example 54

- 10 **N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}cyclopropanecarboxamide**



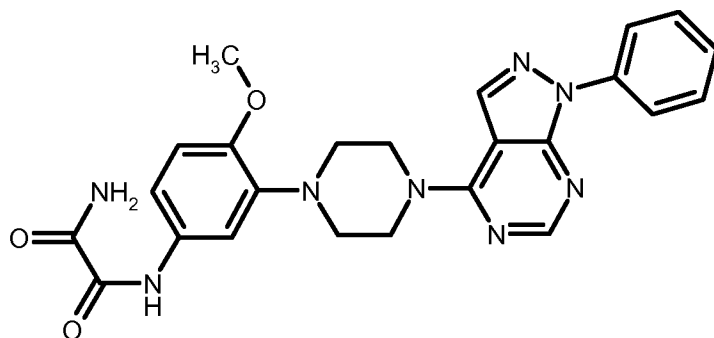
In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 21.4 mg (0.25 mmol) cyclopropyl carboxylic acid gave after HPLC purification the desired material:

- 15 62 mg (50% yield, 95% purity).

- $^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 0.66 - 0.77 (m, 4H), 1.64 - 1.73 (m, 1H), 3.06 - 3.13 (m, 4H), 3.77 (s, 3H), 4.06 - 4.13 (m, 4H), 6.87 (d, 1H), 7.16 (dd, 1H), 7.25 (d, 1H), 7.30 - 7.36 (m, 1H), 7.49 - 7.56 (m, 2H), 8.11 - 8.15 (m, 1H), 8.15 - 8.18 (m, 20 1H), 8.38 (s, 1H), 8.62 (s, 1H), 9.96 (s, 1H).

Example 55

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}ethanediamide



In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 22.2 mg (0.25 mmol) oxamic acid gave after HPLC purification the desired material: 20 mg (16% yield, 90% purity).

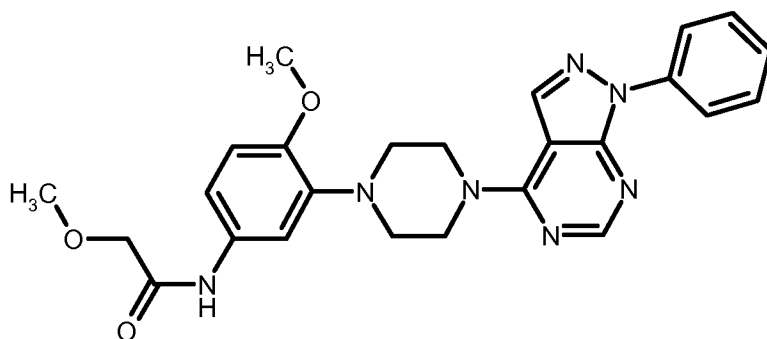
5

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.07 - 3.17 (m, 4H), 3.79 (s, 3H), 4.06 - 4.15 (m, 4H), 6.93 (d, 1H), 7.30 - 7.36 (m, 1H), 7.45 - 7.50 (m, 2H), 7.50 - 7.56 (m, 2H), 7.89 (s, 1H), 8.10 - 8.15 (m, 1H), 8.15 - 8.17 (m, 1H), 8.19 (s, 1H), 8.39 (s, 1H), 8.63 (s, 1H), 10.36 (s, 1H).

10

Example 56

2-methoxy-N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide

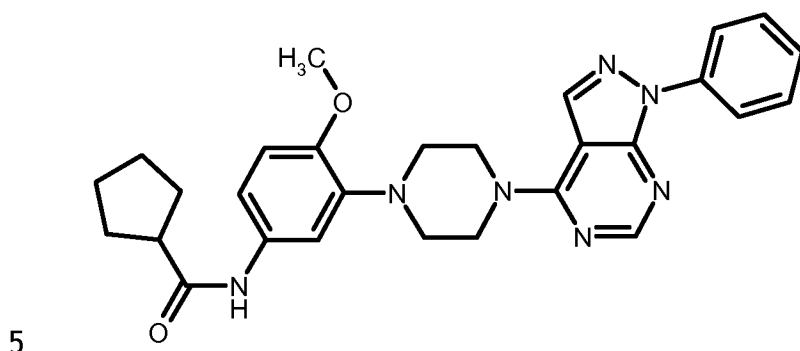


15 In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 22.4 mg (0.25 mmol) methoxyacetic acid gave after HPLC purification the desired material: 64 mg (52% yield, 95% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.06 - 3.14 (m, 4H), 3.33 (s, 3H), 3.78 (s, 3H),
20 3.92 (s, 2H), 4.06 - 4.14 (m, 4H), 6.89 (d, 1H), 7.25 - 7.37 (m, 3H), 7.48 - 7.56 (m, 2H), 8.11 - 8.15 (m, 1H), 8.15 - 8.18 (m, 1H), 8.39 (s, 1H), 8.63 (s, 1H), 9.49 (s, 1H).

Example 57

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}cyclopentanecarboxamide

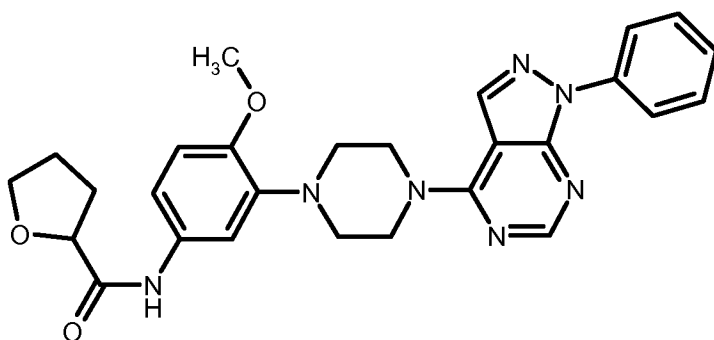


In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 28.4 mg (0.25 mmol) cyclopentanecarboxylic acid gave after HPLC purification the desired material: 56 mg (41% yield, 90% purity).

- 10 $^1\text{H-NMR}$ (400 MHz, DMSO d_6) δ (ppm) = 1.44 - 1.56 (m, 2H), 1.56 - 1.72 (m, 4H), 1.72 - 1.84 (m, 2H), 2.68 (tt, 1H), 3.06 - 3.13 (m, 4H), 3.77 (s, 3H), 4.06 - 4.13 (m, 4H), 6.87 (d, 1H), 7.19 (dd, 1H), 7.27 (d, 1H), 7.30 - 7.36 (m, 1H), 7.49 - 7.57 (m, 2H), 8.14 (d, 1H), 8.15 - 8.18 (m, 1H), 8.39 (s, 1H), 8.63 (s, 1H), 9.63 (s, 1H).

Example 58

(+/-)-N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}tetrahydrofuran-2-carboxamide

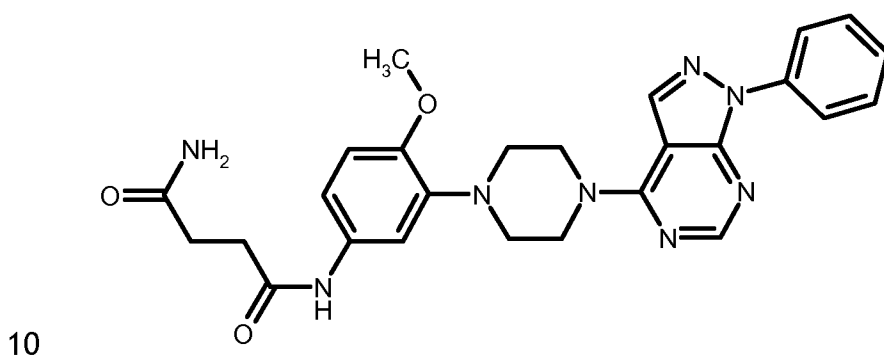


- 20 In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 28.9 mg (0.25 mmol) tetrahydrofuran-2-carboxylic acid gave after HPLC purification the desired material: 68 mg (53% yield, 97% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 1.81 (tt, 2H), 1.88 - 1.97 (m, 1H), 2.08 - 2.18 (m, 1H), 3.07 - 3.14 (m, 4H), 3.73 - 3.82 (m, 4H), 3.94 (dt, 1H), 4.07 - 4.13 (m, 4H), 4.31 (dd, 1H), 6.88 (d, 1H), 7.29 - 7.36 (m, 3H), 7.50 - 7.57 (m, 2H), 8.12 - 8.15 (m, 1H), 8.15 - 8.18 (m, 1H), 8.39 (s, 1H), 8.62 (s, 1H), 9.42 (s, 1H).

Example 59

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}butanediamide

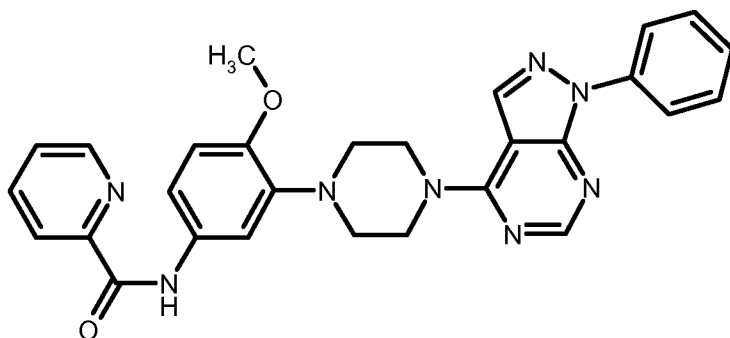


In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 28.2 mg (0.25 mmol) succinamic acid gave after HPLC purification the desired material: 13 mg (9.7% yield, 97% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.32 (t, 2H), 2.44 (t, 2H), 3.04 - 3.13 (m, 4H), 3.76 (s, 3H), 4.06 - 4.14 (m, 4H), 6.72 (br. s., 1H), 6.87 (d, 1H), 7.16 (dd, 1H), 7.24 (d, 1H), 7.28 (br. s., 1H), 7.30 - 7.37 (m, 1H), 7.49 - 7.56 (m, 2H), 8.11 - 8.15 (m, 1H), 8.16 (d, 1H), 8.38 (s, 1H), 8.63 (s, 1H), 9.72 (s, 1H).

Example 60

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-2-carboxamide



In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 30.7 mg (0.25 mmol) picolinic acid gave after HPLC purification the desired material: 28 mg (20% yield, 90% purity).

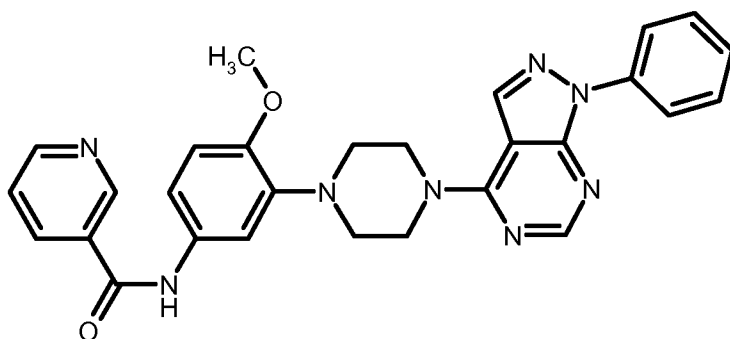
5

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.11 - 3.19 (m, 4H), 3.80 (s, 3H), 4.06 - 4.17 (m, 4H), 6.95 (d, 1H), 7.30 - 7.37 (m, 1H), 7.48 - 7.65 (m, 5H), 7.98 - 8.06 (m, 1H), 8.10 (d, 1H), 8.12 - 8.15 (m, 1H), 8.16 (d, 1H), 8.39 (s, 1H), 8.64 (s, 1H), 8.68 (d, 1H), 10.45 (s, 1H).

10

Example 61

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-3-carboxamide

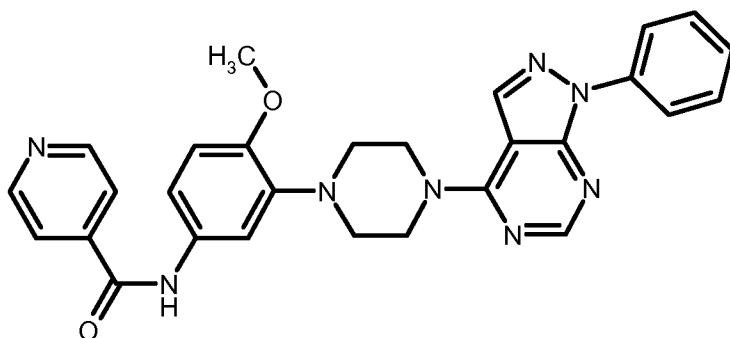


15 In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 30.7 mg (0.25 mmol) nicotinic acid gave after HPLC purification the desired material: 9.0 mg (6.1% yield, 85% purity).

20 ¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 3.23 - 3.33 (m, 4H), 3.94 (s, 3H), 4.16 - 4.28 (m, 4H), 6.90 (d, 1H), 7.23 (d, 1H), 7.29 - 7.47 (m, 3H), 7.52 (t, 2H), 7.91 (s, 1H), 8.08 - 8.15 (m, 2H), 8.15 - 8.24 (m, 2H), 8.48 (s, 1H), 8.76 (d, 1H), 9.08 (s, 1H).

Example 62

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-4-carboxamide



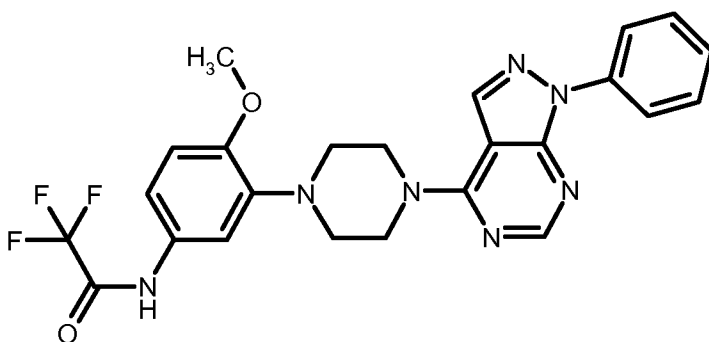
5

In analogy to example 39) 100 mg (0.25 mmol) of example 51) and 30.7 mg (0.25 mmol) isonicotinic acid gave after HPLC purification the desired material: 60 mg (40% yield, 85% purity).

10 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.08 - 3.19 (m, 4H), 3.81 (s, 3H), 4.06 - 4.17 (m, 4H), 6.96 (d, 1H), 7.33 (t, 1H), 7.37 - 7.46 (m, 2H), 7.53 (t, 2H), 7.77 - 7.86 (m, 2H), 8.13 (d, 1H), 8.16 (d, 1H), 8.39 (s, 1H), 8.64 (s, 1H), 8.71 - 8.77 (m, 2H), 10.31 (s, 1H).

Example 63

2,2,2-trifluoro-N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide

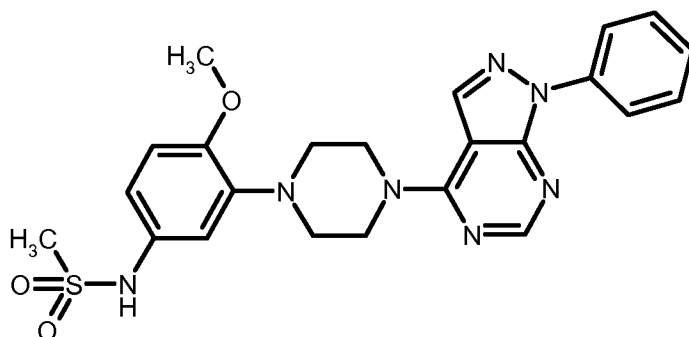


20 In analogy to example 52) 50 mg (0.13 mmol) of example 51) and 11.3 µl (0.15 mmol) trifluoroacetic anhydride gave the desired material: 60 mg (94% yield, 97% purity).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 3.08 - 3.16 (m, 4H), 3.81 (s, 3H), 4.06 - 4.14 (m, 4H), 6.98 (d, 1H), 7.23 (d, 1H), 7.28 - 7.37 (m, 2H), 7.49 - 7.56 (m, 2H), 8.12 - 8.19 (m, 2H), 8.39 (s, 1H), 8.63 (s, 1H), 11.02 (s, 1H).

5 Example 64

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanesulfonamide



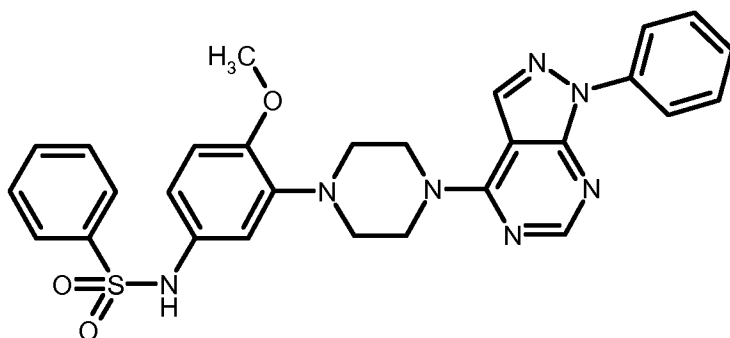
In analogy to example 52) 50 mg (0.13 mmol) of example 51) and 11.3 μL (0.15 mmol)
 10 methanesulfonyl chloride gave the desired material: 40 mg (64% yield, 95% purity).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 2.86 (s, 3H), 3.05 - 3.16 (m, 4H), 3.78 (s, 3H), 4.03 - 4.16 (m, 4H), 6.74 - 6.85 (m, 2H), 6.89 - 6.96 (m, 1H), 7.28 - 7.37 (m, 1H), 7.52 (t, 2H), 8.14 (d, 2H), 8.38 (s, 1H), 8.63 (s, 1H), 9.29 (s, 1H).

15

Example 65

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}benzenesulfonamide

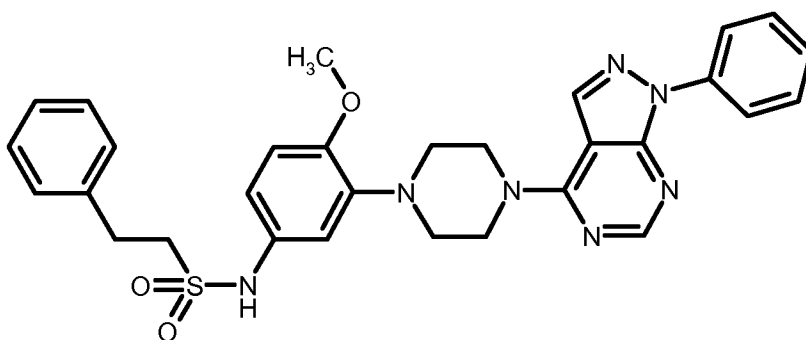


20 In analogy to example 52) 50 mg (0.13 mmol) of example 51) and 11.3 μL (0.15 mmol) benzenesulfonyl chloride gave the desired material: 43 mg (57% yield, 90% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.94 - 3.05 (m, 4H), 3.71 (s, 3H), 4.02 - 4.10 (m, 4H), 6.58 - 6.67 (m, 2H), 6.80 (d, 1H), 7.24 - 7.30 (m, 1H), 7.30 - 7.39 (m, 1H), 7.44 - 7.59 (m, 4H), 7.62 - 7.70 (m, 2H), 8.09 - 8.19 (m, 2H), 8.39 (s, 1H), 8.63 (s, 1H), 9.86 (s, 1H).

Example 66

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}-2-phenylethanesulfonamide

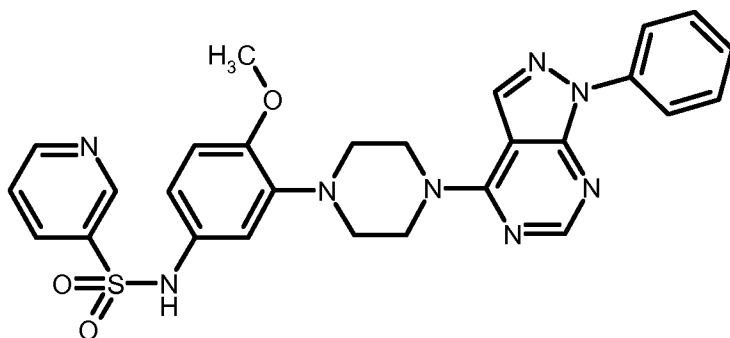


In analogy to example 52) 50 mg (0.13 mmol) of example 51) and 30.6 mg (0.15 mmol) 2-phenylethanesulfonyl chloride gave the desired material: 85 mg (96% yield, 80% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.65 (ddd, 3H), 2.84 (dd, 3H), 2.90 - 2.98 (m, 2H), 3.11 - 3.18 (m, 4H), 3.18 - 3.26 (m, 2H), 3.79 (s, 3H), 4.07 - 4.18 (m, 4H), 5.72 (s, 1H), 6.85 - 6.99 (m, 3H), 7.09 - 7.27 (m, 4H), 7.35 (t, 1H), 7.54 (t, 2H), 8.09 - 8.15 (m, 2H), 8.41 (s, 1H), 8.67 (s, 1H), 9.55 (s, 1H).

Example 67

N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-3-sulfonamide



In analogy to example 52) 50 mg (0.13 mmol) of example 51) and 32.0 mg (0.15 mmol) pyridine-3-sulfonyl chloride hydrochloride gave the desired material: 41 mg (59% yield, 97% purity).

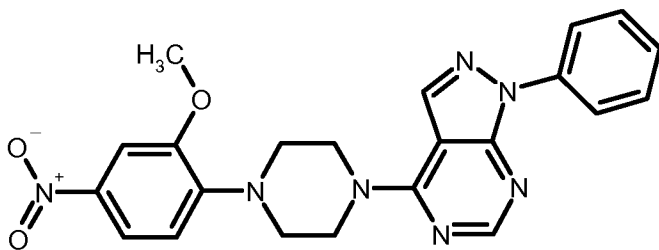
5

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.94 - 3.03 (m, 4H), 3.73 (s, 3H), 4.01 - 4.10 (m, 4H), 6.58 - 6.67 (m, 2H), 6.83 (d, 1H), 7.29 - 7.38 (m, 1H), 7.48 - 7.59 (m, 3H), 8.01 (ddd, 1H), 8.11 - 8.19 (m, 2H), 8.38 (s, 1H), 8.62 (s, 1H), 8.73 (dd, 1H), 8.75 (d, 1H), 10.05 (s, 1H).

10

Example 68

4-[4-(2-methoxy-4-nitrophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine



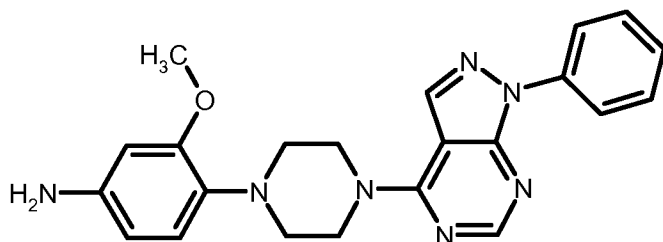
15 In analogy to example 31) 14.7 g (63.5 mmol) of intermediate 1A) and 20.9 g (76.2 mmol) 1-(2-methoxy-4-nitrophenyl)piperazine hydrochloride (commercially available) gave the desired material: 24.2 g (80% yield, 90% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.38 - 3.44 (m, 4H), 3.93 (s, 3H), 4.08 - 4.17 (m, 4H), 7.04 (d, 1H), 7.30 - 7.36 (m, 1H), 7.50 - 7.56 (m, 2H), 7.71 (d, 1H), 7.84 (dd, 1H), 8.12 - 8.17 (m, 2H), 8.39 (s, 1H), 8.60 (s, 1H).

20

Example 69

3-methoxy-4-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]aniline



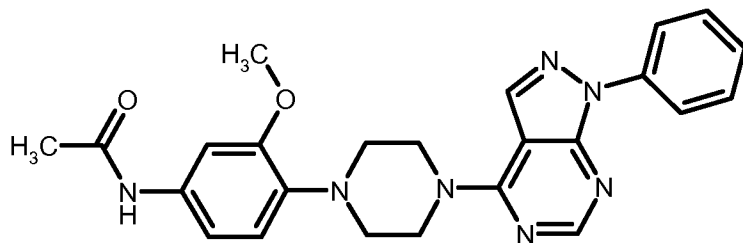
- 5 In analogy to example 51) 150 mg (0.35 mmol) of example 68) gave the desired material: 106 mg (74% yield, 97% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.88 - 2.98 (m, 4H), 3.29 (br. s., 2H), 3.70 (s, 3H), 4.00 - 4.09 (m, 4H), 6.05 (dd, 1H), 6.24 (d, 1H), 6.62 (d, 1H), 7.29 - 7.36 (m, 1H), 7.48 - 7.57 (m, 2H), 8.10 - 8.19 (m, 2H), 8.36 (s, 1H), 8.59 (s, 1H).

10

Example 70

N-{3-methoxy-4-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide

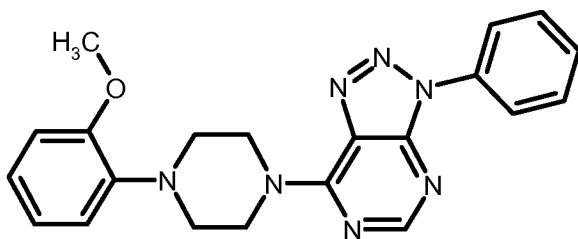


15

In analogy to example 51) 40 mg (0.10 mmol) of example 69) and 11.3 µl (0.12 mmol) acetic anhydride gave the desired material: 25 mg (55% yield, 97% purity).

Example 71

20 **7-[4-(2-methoxyphenyl)piperazin-1-yl]-3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine**



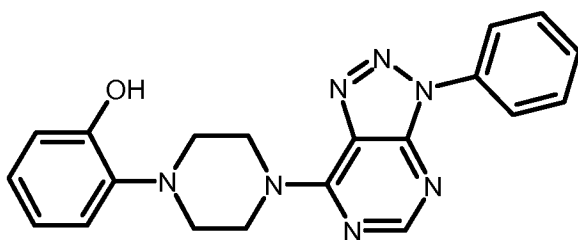
In analogy to example 27) 86 mg (0.37 mmol) of intermediate 11A) and 71.2 mg (0.37 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 114 mg (75% yield, 95% purity).

5

¹H-NMR (500 MHz, DMSO *d*₆) δ (ppm) = 3.16 (br. s., 2H), 3.24 (br. s., 2H), 3.85 (s, 3H), 4.22 (br. s., 2H), 4.79 (br. s., 2H), 6.88 - 6.94 (m, 1H), 6.95 - 6.99 (m, 1H), 6.99 - 7.04 (m, 2H), 7.56 (t, 1H), 7.69 (t, 2H), 8.12 - 8.17 (m, 2H), 8.52 (s, 1H).

10 Example 72

2-[4-(3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)piperazin-1-yl]phenol



In analogy to example 27) 88 mg (0.38 mmol) of intermediate 11A) and 67.7 mg (0.38 mmol) 1-(2-hydroxyphenyl)piperazine gave the desired material: 142 mg (97% yield, 97% purity).

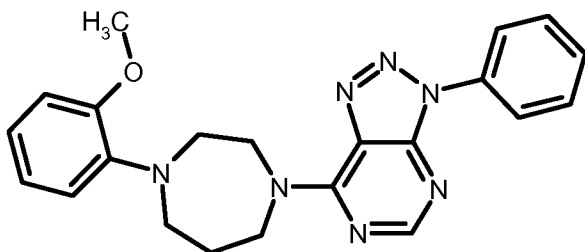
15

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.08 (br. s., 2H), 3.15 (br. s., 2H), 3.27 (s, 3H), 4.20 (br. s., 2H), 4.76 (br. s., 2H), 6.72 (td, 1H), 6.78 - 6.88 (m, 2H), 6.91 (dd, 1H), 7.49 - 7.54 (m, 1H), 7.61 - 7.67 (m, 2H), 8.07 - 8.13 (m, 2H), 8.46 (s, 1H), 9.05 (s, 1H).

20

Example 73

7-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine



In analogy to example 27) 88 mg (0.38 mmol) of intermediate 11A) and 78.4 mg (0.38 mmol) 1-(2-methoxyphenyl)-1,4-diazepane gave the desired material: 127 mg (81% yield, 97% purity).

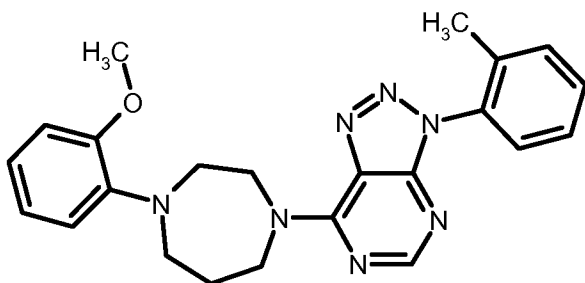
5

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.01 (t, 1H), 2.11 (t, 1H), 3.18 - 3.25 (m, 2H), 3.42 (t, 1H), 3.52 (t, 1H), 3.70 (d, 3H), 4.10 (t, 1H), 4.17 (t, 1H), 4.55 (t, 1H), 4.64 (t, 1H), 6.69 - 6.90 (m, 4H), 7.47 - 7.53 (m, 1H), 7.58 - 7.66 (m, 2H), 8.05 - 8.13 (m, 2H), 8.43 (d, 1H).

10

Example 74

7-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine

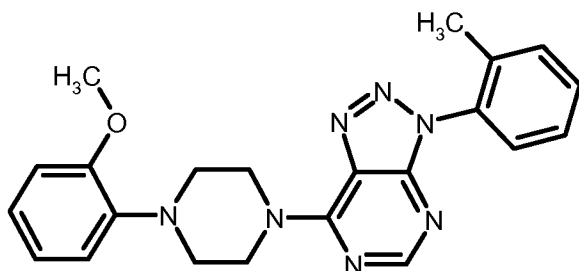


15 In analogy to example 27) 125 mg (0.51 mmol) of intermediate 12A) and 126 mg (0.61 mmol) 1-(2-methoxyphenyl)-1,4-diazepane gave the desired material: 110 mg (50% yield, 97% purity).

20 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 1.96 - 2.07 (m, 4H), 2.07 - 2.18 (m, 1H), 3.24 (br. s., 2H), 3.42 (t, 1H), 3.54 (t, 1H), 3.71 (s, 3H), 4.09 (t, 1H), 4.17 (t, 1H), 4.57 (t, 1H), 4.66 (t, 1H), 6.68 - 6.91 (m, 4H), 7.37 - 7.56 (m, 4H), 8.33 (d, 1H).

Example 75

7-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine

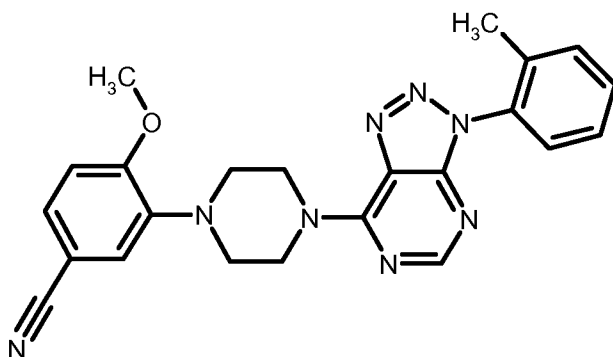


- 5 In analogy to example 27) 125 mg (0.51 mmol) of intermediate 12A) and 117 mg (0.61 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 131 mg (62% yield, 97% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.05 (s, 3H), 3.07 - 3.24 (m, 4H), 3.81 (s, 3H),
 10 4.18 (br. s., 2H), 4.76 (br. s., 2H), 6.82 - 7.01 (m, 4H), 7.38 - 7.57 (m, 4H), 8.37 (s, 1H).

Example 76

15 4-methoxy-3-{4-[3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]piperazin-1-yl}benzonitrile

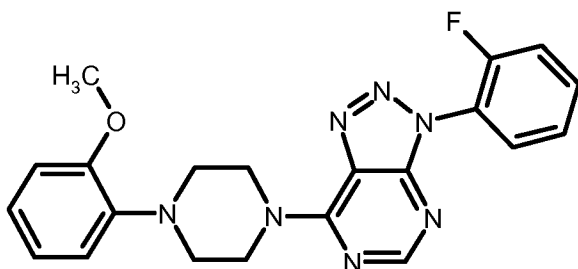


In analogy to example 27) 129 mg (0.53 mmol) of intermediate 12A) and 159 mg (0.63 mmol) of intermediate 2B) gave the desired material: 31 mg (13% yield, 92% purity).

20 ¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.05 (s, 3H), 3.09 - 3.27 (m, 4H), 3.90 (s, 3H), 4.17 (br. s., 2H), 4.75 (br. s., 2H), 7.13 (d, 1H), 7.30 (d, 1H), 7.40 - 7.56 (m, 5H), 8.38 (s, 1H).

Example 77

3-(2-fluorophenyl)-7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine



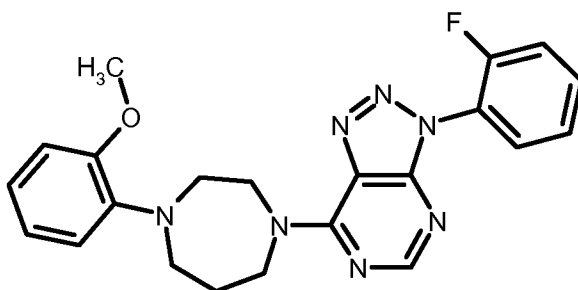
- 5 In analogy to example 27) 100 mg (0.40 mmol) of intermediate 13A) and 77 mg (0.40 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 13 mg (8.2% yield, 97% purity).

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.11 (br. s., 2H), 3.19 (br. s., 2H), 3.81 (s, 3H), 4.18 (br. s., 2H), 4.73 (br. s., 2H), 6.82 - 7.02 (m, 4H), 7.44 - 7.51 (m, 1H), 7.54 - 7.63 (m, 1H), 7.65 - 7.80 (m, 2H), 8.40 (s, 1H).

Example 78

3-(2-fluorophenyl)-7-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3H-

[1,2,3]triazolo[4,5-d]pyrimidine



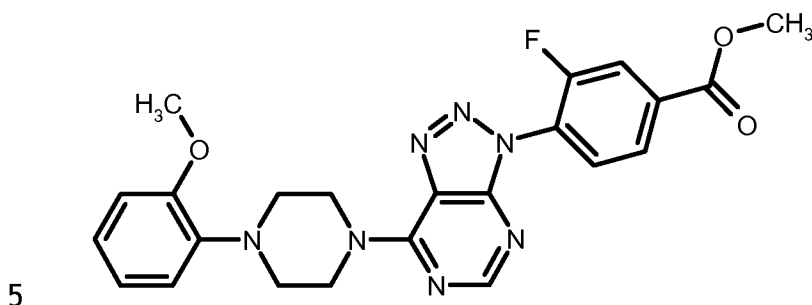
In analogy to example 27) 100 mg (0.40 mmol) of intermediate 13A) and 83 mg (0.40 mmol) 1-(2-methoxyphenyl)-1,4-diazepane gave the desired material: 88 mg (53% yield, 97% purity).

20

¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 2.01 (br. s., 1H), 2.12 (br. s, 1H), 3.22 (br. s., 2H), 3.41 (t, 1H), 3.52 (t, 1H), 3.70 (d, 3H), 4.10 (t, 1H), 4.17 (t, 1H), 4.55 (t, 1H), 4.64 (t, 1H), 6.69 - 6.91 (m, 4H), 7.42 - 7.50 (m, 1H), 7.52 - 7.61 (m, 1H), 7.63 - 7.81 (m, 2H), 8.36 (d, 1H).

Example 79

methyl 3-fluoro-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}benzoate

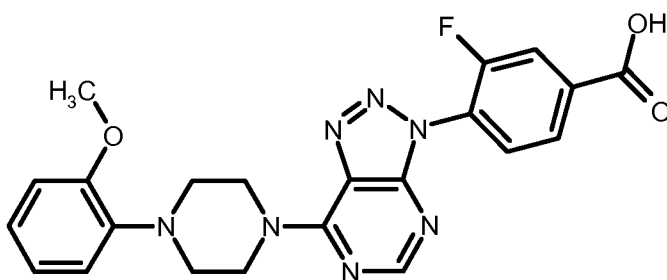


In analogy to example 27) 286 mg (0.93 mmol) of intermediate 14A) and 179 mg (0.93 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 404 mg (89% yield, 95% purity).

- 10 $^1\text{H-NMR}$ (400 MHz, DMSO d_6) δ (ppm) = 3.12 (br. s., 2H), 3.21 (br. s., 2H), 3.81 (s, 3H), 3.91 (s, 3H), 4.18 (br. s., 2H), 4.73 (br. s., 1H), 6.83 - 7.01 (m, 4H), 7.95 - 8.01 (m, 1H), 8.02 - 8.09 (m, 2H), 8.43 (s, 1H).

Example 80

- 15 **3-fluoro-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}benzoic acid**



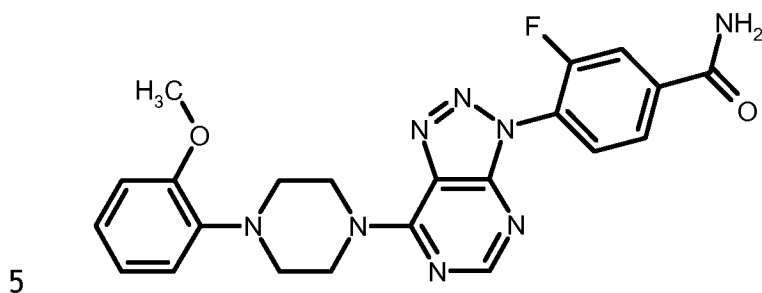
In analogy to example 38) 300 mg (0.84 mmol) of example 79) gave the desired material: 338 mg (89% yield, about 100% purity).

20

- $^1\text{H-NMR}$ (300 MHz, DMSO d_6) δ (ppm) = 3.11 (br. s., 2H), 3.20 (br. s., 2H), 3.80 (s, 3H), 4.18 (br. s., 2H), 4.73 (br. s., 2H), 6.82 - 7.01 (m, 4H), 7.90 - 7.97 (m, 1H), 7.98 - 8.04 (m, 2H), 8.43 (s, 1H), 13.66 (br. s., 1H).

Example 81

3-fluoro-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}benzamide

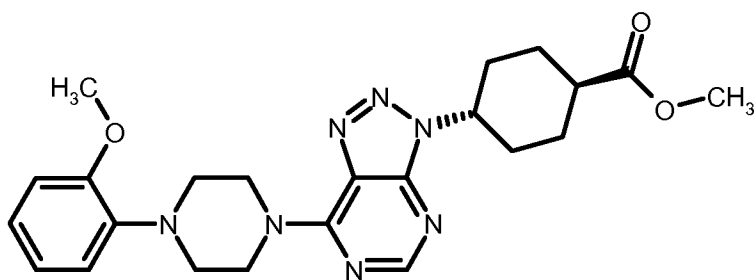


In analogy to example 39) 100 mg (0.22 mmol) of example 80) gave only via HPLC purification the desired material: 56 mg (54% yield, 95% purity).

10 ¹H-NMR (300 MHz, DMSO *d*₆) δ (ppm) = 3.12 (br. s., 2H), 3.20 (br. s., 2H), 3.81 (s, 3H), 4.18 (br. s., 2H), 4.73 (br. s., 2H), 6.83 - 7.01 (m, 4H), 7.70 (br. s., 1H), 7.85 - 7.92 (m, 1H), 7.92 - 7.97 (m, 1H), 8.00 (dd, 1H), 8.21 (br. s., 1H), 8.42 (s, 1H).

Example 82

15 **methyl trans-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}cyclohexanecarboxylate**

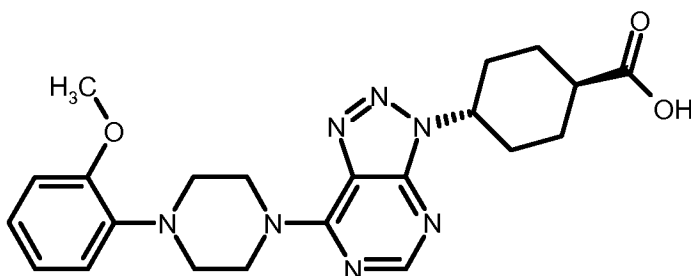


20 In analogy to example 27) 2.92 g (9.87 mmol) of intermediate 15A) and 2.28 g (11.8 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 1.74 g (38% yield, 97% purity).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.52 - 1.70 (m, 2H), 2.02 - 2.16 (m, 5H), 3.02 - 3.20 (m, 4H), 3.60 (s, 3H), 3.80 (s, 3H), 4.12 (br. s., 1H), 4.61 - 4.80 (m, 3H), 6.81 - 6.99 (m, 4H), 8.36 (s, 1H).

5 Example 83

trans-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}cyclohexanecarboxylic acid

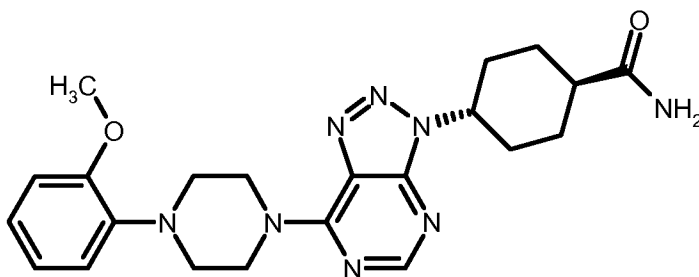


In analogy to example 38) 1.74 g (3.85 mmol) of example 82) gave the desired material: 1.5 g (85% yield, 95% purity).

$^1\text{H-NMR}$ (300 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.47 - 1.67 (m, 2H), 1.99 - 2.15 (m, 6H), 2.35 (t, 1H), 3.01 - 3.19 (m, 4H), 3.79 (s, 3H), 4.11 (br. s., 2H), 4.62 - 4.79 (m, 3H), 6.80 - 7.01 (m, 4H), 8.36 (s, 1H), 12.12 (br. s., 1H).

Example 84

trans-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}cyclohexanecarboxamide

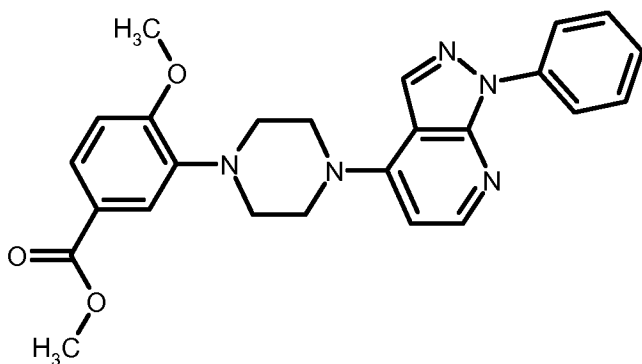


In analogy to example 39) 150 mg (0.34 mmol) of example 83) gave the desired material: 27 mg (18% yield, 97% purity).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO } d_6$) δ (ppm) = 1.54 - 1.68 (m, 2H), 1.95 (d, 2H), 2.05 - 2.16 (m, 4H), 2.20 - 2.30 (m, 1H), 3.04 - 3.22 (m, 4H), 3.82 (s, 3H), 4.15 (br. s., 2H), 4.65 - 4.80 (m, 3H), 6.76 (br. s., 1H), 6.84 - 7.02 (m, 4H), 7.26 (br. s., 1H), 8.38 (s, 1H).

5 Example 85

methyl 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)piperazin-1-yl]benzoate

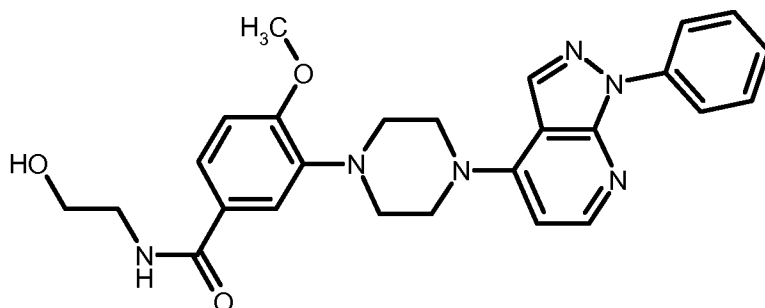


To a solution of 100 mg (0.38 mmol) of intermediate 1C) in 1.6 mL DMF 129 mg (0.45 mmol) of intermediate 1B) and 0.17 mL (1.13 mmol) DBU were added and the reaction mixture was heated at 125°C for 3 hours. A second experiment with 500 mg (1.88 mmol) of intermediate 1C) was performed. Both mixture together were concentrated in vacuum and purified twice via a Biotage chromatography system (25 g snap column, hexane / 0 - 100% ethyl acetate, then ethyl acetate / 0 - 15% methanol). This procedure gave 520 mg of a mixture of the desired material and the regioisomer methyl 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[4,3-c]pyridin-4-yl)piperazin-1-yl]benzoate. A sample of 70 mg of this mixture was purified further via HPLC and gave the desired material: 15 mg (1.5% yield, 85% purity).

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm) = 3.33 - 3.39 (m, 4H), 3.85 - 3.90 (m, 4H), 3.93 (s, 3H), 4.01 (s, 3H), 6.50 (d, 1H), 6.96 (d, 1H), 7.30 - 7.36 (m, 1H), 7.55 (t, 2H), 7.70 (d, 1H), 7.82 (dd, 1H), 8.18 - 8.26 (m, 3H), 8.34 (d, 1H).

Example 86

N-(2-hydroxyethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)piperazin-1-yl]benzamide

**Step1:**

In analogy to example 38) 450 mg (1.02 mmol) of the mixture of example 85 and its regioisomer gave the desired material together with the acid of its regioisomer and
 5 was used without any further purification: 354 mg (81% yield).

Step2:

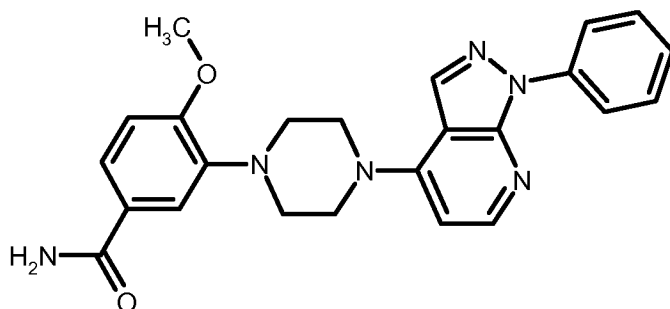
In analogy to example 39) 177 mg (0.41 mmol) of the mixture of acids of step 1) and
 25.2 mg (0.41 mmol) 2-aminoethanol gave the desired material: 17 mg (7.9% yield,
 10 90% purity).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 3.25 - 3.34 (m, 4H), 3.63 (q, 2H), 3.79 - 3.88 (m, 6H), 3.96 (s, 3H), 5.32 (s, 1H), 6.47 (d, 1H), 6.83 - 6.94 (m, 2H), 7.33 (t, 1H), 7.45 - 7.59 (m, 4H), 8.16 (d, 2H), 8.22 (s, 1H), 8.31 (d, 1H).

15

Example 87

4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)piperazin-1-yl]benzamide



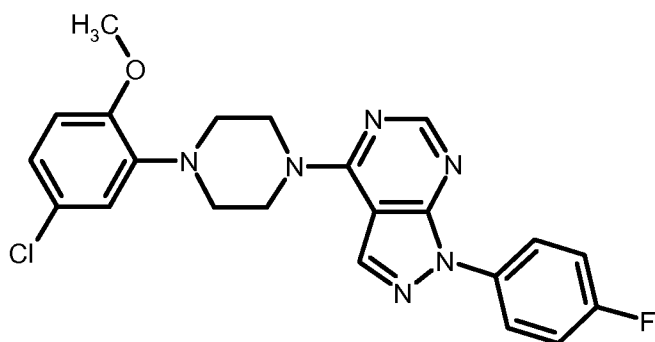
20 In analogy to example 39) 177 mg (0.41 mmol) of the mixture of acids of step 1) in example 86) and 0.82 mL 0.5M ammonia in dioxane gave the desired material: 18 mg (9.1% yield, 90% purity).

¹H-NMR (300 MHz, CDCl₃) δ (ppm) = 3.34 - 3.42 (m, 4H), 3.84 - 3.95 (m, 4H), 4.00 (s, 3H), 5.48 - 6.18 (m, 2H), 6.52 (d, 1H), 6.96 (d, 1H), 7.36 (t, 1H), 7.46 - 7.64 (m, 4H), 8.15 (d, 2H), 8.26 (s, 1H), 8.34 (d, 1H).

5

Example 88

4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine



10

200 mg (0.76 mmol) 4-Chloro-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (intermediate 2A) were dissolved in 0.59 mL DMF and given in a sealable glass tube. 201 mg (0.76 mmol) 1-(5-Chloro-2-methoxyphenyl)piperazine hydrochloride, 0.34 mL (2.29 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en and 0.11 mL (0.76 mmol) triethylamine were added, and the glass tube was sealed with a teflon screw top. The reaction mixture was heated for 2.5 hours at 120°C (heating block). After the cooling the reaction mixture was diluted with 3 mL methyl-tert.butylether and 0.5 mL methanol. The precipitate was sucked off, washed with methyl-tert.butylether and little methanol yielding 270 mg (78.9 %) of the title compound.

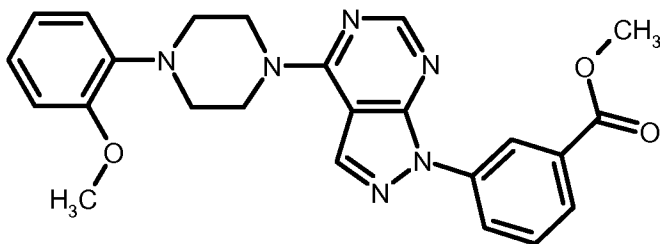
20

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 3.10 - 3.17 (m, 4H), 3.80 (s, 3H), 4.05 - 4.12 (m, 4H), 6.88 (d, 1H), 6.94 - 7.02 (m, 2H), 7.33 - 7.41 (m, 2H), 8.13 - 8.20 (m, 2H), 8.38 (s, 1H), 8.60 (s, 1H).

25

Example 89

methyl 3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzoate



5

2.7 g Methyl 3-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate (strongly contaminated, content ~ 30%) were dissolved in 1.59 mL DMF. After addition of 0.38 g (1.97 mmol) 1-(2-methoxyphenyl)piperazine hydrochloride and 0.884 mL (5.9 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en the reaction mixture was heated for 10 hours at 60 °C. Due to an incomplete reaction heating was continued for 15 h at 80 °C. After the cooling the reaction mixture was diluted with 3 mL methyl-tert.butylether/ ethanol (10%). The precipitate was sucked off and washed with methyl-tert.butylether/ethanol. After further purification via HPLC 398.4 mg (40.9 %) of the title compound were obtained.

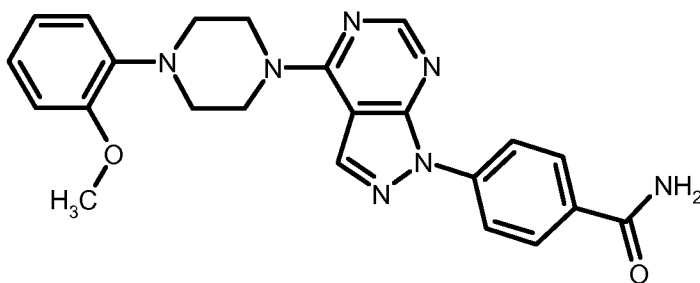
15

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 3.09 - 3.17 (m, 4H), 3.81 (s, 3H), 3.88 (s, 3H), 4.08 - 4.14 (m, 4H), 6.84 - 6.99 (m, 4H), 7.69 (t, 1H), 7.90 (dt, 1H), 8.43 (s, 1H), 8.48 - 8.53 (m, 1H), 8.67 (s, 1H), 8.81 (t, 1H).

20

Example 90

4-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzamide



Step 1:

0.77 g (2.68 mmol) Methyl 4-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzoate
 5 were dissolved in 2.06 mL DMF. After addition of 0.77 g (2.68 mmol) 1-(2-methoxyphenyl)piperazine and 1.20 mL (8.03 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en the reaction mixture was heated for 3 hours at 120 °C. The reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 0.570 g (45.6%) of methyl 4-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzoate.
 10 UPLC-MS: RT = 1.42 min; m/z = 445 (ES⁺, M+1)

Step 2:

50 mg (0.11 mmol) Methyl 4-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzoate were given in 0.8 mL 7M NH₃ in MeOH
 15 and heated for one week at 110 °C (sealed tube, heating block; caution: pressure build-up). The reaction mixture was evaporated to dryness and the residue was purified by chromatography yielding 7.3 mg (14.4%) of the title compound.

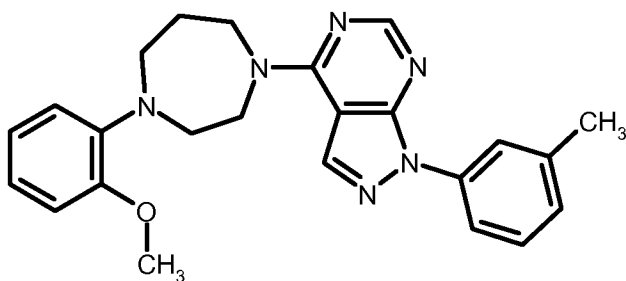
20

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 3.07 - 3.15 (m, 4H), 3.80 (s, 3H), 4.06 - 4.15 (m, 4H), 6.83 - 7.00 (m, 4H), 7.37 (br. s., 1H), 7.96 - 8.06 (m, 3H), 8.26 - 8.34 (m, 2H), 8.42 (s, 1H), 8.66 (s, 1H).

25

Example 91

4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

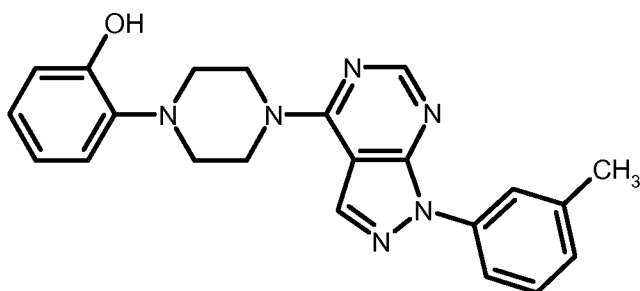


246 mg (70% pure) 4-Chloro-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine
 5 (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.54 mL DMF
 and given in a sealable glass tube. 145.2 mg (0.70 mmol) 1-(2-Methoxyphenyl)-1,4-
 diazepane and 0.32 mL (2.11 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added,
 and the glass tube was sealed with a teflon screw top. The reaction mixture was
 heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was
 10 diluted with dichloromethane, washed with brine, dried over sodium sulfate and
 evaporated to dryness. The residue was purified by HPLC chromatography yielding
 6.6 mg (2.2%) of the title compound.

1H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 1.95 (br. s., 1H), 2.10 (br. s., 1H), 2.38 (s,
 15 3H), 3.17 (br. s., 2H), 3.35 (br. s., 1H), 3.47 (br. s., 1H), 3.71 (s, 3H), 3.99 - 4.19 (m,
 4H), 6.72 - 6.92 (m, 4H), 7.14 (d, 1H), 7.39 (t, 1H), 7.91 - 7.99 (m, 2H), 8.34 (br. s.,
 1H), 8.45 (s, 1H).

Example 92

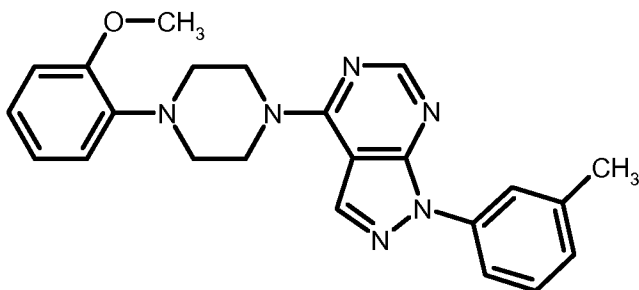
20 2-{4-[1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol



- 246 mg (70% pure) 4-Chloro-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.54 mL DMF and given in a sealable glass tube. 125.4 mg (0.70 mmol) 2-(Piperazin-1-yl)phenol and 0.32 mL (2.11 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added, and the glass tube was sealed. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was diluted with dichloromethane, washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by HPLC chromatography yielding 6.7 mg (2.3%) of the desired compound.
- 1H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 2.38 (s, 3H), 3.01 - 3.13 (m, 4H), 4.04 - 4.18 (m, 4H), 6.67 - 6.93 (m, 4H), 7.15 (d, 1H), 7.40 (t, 1H), 7.90 - 8.00 (m, 2H), 8.39 (s, 1H), 8.60 (s, 1H), 9.06 (s, 1H).

Example 93

- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



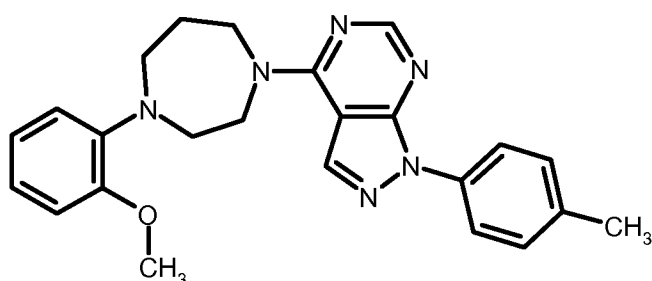
- 246 mg (70% pure) 4-Chloro-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.54 mL DMF and given in a sealable glass tube. 135.3 mg (0.71 mmol) 1-(2-Methoxyphenyl)piperazine and 0.32 mL (2.11 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added, and the glass tube was sealed. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was diluted with dichloromethane, washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by HPLC chromatography yielding 7 mg (2.4%) of the desired compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.38 (s, 3H), 3.03 - 3.16 (m, 4H), 3.80 (s, 3H), 4.02 - 4.14 (m, 4H), 6.82 - 7.00 (m, 4H), 7.15 (d, 1H), 7.40 (t, 1H), 7.88 - 8.02 (m, 2H), 8.38 (s, 1H), 8.60 (s, 1H).

5

Example 94

4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



10

150 mg (0.58 mmol, 95% pure) 4-Chloro-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.45 mL DMF (sealable glass tube). 120 mg (0.58 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.26 mL (1.75 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 2.5 hours at 120 °C (heating block). After cooling the DMF was removed by evaporation, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 135.5 mg (56.1%) of the title compound.

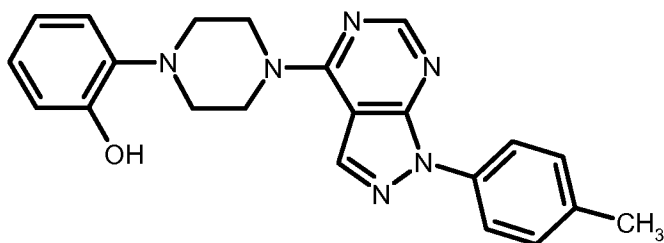
20

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 1.95 (br. s., 1H), 2.10 (br. s., 1H), 2.33 (s, 3H), 3.04 - 3.21 (m, 2H), 3.35 (br. s., 1H), 3.46 (br. s., 1H), 3.71 (s, 3H), 3.95 - 4.29 (m, 4H), 6.70 - 6.90 (m, 4H), 7.27 - 7.37 (m, 2H), 7.94 - 8.05 (m, 2H), 8.32 (br. s., 1H), 8.43 (s, 1H).

25

Example 95

2-{4-[1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol



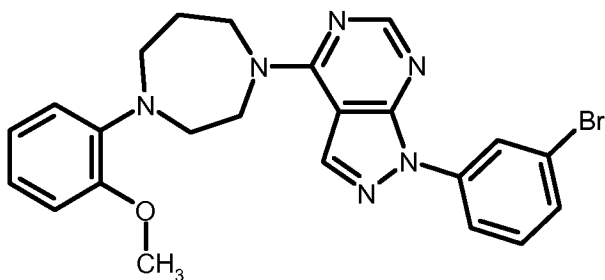
150 mg (0.58 mmol, 95% pure) 4-Chloro-1-(4-methylphenyl)-1H-pyrazolo[3,4-
d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in
5 0.45 mL DMF (sealable glass tube). 103.8 mg (0.58 mmol) 2-(Piperazin-1-yl)phenol
and 0.26 mL (1.75 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added, and the
glass tube was sealed. The reaction mixture was heated for 2 hours at 120°C (heating
block). After cooling the DMF was removed by evaporation, and the residue was
purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 98.4
10 mg (43.7%) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 2.34 (s, 3H), 3.01 - 3.11 (m, 4H), 4.00 - 4.17
(m, 4H), 6.69 - 6.94 (m, 4H), 7.32 (d, 2H), 8.01 (d, 2H), 8.36 (s, 1H), 8.58 (s, 1H),
9.06 (s, 1H).

15

Example 96

1-(3-bromophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-
d]pyrimidine



20

150 mg (0.49 mmol) 4-Chloro-1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidine
(commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.30 mL DMF
(sealable glass tube). 99.96 mg (0.49 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and

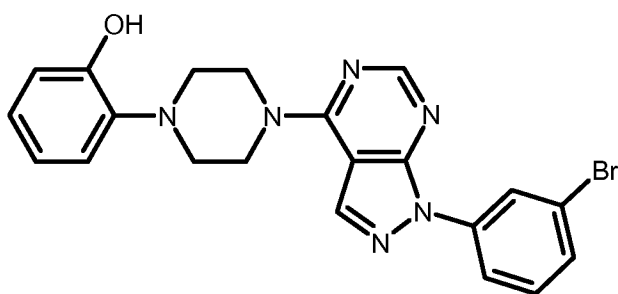
0.22 mL (1.45 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the DMF was removed by evaporation, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 140 mg (57.3%) of the title compound.

5

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 1.98 (br. s., 1H), 2.12 (br. s., 1H), 3.19 (br. s., 2H), 3.49 (br. s., 2H), 3.73 (s, 3H), 3.96 - 4.27 (m, 4H), 6.72 - 6.96 (m, 4H), 7.44 - 7.59 (m, 2H), 8.17 - 8.29 (m, 1H), 8.40 (br. s., 1H), 8.47 - 8.59 (m, 2H).

10 Example 97

2-{4-[1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol



15 150 mg (0.49 mmol) 4-Chloro-1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.37 mL DMF (sealable glass tube). 83.37 mg (0.49 mmol) 2-(Piperazin-1-yl)phenol and 0.22 mL (1.45 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the DMF was removed by evaporation, and the residue was purified by HPLC chromatography yielding 37.1 mg (16.1%) of the desired title compound.

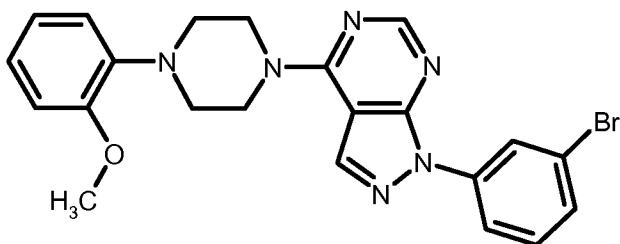
20

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 3.02 - 3.13 (m, 4H), 4.05 - 4.17 (m, 4H), 6.67 - 6.93 (m, 4H), 7.43 - 7.60 (m, 2H), 8.22 (dt, 1H), 8.48 (s, 1H), 8.52 (s, 1H), 8.65 (s, 1H), 9.12 (br. s, 1H).

25

Example 98

1-(3-bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



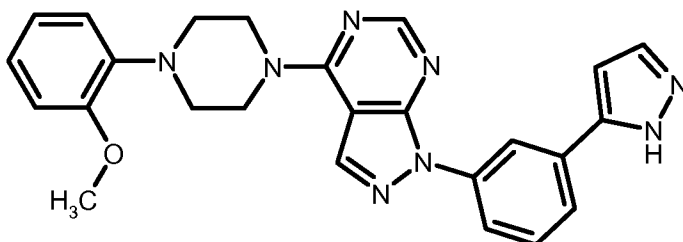
5

0.69 g (2.23 mmol) 4-Chloro-1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 1.7 mL DMF (sealable glass tube). 0.43 g (2.23 mmol) 1-(2-Methoxyphenyl)piperazine and 1 mL (6.69 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was diluted with dichloromethane. The precipitate was sucked off, washed and dried yielding 0.74 g (71.8%) of the desired compound.

1H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.03 - 3.15 (m, 4H), 3.80 (s, 3H), 4.01 - 4.16 (m, 4H), 6.80 - 7.04 (m, 4H), 7.43 - 7.59 (m, 2H), 8.15 - 8.27 (m, 1H), 8.38 - 8.44 (m, 1H), 8.46 - 8.53 (m, 1H), 8.65 (s, 1H).

Example 99

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[3-(1H-pyrazol-5-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine

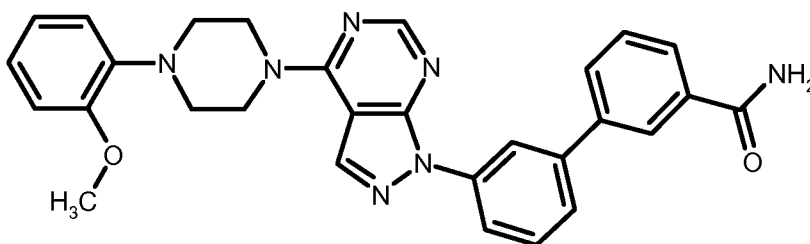


150 mg (0.32 mmol) 1-(3-Bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, 136.7 mg (0.65 mmol) [1-(tert-butoxycarbonyl)-1H-pyrazol-5-yl]boronic acid, 26.3 mg (0.03 mmol) 1,1' bis-(diphenyl-phosphino)ferrocenedichloropalladium(II) and 102.5 mg (0.97 mmol) sodium carbonate were given in a degassed mixture of 0.5 mL water and 3.5 mL dioxane. After purging the vial with nitrogen the reaction mixture was heated in the microwave for 90 minutes at 105 °C. The reaction mixture was poured on saturated ammonium chloride solution (50 mL) and dichloromethane (150 mL). After vigorous stirring for 30 minutes the organic phase was separated and the aqueous phase was reextracted once more with 50 mL dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, and the solvent was evaporated. The residue was purified via HPLC chromatography yielding 76.1 mg (49.6%) of the title compound.

1H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.05 - 3.16 (m, 4H), 3.80 (s, 3H), 4.01 - 4.19 (m, 4H), 6.74 (s, 1H), 6.79 - 7.03 (m, 4H), 7.47 - 7.60 (m, 1H), 7.69 - 7.89 (m, 2H), 8.09 (d, 1H), 8.41 (s, 1H), 8.63 (s, 2H), 12.93 (br. s., 1H).

Example 100

3'-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}biphenyl-3-carboxamide



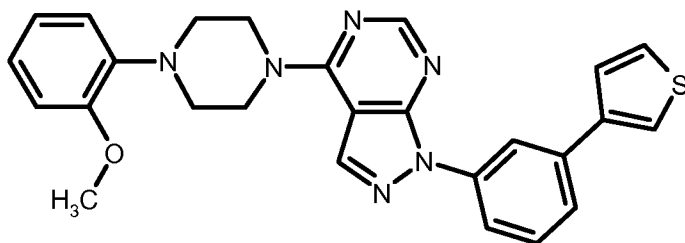
150 mg (0.32 mmol) 1-(3-Bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, 106.3 mg (0.65 mmol) (3-carbamoylphenyl)boronic acid, 26.3 mg (0.03 mmol) 1,1' bis-(diphenyl-phosphino)ferrocene-

dichloropalladium(II) and 102.5 mg (0.97 mmol) sodium carbonate were given in a degassed mixture of 0.5 mL water and 3.5 mL dioxane. After purging the vial with nitrogen the reaction mixture was heated in the microwave for 90 minutes at 105 °C. The reaction mixture was poured on saturated ammonium chloride solution (50 mL) and dichloromethane (150 mL). After vigorous stirring for 30 minutes the organic phase was separated, and the aqueous phase was reextracted once more with 50 mL dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, and the solvent was evaporated. The residue was purified via HPLC chromatography yielding 31.9 mg (18.6%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.04 - 3.17 (m, 4H), 3.80 (s, 3H), 4.06 - 4.15 (m, 4H), 6.80 - 7.01 (m, 4H), 7.40 (br. s., 1H), 7.50 - 7.72 (m, 3H), 7.87 (t, 2H), 8.10 (br. s., 1H), 8.15 - 8.24 (m, 2H), 8.41 (s, 1H), 8.46 (s, 1H), 8.65 (s, 1H).

Example 101

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[3-(thiophen-3-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine



20

150 mg (0.32 mmol) 1-(3-Bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, 82.5mg (0.65 mmol) 3-thienylboronic acid, 26.3 mg (0.03 mmol) 1,1' bis-(diphenyl-phosphino)ferrocenedichloropalladium(II) and 102.5 mg (0.97 mmol) sodium carbonate were given in a degassed mixture of 0.5 mL water and 3.5 mL dioxane. After purging the vial with nitrogen the reaction mixture was heated in the microwave for 90 minutes at 105 °C. The reaction mixture was poured on saturated ammonium chloride solution (50 mL) and dichloromethane (150 mL). After vigorous stirring for 30 minutes the organic phase was separated, and the aqueous

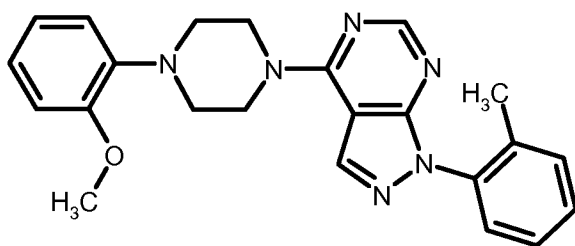
phase was reextracted once more with 50 mL dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate, and the solvent was evaporated. The residue was purified via HPLC chromatography yielding 74.6 mg (46.9%) of the title compound.

5

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.07 - 3.17 (m, 4H), 3.80 (s, 3H), 4.05 - 4.16 (m, 4H), 6.80 - 7.01 (m, 4H), 7.51 - 7.60 (m, 2H), 7.62 - 7.71 (m, 2H), 7.92 (dd, 1H), 8.04 - 8.12 (m, 1H), 8.36 - 8.47 (m, 2H), 8.64 (s, 1H).

10 Example 102

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



15

130 mg (70% pure) 4-Chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.29 mL DMF (sealable glass tube). 71.5 mg (0.37 mmol) 1-(2-Methoxyphenyl)piperazine and 0.17 L (1.12 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 2 hours at 120 °C (heating block). After cooling the reaction mixture was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 75.5 mg (50.7%) of the title compound.

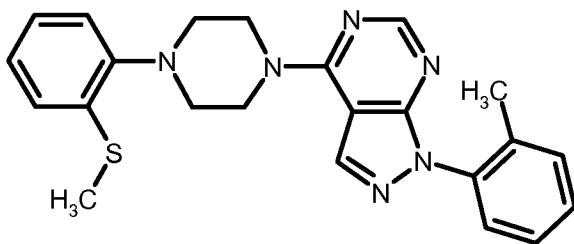
20

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.02 (s, 3H), 3.04 - 3.16 (m, 4H), 3.80 (s, 3H), 4.03 - 4.16 (m, 4H), 6.77 - 7.01 (m, 4H), 7.26 - 7.47 (m, 4H), 8.19 - 8.28 (m, 1H), 8.58 (s, 1H).

25

Example 103

1-(2-methylphenyl)-4-{4-[2-(methylsulfanyl)phenyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine



5

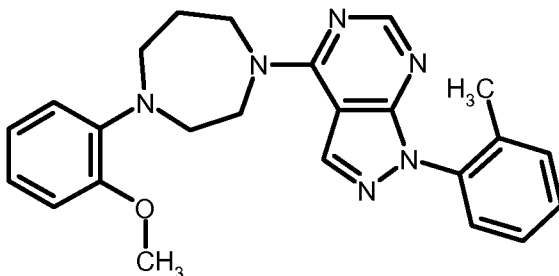
130 mg (70% pure) 4-Chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.29 mL DMF (sealable glass tube). 77.5 mg (0.37 mmol) 1-(2-Methylmercaptophenyl)piperazine and 0.17 mL (1.12 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 2.5 hours at 120°C (heating block). After cooling the reaction mixture was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 75.9 mg (49%) of the title compound.

15

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.02 (s, 3H), 2.39 (s, 3H), 3.04 (t, 4H), 4.10 (br. , 4H), 7.06 - 7.20 (m, 4H), 7.26 - 7.46 (m, 4H), 8.19 - 8.26 (m, 1H), 8.58 (s, 1H).

Example 104

4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine



20

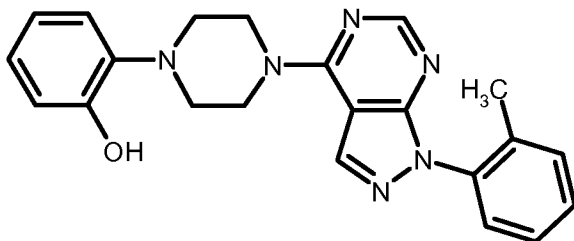
130 mg (0.51 mmol, 95% pure) 4-Chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.39 mL DMF (sealable glass tube). 104.1 mg (0.51 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.23 mL (1.51 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added.

- 5 The reaction mixture was heated for 2.5 hours at 120 °C (heating block). After cooling the reaction mixture was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 104.4 mg (49.9%) of the title compound.

- 10 ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 1.95 (br. s., 1H), 2.01 (s, 3H), 2.11 (br. s., 1H), 3.18 (br. s., 2H), 3.34 (br. s., 1H), 3.47 (br. s., 1H), 3.72 (s, 3H), 4.04 - 4.22 (m, 4H), 6.70 - 6.92 (m, 4H), 7.27 - 7.47 (m, 4H), 8.19 (s, 1H), 8.37 - 8.49 (m, 1H).

Example 105

- 15 2-{4-[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol

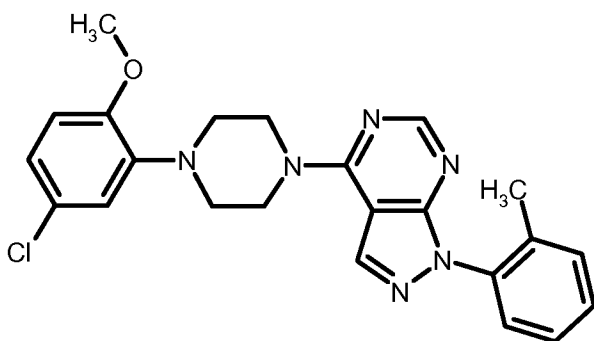


- 140 mg (0.54 mmol, 95% pure) 4-Chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.39 mL DMF (sealable glass tube). 96.88 mg (0.54 mmol) 2-(Piperazin-1-yl)phenol and 0.24 mL (1.63 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 1 hour at 120 °C (heating block). After cooling the reaction mixture was evaporated to dryness. The residue was purified by
- 25 chromatography (silicagel, eluents: ethyl acetate/ hexane) followed by an additional HPLC chromatography yielding 4.6 mg (2.1%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.02 (s, 3H), 3.02-3.15 (m, 4H), 4.02-4.19 (m, 4H), 6.66 - 7.03 (m, 4H), 7.24 - 7.54 (m, 4H), 8.25 (s, 1H), 8.59 (s, 1H), 9.08 (s, 1H).

5 Example 106

4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

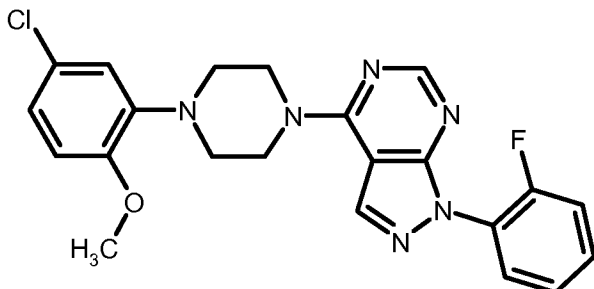


130 mg (0.51 mmol, 95% pure) 4-Chloro-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 0.39 mL DMF (sealable glass tube). 132.83 mg (0.51 mmol) 1-(5-Chloro-2-methoxyphenyl)piperazine hydrochloride, 0.23 mL (1.54 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en and 0.07 mL (0.51 mmol) triethylamine were added. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 54.9 mg (25%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.02 (s, 3H), 3.04-3.22 (m, 4H), 3.80 (s, 3H), 4.02 - 4.14 (m, 4H), 6.89 (d, 1H), 6.92 - 7.06 (m, 2H), 7.23 - 7.46 (m, 4H), 8.23 (s, 1H), 8.57 (s, 1H).

Example 107

4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine

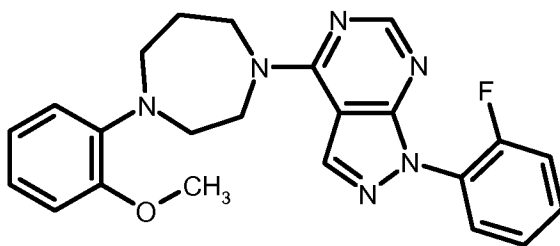


200 mg (50% pure) 4-Chloro-1-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (intermediate 4A) were dissolved in 0.31 mL DMF (sealable glass tube). 105.84 mg (0.40 mmol) 1-(5-Chloro-2-methoxyphenyl)piperazine hydrochloride, 0.18 mL (1.21 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en and 0.06 mL (0.40 mmol) triethylamine were added. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was evaporated to dryness. The residue was purified by HPLC chromatography yielding 42 mg (22.6%) of the title compound.

10 ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.06 - 3.18 (m, 4H), 3.80 (s, 3H), 4.02 - 4.13 (m, 4H), 6.88 (d, 1H), 6.92 - 7.03 (m, 2H), 7.32 - 7.69 (m, 4H), 8.28 (s, 1H), 8.62 (s, 1H).

Example 108

15 1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



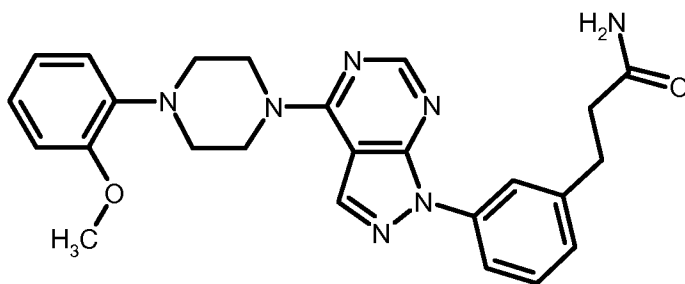
20 200 mg (50% pure) 4-Chloro-1-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (intermediate 4A) were dissolved in 0.62 mL DMF (sealable glass tube). 165.93 mg (0.80 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.36 mL (2.41 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 3 hours at 120°C (heating block). After cooling the reaction mixture was evaporated to

dryness. The residue was purified by HPLC chromatography yielding 35 mg (9.9%) of the title compound.

1H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 1.96 (br. s., 1H), 2.11 (br. s., 1H), 3.18 (br. s., 2H), 3.35 (br. s., 1H), 3.47 (br. s., 1H), 3.72 (s, 3H), 3.99 - 4.22 (m, 4H), 6.72 - 6.93 (m, 4H), 7.31 - 7.39 (m, 1H), 7.41 - 7.49 (m, 1H), 7.50 - 7.66 (m, 2H), 8.23 (br. s., 1H), 8.48 (s, 1H).

Example 109

3-(3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}phenyl)propanamide



163.5 mg (0.35 mmol) 1-(3-Bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, 42.9 mg (0.70 mmol) acrylamide, 18.2 mg (0.06 mmol) tri-
2-tolylphosphine and 7.9 mg (0.04 mmol) palladium(II)-acetate were dissolved in 2.5 mL acetonitrile. After addition of 0.06 mL (0.40 mmol) triethylamine the reaction mixture was heated in the microwave for 60 minutes at 110 °C. Due to an incomplete reaction heating was continued for 48 hours (heating block). The reaction mixture was poured on saturated ammonium chloride solution (50 mL) and dichloromethane (150 mL). After vigorous stirring for 30 minutes the organic phase was separated. The organic extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated. The crude residue (90 mg, 52% pure) was used in the next step without further purification.

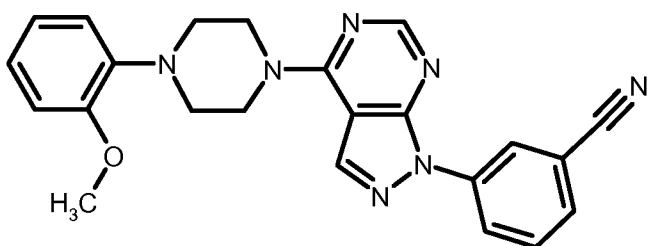
The crude residue (90 mg) was dissolved in ethanol (10 mL). 10 mg Pd/C were added, and the reaction was stirred overnight under a H₂ atmosphere. The catalyst was sucked off via a glass fibre filter, and the filtrate was evaporated to dryness yielding 4.5 mg (4.7%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.32 - 2.43 (m, 2H), 2.89 (t, 2H), 3.02-3.21 (m, 4H), 3.80 (s, 3H), 4.03 - 4.14 (m, 4H), 6.73 (br. s., 1H), 6.81 - 7.01 (m, 4H), 7.18 (d, 1H), 7.28 (br. s., 1H), 7.42 (t, 1H), 7.91 - 8.04 (m, 2H), 8.38 (s, 1H), 8.60 (s, 1H).

5

Example 110

3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzonitrile



10

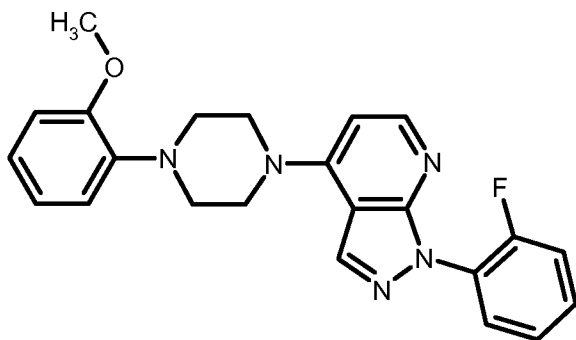
160 mg (0.34 mmol) 1-(3-Bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine were dissolved in 1.42 mL dimethylformamide. After addition of 40.4 mg (0.34 mmol) zinc cyanide and 19.9 mg (0.02 mmol)

15 tetrakis(triphenyl)phosphine-palladium(0) the reaction mixture was stirred for three hours at 100 °C and after cooling diluted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, and the solvent was evaporated. Purification of the residue via HPLC yielded 22 mg, (15.6%) of the desired compound.

20 ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.04 - 3.16 (m, 4H), 3.80 (s, 3H), 4.03 - 4.14 (m, 4H), 6.91 - 7.01 (m, 3H), 7.27 - 7.38 (m, 1H), 7.45 - 7.58 (m, 2H), 8.15 (dd, 2H), 8.38 (s, 1H), 8.61 (s, 1H).

Example 111

25 1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-b]pyridine

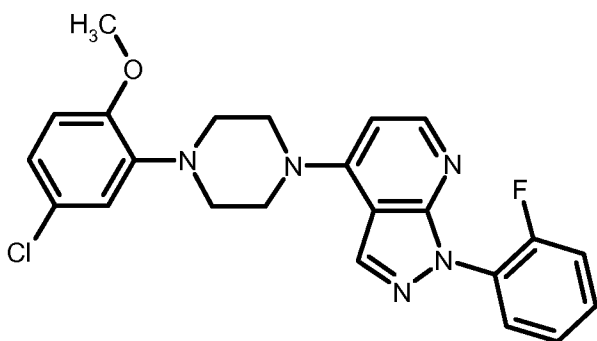


23,51 mg (0.03 mmol) Tris(dibenzylidene-acetone)dipalladium (0), 234,23 mg (0.72 mmol) cesium carbonate, 12.24 mg (0.03 mmol) 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl, 150 mg (0.51 mmol) 4-bromo-1-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine and 118.47 mg (0.62 mmol) 1-(2-methoxyphenyl)piperazine in 0.7 mL dioxane (microwave vial) were heated for 16 hours at 80 °C (heating block). The reaction mixture was filtered via a glass fibre filter. The filter was washed with ethyl acetate and the filtrate was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 122.3 mg (56.1%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.06 - 3.18 (m, 4H), 3.69 - 3.85 (m, 7H), 6.58 (d, 1H), 6.80 - 7.02 (m, 4H), 7.30 - 7.66 (m, 4H), 8.08 (d, 1H), 8.57 (s, 1H).

Example 112

4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine



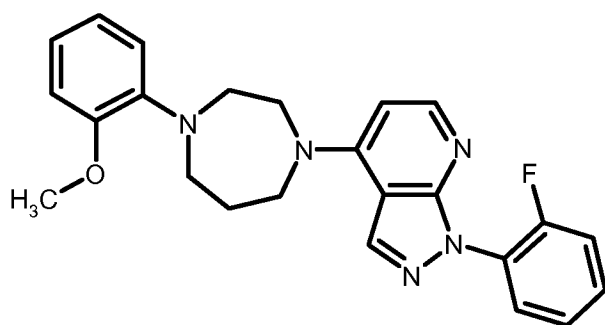
23,51 mg (0.03 mmol) Tris(dibenzylidene-acetone)dipalladium (0), 234,23 mg (0.72 mmol) cesium carbonate, 12.24 mg (0.03 mmol) 2-dicyclohexylphosphino-2,4,6-

triisopropylbiphenyl, 150 mg (0.51 mmol) 4-bromo-1-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine and 162.16 mg (0.62 mmol) 1-(5-chloro-2-methoxyphenyl)piperazine in 0.7 mL dioxane (microwave vial) were heated for 16 hours at 80 °C (heating block). The reaction mixture was filtered via a glass fibre filter. The filter was washed with ethyl acetate and the filtrate was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 46 mg (19.4%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.09 - 3.22 (m, 4H), 3.67 - 3.85 (m, 7H), 6.58 (d, 1H), 6.89 (d, 1H), 6.91 - 7.04 (m, 2H), 7.29 - 7.67 (m, 4H), 8.08 (d, 1H), 8.56 (s, 1H).

Example 113

1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-b]pyridine

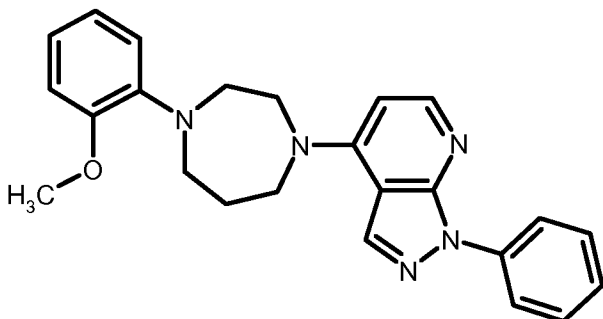


23,51 mg (0.03 mmol) Tris(dibenzylidene-acetone)dipalladium (0), 234,23 mg (0.72 mmol) cesium carbonate, 12.24 mg (0.03 mmol) 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl, 150 mg (0.51 mmol) 4-bromo-1-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine and 127.1 mg (0.62 mmol) 1-(2-methoxyphenyl)-1,4-diazepane in 0.7 mL dioxane (microwave vial) were heated for 16 hours at 80 °C (heating block). The reaction mixture was filtered via a glass fibre filter. The filter was washed with ethyl acetate and the filtrate was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 92.2 mg (40.9%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.05 (br. s., 2H), 3.03 - 3.21 (m, 2H), 3.41 (t, 2H), 3.71 (s, 3H), 3.81 - 3.99 (m, 4H), 6.37 (d, 1H), 6.71 - 6.95 (m, 4H), 7.28 - 7.67 (m, 4H), 7.95 (d, 1H), 8.42 (s, 1H).

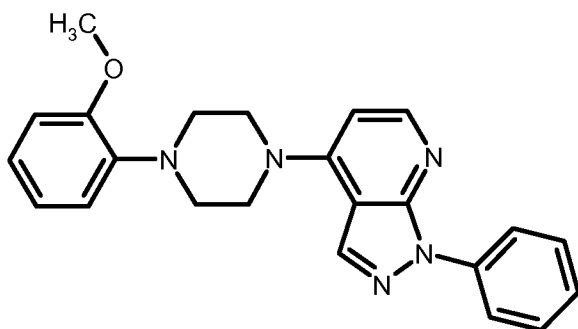
5 Example 114

4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine



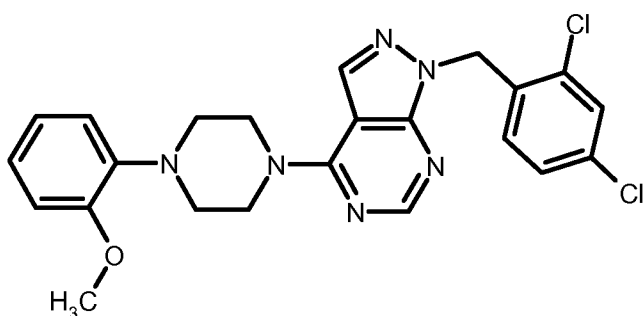
25.05 mg (0.03 mmol) Tris(dibenzylidene-acetone)dipalladium (0), 249.61 mg (0.77 mmol) cesium carbonate, 13.04 mg (0.03 mmol) 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl, 150 mg (0.55 mmol) 4-bromo-1-phenyl-1H-pyrazolo[3,4-b]pyridine and 135.46 mg (0.66 mmol) 1-(2-methoxyphenyl)-1,4-diazepane in 0.7 mL dioxane (microwave vial) were heated for 16 hours at 80 °C (heating block). The reaction mixture was filtered via a glass fibre filter. The filter was washed with ethyl acetate and the filtrate was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 71 mg (30.9%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.05 (br. s., 2H), 3.08 - 3.18 (m, 2H), 3.41 (t, 2H), 3.71 (s, 3H), 3.83 - 4.00 (m, 4H), 6.42 (d, 1H), 6.71 - 6.92 (m, 4H), 7.20 - 7.30 (m, 1H), 7.42 - 7.54 (m, 2H), 8.07 (d, 1H), 8.24 (dd, 2H), 8.41 (s, 1H).

Example 115**4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine**

23,55 mg (0.03 mmol) Tris(dibenzylidene-acetone)dipalladium (0), 224,65 mg (0.69
 5 mmol) cesium carbonate, 11.74 mg (0.03 mmol) 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl, 135 mg (0.51 mmol) 4-bromo-1-phenyl-1H-pyrazolo[3,4-b]pyridine and 113.67 mg (0.59 mmol) 1-(2-methoxyphenyl)piperazine in 0.7 mL dioxane (microwave vial) were heated for 16 hours at 80 °C (heating block). The reaction mixture was filtered via a glass fibre filter. The filter was washed with ethyl
 10 acetate and the filtrate was evaporated to dryness. The residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 94.6 mg (47.3%) of the title compound.

1H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.09 - 3.21 (m, 4H), 3.70 - 3.89 (m, 7H), 6.63
 15 (d, 1H), 6.80 - 7.02 (m, 4H), 7.22-7.32 (m, 1H), 7.45-7.58 (m, 2H), 8.15-8.30 (m, 3H), 8.58 (s, 1H).

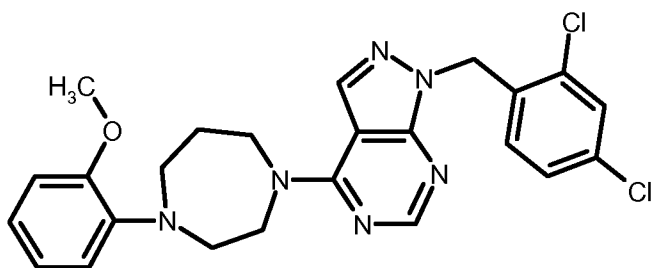
Example 116**1-(2,4-dichlorobenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine**

2.85 g (9.09 mmol) 4-Chloro-1-(2,4-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Journal of Heterocyclic Chemistry, 1989, vol.26, p.613 - 618) were dissolved in 10 mL DMF. 2.10 g (10.91 mmol) 1-(2-Methoxyphenyl)piperazine and 4.07 mL (27.27 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 4 hours at 130°C. After cooling the reaction mixture was evaporated to dryness. The residue was diluted with dichloromethane and extracted twice with brine. After evaporation of the solvent the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 341 mg (7.7 %) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 3.12 - 3.39 (m, 4 H), 3.94 (s, 3 H), 4.21 (br. s., 4 H), 5.69 (s, 2 H), 6.81 (d, 1 H), 6.89 - 7.01 (m, 3 H), 7.03 - 7.21 (m, 2 H), 7.43 (s, 1 H), 8.07 (s, 1 H), 8.42 (s, 1 H).

Example 117

1-(2,4-dichlorobenzyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine

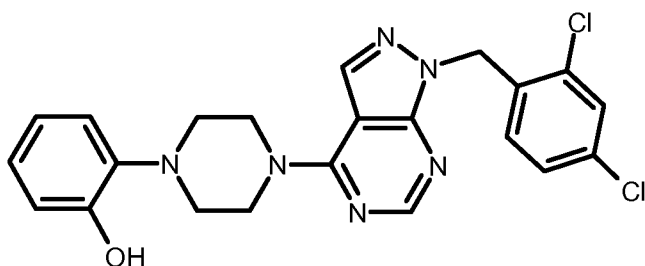


185 mg (59% pure) 4-Chloro-1-(2,4-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Journal of Heterocyclic Chemistry, 1989, vol.26, p.613 - 618) were dissolved in 0.69 mL DMF. 90 mg (0.42 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.16 mL (1.04 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 18 hours at 110°C (heating block). After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 59 mg (32.3 %) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.08 (s, 2 H), 3.18 (br. s., 2 H), 3.47 (br. s., 2 H), 3.73 (s, 3 H), 4.02 (br. s., 1 H), 4.08 (br. s., 2 H), 4.15 (br. s., 1 H), 5.59 (s, 2 H), 6.79 - 6.97 (m, 5 H), 7.36 (dd, 1 H), 7.67 (d, 1 H), 8.24 - 8.32 (m, 2 H).

5 Example 118

2-{4-[1-(2,4-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol



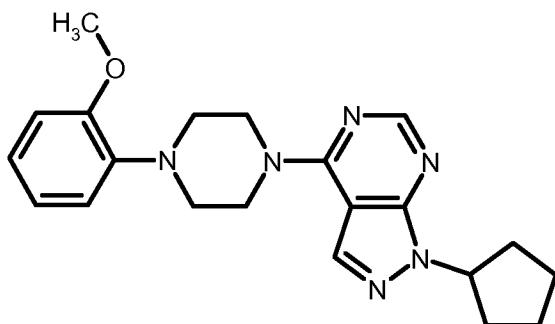
- 10 260 mg (59% pure) 4-Chloro-1-(2,4-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidine (preparation known: Journal of Heterocyclic Chemistry, 1989, vol.26, p.613 - 618) were dissolved in 1 mL DMF. 100 mg (0.56 mmol) 2-(Piperazin-1-yl)phenol and 0.21 mL (1.39 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated over night at 130° C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 37 mg (17.2 %) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.02 - 3.15 (m, 4 H), 4.05 - 4.18 (m, 4 H), 5.61 (s, 2 H), 6.74 - 6.99 (m, 5 H), 7.36 (d, 1 H), 7.67 (d, 1 H), 8.32 (s, 1 H), 8.43 (s, 1 H), 9.09 (s, 1 H).

Example 119

1-cyclopentyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine

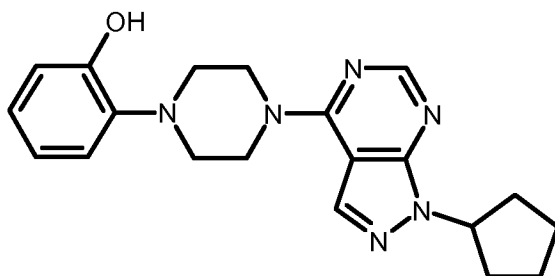
25



- 30 mg (0.13 mmol) 4-Chloro-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. UkrOrgSynthesis Ltd.) were dissolved in 1 mL DMF. 23
- 5 mg (0.12 mmol) 1-(2-Methoxyphenyl)piperazine and 0.06 mL (0.40 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 4 hours at 90°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by HPLC yielding 6.7 mg (13.1 %) of the title compound.
- 10 ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 1.63 - 1.74 (m, 2 H), 1.84 - 2.01 (m, 4 H), 2.02 - 2.13 (m, 2 H), 3.04 - 3.15 (m, 4 H), 3.83 (s, 3 H), 4.02 - 4.10 (m, 4 H), 5.18 - 5.28 (m, 1 H), 6.85 - 7.03 (m, 4 H), 8.28 (s, 1 H), 8.33 (s, 1 H) ppm.

Example 120

- 15 2-[4-(1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol

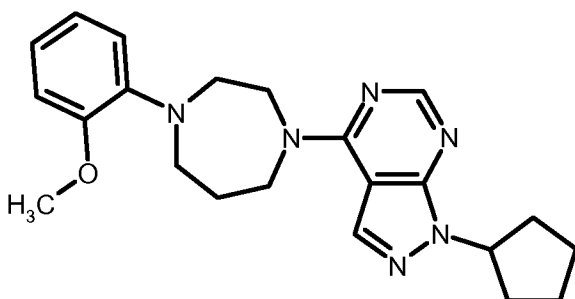


- 100 mg (0.45 mmol) 4-Chloro-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. UkrOrgSynthesis Ltd.) were dissolved in 1 mL DMF. 72
- mg (0.40 mmol) 2-(Piperazin-1-yl)phenol and 0.20 mL (1.34 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 4
- 20 hours at 95°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by HPLC yielding 26 mg (14.5 %) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 1.63 - 1.73 (m, 2 H), 1.84 - 2.09 (m, 6 H), 3.01 - 3.12 (m, 4 H), 4.03 - 4.13 (m, 4 H), 5.23 (q, 1 H), 6.71 - 6.78 (m, 1 H), 6.80 - 6.95 (m, 3 H), 8.28 (s, 1 H), 8.34 (s, 1 H), 9.08 (br. s., 1 H) ppm.

5 Example 121

1-cyclopentyl-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



10

100 mg (0.45 mmol) 4-Chloro-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidine (commercially available, e.g. UkrOrgSynthesis Ltd.) were dissolved in 1 mL DMF. 90 mg (0.45 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.20 mL (1.34 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 4 hours at 95°C. Due to an incomplete reaction heating was continued for additional two hours. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by HPLC yielding 29.6 mg (16.6 %) of the title compound.

15

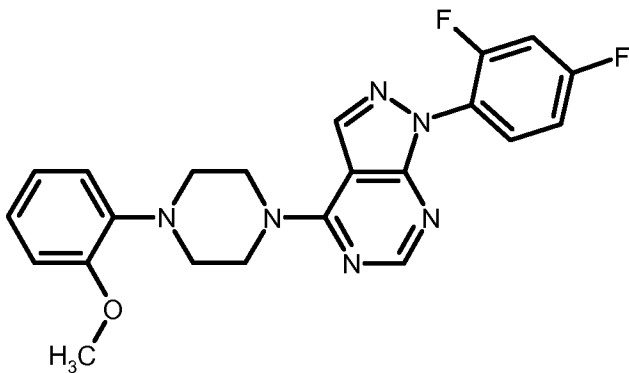
¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 1.63 - 1.74 (m, 2 H), 1.83 - 2.12 (m, 8 H), 3.17 (br. s., 2 H), 3.35 (br. s., 1 H), 3.45 (br. s., 1 H), 3.74 (s, 3 H), 4.01 (br. s., 1 H), 4.08 (br. s., 2 H), 4.13 (br. s., 1 H), 5.20 (t, 1 H), 6.74 - 6.93 (m, 4 H), 8.19 (s, 1 H), 8.23 (s, 1 H) ppm.

20

Example 122

1-(2,4-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine

25

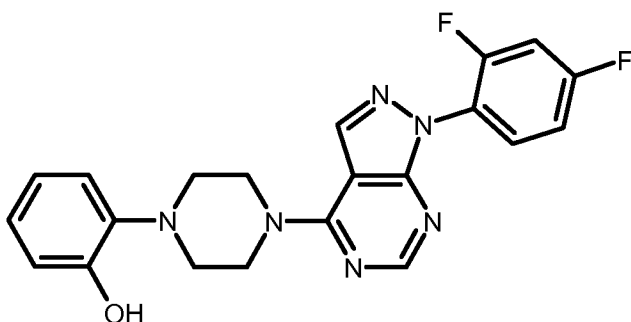


181 mg (0.60 mmol) 4,6-Dichloro-5-{(E)-[(2,4-difluorophenyl)hydrazono]methyl}pyrimidine (commercially available, e.g. Kingsh
 5 Chemicals Ltd.) were dissolved in 1 mL DMF. 138 mg (0.72 mmol) 1-(2-Methoxyphenyl)piperazine and 0.27 mL (1.80 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 73 mg (28.9%) of
 10 the desired compound.

1H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.07 - 3.19 (m, 4 H), 3.83 (s, 3 H), 4.06 - 4.19 (m, 4 H), 6.86 - 7.03 (m, 4 H), 7.26 - 7.38 (m, 1 H), 7.55 - 7.65 (m, 1 H), 7.67 - 7.78 (m, 1 H), 8.31 (s, 1 H), 8.67 (s, 1 H).
 15

Example 123

2-{4-[1-(2,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol



20

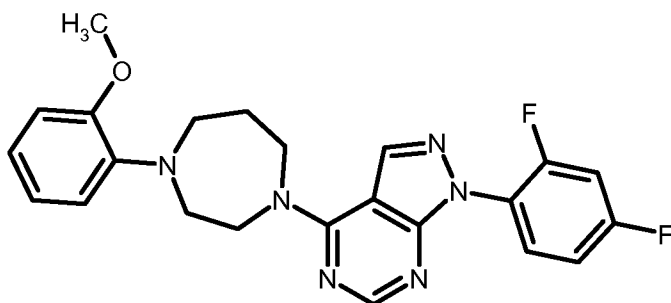
407 mg (1.34 mmol) 4,6-Dichloro-5-[(E)-[(2,4-difluorophenyl)hydrazono]methyl]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 2 mL DMF. 287 mg (1.61 mmol) 2-(Piperazin-1-yl)phenol and 0.60 mL (4.03 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added.

- 5 The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 72 mg (12%) of the desired compound.

- 10 ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 3.07 - 3.14 (m, 4 H), 4.10 - 4.20 (m, 4 H), 6.73 - 6.80 (m, 1 H), 6.81 - 6.90 (m, 2 H), 6.93 (dd, 1 H) 7.28 - 7.36 (m, 1 H), 7.59 (ddd, 1 H), 7.72 (td, 1 H), 8.31 (s, 1 H), 8.67 (s, 1 H), 9.10 (s, 1 H).

Example 124

- 15 1-(2,4-difluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine

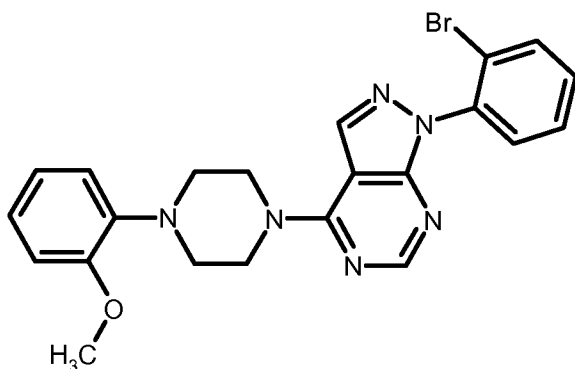


- 163 mg (0.54 mmol) 4,6-Dichloro-5-[(E)-[(2,4-difluorophenyl)hydrazono]methyl]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 1 mL DMF. 133.1 mg (0.65 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.24 mL (1.60 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and
- 25 the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) yielding 47 mg (20%) of the desired compound.

¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 2.15 (br. s., 2 H), 3.21 (br. s., 2 H), 3.38 (br. s., 1 H), 3.51 (br. s., 1 H), 3.75 (s, 3 H), 4.13 (br. s., 4 H), 6.76 - 6.91 (m, 4 H), 7.26 - 7.35 (m, 1 H), 7.58 (ddd, 1 H), 7.72 (td, 1 H), 8.27 (s, 1 H), 8.52 (s, 1 H).

5 Example 125

1-(2-bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine

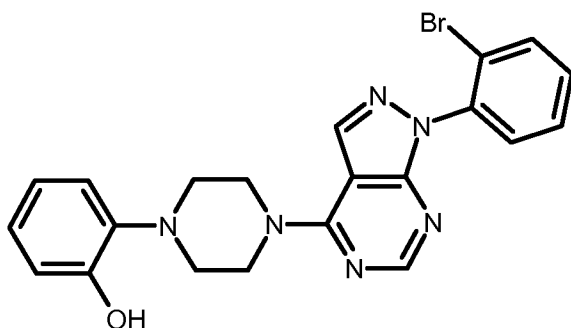


- 10 1,67 g (4.82 mmol) 4,6-Dichloro-5-[(E)-[(2-bromophenyl)hydrazono]methyl]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 10 mL DMF. 1.11 g (5.78 mmol) 1-(2-Methoxyphenyl)piperazine and 2.16 mL (14.45 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and
- 15 the residue was purified by chromatography (silicagel, eluents: ethyl acetate/hexane) followed by an additional HPLC yielding 0.40 g (17%) of the desired compound.

- ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.10 - 3.18 (m, 4 H), 3.84 (s, 3 H), 4.10 - 4.17 (m, 4 H), 6.86 - 7.05 (m, 4 H), 7.49 - 7.64 (m, 3 H), 7.88 (dd, 1 H), 8.27 (s, 1 H), 8.64 (s, 1 H).
- 20

Example 126

2-{4-[1-(2-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol

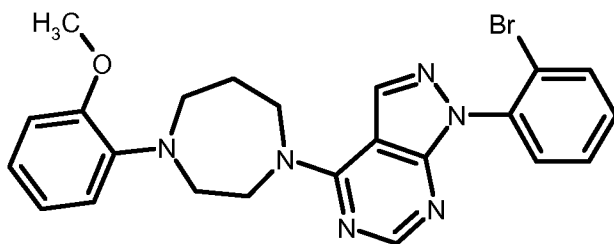


500 mg (1.45 mmol) 4,6-Dichloro-5-[(E)-[(2-bromophenyl)hydrazono]methyl]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 3 mL DMF. 310 mg (1.73 mmol) 2-(Piperazin-1-yl)phenol and 0.65 mL (4.34 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction mixture was evaporated to dryness and the residue was purified by HPLC yielding 42 mg (6.2%) of the title compound.

10 ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.05 - 3.17 (m, 4 H), 4.10 - 4.18 (m, 4 H), 6.77 (dd, 1 H), 6.80 - 6.89 (m, 2 H), 6.93 (d, 1 H), 7.49 - 7.63 (m, 3 H), 7.88 (dd, 1 H), 8.27 (s, 1 H), 8.64 (s, 1 H), 9.15 (s, 1 H).

Example 127

15 1-(2-bromophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



20 160 mg (0.46 mmol) 4,6-Dichloro-5-[(E)-[(2-bromophenyl)hydrazono]methyl]pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 1 mL DMF. 110 mg (0.55 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.21 mL (1.39 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6

hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/hexane) followed by an additional HPLC yielding 9.4 mg (4.2%) of the desired compound.

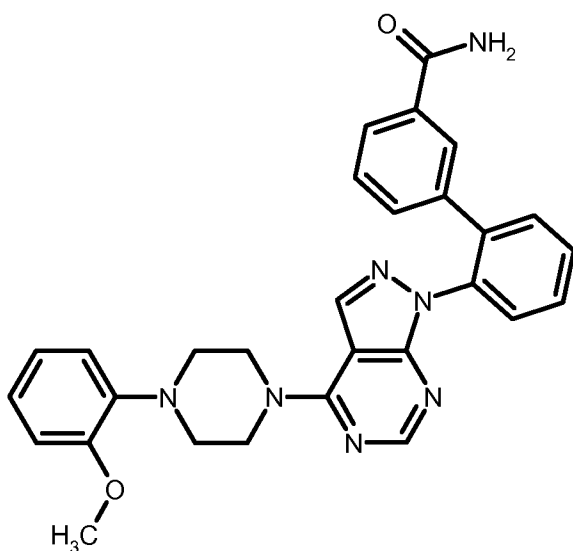
5

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 2.10 - 2.37 (m, 2 H), 3.32 (t, 2 H), 3.48 (br. s., 1 H), 3.58 (br. s., 1 H), 3.88 (s, 3 H), 4.10 - 4.36 (m, 4 H), 6.86 - 6.93 (m, 2 H), 6.94 - 7.02 (m, 2 H), 7.34 - 7.43 (m, 1 H), 7.48 - 7.54 (m, 2 H), 7.78 (d, 1 H), 8.18 (s, 1 H), 8.42 (s, 1 H).

10

Example 128

2'-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}biphenyl-3-carboxamide



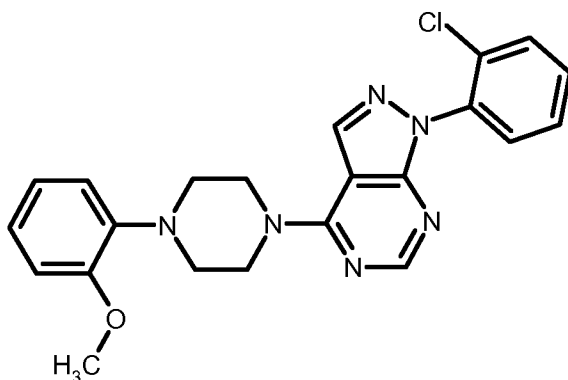
- 15 100 mg (0.21 mmol) 1-(2-Bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, 70.9 mg (0.43 mmol) (3-carbamoylphenyl)boronic acid, 17.6 mg (0.02 mmol) 1,1' bis-(diphenyl-phosphino)ferrocenedichloropalladium(II) and 68.3 mg (0.64 mmol) sodium carbonate were given in a degassed mixture of 0.3 mL water and 2.3 mL dioxane. After purging the vial with nitrogen the reaction mixture
- 20 was heated in the microwave for 90 minutes at 105 °C. The reaction mixture was poured on saturated ammonium chloride solution and dichloromethane. After vigorous stirring for 30 minutes the organic phase was separated and washed twice with brine, dried over sodium sulfate, and the solvent was evaporated. The residue

was purified via HPLC chromatography yielding 6.5 mg (6%) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) = 3.06 - 3.14 (m, 4 H), 3.82 (s, 3 H), 4.01 - 4.09 (m, 4 H), 6.86 - 6.95 (m, 2 H), 6.95 - 7.01 (m, 3 H), 7.19 (t, 1 H), 7.28 (br. s., 1 H), 7.51 - 7.55 (m, 1 H), 7.58 - 7.70 (m, 4 H), 7.71 (t, 1 H), 7.90 (br. s., 1 H), 8.13 (s, 1 H), 8.44 (s, 1 H).

Example 129

10 1-(2-chlorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



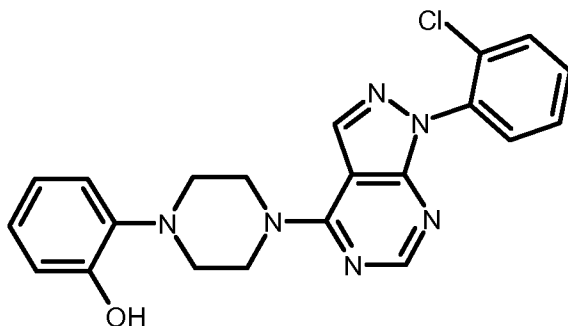
175 mg (0.58 mmol) 4,6-Dichloro-5-{(E)-[(2-chlorophenyl)hydrazono]methyl}pyrimidine (commercially available, e.g. Kingsh
15 Chemicals Ltd.) were dissolved in 1 mL DMF. 180 mg (0.58 mmol) 1-(2-Methoxyphenyl)piperazine and 0.26 mL (1.74 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/ hexane) followed by an additional
20 HPLC yielding 37 mg (14.9%) of the desired compound.

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 3.23 - 3.33 (m, 4 H), 3.95 (s, 3 H), 4.20 - 4.31 (m, 4 H), 6.91 - 7.02 (m, 4 H), 7.42 - 7.50 (m, 2 H), 7.53 (d, 1 H), 7.60 (d, 1 H), 8.25 (s, 1 H), 8.44 (s, 1 H).

25

Example 130

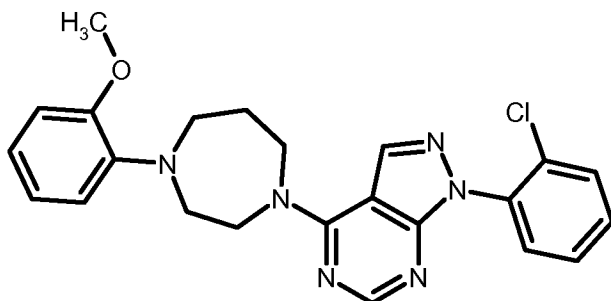
2-{4-[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol



- 5 500 mg (1.66 mmol) 4,6-Dichloro-5-{(E)-[(2-chlorophenyl)hydrazono]methyl}pyrimidine (commercially available, e.g. Kingsh Chemicals Ltd.) were dissolved in 5 mL DMF. 360 mg (1.99 mmol) 2-(Piperazin-1-yl)phenol and 0.74 mL (4.97 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 6 hours at 130°C. After cooling the reaction
- 10 mixture was evaporated to dryness, and the residue was diluted with dichloromethane. The organic phase was washed with water and brine, dried (MgSO₄) and the solvent was removed. The residue was purified by HPLC yielding 65 mg (7.6%) of the title compound.
- 15 ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) = 3.07 - 3.16 (m, 4 H), 4.09 - 4.20 (m, 4 H), 6.77 (dd, 1 H), 6.80 - 6.89 (m, 2 H) 6.93 (d, 1 H), 7.54 - 7.65 (m, 3 H), 7.70 - 7.76 (m, 1 H), 8.27 (s, 1 H), 8.65 (s, 1 H), 9.14 (s, 1 H).

Example 131

- 20 **1-(2-chlorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine**

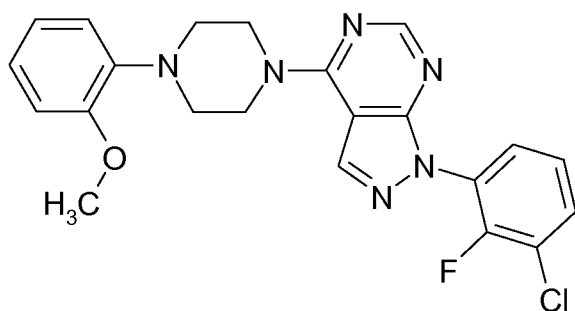


150 mg (0.50 mmol) 4,6-Dichloro-5-[(E)-[(2-chlorophenyl)hydrazono]methyl]pyrimidine (commercially available, e.g. Kingsh
 5 Chemicals Ltd.) were dissolved in 1 mL DMF. 126 mg (0.60 mmol) 1-(2-Methoxyphenyl)-1,4-diazepane and 0.22 mL (1.49 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en were added. The reaction mixture was heated for 3 hours at 130°C. After cooling the reaction mixture was evaporated to dryness, and the residue was purified by chromatography (silicagel, eluents: ethyl acetate/
 10 hexane) followed by an additional HPLC yielding 19.5 mg (9%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ (ppm) = 2.09 - 2.40 (m, 3 H), 3.32 (t, 2 H), 3.49 (br. s., 1 H), 3.57 (br. s., 1 H), 3.88 (s, 3 H), 4.22 (br. s., 4 H), 6.85 - 6.93 (m, 2 H), 6.94 - 7.03 (m, 2 H), 7.43 - 7.50 (m, 2 H), 7.51 - 7.57 (m, 1 H), 7.58 - 7.64 (m, 1 H), 8.18 (s, 1
 15 H), 8.42 (s, 1 H).

Example 132

1-(3-chloro-2-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-*d*]pyrimidine



20

To 210 mg (0.74 mmol) 4-chloro-1-(3-chloro-2-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidine in 3 mL anhydrous DMF were added 143 mg (0.74 mmol) 1-(2-methoxyphenyl)piperazine and 0.332 mL (2.23 mmol) DBU. The mixture was stirred 3

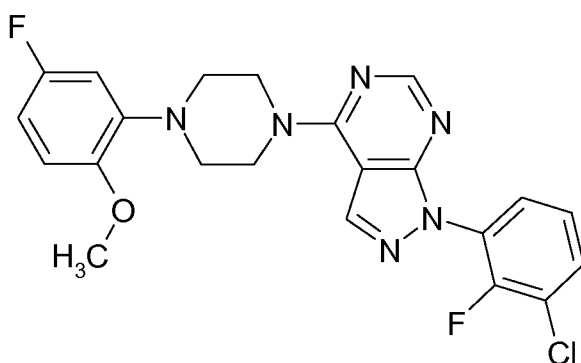
h at 120°C. The mixture was allowed to reach rt and concentrated on a rotavap. The residue was purified by HPLC to yield 159 mg (49%) product.

LC-MS (analytical method 3): R_t = 1.35 min, MS (ESIpos): m/z = 439 ($M+H$)⁺.

- 5 ¹H-NMR (400MHz, DMSO- d_6): δ [ppm]= 3.14 (br. s., 4H), 3.83 (s, 3H), 4.08 - 4.17 (m, 4H), 6.86 - 7.04 (m, 4H), 7.44 (s, 1H), 7.66 (s, 1H), 7.78 (s, 1H), 8.33 (s, 1H), 8.70 (s, 1H).

Example 133

- 10 **1-(3-chloro-2-fluorophenyl)-4-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-*d*]pyrimidine**



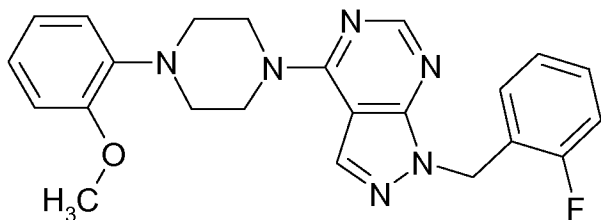
- To 106 mg (0.37 mmol) 4-chloro-1-(3-chloro-2-fluorophenyl)-1H-pyrazolo[3,4-*d*]pyrimidine in 1.5 mL anhydrous DMF were added 78.7 mg (0.37 mmol) 1-(5-fluoro-2-methoxyphenyl)piperazine and 0.168 mL (1.12 mmol) DBU. The mixture was stirred
 15 3 h at 120°C. The mixture was allowed to reach rt and concentrated on a rotavap. The residue was purified by HPLC to yield 14 mg (8%) product.

LC-MS (analytical method 3): R_t = 1.42 min, MS (ESIpos): m/z = 457 ($M+H$)⁺.

- 20 ¹H-NMR (500MHz, DMSO- d_6): δ [ppm]= 3.12 - 3.21 (m, 4H), 3.82 (s, 3H), 4.09 - 4.15 (m, 4H), 6.74 - 6.80 (m, 2H), 6.94 - 6.99 (m, 1H), 7.41 - 7.47 (m, 1H), 7.63 - 7.68 (m, 1H), 7.76 - 7.81 (m, 1H), 8.33 (s, 1H), 8.70 (s, 1H).

Example 134

- 25 **1-(2-fluorobenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-*d*]pyrimidine**



Step 1:

- 100 mg (0.57 mmol) 4,6-dichloropyrimidine-5-carbaldehyde, 79.2 mg 0.57 mmol (2-fluorobenzyl)hydrazine and 0.079 mL (0.57 mmol) *N,N*-diethylethanamine in 5 mL anhydrous 1,2-dimethoxyethane were stirred 1.5 h under reflux. The reaction mixture was allowed to reach rt and concentrated on a rotavap. This material was used without further purification in the next step

Step 2:

- To 148.8 mg (0.57 mmol) 4-chloro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (from step 1) in 2 mL anhydrous DMF were added 108.6 mg (0.57 mmol) 1-(2-methoxyphenyl)piperazine and 0.253 mL (1.70 mmol) DBU. The mixture was stirred 3 h at 120°C. The mixture was allowed to reach rt and concentrated on a rotavap. The residue was purified by HPLC to yield 98.4 mg (40%) product.

15

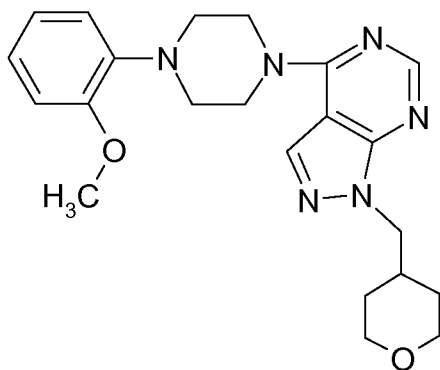
LC-MS (analytical method 3): $R_t = 1.32$ min, MS (ESIpos): $m/z = 419$ ($M+H$)⁺.

¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 3.02 - 3.12 (m, 4H), 3.78 (s, 3H), 4.00 - 4.10 (m, 4H), 5.55 (s, 2H), 6.81 - 7.00 (m, 4H), 7.03 - 7.22 (m, 3H), 7.26 - 7.36 (m, 1H), 8.29 (s, 1H), 8.36 (s, 1H).

20

Example 135

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



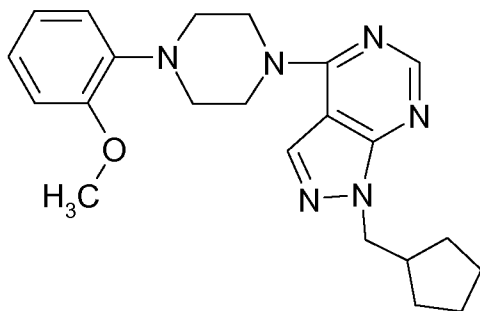
At 0-5°C were added 0.133 mL (0.68 mmol) diisopropyl-diazene-1,2-dicarboxylate to 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 74.9 mg (0.64 mmol) tetrahydro-2*H*-pyran-4-ylmethanol and 169 mg (0.64 mmol) triphenylphosphine in 5 mL anhydrous THF. It was stirred 27 h at rt. It was concentrated on a rotavap. The residue was purified on silicagel (dichloromethane/methanol 95:5 gradient) and by HPLC yielding 13 mg (5%) product.

LC-MS (analytical method 3): R_t = 1.13 min, MS (ESIpos): m/z = 409 ($M+H$)⁺.

¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 1.31 (br. s., 4H), 2.02 - 2.20 (m, 1H), 3.02 - 3.12 (m, 4H), 3.18 (d, 2H), 3.71 - 3.84 (m, 5H), 3.98 - 4.10 (m, 4H), 4.18 (d, 2H), 6.82 - 7.01 (m, 4H), 8.25 (s, 1H), 8.33 (s, 1H).

Example 136

1-(cyclopentylmethyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine

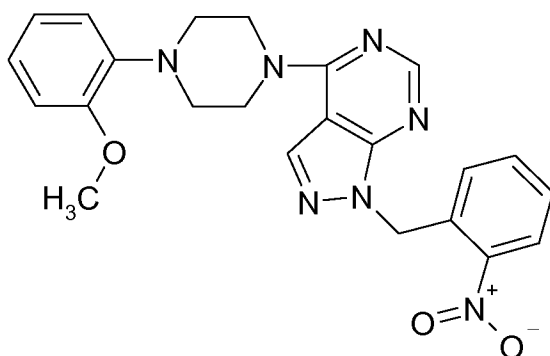


At 0-5°C were added 0.133 mL (0.68 mmol) diisopropyl-diazene-1,2-dicarboxylate to 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 64.5 mg (0.64 mmol) cyclopentylmethanol and 169 mg (0.64 mmol) triphenylphosphine in 5 mL anhydrous THF. It was stirred 20 h at rt. It was

concentrated on a rotavap. The residue was purified on silicagel (dichloromethane/methanol 95:5 gradient) and by HPLC yielding 37 mg (31%) product.

- 5 LC-MS (analytical method 3): $R_t = 1.39$ min, MS (ESIpos): $m/z = 393$ ($M+H$)⁺.
¹H-NMR (300MHz, DMSO- d_6): δ [ppm]= 1.25 (br. s., 2H), 1.37 - 1.61 (m, 6H), 2.36 - 2.44 (m, 1H), 3.02 - 3.11 (m, 4H), 3.79 (s, 3H), 3.99 - 4.09 (m, 4H), 4.19 (d, 2H), 6.82 - 7.00 (m, 4H), 8.25 (s, 1H), 8.31 (s, 1H).

10 **Example 137**
4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(2-nitrobenzyl)-1H-pyrazolo[3,4-*d*]pyrimidine



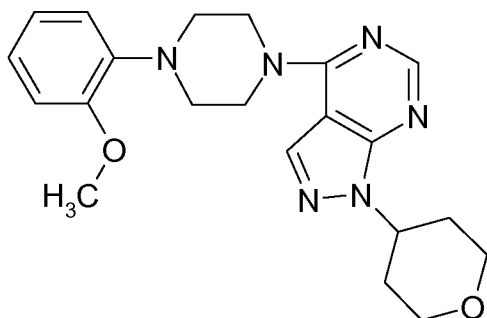
- 15 18.3 mg (0.42 mmol) sodium hydride (55% in oil) and 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-*d*]pyrimidine in 3 mL anhydrous DMF were stirred for 30 minutes. Then were added 90.5 mg (0.42 mmol) 1-(bromomethyl)-2-nitrobenzene. It was stirred over night at rt. A small spatula tip of sodium hydride was added and it was stirred 2 additional h at rt. The mixture was concentrated on a rotavap. The residue was purified by HPLC yielding 10 mg (7%) product.

- 20 LC-MS (analytical method 3): $R_t = 1.31$ min, MS (ESIpos): $m/z = 446$ ($M+H$)⁺.
¹H-NMR (400MHz, DMSO- d_6): δ [ppm]= 3.12 (br. s., 4H), 3.82 (s, 3H), 4.09 (br. s., 4H), 5.90 (s, 2H), 6.80 - 6.85 (m, 1H), 6.98 (s, 4H), 7.54 - 7.60 (m, 1H), 7.60 - 7.67 (m, 1H), 8.09 - 8.13 (m, 1H), 8.29 (s, 1H), 8.45 (s, 1H).

25

Example 138

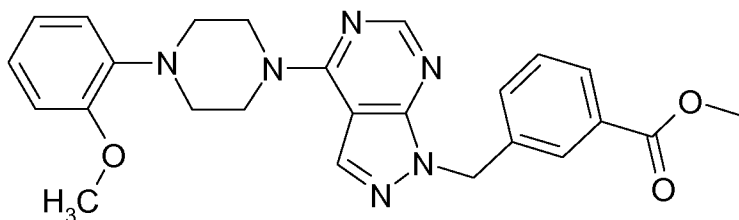
4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidine



- 5 To 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine, 525 mg (1.61 mmol) cesium carbonate and 12.3 mg (0.08 mmol) sodium iodide in 4 mL anhydrous DMF were added 160 mg (0.97 mmol) 4-bromotetrahydro-2H-pyran. It was stirred over night at rt and then 4 h at 50°C. The mixture was concentrated on a rotavap. 20 mL water and 15 mL dichloromethane were added.
- 10 The layers were separated and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by HPLC yielding 44 mg (34%) product.
- 15 LC-MS (analytical method 3): $R_t = 1.14$ min, MS (ESIpos): $m/z = 395$ ($M+H$)⁺.
¹H-NMR (300MHz, DMSO- d_6): δ [ppm]= 1.76 - 1.87 (m, 2H), 2.05 - 2.22 (m, 2H), 3.05 - 3.14 (m, 4H), 3.47 - 3.60 (m, 2H), 3.82 (s, 3H), 3.94 - 4.03 (m, 2H), 4.03 - 4.11 (m, 4H), 4.85 - 4.99 (m, 1H), 6.84 - 7.03 (m, 4H), 8.28 (s, 1H), 8.33 - 8.38 (m, 1H).

Example 139

methyl 3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}methyl)benzoate



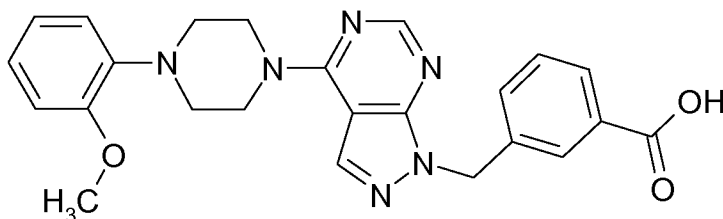
To 1.5 g (4.83 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 7.87 g (24.17 mmol) cesium carbonate and 185 mg (1.23 mmol) sodium iodide in 60 mL anhydrous DMF were added 1.33 g (5.80 mmol) methyl 3-(bromomethyl)benzoate. It was stirred over night at rt. The reaction mixture was concentrated on a rotavap and water and dichloromethane were added. The layers were separated and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed three times with water, dried over magnesium sulfate and concentrated. The residue was purified on silica gel (gradient of hexane and ethyl acetate) yielding 1.3 g (59%) product.

LC-MS (analytical method 3): R_t = 1.29 min, MS (ESIpos): m/z = 459 ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 3.04 - 3.11 (m, 4H), 3.79 (d, 6H), 4.01 - 4.09 (m, 4H), 5.59 (s, 2H), 6.88 (s, 2H), 6.92 - 6.99 (m, 2H), 7.42 - 7.50 (m, 2H), 7.82 (d, 2H), 8.30 (s, 1H), 8.38 (s, 1H).

Example 140

3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)benzoic acid



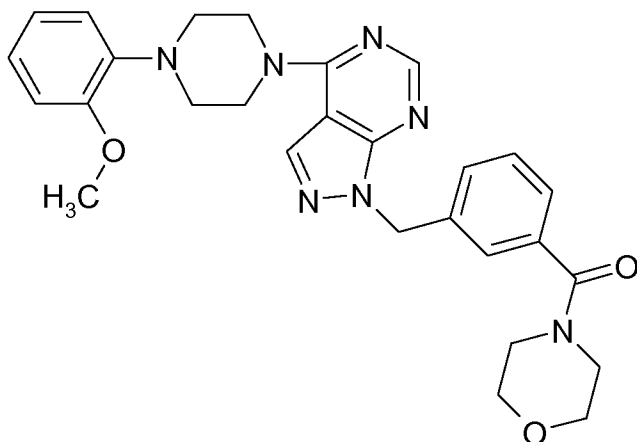
To 1.3 g (2.84 mmol) methyl 3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)benzoate in 5.7 mL methanol and 23 mL THF were added 203.7 mg (8.51 mmol) lithium hydroxide. It was stirred 30 h at 40°C. The reaction mixture was concentrated on a rotavap. Water was added and the pH was adjusted to 5 with 1 M hydrochloric acid. It was stirred 2 h. The precipitate was filtered off under suction and dried 48 h at 45°C under vacuum to afford 1.04 g (83%) product.

LC-MS (analytical method 3): R_t = 1.13 min, MS (ESIpos): m/z = 445 ($M+H$)⁺.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 3.07 (br. s., 4H), 3.79 (s, 3H), 4.05 (br. s., 4H), 5.58 (s, 2H), 6.80 - 7.01 (m, 4H), 7.36 - 7.50 (m, 2H), 7.73 - 7.85 (m, 2H), 8.30 (s, 1H), 8.37 (s, 1H), 12.80 - 13.10 (m, 1H).

5 Example 141

[3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)phenyl](morpholin-4-yl)methanone



To 75 mg (0.17 mmol) 3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)benzoic acid, 19.1 mg (0.22 mmol) morpholine and 0.176 mL (1.01 mmol) *N*-ethyl-*N*-isopropylpropan-2-amine in 4 mL ethyl acetate were added 0.151 mL (0.25 mmol) 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (50% in ethyl acetate). It was stirred over night at rt. The residue was purified by HPLC giving 54 mg (62%) product.

15

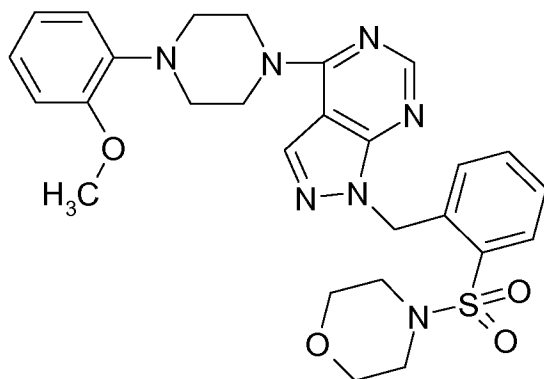
LC-MS (analytical method 5): *R*_t = 1.11 min, MS (ESIpos): *m/z* = 514 (*M*+*H*)⁺.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 3.11 (d, 4H), 3.40 - 3.70 (m, 6H), 3.81 (s, 3H), 4.07 (d, 4H), 5.58 (s, 2H), 6.91 (s, 2H), 6.95 - 7.02 (m, 2H), 7.22 (s, 1H), 7.27 - 7.32 (m, 2H), 7.35 - 7.41 (m, 1H), 8.32 (s, 1H), 8.40 (s, 1H).

20

Example 142

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[2-(morpholin-4-ylsulfonyl)benzyl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



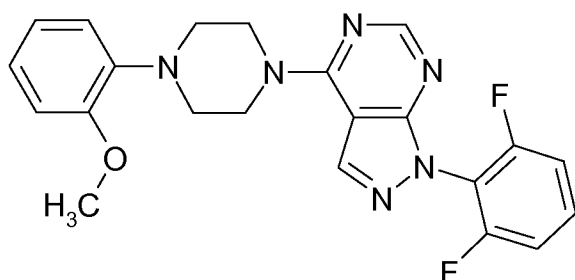
To 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-
 d]pyrimidine, 525 mg (1.61 mmol) cesium carbonate and 12.3 mg (0.08 mmol) sodium
 iodide in 4 mL anhydrous DMF were added 134.1 mg (0.42 mmol) 4-
 5 (bromomethyl)phenyl]sulfonyl}morpholine. It was stirred over night at rt. The
 mixture was concentrated on a rotavap. The residue was purified by HPLC yielding 69
 mg (35%) product.

LC-MS (analytical method 3): $R_t = 1.25$ min, MS (ESIpos): $m/z = 550$ ($M+H$)⁺.

10 ¹H-NMR (600MHz, DMSO-*d*₆): δ [ppm]= 3.13 - 3.18 (m, 8H), 3.68 - 3.72 (m, 4H), 3.85
 (s, 3H), 4.13 (br. s., 4H), 5.96 (s, 2H), 6.54 - 6.57 (m, 1H), 6.90 - 6.94 (m, 1H), 6.95 -
 6.98 (m, 1H), 7.01 (d, 2H), 7.53 - 7.59 (m, 2H), 7.91 - 7.94 (m, 1H), 8.32 (s, 1H), 8.53
 (s, 1H).

15 Example 143

1-(2,6-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-
 d]pyrimidine



To 77 mg (0.29 mmol) 4-chloro-1-(2,6-difluorophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine
 20 and 56 mg (0.29 mmol) 1-(2-methoxyphenyl)piperazine in 0.22 mL anhydrous DMF
 were added 0.130 mL (0.86 mmol) DBU. The mixture was stirred 3 h at 120°C. The
 mixture was allowed to reach rt and water was added. The solid material was

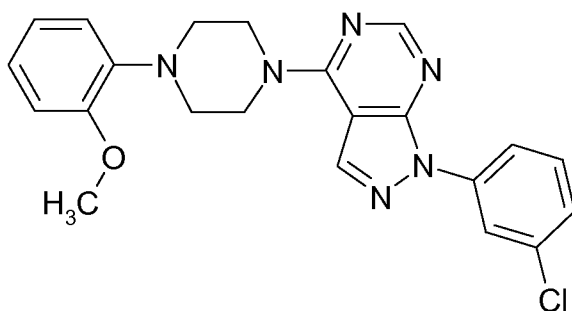
filtered off under suction and washed three times with water. The solid material was dried under vacuum providing 66 mg (56%) product.

LC-MS (analytical method 3): R_t = 1.25 min, MS (ESIpos): m/z = 423 ($M+H$)⁺.

- 5 ¹H-NMR (300MHz, DMSO- d_6): δ [ppm]= 3.11 (br. s., 4H), 3.80 (s, 3H), 4.09 (d, 4H), 6.81 - 7.02 (m, 4H), 7.35 - 7.44 (m, 2H), 7.62 - 7.74 (m, 1H), 8.27 (s, 1H), 8.69 (s, 1H).

Example 144

- 10 1-(3-chlorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



Step1:

- 100 mg (0.57 mmol) 4,6-dichloropyrimidine-5-carbaldehyde and 101.2 mg (0.57 mmol) (3-chlorophenyl)hydrazine hydrochloride were dissolved in 2.5 mL 1,2-dimethoxyethane. 0.158 mL (1.13 mmol) *N,N*-diethylethanamine were added and it was stirred 3 h at 75°C and 2 h at 120°C. The reaction mixture was concentrated on a rotavap to provide 149 mg of crude material which was used without further purification in the next step.

20

Step 2:

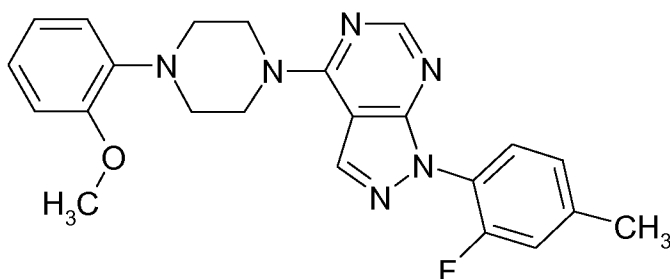
- To 149 mg material from step 1 and 108 mg (0.56 mmol) 1-(2-methoxyphenyl)piperazine in 1 mL anhydrous DMF were added 0.252 mL (1.69 mmol) DBU. The mixture was stirred 3 h at 120°C. The mixture was allowed to reach rt and and was then concentrated on a rotavap. The residue was purified by HPLC providing 5 mg (2%) product.

LC-MS (analytical method 3): R_t = 1.54 min, MS (ESIpos): m/z = 421 ($M+H$)⁺.

¹H-NMR (300MHz, CHLOROFORM-d): δ [ppm]= 3.22 - 3.30 (m, 4H), 3.93 (s, 3H), 4.17 - 4.26 (m, 4H), 6.90 - 6.99 (m, 3H), 7.05 (d, 1H), 7.27 - 7.33 (m, 1H), 7.44 (t, 1H), 8.15 - 8.22 (m, 2H), 8.29 (t, 1H), 8.49 (s, 1H).

5 Example 145

1-(2-fluoro-4-methylphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



Step 1:

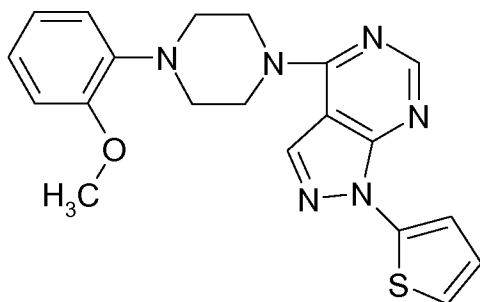
- 10 100 mg (0.71 mmol) (2-fluoro-4-methylphenyl)hydrazine, 126.3 mg (0.71 mmol) 4,6-dichloropyrimidine-5-carbaldehyde and 0.099 mL (0.71 mmol) *N,N*-diethylethanamine were heated 3 h in 3.2 mL 1,2-dimethoxyethane. The reaction was allowed to reach rt and concentrated on a rotavap yielding 213 mg (99.8%) product which was used without further purification in the next step.
- 15 LC-MS (analytical method 3): R_t = 1.36 min, MS (ESIpos): m/z = 263 ($M+H$)⁺.

Step 2:

- To 187 mg (0.63 mmol) 4,6-dichloro-5-[(2-fluoro-4-methylphenyl)hydrazono]methylpyrimidine (step 1) and 120.2 mg (0.63 mmol) 1-(2-methoxyphenyl)piperazine in 2.2 mL anhydrous DMF were added 0.280 mL (1.88 mmol) DBU. The mixture was stirred 4 h at 120°C. The mixture was allowed to reach rt and was then concentrated on a rotavap. The residue was purified by HPLC giving 112 mg (42%) product.
- LC-MS (analytical method 3): R_t = 1.36 min, MS (ESIpos): m/z = 419 ($M+H$)⁺.
- 25 ¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 2.39 (s, 3H), 3.11 (d, 4H), 3.80 (s, 3H), 4.04 - 4.14 (m, 4H), 6.81 - 7.01 (m, 4H), 7.19 (s, 1H), 7.24 - 7.32 (m, 1H), 7.46 (s, 1H), 8.26 (s, 1H), 8.59 (s, 1H).

Example 147

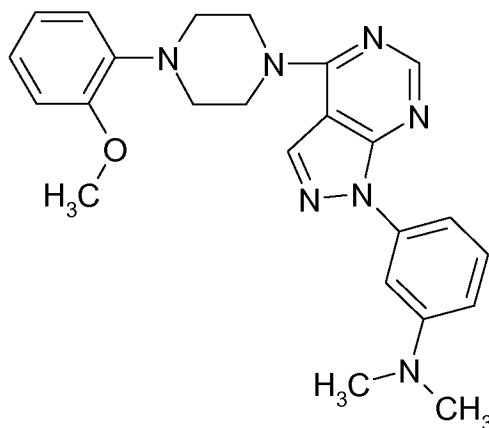
4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(thiophen-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



- 5 80 mg (0.26 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 63 mg (0.39 mmol) 2-bromothiophene, 14.7 mg (0.08 mmol) copper(I) iodide, 115 mg (0.54 mmol) tripotassium phosphate and 22 mg (0.16 mmol) trans-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C for 4 h. The reaction mixture was poured into water
- 10 and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with water, dried over magnesium sulfate and concentrated. The residue was purified by HPLC affording 16 mg (16%) product.
- 15 LC-MS (analytical method 3): $R_t = 1.39$ min, MS (ESIpos): $m/z = 393$ ($M+H$)⁺.
¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 3.13 (br. s., 4H), 3.82 (s, 3H), 4.11 (br. s., 4H), 6.85 - 7.04 (m, 4H), 7.09 (s, 1H), 7.35 (s, 1H), 7.67 - 7.71 (m, 1H), 8.44 (s, 1H), 8.62 (s, 1H).

Example 148

3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-*N,N*-dimethylaniline



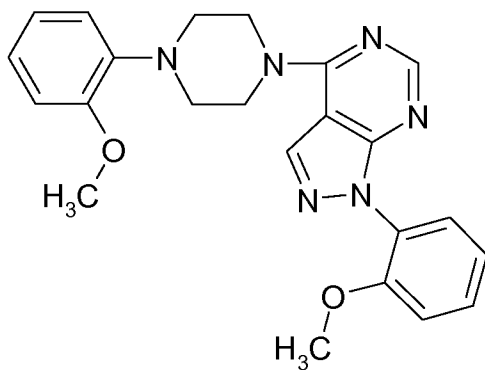
80 mg (0.26 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-
 d]pyrimidine, 77.4 mg (0.39 mmol) 3-bromo-*N,N*-dimethylaniline, 14.7 mg (0.08
 mmol) copper(I) iodide, 115 mg (0.54 mmol) tripotassium phosphate and 22 mg (0.16
 5 mmol) *trans-N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were
 heated under microwave irradiation at 180°C for 4 h. The reaction mixture was
 poured into water and extracted three times with ethyl acetate. The combined
 organic phases were washed with 0.5 M aqueous EDTA solution and three times with
 water, dried over magnesium sulfate and concentrated. The residue was purified by
 10 HPLC affording 32 mg (29%) product.

LC-MS (analytical method 3): R_t = 1.42 min, MS (ESIpos): m/z = 430 ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 2.96 (s, 6H), 3.13 (br. s., 4H), 3.83 (s, 3H),
 4.12 (br. s., 4H), 6.68 - 6.74 (m, 1H), 6.98 (s, 4H), 7.28 - 7.35 (m, 1H), 7.44 - 7.48
 15 (m, 1H), 7.48 - 7.52 (m, 1H), 8.39 (s, 1H), 8.59 (s, 1H).

Example 149

1-(2-methoxyphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-
 d]pyrimidine



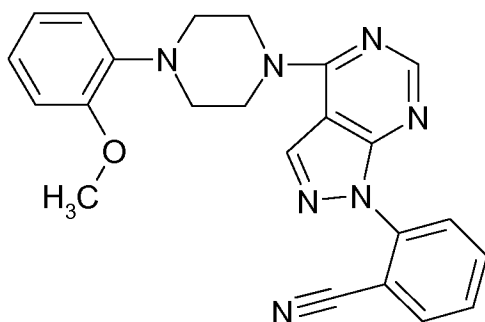
80 mg (0.26 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-
 d]pyrimidine (for preparation see Intermediate 19A), 90.5 mg (0.39 mmol) 1-iodo-2-
 methoxybenzene, 14.7 mg (0.08 mmol) copper(I) iodide, 115 mg (0.54 mmol)
 5 tripotassium phosphate and 22 mg (0.16 mmol) trans-*N,N*-dimethylcyclohexane-1,2-
 diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C
 for 4 h. The reaction mixture was poured into water and extracted three times with
 ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA
 solution and three times with water, dried over magnesium sulfate and concentrated.
 10 The residue was purified by HPLC affording 4 mg (4%) product.

LC-MS (analytical method 3): R_t = 1.02 min, MS (ESIpos): m/z = 417 ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 3.08 - 3.18 (m, 4H), 3.70 (s, 3H), 3.83 (s, 3H),
 4.08 - 4.15 (m, 4H), 6.87 - 7.03 (m, 4H), 7.07 - 7.13 (m, 1H), 7.22 - 7.27 (m, 1H),
 15 7.33 - 7.38 (m, 1H), 7.48 - 7.56 (m, 1H), 8.22 (s, 1H), 8.53 (s, 1H).

Example 150

2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-*d*]pyrimidin-1-
 yl}benzonitrile



80 mg (0.26 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 70.4 mg (0.39 mmol) 2-bromobenzonitrile, 49.1 mg (0.26 mmol) copper(I) iodide, 3.9 mg (0.03 mmol) sodium iodide, 115 mg (0.54 mmol) tripotassium phosphate and 22 mg (0.16 mmol) trans-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C for 2 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with water, dried over magnesium sulfate and concentrated. The residue was purified by HPLC affording 3 mg (3%) product.

10

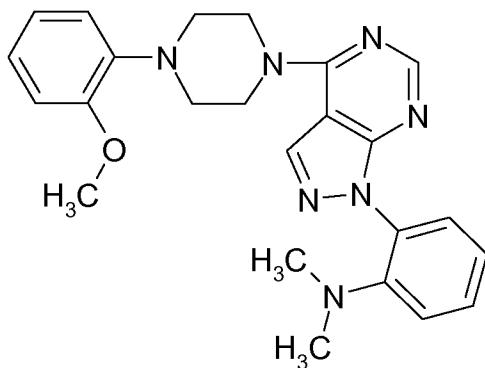
LC-MS (analytical method 3): R_t = 1.23 min, MS (ESIpos): m/z = 412 ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 3.08 - 3.18 (m, 4H), 3.70 (s, 3H), 3.83 (s, 3H), 4.08 - 4.15 (m, 4H), 6.87 - 7.03 (m, 4H), 7.07 - 7.13 (m, 1H), 7.22 - 7.27 (m, 1H), 7.33 - 7.38 (m, 1H), 7.48 - 7.56 (m, 1H), 8.22 (s, 1H), 8.53 (s, 1H).

15

Example 151

2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-*N,N*-dimethylaniline



20 80 mg (0.26 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 77.4 mg (0.39 mmol) 2-bromo-*N,N*-dimethylaniline, 14.7 mg (0.08 mmol) copper(I) iodide, 115 mg (0.54 mmol) tripotassium phosphate and 22 mg (0.16 mmol) trans-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C for 8 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with

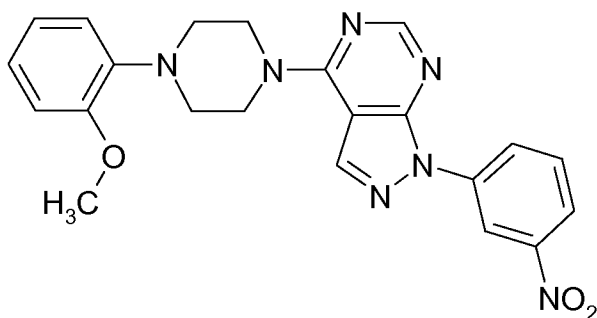
25

water, dried over magnesium sulfate and concentrated. The residue was purified by HPLC affording 3 mg (3%) product.

LC-MS (analytical method 3): $R_t = 1.09$ min, MS (ESIpos): $m/z = 430$ ($M+H$)⁺.

- 5 ¹H-NMR (300MHz, CHLOROFORM-*d*): δ [ppm]= 2.52 (s, 6H), 3.25 - 3.33 (m, 4H), 3.96 (s, 3H), 4.22 - 4.30 (m, 4H), 6.92 - 7.16 (m, 6H), 7.31 (d, 1H), 7.36 - 7.45 (m, 1H), 8.25 (s, 1H), 8.45 (s, 1H).

10 **Example 152**
4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine



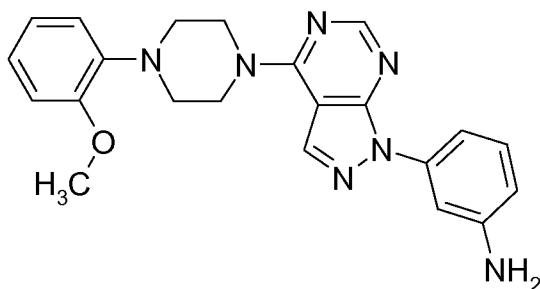
- To 6.2 g (22.49 mmol) 4-chloro-1-(3-nitrophenyl)-3a,7a-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine in 88 mL anhydrous DMF were added 4.324 g (22.49 mmol) 1-(2-methoxyphenyl)piperazine and 10.07 mL (67.48 mmol) DBU. The mixture was stirred 3 h at 120°C. The mixture was allowed to reach rt and concentrated on a rotavap. Water was added and the mixture was stirred 0.5 h. The solid was filtered off under suction and washed five times with water. The solid was dried 48 h at 45°C under vacuum. The material was dissolved in dichloromethane and water. The layers were separated and the organic phase was extracted three times with water. The dichloromethane phase was dried over magnesium sulfate and concentrated yielding 9.6 g (94%) product.

- 25 LC-MS (analytical method 3): $R_t = 1.48$ min, MS (ESIpos): $m/z = 432$ ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 3.09 - 3.15 (m, 4H), 3.81 (s, 3H), 4.08 - 4.14 (m, 4H), 6.84 - 7.00 (m, 4H), 7.83 (t, 1H), 8.16 (s, 1H), 8.47 (s, 1H), 8.69 (d, 1H), 8.72 (s, 1H), 9.18 (t, 1H).

Example 153

3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}aniline



5

1.2 g 10% Pd/C (50% water) were added to a suspension of 8 g (18.54 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine in 500 mL of THF and methanol (1:1). It was hydrogenated 2.5 h under an atmosphere of hydrogen. The catalyst was filtered off. The catalyst was washed with 100 mL THF and 100 mL methanol. The filtrate was concentrated on a rotavap and the solid was dried under vacuum at 45° C to afford 7 g (94%) product.

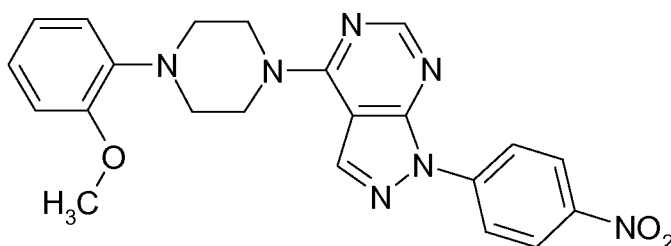
LC-MS (analytical method 3): R_t = 1.13 min, MS (ESIpos): m/z = 402 ($M+H$)⁺.
¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm] = 3.07 - 3.17 (m, 4H), 3.82 (s, 3H), 4.04 - 4.18 (m, 4H), 5.37 (s, 2H), 6.48 - 6.56 (m, 1H), 6.83 - 7.04 (m, 4H), 7.13 (s, 1H), 7.27 - 7.32 (m, 1H), 7.37 (s, 1H), 8.37 (s, 1H), 8.57 (s, 1H).

15

Example 154

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine

20



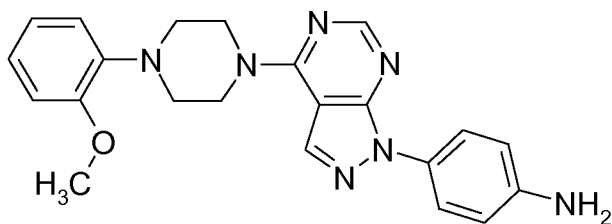
To 9.879 g (25.09 mmol) 4-chloro-1-(4-nitrophenyl)-3a,7a-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine in 60 mL anhydrous DMF were added 11.233 mL (75.26 mmol) DBU and 5.788 g (30.10 mmol) 1-(2-methoxyphenyl)piperazine. It was stirred over night at

130°C. The mixture was allowed to reach rt. The solid was filtered off and washed with diethyl ether and acetonitrile. The crude material was purified on silica gel (2vol% isopropanol in dichloromethane) yielding 6.815 g (63%) product.

- 5 LC-MS (analytical method 6): $R_t = 1.48$ min, MS (ESIpos): $m/z = 432$ ($M+H$)⁺.
¹H-NMR (300MHz, CHLOROFORM-*d*): δ [ppm]= 3.22 - 3.32 (m, 4H), 3.93 (s, 3H), 4.18 - 4.28 (m, 4H), 6.89 - 7.01 (m, 3H), 7.03 - 7.12 (m, 1H), 8.24 (s, 1H), 8.35 - 8.43 (m, 2H), 8.51 (s, 1H), 8.62 (d, 2H).

10 Example 155

4-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}aniline



- 0.8 g 10% Pd/C (50% water) were added to a suspension of 5.3 g (12.28 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(4-nitrophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine in 400 mL of THF and methanol (1:1). It was hydrogenated 2.5 h under an atmosphere of hydrogen. The catalyst was filtered off and washed with 150 mL THF and 150 mL methanol. The filtrate was concentrated on a rotavap and the solid was dried under vacuum at 45°C to yield 3.8 g (73%) product.

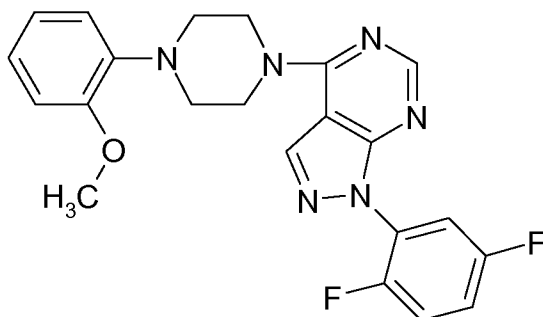
20

LC-MS (analytical method 3): $R_t = 1.02$ min, MS (ESIpos): $m/z = 402$ ($M+H$)⁺.
¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 3.06 - 3.17 (m, 4H), 3.82 (s, 3H), 4.04 - 4.17 (m, 4H), 5.39 (br. s., 2H), 6.65 - 6.72 (m, 2H), 6.85 - 7.03 (m, 4H), 7.58 - 7.66 (m, 2H), 8.32 (s, 1H), 8.50 (s, 1H).

25

Example 156

1-(2,5-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



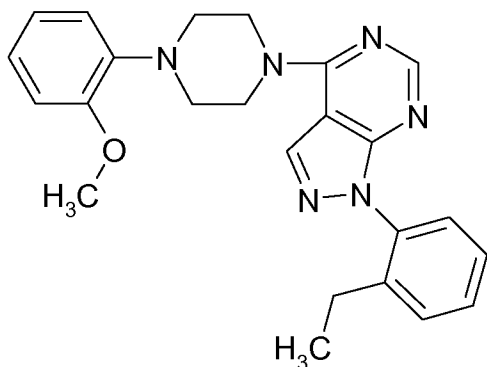
100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-
 d]pyrimidine, 93.3 mg (0.48 mmol) 2-bromo-1,4-difluorobenzene, 18.4 mg (0.10
 mmol) copper(I) iodide, 144 mg (0.68 mmol) tripotassium phosphate and 27.5 mg
 5 (0.19 mmol) *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP
 were heated under microwave irradiation at 180°C for 4 h. The reaction mixture was
 poured into water and extracted three times with ethyl acetate. The combined
 organic phases were washed with 0.5 M aqueous EDTA solution and three times with
 water, dried over magnesium sulfate and concentrated. The residue was purified by
 10 HPLC to afford 12 mg (9%) product.

LC-MS (analytical method 3): $R_t = 1.31$ min, MS (ESIpos): $m/z = 423$ ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 3.08 - 3.18 (m, 4H), 3.83 (s, 3H), 4.08 - 4.17
 (m, 4H), 6.86 - 7.03 (m, 4H), 7.42 - 7.50 (m, 1H), 7.53 - 7.65 (m, 2H), 8.32 (s, 1H),
 15 8.68 (s, 1H).

Example 157

1-(2-ethylphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-
 d]pyrimidine



20

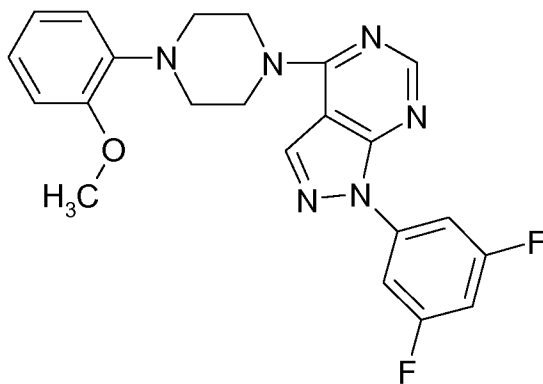
100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 112.2 mg (0.48 mmol) 1-ethyl-2-iodobenzene, 18.4 mg (0.10 mmol) copper(I) iodide, 144 mg (0.68 mmol) tripotassium phosphate and 27.5 mg (0.19 mmol) trans-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation 4 h at 180°C. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with water, dried over magnesium sulfate and concentrated. The residue was purified by HPLC affording 11 mg (8%) product.

LC-MS (analytical method 3): R_t = 1.45 min, MS (ESIpos): m/z = 415 ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 0.93 (t, 3H), 2.38 (d, 2H), 3.10 - 3.18 (m, 4H), 3.83 (s, 3H), 4.08 - 4.17 (m, 4H), 6.85 - 7.04 (m, 4H), 7.32 (s, 1H), 7.35 - 7.40 (m, 1H), 7.43 - 7.51 (m, 2H), 8.25 (s, 1H), 8.59 (s, 1H).

Example 158

1-(3,5-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine



100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 93.3 mg (0.48 mmol) 1-bromo-3,5-difluorobenzene, 18.4 mg (0.10 mmol) copper(I) iodide, 144 mg (0.68 mmol) tripotassium phosphate and 27.5 mg (0.19 mmol) trans-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C for 4 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with

water, dried over magnesium sulfate and concentrated. The residue was purified by HPLC to give 20.3 mg (14%) product.

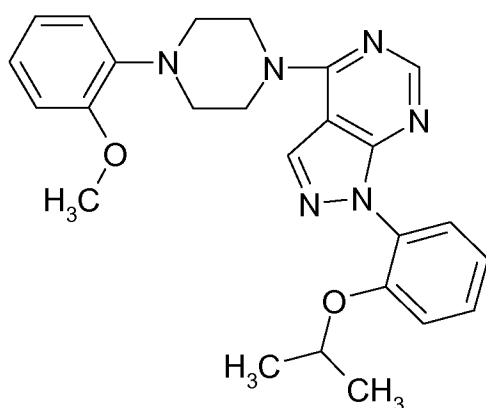
LC-MS (analytical method 3): R_t = 1.58 min, MS (ESIpos): m/z = 423 ($M+H$)⁺.

- 5 ¹H-NMR (400MHz, DMSO- d_6): δ [ppm]= 3.14 (br. s., 4H), 3.83 (s, 3H), 4.12 (br. s., 4H), 6.98 (d, 4H), 7.20 - 7.28 (m, 1H), 8.03 - 8.12 (m, 2H), 8.47 (s, 1H), 8.71 (s, 1H).

Example 159

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[2-(propan-2-yloxy)phenyl]-1*H*-

- 10 pyrazolo[3,4-*d*]pyrimidine



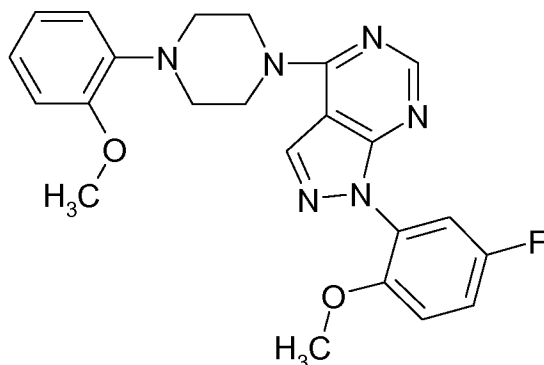
- 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 104 mg (0.48 mmol) 1-bromo-2-isopropoxybenzene, 18.4 mg (0.10 mmol) copper(I) iodide, 144 mg (0.68 mmol) tripotassium phosphate and 27.5 mg
 15 (0.19 mmol) *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C for 4 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with water, dried over magnesium sulfate and concentrated. The residue was purified by
 20 HPLC affyielding 2.1 mg (1.5%) product.

LC-MS (analytical method 3): R_t = 1.37 min, MS (ESIpos): m/z = 445 ($M+H$)⁺.

- ¹H-NMR (400MHz, CHLOROFORM- d): δ [ppm]= 1.18 (d, 6H), 3.24 - 3.33 (m, 4H), 3.96 (s, 3H), 4.22 - 4.30 (m, 4H), 4.44 - 4.55 (m, 1H), 6.93 - 7.03 (m, 3H), 7.06 - 7.15 (m,
 25 3H), 7.41 - 7.48 (m, 2H), 8.21 (s, 1H), 8.43 (s, 1H).

Example 160

1-(5-fluoro-2-methoxyphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine

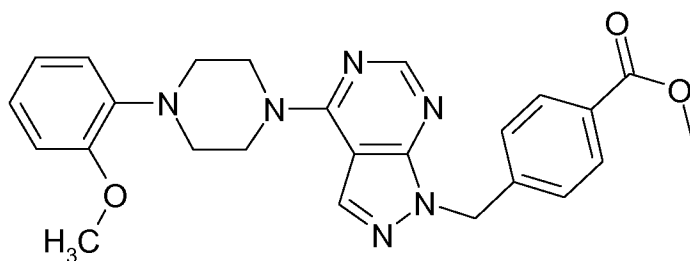


5 100 mg (0.32 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 99.1 mg (0.48 mmol) 2-bromo-4-fluoro-1-methoxybenzene, 18.4 mg (0.10 mmol) copper(I) iodide, 144 mg (0.68 mmol) tripotassium phosphate and 27.5 mg (0.19 mmol) trans-*N,N*-dimethylcyclohexane-1,2-diamine in 3 mL anhydrous NMP were heated under microwave irradiation at 180°C for 4 h. The reaction mixture was
10 poured into water and extracted three times with ethyl acetate. The combined organic phases were washed with 0.5 M aqueous EDTA solution and three times with water, dried over magnesium sulfate and concentrated. The residue was purified by HPLC affording 8 mg (6%) product.

15 LC-MS (analytical method 3): R_t = 1.24 min, MS (ESIpos): m/z = 435 ($M+H$)⁺.
¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 3.12 (br. s., 4H), 3.69 (s, 3H), 3.83 (s, 3H), 4.05 - 4.16 (m, 4H), 6.84 - 7.05 (m, 4H), 7.28 (s, 1H), 7.35 (d, 2H), 8.25 (s, 1H), 8.57 (s, 1H).

Example 161

methyl 4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)benzoate



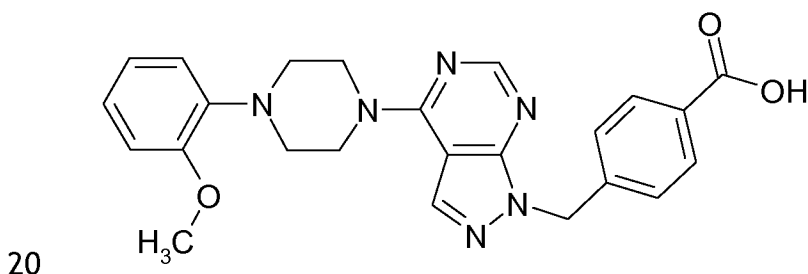
To 10 g (32.2 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidine, 52.49 g (161.1 mmol) cesium carbonate and 1.232 g (8.22 mmol) sodium iodide in 400 mL anhydrous DMF were added 9.964 g (43.5 mmol) methyl 4-(bromomethyl)benzoate. It was stirred over night at rt. The reaction mixture was concentrated on a rotavap and 200 mL water and 150 mL dichloromethane were added. The layers were separated and the aqueous phase was extracted three times with 150 mL dichloromethane. The combined organic phases were washed three times with 100 mL water, dried over magnesium sulfate and concentrated. The residue was purified on silica gel (gradient of hexane and ethyl acetate) yielding 9.5 g (64%) product.

LC-MS (analytical method 3): $R_t = 1.29$ min, MS (ESIpos): $m/z = 459$ ($M+H$)⁺.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm]= 3.07 - 3.13 (m, 4H), 3.82 (d, 6H), 4.04 - 4.11 (m, 4H), 5.62 (s, 2H), 6.91 (s, 2H), 6.95 - 7.02 (m, 2H), 7.31 (d, 2H), 7.90 (d, 2H), 8.31 (s, 1H), 8.41 (s, 1H).

Example 162

4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)benzoic acid



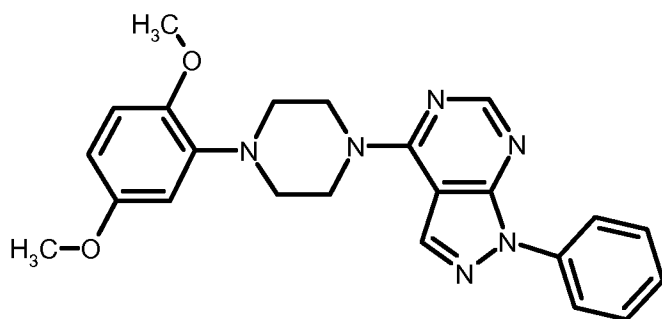
To 11.64 g (25.4 mmol) methyl 4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}methyl)benzoate in 51.4 mL methanol and 206 mL THF were added 1.824 g (76.2 mmol) lithium hydroxide. It was stirred over the weekend at 40°C. The reaction mixture was concentrated on a rotavap. 1 L of water was added and the pH was adjusted to 5 with 2 M hydrochloric acid. It was stirred 3 h. The precipitate was filtered off under suction and dried at 45°C under vacuum to afford 7.4 g (66%) product.

LC-MS (analytical method 3): $R_t = 1.11$ min, MS (ESIpos): $m/z = 445$ ($M+H$)⁺.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 3.07 (br. s., 4H), 3.78 (s, 3H), 4.05 (br. s., 4H), 5.58 (s, 2H), 6.81 - 7.01 (m, 4H), 7.25 (d, 2H), 7.84 (d, 2H), 8.29 (s, 1H), 8.39 (s, 1H), 12.83 - 13.01 (m, 1H).

5 Example 163

4-[4-(2,5-dimethoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine



- To a suspension of 42 mg (0.15 mmol) 1-phenyl-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine in a mixture of 0.5 mL toluene and 0.5 mL tert-butanol were added 39 mg (0.18 mmol) 2-bromo-1,4-dimethoxybenzene in 0.31 mL N,N-dinethylformamide. A mixture of 14.3 mg (0.03 mmol) 2-(*dicyclohexylphosphino*)-2',4',6'-*triisopropylbiphenyl* and 6.7 mg (0.03 mmol) palladium-(II)-acetate in 0.3 mL N,N-dinethylformamide was added. 49 mg (0.15 mmol) cesium carbonate were added.
- The reaction mixture was heated to 110°C for 12 h.

The reaction mixture was concentrated and suspended in a 1:1 mixture of dimethylsulfoxide and methanol. Insoluble material was filtered off and the crude product was purified by HPLC to give 12 mg of the title compound as solid material.

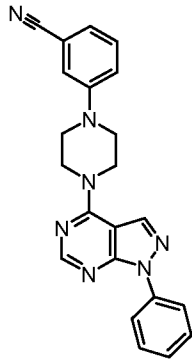
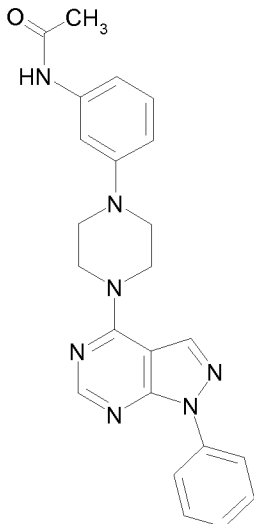
- LCMS: R_t = 1.41 min; MS found (ESIpos) m/z = 417 [M+H]⁺.

(Instrument MS: Waters ZQ; Instrument HPLC: Waters UPLC Acquity; Column: Acquity BEH C18 (Waters), 50mm x 2.1mm, 1.7μm; eluent A: water +0,1 vol% formic acid, eluent B: acetonitrile (Lichrosolv Merck); gradient: 0.0 min 99% A-1.6min 1% A-1.8 min 1%A - 1.81 min 99% A - 2.0min 99 % A; temperature: 60°C; flow: 0.8 mL/min;

- UV-Detection PDA 210-400nm).

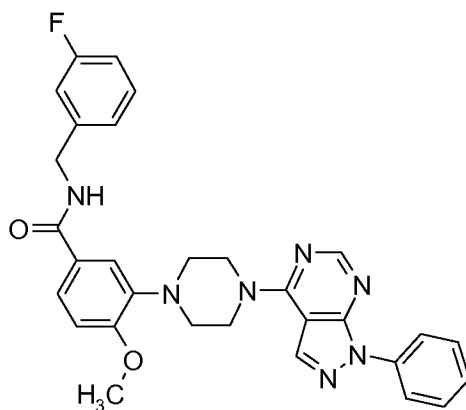
The examples in table 1 were prepared in analogy to example 164:

Table 1:

Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
164		3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzonitrile	382	1.36
165		N-{3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide	414	1.18

5 Example 166

N-(3-fluorobenzyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide



To 65 mg (0.15 mmol) 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoic acid and 50 mg (0.39 mmol) N,N-diethylpropan-2-amine in 1 mL N,N-dimethylformamide were added 24 mg (0.195 mmol) 1-(3-fluorophenyl)methanamine in 0.35 mL N,N-dimethylformamide. 83 mg (0.195 mmol) N-[[[(1Z)-1-cyano-2-ethoxy-2-oxoethylidene]amino}oxy](morpholin-4-yl)methylene]-N-methylmethanaminium hexafluorophosphate (COMU) in 0.4 mL N,N-dimethylformamide were added. The reaction mixture was shaken at room temperature for 12 h.

0.25 mL methanol were added. Insoluble material was filtered off and the crude product solution was purified by HPLC to give 8 mg of the title compound as solid material.

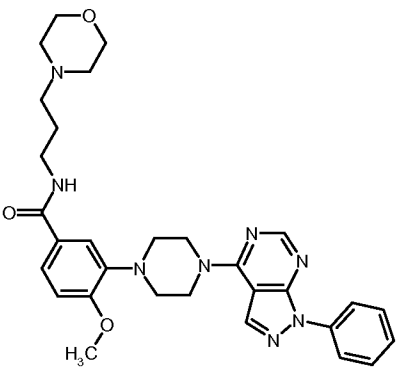
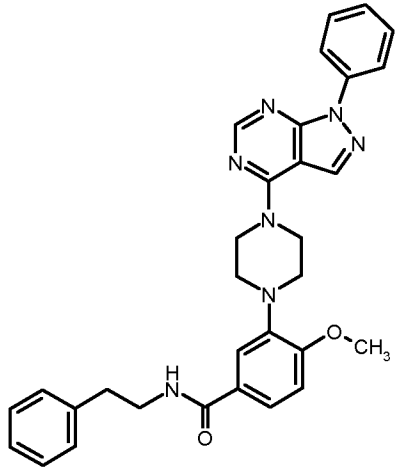
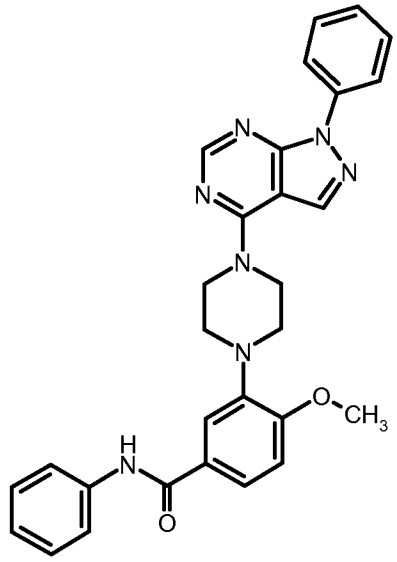
LCMS: $R_t = 1.39$ min; MS found (ESIpos) $m/z = 539$ $[M+H]^+$.

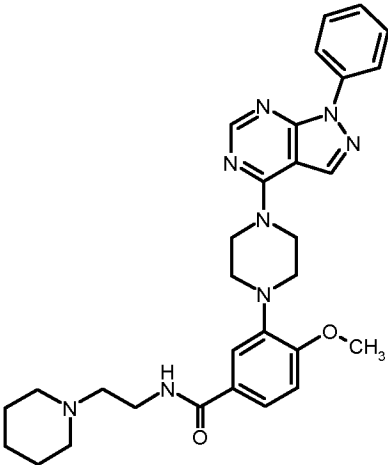
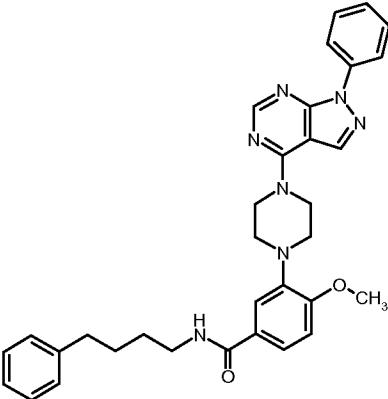
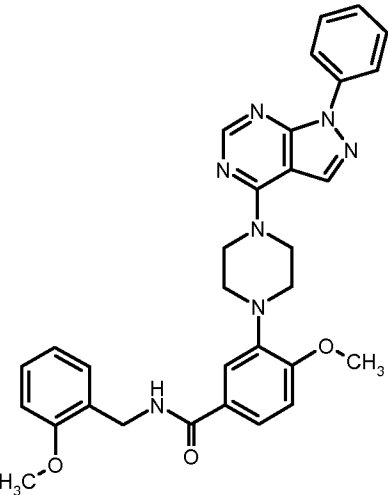
(Instrument MS: Waters ZQ; Instrument HPLC: Waters UPLC Acquity; Column: Acquity BEH C18 (Waters), 50mm x 2.1mm, 1.7 μ m; eluent A: water +0,1 vol% formic acid, eluent B: acetonitrile (Lichrosolv Merck); gradient: 0.0 min 99% A-1.6min 1% A-1.8 min 1%A - 1.81 min 99% A - 2.0min 99 % A; temperature: 60°C; flow: 0.8 mL/min;

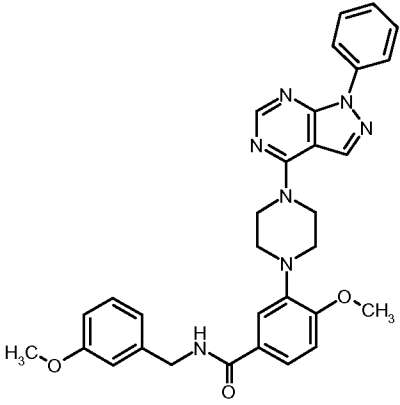
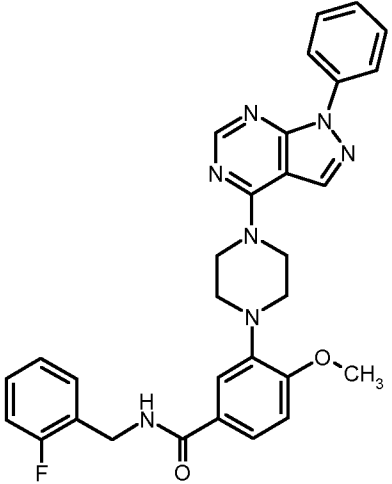
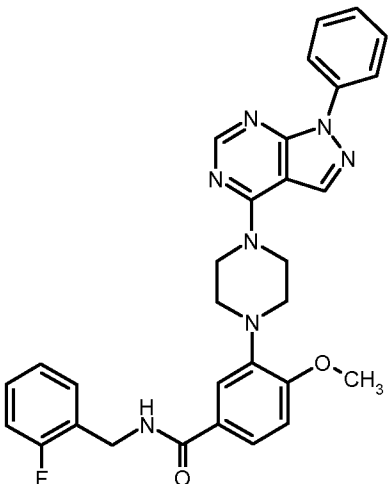
UV-Detection PDA 210-400nm).

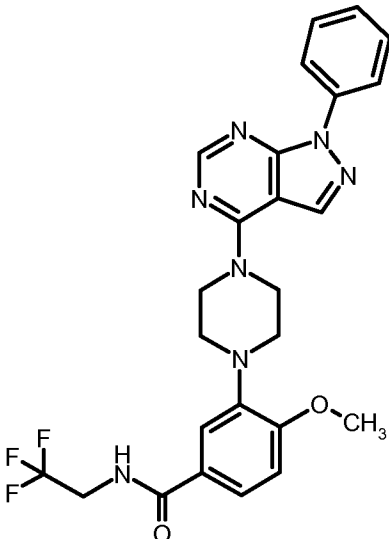
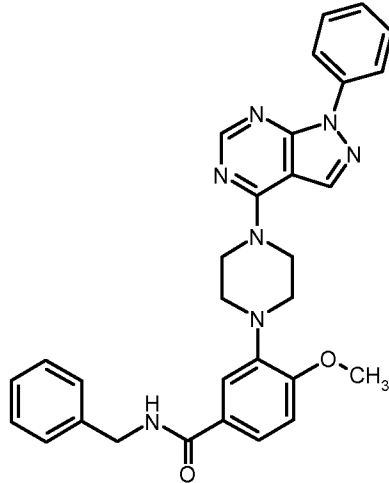
The examples in table 2 were prepared in analogy to example 149:

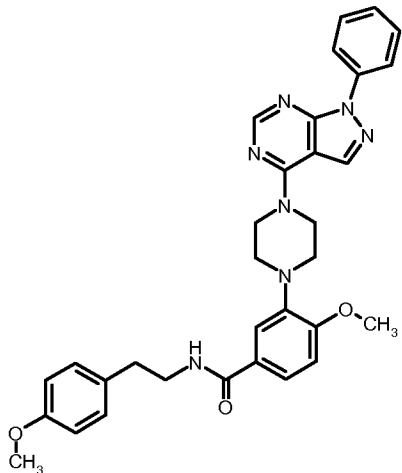
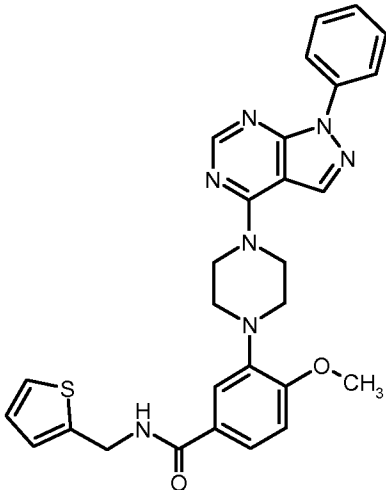
Table 2:

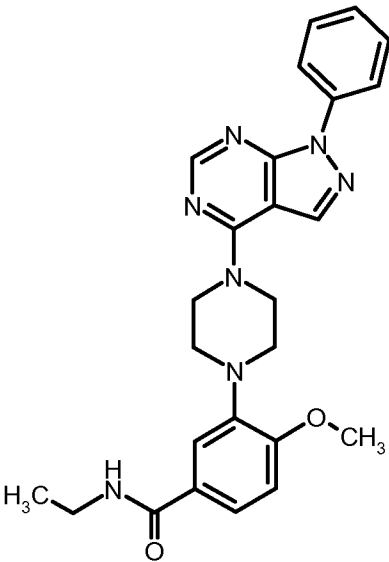
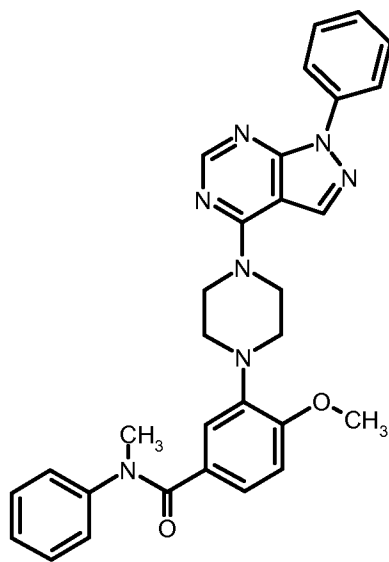
Example	Structure	Name	Mass found m/z [M+H] +	Retention time [min]
167		4-methoxy-N-[3-(morpholin-4-yl)propyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	558	0.9
168		4-methoxy-N-(2-phenylethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	535	1.4
169		4-methoxy-N-phenyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	507	1.41

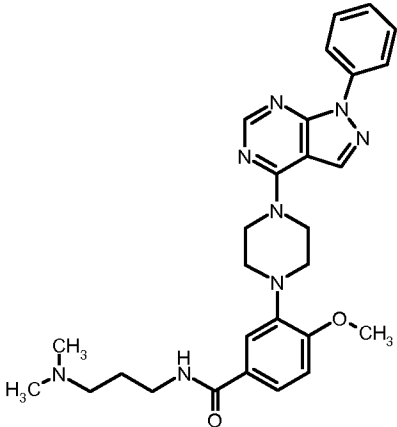
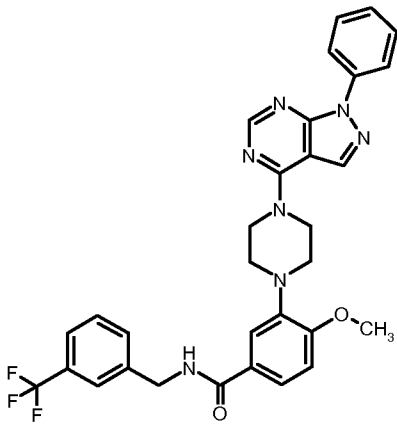
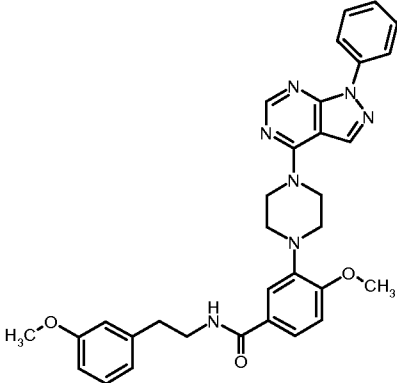
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
170		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(piperidin-1-yl)ethyl]benzamide	542	0.93
171		4-methoxy-N-(4-phenylbutyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	563	1.5
172		4-methoxy-N-(2-methoxybenzyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	551	1.4

Example	Structure	Name	Mass found m/z [M+H] +	Retention time [min]
173		4-methoxy-N-(3-methoxybenzyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	551	1.37
174		N-(2-fluorobenzyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	539	1.39
175		N-(4-fluorobenzyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	539	1.39

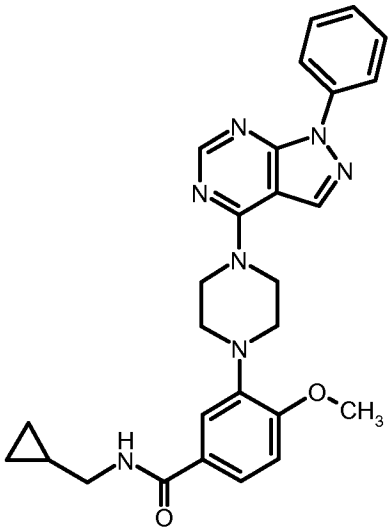
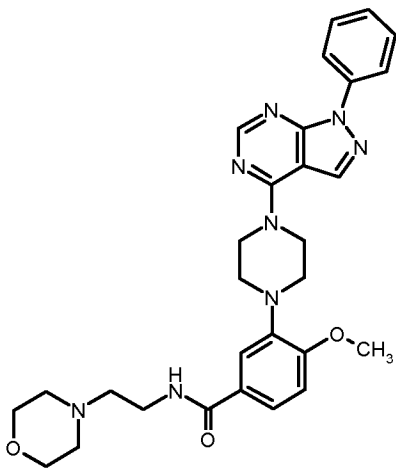
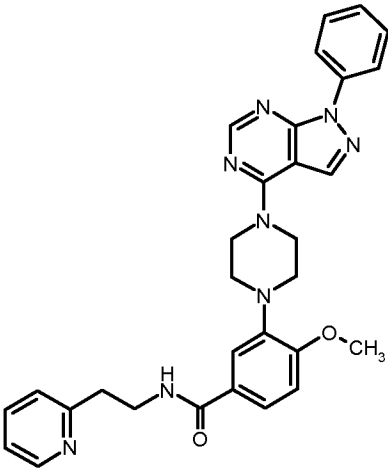
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
176		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(2,2,2-trifluoroethyl)benzamide	513	1.33
177		N-benzyl-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	521	1.38

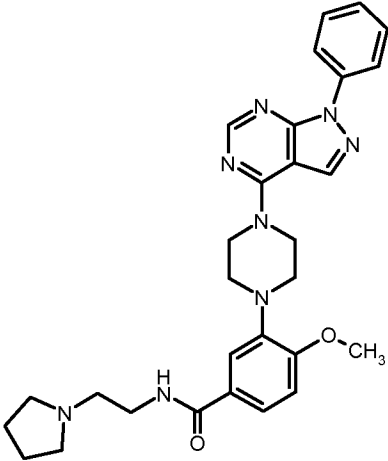
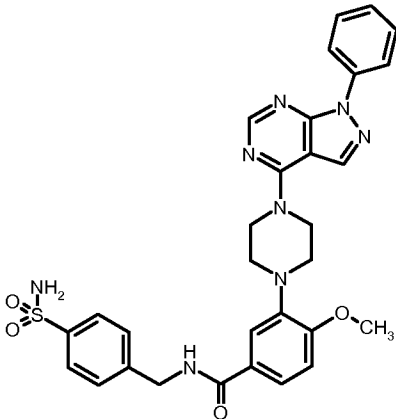
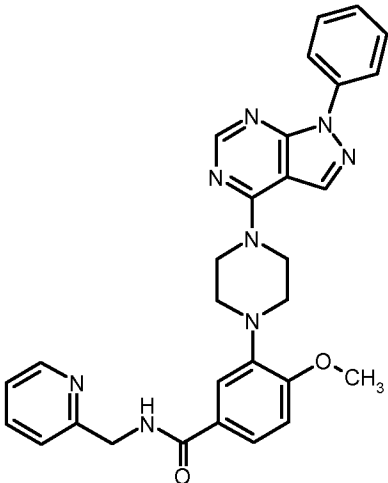
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
178		4-methoxy-N-[2-(4-methoxyphenyl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	565	1.39
179		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(thiophen-2-ylmethyl)benzamide	527	1.36

Example	Structure	Name	Mass found m/z [M+H] +	Retention time [min]
180		N-ethyl-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	459	1.22
181		4-methoxy-N-methyl-N-phenyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	521	1.41

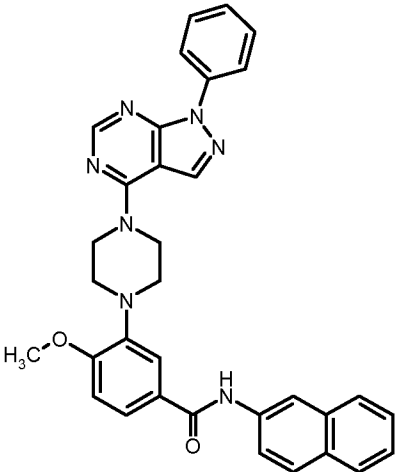
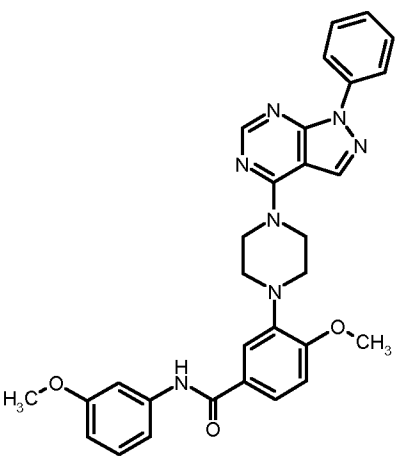
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
182		N-[3-(dimethylamino)propyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	516	0.9
183		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[3-(trifluoromethyl)benzyl]benzamide	589	1.48
184		4-methoxy-N-[2-(3-methoxyphenyl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	565	1.4

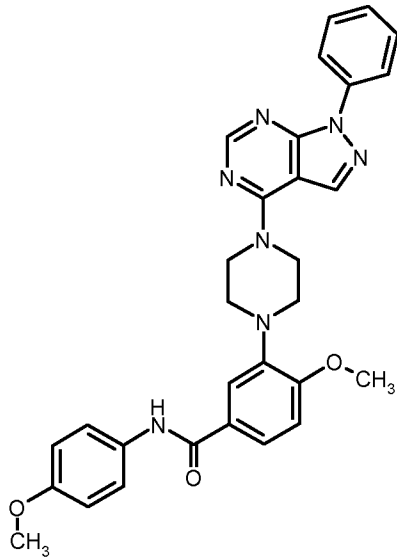
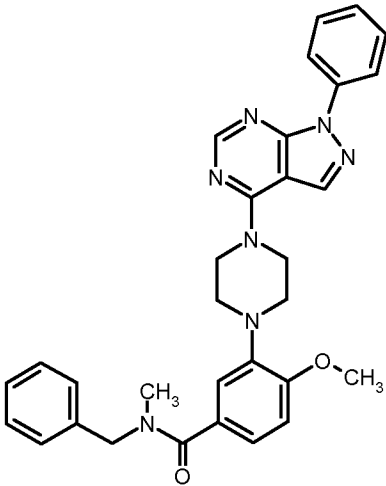
Example	Structure	Name	Mass found m/z [M+H] +	Retention time [min]
185		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-4-yl)benzamide	508	0.97
186		N-(4-carbamoylphenyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	550	1.18

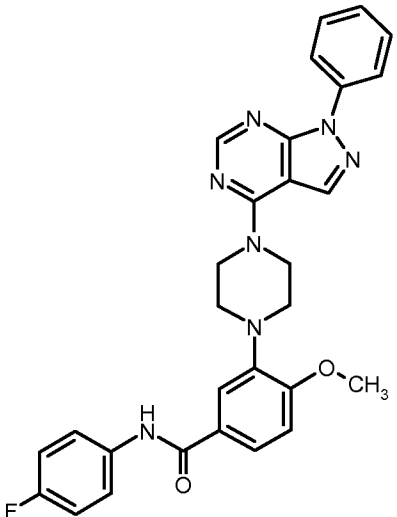
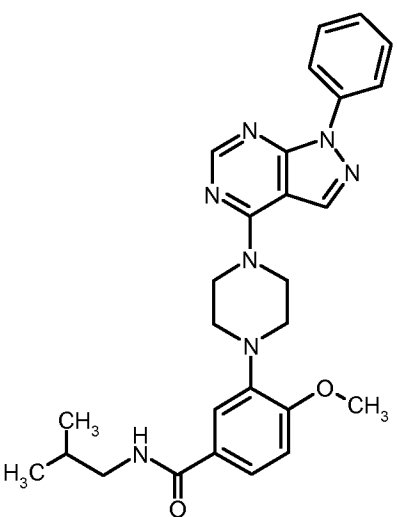
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
187		N-(cyclopropylmethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	485	1.31
188		4-methoxy-N-[2-(morpholin-4-yl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	544	0.9
189		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyridin-2-yl)ethyl]benzamide	536	0.97

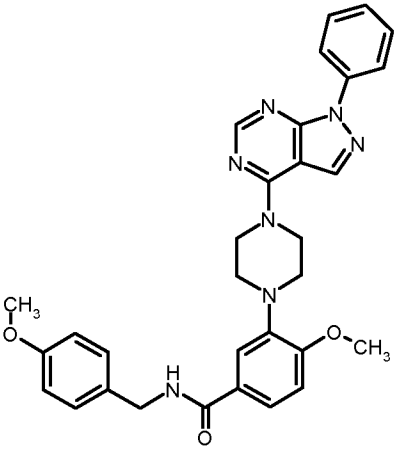
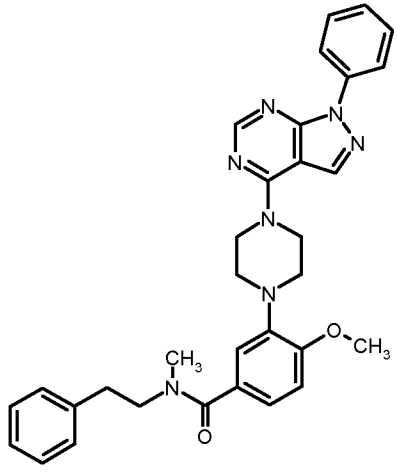
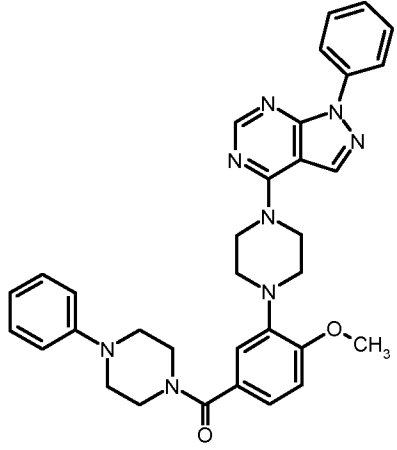
Example	Structure	Name	Mass found m/z [M+H] +	Retention time [min]
190		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyrrolidin-1-yl)ethyl]benzamide	528	0.91
191		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(4-sulfamoylbenzyl)benzamide	600	1.18
192		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-2-ylmethyl)benzamide	522	1.08

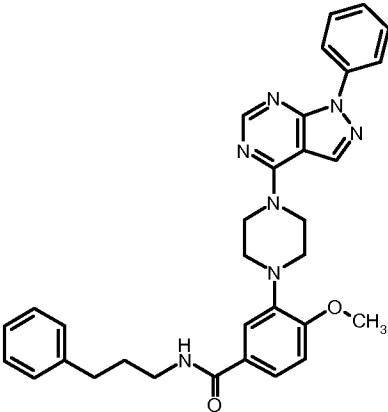
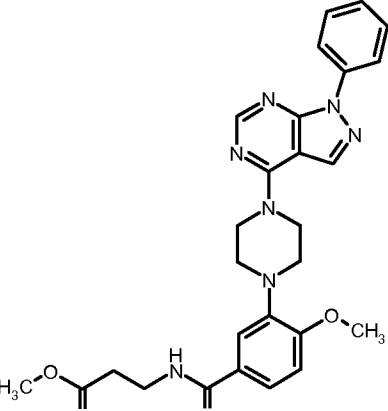
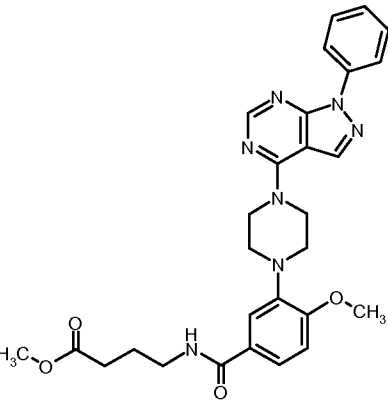
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
193		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-3-ylmethyl)benzamide	522	0.98
194		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-4-ylmethyl)benzamide	522	0.94
195		4-methoxy-N-(naphthalen-1-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	557	1.45

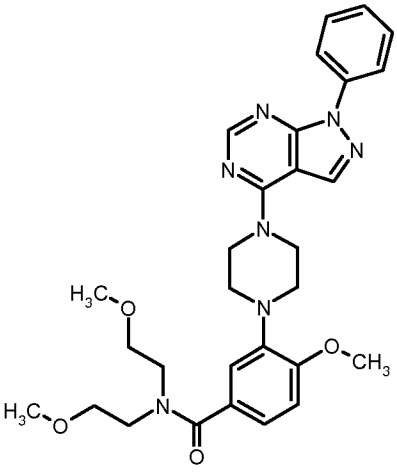
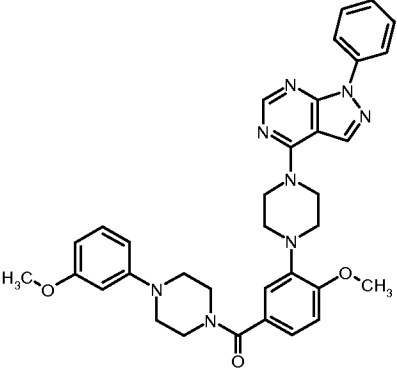
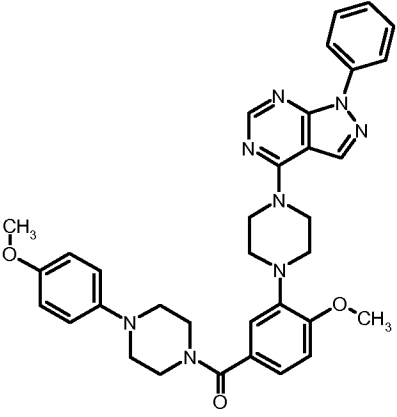
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
196		4-methoxy-N-(naphthalen-2-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	557	1.52
197		4-methoxy-N-(3-methoxyphenyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	537	1.41

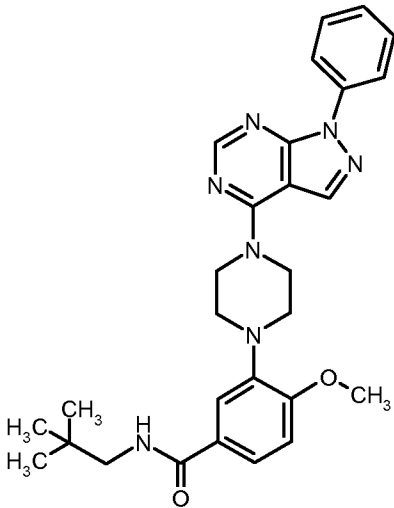
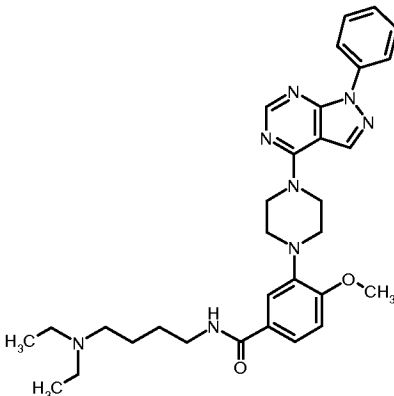
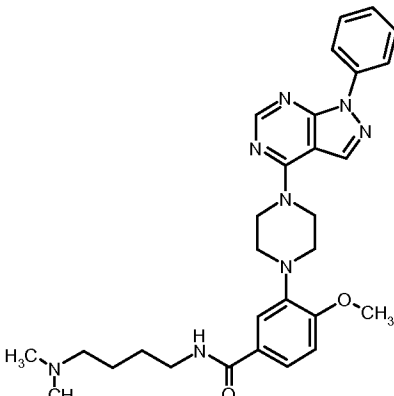
Example	Structure	Name	Mass found m/z [M+H] +	Retention time [min]
198		4-methoxy-N-(4-methoxyphenyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	537	1.38
199		N-benzyl-4-methoxy-N-methyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	535	1.44

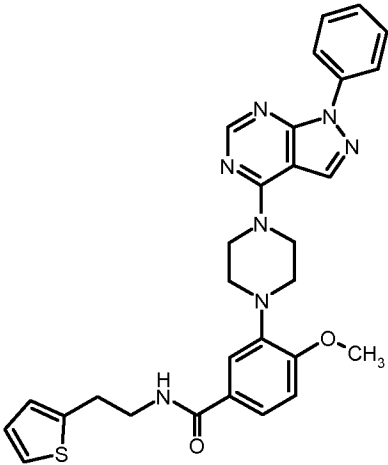
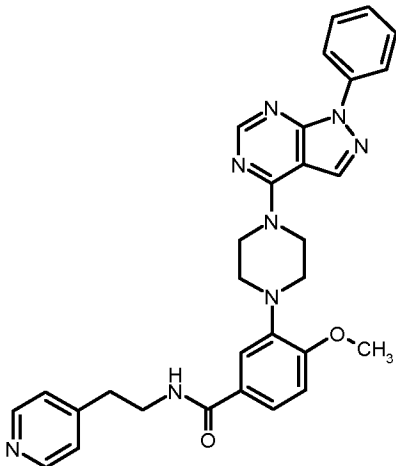
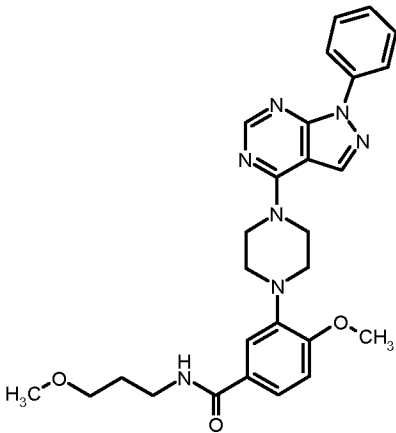
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
200		N-(4-fluorophenyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	525	1.42
201		4-methoxy-N-(2-methylpropyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	487	1.36

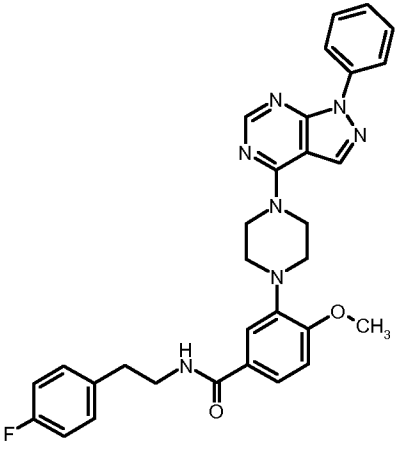
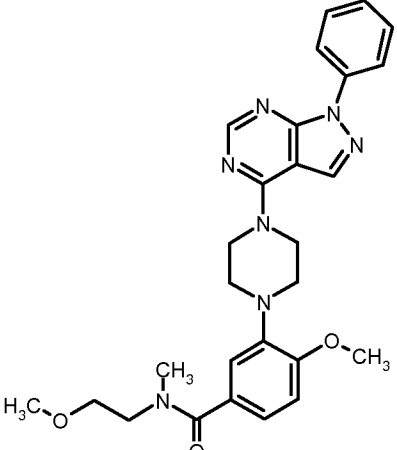
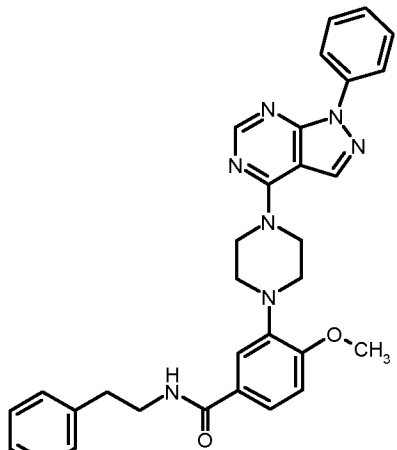
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
202		4-methoxy-N-(4-methoxybenzyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	551	1.37
203		4-methoxy-N-methyl-N-(2-phenylethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	549	1.45
204		{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}(4-phenylpiperazin-1-yl)methanone	576	1.47

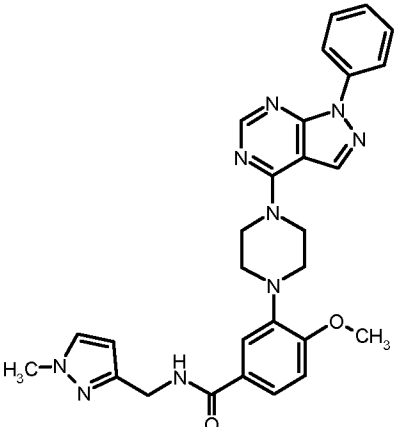
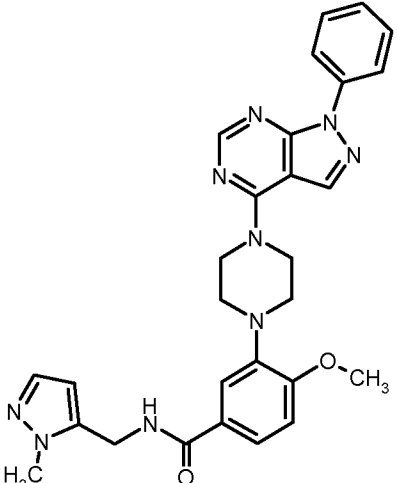
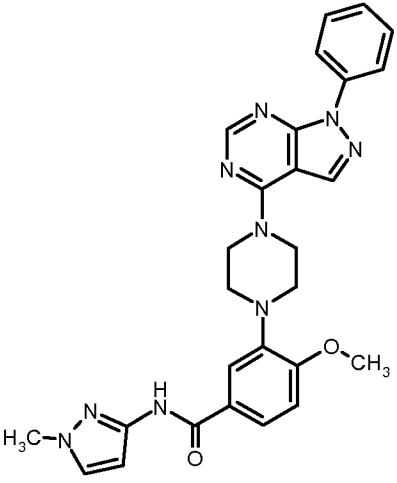
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
205		4-methoxy-N-(3-phenylpropyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	549	1.46
206		methyl N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoyl}-beta-alaninate	517	1.22
207		methyl 4-({4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoyl}amino) butanoate	531	1.24

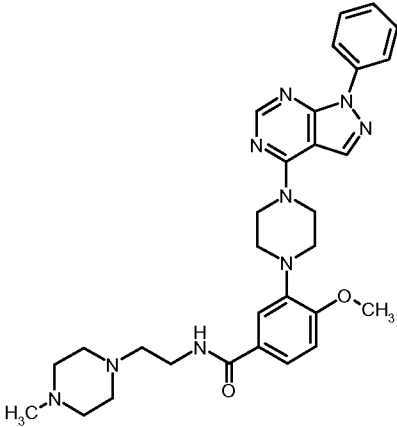
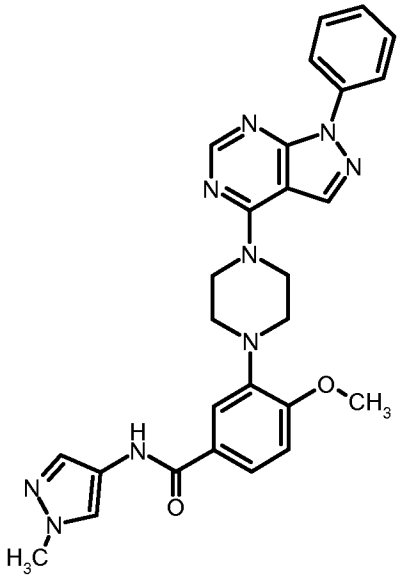
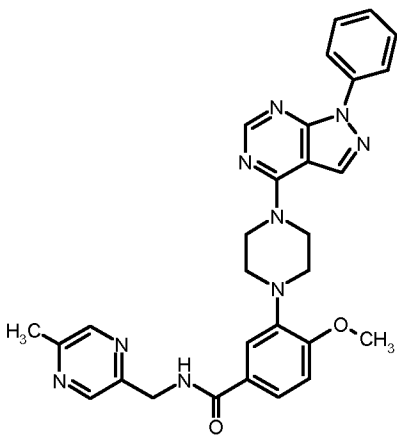
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
208		4-methoxy-N,N-bis(2-methoxyethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	547	1.28
209		[4-(3-methoxyphenyl)piperazin-1-yl]{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanone	606	1.45
210		[4-(4-methoxyphenyl)piperazin-1-yl]{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanone	606	1.41

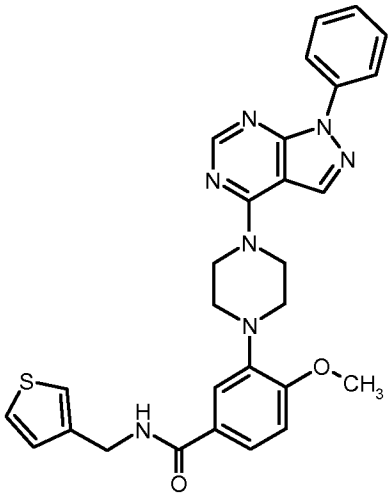
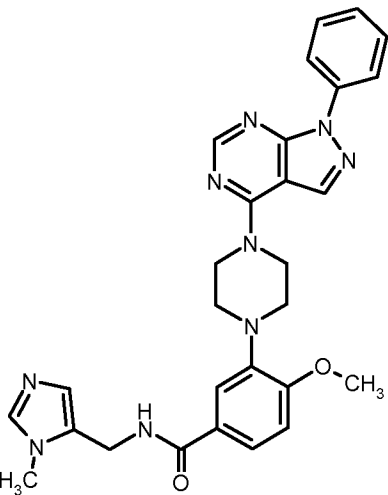
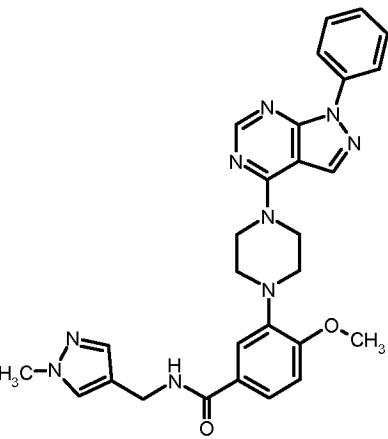
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
211		N-(2,2-dimethylpropyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	501	1.42
212		N-[4-(diethylamino)butyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	558	0.94
213		N-[4-(dimethylamino)butyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	530	0.9

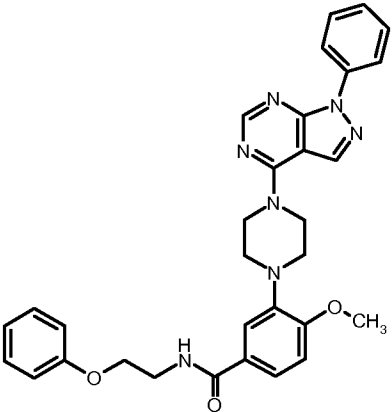
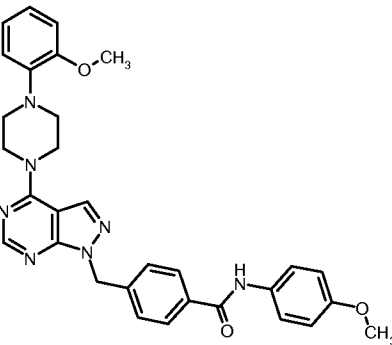
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
214		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(thiophen-2-yl)ethyl]benzamide	541	1.39
215		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyridin-4-yl)ethyl]benzamide	536	0.93
216		4-methoxy-N-(3-methoxypropyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	503	1.23

Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
217		N-[2-(4-fluorophenyl)ethyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	553	1.41
218		4-methoxy-N-(2-methoxyethyl)-N-methyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	503	1.25
219		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyridin-3-yl)ethyl]benzamide	536	0.95

Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
220		4-methoxy-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	525	1.18
221		4-methoxy-N-[(1-methyl-1H-pyrazol-5-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	525	1.18
222		4-methoxy-N-(1-methyl-1H-pyrazol-3-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	511	1.22

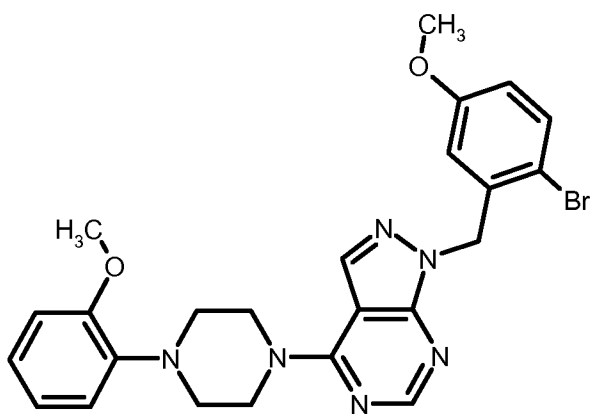
Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
223		4-methoxy-N-[2-(4-methylpiperazin-1-yl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	557	0.87
224		4-methoxy-N-(1-methyl-1H-pyrazol-4-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	511	1.19
225		4-methoxy-N-[(5-methylpyrazin-2-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	537	1.19

Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
226		4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(thiophen-3-ylmethyl)benzamide	527	1.35
227		4-methoxy-N-[(1-methyl-1H-imidazol-5-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	525	0.9
228		4-methoxy-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	525	1.16

Example	Structure	Name	Mass found m/z [M+H] +	Retent ion time [min]
229		4-methoxy-N-(2-phenoxyethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide	551	1.41
230		N-(4-methoxyphenyl)-4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}methyl)benzamide	550.62	1.18

Example 231

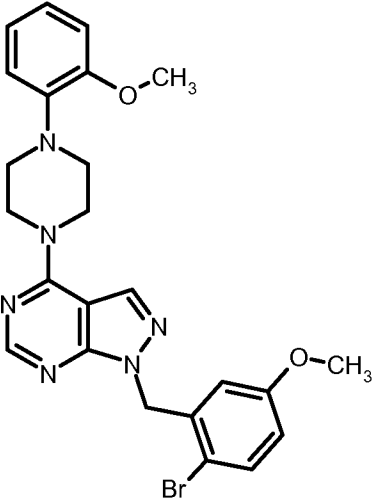
1-(2-bromo-5-methoxybenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine



To a solution of 47 mg (0.15 mmol) 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine in 0.75 mL N,N-dimethylformamide were added 84 mg (0.3 mmol) 1-bromo-2-(bromomethyl)-4-methoxybenzene in 0.6 mL N,N-dimethylformamide, 244 mg cesium carbonate in 1.5 mL N,N-dimethylformamide as suspension and 5 mg solid sodium iodide and the reaction mixture was heated at 50°C for 12 h.

The reaction mixture was filtered and the crude product was purified by preparative HPLC to give 11 mg of the title compound as solid material.

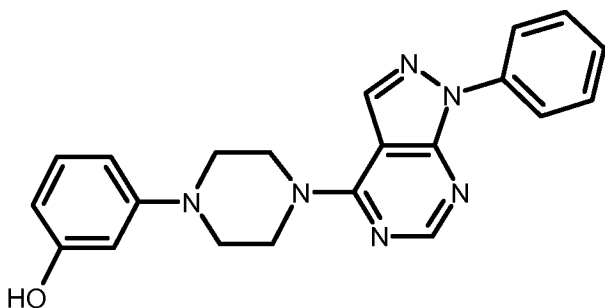
(Instrument MS: Waters ZQ; Instrument HPLC: Waters UPLC Acquity; Column: Acquity BEH C18 (Waters), 50mm x 2.1mm, 1.7µm; eluent A: water +0,1 vol% formic acid, eluent B: acetonitrile (Lichrosolv Merck); gradient: 0.0 min 99% A-1.6min 1% A-1.8 min 1%A - 1.81 min 99% A - 2.0min 99 % A; temperature: 60°C; flow: 0.8 mL/min; UV-Detection PDA 210-400nm).

Example	Structure	Name	Mass found m/z [M+H] ⁺	Retention time [min]
231		1-(2-bromo-5-methoxybenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine	510.40	1.29

15

Example 232

3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol

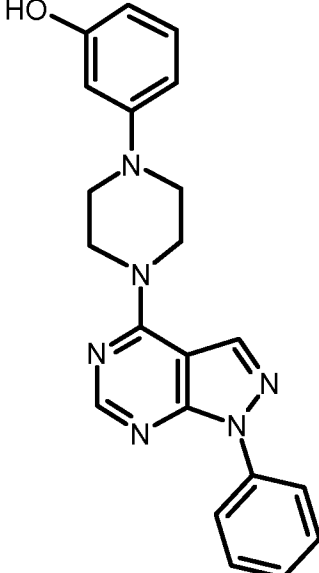


To A solution of 0.1 mmol (23 mg) of 4-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine in N-methyl-2-pyrrolidone was added to 0.3 mmol (53 mg) 3-(piperazin-1-yl)phenol followed by 0.5 mol (69 mg) potassium carbonate. The
5 resulting mixture was shaken for 1 hour under microwave irradiation at 150°C. After cooling to room temperature, the reaction mixture was filtered off and the filtrate was purified by LC-MS with the following method:

Instrument MS: Waters, Instrument HPLC: Waters (column Phenomenex Luna 5µ C18(2) 100A, AXIA Tech. 50 x 21.2 mm, Eluent A: water + 0.05% formic acid, Eluent
10 B: methanol (ULC) + 0.05% formic acid, gradient elution; flow: 40 ml/min; UV-Detection: DAD; 210 - 400 nm).

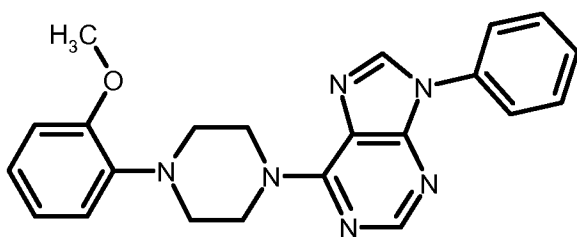
Method for analytical LC-MS:

Instrument MS: Waters SQD; Instrument HPLC: Waters UPLC; column: Zorbax SB-Aq (Agilent), 50 mm x 2.1 mm, 1.8 µm; Eluent A: water + 0.025% formic acid, Eluent B:
15 acetonitrile (ULC) + 0.025% formic acid; gradient: 0.0 min 98%A - 0.9 min 25%A - 1.0 min 5%A - 1.4 min 5%A - 1.41 min 98%A - 1.5 min 98%A; oven: 40°C; flow: 0.600 ml/min; UV-detection: DAD; 210 nm

Example	Structure	Name	Mass found m/z [M+H] ⁺	Retention time [min]
232		3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol	373.0	1.10

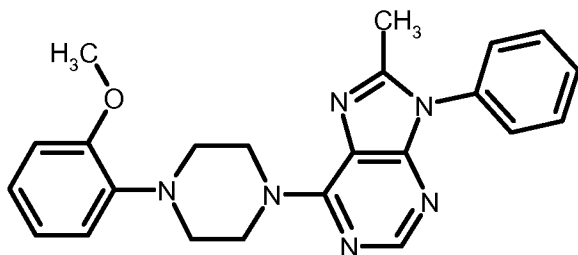
5 Example 233

6-[4-(2-methoxyphenyl)piperazin-1-yl]-9-phenyl-9H-purine



In analogy to example 27) 139 mg (0.60 mmol) of intermediate 16A) and 139 mg (0.72 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 81 mg (33% yield, 95% purity).

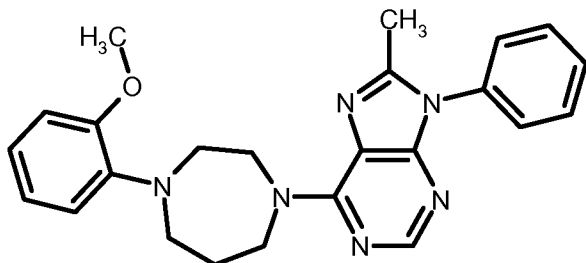
¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 3.04 - 3.10 (m, 4H), 3.80 (s, 3H), 4.29 - 4.50 (m, 4H), 6.82 - 6.98 (m, 4H), 7.41 - 7.48 (m, 1H), 7.53 - 7.60 (m, 2H), 7.81 - 7.84 (m, 1H), 7.84 - 7.86 (m, 1H), 8.29 (s, 1H), 8.58 (s, 1H).

Example 234**6-[4-(2-methoxyphenyl)piperazin-1-yl]-8-methyl-9-phenyl-9H-purine**

In analogy to example 27) 100 mg (0.41 mmol) of intermediate 17A) and 94.3 mg
 5 (0.49 mmol) 1-(2-methoxyphenyl)piperazine gave the desired material: 16 mg (9.4%
 yield, 97% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.38 (s, 3H), 3.04 - 3.10 (m, 4H), 3.79 (s, 3H),
 4.27 - 4.43 (m, 4H), 6.83 - 6.99 (m, 4H), 7.45 - 7.61 (m, 5H), 8.13 (s, 1H).

10

Example 235**6-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-8-methyl-9-phenyl-9H-purine**

In analogy to example 27) 100 mg (0.41 mmol) of intermediate 17A) and 101 mg (0.49
 15 mmol) 1-(2-methoxyphenyl)-1,4-diazepane gave the desired material: 11 mg (6.3%
 yield, 97% purity).

¹H-NMR (400 MHz, DMSO *d*₆) δ (ppm) = 2.01 (br. s., 2H), 2.36 (s, 3H), 3.17 (t, 2H),
 3.39 (br. s., 2H), 3.72 (s, 3H), 3.89 - 4.13 (m, 2H), 4.36 - 4.67 (m, 2H), 6.72 - 6.82
 20 (m, 2H), 6.83 - 6.89 (m, 2H), 7.44 - 7.60 (m, 5H), 8.08 (s, 1H).

Further, the compounds of formula (I) of the present invention can be
 converted to any salt as described herein, by any method which is known to
 the person skilled in the art. Similarly, any salt of a compound of formula (I) of

the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

Biological in vitro assays

5

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

Biological Evaluation

In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety. Demonstration of the activity of the compounds of the present invention may be accomplished through in vitro and in vivo assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent to inhibit glucose transporter GLUT1 and/or GLUT2 the following assays may be used.

Indirect measurement of GLUT activity by quantification of intracellular ATP levels

20

It is well known that a combination of small-molecule inhibitors of mitochondrial electron transport chain and glucose catabolism synergistically suppress ATP production and impair cellular viability (Ulanovskaya et al., 2008,2011; Liu, et al. 2001). We therefore used DLD1 or CHO-K1 cells in combination with an oxidative phosphorylation inhibitor to identify GLUT inhibitors. Cell lines were maintained in DMEM medium supplemented with 10% FCS and 1% Penicillin-Streptomycin solution and 2% Glutamax. The cells were treated with trypsin and seeded into 384 plates at a density of 4000 cells/well. The cells were then cultured overnight in glucose free media containing 1% FCS

30

to reduce intracellular ATP levels. After 24h the cells were incubated at 37°C containing the appropriate glucose or in case of GLUT2 fructose concentration (1 mM and 30 mM respectively) with or without compounds and 1uM Rotenone for 15min. The CellTiter-Glo® Luminescent Cell Viability Assay from Promega was then used to measure ATP levels. Compounds able to reduce the ATP levels within 15 min of glucose application were considered to be glucose uptake inhibitors. The compounds of examples 3 to 14 and 16 to 18 were tested in this assay and showed results in the range of 4 to 667 nM as depicted in detail in the following table.

10

Liu H, Hu YP, Savarai N, Priebe W, Lampadis T. Hypersensitization of tumor cells to glycolytic inhibitors. *Biochemistry*. 2001;40:5542-5547.

Ulanovskaya O, Janjic J, Matsumoto K, Schumacker PT, Kron SJ, Kozmin SA. Synthesis enables identification of the cellular target of leucascandrolide A and neopeltolide. *Nat Chem Biol*. 2008;4:418-424.

Ulanovskaya O, Jiayue Cui, Stephen J. Kron, and Sergey A. Kozmin. A pairwise chemical genetic screen identifies new inhibitors of glucose transport. *Chem Biol*. 2011 February 25; 18(2): 222-230.

20

Table 1: Measured IC₅₀ values of compounds regarding glucose induced ATP increase (GLUT1 inhibition)

Example	IC ₅₀ [nM] ¹	Example	IC ₅₀ [nM] ¹	Example	IC ₅₀ [nM] ¹
1	19	83	18800	164	39
2	11	84	78	165	97
3	4	85	93	166	50
4	260 ²	86	27	167	26
5	35	87	25	168	15
6	13	88	34	169	34
7	9	89	77	170	22
8	24	90	92	171	75
9	7	91	5	172	69
10	5	92	7	173	42

11	186	93	29	174	40
12	257	94	17	175	50
13	305	95	41	176	100
14	414	96	79	177	39
16	5	97	19	178	18
17	40	98	458	179	41
18	22	99	36	180	19
19	13	100	86	181	52
20	48	101	79	182	59
21	44	102	7	183	63
22	55	103	31	184	16
23	27	104	0.9	185	59
24	15	105	7	186	63
25	18	106	11	187	13
26	19	107	4	188	7
27	43	108	2	189	7
28	8	109	61	190	16
29	65	110	33	191	14
30	83	111	61	192	16
31	200	112	28	193	17
32	49	113	4	194	13
33	19	114	16	195	30
34	11	115	94	196	42
35	4	116	56	197	63
36	14	117	15	198	33
37	71	118	31	199	52
38	144	119	24	200	25
39	5	120	4	201	21
40	71	121	5	202	51
41	76	122	12	203	58
42	69	123	3	204	45
43	13	124	3	205	13
44	63	125	10	206	3
45	9	126	5	207	6
46	23	127	3	208	51
47	54	128	41	209	34
48	4	129	25	210	69
49	9	130	8	211	38

51	76	131	13	212	45
52	21	132	8	213	54
53	25	133	45	214	17
54	36	134	86	215	4
55	30	135	88	216	4
56	23	136	25	217	16
57	78	137	37	218	51
58	19	138	57	219	6
59	29	139	264	220	10
60	67	140	2550	221	16
61	61	141	100	222	18
62	28	142	6	223	17
63	42	143	31	224	33
64	76	144	65	225	17
65	30	145	45	226	26
66	42	147	76	227	16
67	36	148	67	228	16
69	45	149	25	229	17
70	100	150	67	230	30
71	55	151	81	231	86
72	15	152	103	232	87
73	19	153	88	233	46
74	0.7	155	52	234	5
75	11	156	24	235	0.3
76	6	157	66	Reference ³	11100
77	49	158	8		
78	11	159	17		
79	9680	160	31		
80	9090	161	4090		
81	42	162	18100		
82	16700	163	15		

¹ DLD1 cells used for ATP level measurements, all IC₅₀ values were standardized to cytochalasin B IC₅₀ values;

² CHO-K1 cells were used for ATP level measurements

5 ³ Reference = 3-bromo-4-[4-(2,5-difluorophenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine (WO2005/117909, entry 131 on page 187)

Table 2: Measured IC₅₀ values of compounds regarding fructose induced ATP increase (GLUT2 inhibition)

Example	IC ₅₀ [nM] ¹
1	36100
15	1200
39	103
45	156
111	1480

5

Biological Assay: Glucose uptake assay

Cells (e.g. H460 or CHO-K1) were cultured under standard conditions. 10000 cells per well were seeded in clear 96 well tissue culture isoplate plates and cultured overnight (PerkinElmer, 1450-516) under standard conditions. Culture medium was removed and cells were washed two times with 100 µl KRP buffer and then incubated for 45 minutes at 37°C (KRP buffer: 10 mM sodium hydrogen phosphate, 130 mM sodium chloride, 5 mM potassium chloride, 1.3 mM magnesium sulfate, 1.3 mM calcium chloride (pH 7.5), 50 mM HEPES (pH 7.5), 4.7 mM potassium chloride, 1.25 mM magnesium sulfate, 1.25 mM calcium chloride) each. KRP wash buffer was removed and compound 1 (diluted in KRP buffer) was added and incubated for 30 minutes at 37°C. 200 nM radioligand (radioligand 2[1,2] 3H-Deoxy D-Glucose in KRP buffer) were added and incubated for 5 minutes at room temperature. The supernatant was removed and cells were washed with 100 µl ice-cold KRP for two times each. 25 µl of lysis buffer (1 % Triton-X, 0,5N sodium hydroxide) were added and incubated at room temperature for 5 minutes. 75 µl scintillation solution (Microscint-20, PerkinElmer) were added and the plates were shaken for 1 minute. The plates were incubated for 3h at room temperature and the counts were determined by using a Wallace MicroBeta counter (60 seconds per well).

25

Table 3: Measured IC₅₀ values of example 1 regarding GLUT1 inhibition in different cell lines

Example	Cell line	IC ₅₀ [nM]
1	CHO-K1	311
1	H460	132
1	RCC(-VHL)	8
1	RCC(+VHL)	15

Biological assay: Proliferation Assay

- 5 Cultivated tumor cells (MCF7, hormone dependent human mammary carcinoma cells, ATCC HTB22; NCI-H460, human non-small cell lung carcinoma cells, ATCC HTB-177; DU 145, hormone-independent human prostate carcinoma cells, ATCC HTB-81; HeLa-MaTu, human cervical carcinoma cells, EPO-GmbH, Berlin; HeLa-MaTu-ADR, multidrug-resistant human cervical carcinoma cells, EPO-GmbH,
- 10 Berlin; HeLa human cervical tumor cells, ATCC CCL-2; B16F10 mouse melanoma cells, ATCC CRL-6475) were plated at a density of 5000 cells/well (MCF7, DU145, HeLa-MaTu-ADR), 3000 cells/well (NCI-H460, HeLa-MaTu, HeLa), or 1000 cells/well (B16F10) in a 96-well multititer plate in 200 µl of their respective growth medium supplemented 10% fetal calf serum. After 24 hours,
- 15 the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 µl), to which the test substances were added in various concentrations (0 µM, as well as in the range of 0.01-30 µM; the final concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were
- 20 incubated for 4 days in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 µl/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells with water, the plates were dried at room temperature. The cells were stained
- 25 by adding 100 µl/measuring point of a 0.1% crystal violet solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were

dried at room temperature. The dye was dissolved by adding 100 µl/measuring point of a 10% acetic acid solution. The extinction was determined by photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the extinction values of the zero-point plate (=0%) and the extinction of the untreated (0 µm) cells (=100%). The IC₅₀ values were determined by means of a 4 parameter fit.

Determination of metabolic stability *in vitro*

(including calculation of hepatic *in vivo* blood clearance (CL) and of maximal oral bioavailability (F_{max}))

The metabolic stability of test compounds *in vitro* was determined by incubating them at 1 µM with a suspension liver microsomes in 100 mM phosphate buffer, pH7.4 (NaH₂PO₄ x H₂O + Na₂HPO₄ x 2H₂O) at a protein concentration of 0.5 mg/mL and at 37° C. The reaction was activated by adding a co-factor mix containing 1.2 mg NADP, 3 IU glucose-6-phosphate dehydrogenase, 14.6 mg glucose-6-phosphate and 4.9 mg MgCl₂ in phosphate buffer, pH 7.4. Organic solvent in the incubations was limited to <0.2 % dimethylsulfoxide (DMSO) and <1% methanol. During incubation, the microsomal suspensions were continuously shaken and aliquots were taken at 2, 8, 16, 30, 45 and 60 min, to which equal volumes of cold methanol were immediately added. Samples were frozen at -20° C over night, subsequently centrifuged for 15 minutes at 3000 rpm and the supernatant was analyzed with an Agilent 1200 HPLC-system with LCMS/MS detection.

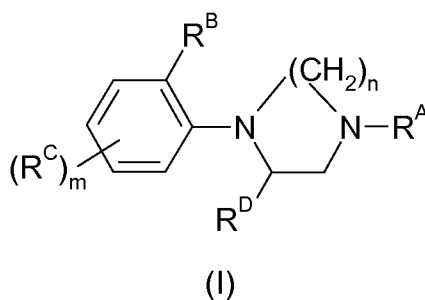
The half-life of a test compound was determined from the concentration-time plot. From the half-life the intrinsic clearances were calculated. Together with the additional parameters liver blood flow, specific liver weight and microsomal protein content the hepatic *in vivo* blood clearance (CL) and the

maximal oral bioavailability ($F_{\max}$) were calculated for the different species. The following parameter values were used: Liver blood flow - 1.3 L/h/kg (human), 2.1 L/h/kg (dog), 4.2 L/h/kg (rat); specific liver weight - 21 g/kg (human), 39 g/kg (dog), 32 g/kg (rat); microsomal protein content - 40 mg/g.

- 5 With the described assay only phase-I metabolism of microsomes is reflected, e.g. typically oxidoreductive reactions by cytochrome P450 enzymes and flavin mono-oxygenases (FMO) and hydrolytic reactions by esterases (esters and amides).

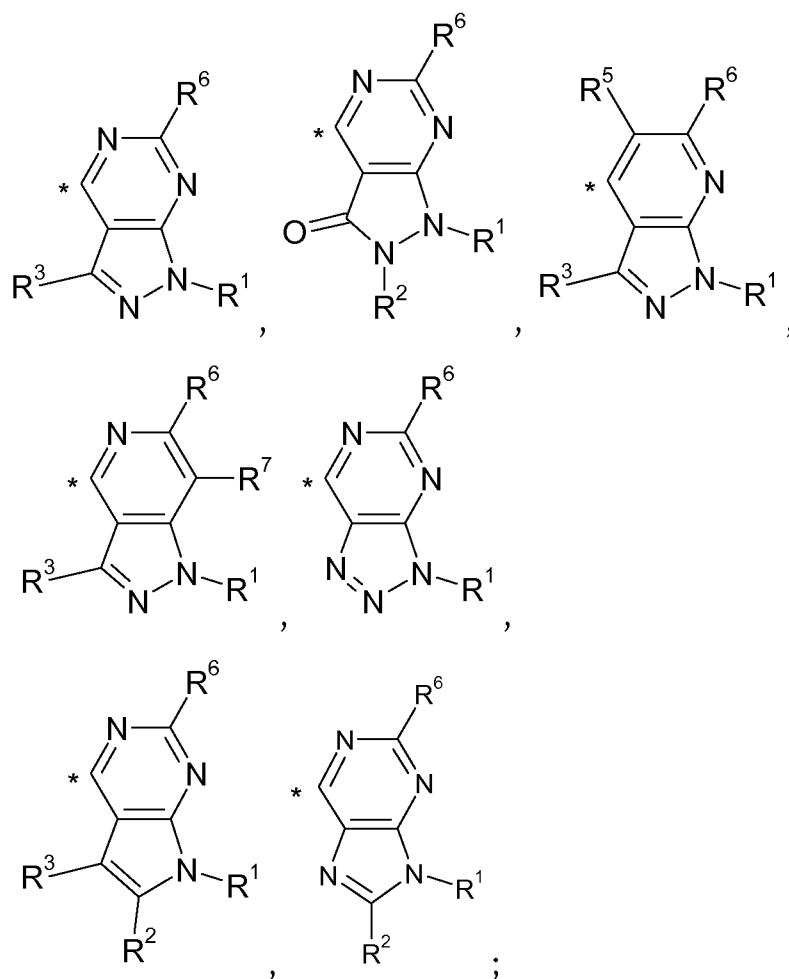
CLAIMS

1. A compound of general formula (I) :



in which :

R^A is selected from the group consisting of:



wherein * indicates the point of attachment of said groups with the rest of the molecule;

R^B represents a hydrogen atom or a -OH, -SH, -NH₂, C₁-C₃-alkoxy-,
 HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, -
 S-(C₁-C₃-alkyl), -S-(halo-C₁-C₃-alkyl), -N(H)(C₁-C₃-alkyl),
 5 -N(C₁-C₃-alkyl)(C₁-C₃-alkyl) or a H₂N-C₁-C₃-alkyl- group;

each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-,
 C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-,
 10 C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 aryl-, heteroaryl-, 3- to 10-membered heterocycloalkyl-,
 4- to 10-membered heterocycloalkenyl-, C₃-C₇-cycloalkyl-,
 -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂,
 -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 15 -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)₂R⁸,
 -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;

or

20 when two R^C groups are present ortho to each other on the phenyl-
 group, said two R^C groups together form a bridge :

O(CH₂)₂O, *O(CH₂)O*, *O(CF₂)O*, *CH₂C(R^{8a})(R^{8b})O*, *C(=O)N(R^{8a})CH₂*,
 N(R^{8a})C(=O)CH₂O, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents
 the point of attachment to said phenyl- group;

25

R^D represents a hydrogen atom or a methyl- group;

R^I represents a hydrogen atom or a C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 C₂-C₆-alkynyl-, C₁-C₆-alkoxy-, C₁-C₆-alkoxy-C₁-C₆-alkyl-,
 30 C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,

- C₄-C₈-cycloalkenyl-, -(CH₂)_p-C₄-C₈-cycloalkenyl,
 3- to 10-membered heterocycloalkyl-,
 -(CH₂)_p-(3- to 10-membered heterocycloalkyl),
 4- to 10-membered heterocycloalkenyl-,
 5 -(CH₂)_p-(4- to 10-membered heterocycloalkenyl),
 aryl-, -(CH₂)_p-aryl, heteroaryl- or -(CH₂)_p-heteroaryl group,
 wherein said group is optionally substituted, identically or differently,
 with 1, 2, 3, 4 or 5 R⁹ groups ;
- 10 R² represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group ;
- R³ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,
 15 -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,
 -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸ or -O(C=O)N(R^{8a})R^{8b} group ;
 wherein said C₁-C₃-alkyl- group is optionally substituted with a group
 20 selected from: -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸,
 -OR⁸, -O(C=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} and
 -S(=O)(=NR^{8c})R⁸ ;
- 25 R⁵ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group;
- R⁶ represents a hydrogen atom or a C₁-C₃-alkyl-, C₁-C₃-alkoxy-,
 halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, -C(=O)R⁸,
 30 -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸,

-N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸ or
 -O(C=O)R⁸ group ;

wherein said C₁-C₃-alkyl- group is optionally substituted with a group
 5 selected from: -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 -N(R^{8a})R^{8b}, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸,
 -OR⁸, -O(C=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} and
 -S(=O)(=NR^{8c})R⁸ ;

10 R⁷ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or
 C₃-C₇-cycloalkyl- group;

R⁸, R^{8a}, R^{8b}, R^{8c}

represent, independently from each other, a hydrogen atom or a
 15 C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,
 C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-,
 (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, heteroaryl-,
 aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-C₁-C₆-alkyl- or
 (aryl)-(3- to 10-membered heterocycloalkyl)- group;

20 said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,
 3- to 10-membered heterocycloalkyl-,
 (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-,
 aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-,
 heteroaryl-C₁-C₆-alkyl-, (aryl)-(3- to 10-membered heterocycloalkyl)-
 25 group being optionally substituted one or more times, identically or
 differently, with R¹⁰;

or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a
 4- to 7-membered heterocycloalkyl- group, which is optionally
 30 substituted once with C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group,

the phenyl- group being optionally substituted 1, 2 or 3 times,
identically or differently, with halogen, C₁-C₃-alkyl- or C₁-C₃-alkoxy;

5 R⁹ represents a halogen atom, or a -CN, C₁-C₆-alkoxy-, C₁-C₆-alkyl-,
halo-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₆-alkyl)-,
HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-,
C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-,
aryl-, heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
-N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b},
10 -N(R^{8c})C(=O)N(R^{8a})R^{8b}, -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸,
-N(R^{8c})S(=O)₂R⁸, -OR⁸, -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸,
-S(=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or
-S(=O)(=NR^{8c})R⁸ group;

wherein the aryl- and heteroaryl- group is optionally substituted, one or
15 more times, identically or differently, with R^c ;

R¹⁰ represents a halogen atom, or a C₁-C₃-alkyl-, halo-C₁-C₃-alkyl-, -CN,
-C(=O)R¹¹, -C(=O)N(H)R¹¹, -C(=O)N(R^{11a})R^{11b}, -C(=O)O-R¹¹, -N(R^{11a})R^{11b},
-NO₂, -N(H)C(=O)R¹¹, -N(R^{11a})C(=O)R^{11b}, -N(H)C(=O)N(R^{11a})R^{11b},
20 -N(R^{11a})C(=O)N(R^{11b})R^{11c}, -N(H)C(=O)OR¹¹, -N(R^{11a})C(=O)OR^{11b},
-N(H)S(=O)₂R¹¹, -N(R^{11a})S(=O)₂R^{11b}, -OR¹¹, -O(C=O)R¹¹, -O(C=O)N(R^{11a})R^{11b},
-O(C=O)OR¹¹, -SR¹¹, -S(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(H)R¹¹,
-S(=O)₂N(R^{11a})R^{11b} or -S(=O)(=NR^{11a})R^{11b} group;

25 R¹¹, R^{11a}, R^{11b}, R^{11c}

represent, independently from each other, a hydrogen atom or a
C₁-C₆-alkyl- group;

m is an integer of 0, 1, 2 or 3 ;

30 n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

t is an integer of 3, 4 or 5 ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
5 of same ;

wherein the following compounds are excluded:

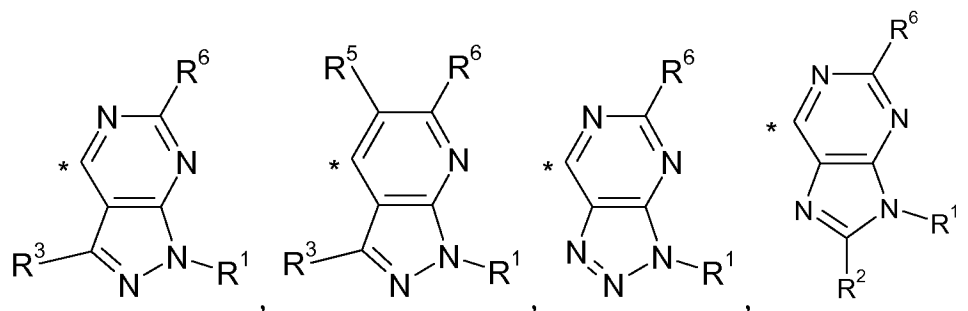
4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,

1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-
1H-pyrazolo[3,4-d]pyrimidine,

10 4-[4-(2-fluorophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine.

2. A compound according to claim 1, wherein :

R^A is selected from the group consisting of:

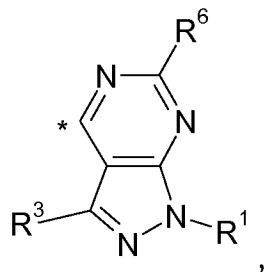


15 wherein * indicates the point of attachment of said groups with the rest
of the molecule;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
of same.

20 3. A compound according to claim 1 or 2, wherein :

R^A represents



wherein * indicates the point of attachment of said groups with the rest of the molecule;

5 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

4. A compound according to any one of claims 1 to 3, wherein :

R^B represents a -OH, -NH₂, C₁-C₂-alkoxy- or a -S-(C₁-C₂-alkyl)- group;

10 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. A compound according to any one of claims 1 to 4, wherein :

each R^C independently represents

15 a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, fluoro-C₁-C₃-alkyl-, HO-C₁-C₆-alkyl-, phenyl-, 5- or 6-membered heteroaryl-, -C(=O) R^8 , -C(=O)N(H) R^{8a} , -C(=O)N(R^{8a}) R^{8b} , -C(=O)O- R^8 , -N(R^{8a}) R^{8b} , -N(H)C(=O) R^8 , -N(R^{8c})C(=O) R^8 , -N(R^{8c})C(=O)C(=O)N(R^{8a}) R^{8b} , -N(H)S(=O)₂ R^8 , -S(=O)₂ R^8 , -S(=O)₂N(H) R^8 or
20 -S(=O)₂N(R^{8a}) R^{8b} group;

or when two R^C groups are present ortho to each other on the phenyl-group, said two R^C groups together form a bridge :

O(CH₂)O or *(CH₂)_t*; wherein each * represents the point of attachment to said phenyl- group;

25 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

6. A compound according to any one of claims 1 to 5, wherein :

R^D represents a hydrogen atom ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
5 of same.

7. A compound according to any one of claims 1 to 6, wherein :

R¹ represents a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
4- to 7-membered heterocycloalkyl-,

10 -(CH₂)_p-(4- to 7-membered heterocycloalkyl), phenyl-,

-(CH₂)_p-phenyl or 5- or 6-membered heteroaryl- group,

wherein said group is optionally substituted, identically or differently,
with 1 or 2 R⁹ groups ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
15 of same.

8. A compound according to any one of claims 1 to 7, wherein :

R² represents a hydrogen atom or a methyl- group;

R³ represents a hydrogen atom ;

20 R⁵ represents a hydrogen atom ;

and

R⁶ represents a hydrogen atom ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
of same.

25

9. A compound according to any one of claims 1 to 8, wherein :

R⁸ and R^{8a}

represent, independently from each other, a hydrogen atom, or

a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-,

30 4- to 7-membered heterocycloalkyl-,

(4- to 7-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, phenyl-, naphthyl-,
 5- or 6-membered heteroaryl-, phenyl-C₁-C₆-alkyl-,
 (phenyl)-O-(C₁-C₆-alkyl)- or
 (5- or 6-membered heteroaryl)-C₁-C₆-alkyl- group; said C₁-C₆-alkyl-,
 5 phenyl-, naphthyl-, phenyl-C₁-C₆-alkyl-, (phenyl)-O-(C₁-C₆-alkyl)-, 5- or
 6-membered heteroaryl-, (5- or 6-membered heteroaryl)-C₁-C₆-alkyl-
 group being optionally substituted one or more times, identically or
 differently, with R¹⁰;

10 R^{8b} and R^{8c}

represent, independently from each other, a hydrogen atom or a
 C₁-C₃-alkyl- or a methoxy-C₁-C₃-alkyl- group ;

or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a
 15 4- to 7-membered heterocycloalkyl- group, which is optionally
 substituted once with a C₁-C₃-alkyl- or a phenyl- group, the phenyl-
 group being optionally substituted once with fluoro, chloro, methyl- or
 methoxy-;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
 20 of same.

10. A compound according to any one of claims 1 to 9, wherein :

R⁹ represents a halogen atom, or a -CN, C₁-C₃-alkoxy-, C₁-C₃-alkyl-,
 trifluoromethyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₃-alkyl)-, aryl-,
 25 5- or 6-membered heteroaryl-, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -N(R^{8a})R^{8b},
 -NO₂, -N(H)C(=O)R⁸, -N(H)S(=O)₂R⁸, -OR⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸ or
 -S(=O)₂N(R^{8a})R^{8b} group;
 wherein the aryl- and heteroaryl- group is optionally substituted, one or
 more times, identically or differently, with R^c;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

11. A compound according to any one of claims 1 to 10, wherein :

5 m is an integer of 0 or 1 ;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

12. A compound according to claim 1, which is selected from the group
10 consisting of:

2-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol,

4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,

15 4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,

1-(3-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,

2-[4-(1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol,

20 1-(3-fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,

2-[4-(1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol,

25 1-(4-fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,

4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[4-(methylsulfonyl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine,

4-[4-(2-ethoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,

- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(pyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidine,
- 2-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]aniline,
- 1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(2-fluorophenyl)-4-{4-[2-(methylsulfanyl)phenyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine,
- {2-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanol,
- 4-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(4-chloro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2,4-dimethoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 3-methoxy-4-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzonitrile,
- 4-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2-methoxy-5-methylphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- methyl 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoate,
- {4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanol,

- 1-cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-cyclohexyl-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 5 1-(cyclohexylmethyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(4-bromo-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(5-bromo-2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 10 d]pyrimidine,
- 4-{4-[2-methoxy-5-(pyridin-3-yl)phenyl]piperazin-1-yl}-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 15 4-[4-(4-fluoro-2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 4-methoxy-3-{4-[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}benzonitrile,
- (+/-)-4-[4-(2-methoxyphenyl)-3-methylpiperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 20 4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoic acid,
- 25 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,

- N-(2-aminoethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-[2-(dimethylamino)ethyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 5 4-methoxy-N-[2-(methylamino)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-[2-(acetylamino)ethyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-(3-aminopropyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 10 N-(2-hydroxyethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-(2-hydroxypropyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 15 azetidin-1-yl{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanone,
- 4-methoxy-N-[2-(2-oxoimidazolidin-1-yl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(2-methoxyethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 20 4-[4-(2-methoxy-5-nitrophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]aniline,
- 25 N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide,

- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}-2-phenylacetamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}cyclopropanecarboxamide,
- 5 N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}ethanediamide,
- 2-methoxy-N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}cyclopentanecarboxamide,
- 10 (+/-)-N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}tetrahydrofuran-2-carboxamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}butanediamide,
- 15 N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-2-carboxamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-3-carboxamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-4-carboxamide,
- 20 2,2,2-trifluoro-N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanesulfonamide,
- 25 N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}benzenesulfonamide,

- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}-2-phenylethanesulfonamide,
- N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}pyridine-3-sulfonamide,
- 5 4-[4-(2-methoxy-4-nitrophenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 3-methoxy-4-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]aniline,
- N-{3-methoxy-4-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide,
- 10 7-[4-(2-methoxyphenyl)piperazin-1-yl]-3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine,
- 2-[4-(3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)piperazin-1-yl]phenol,
- 7-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3-phenyl-3H-[1,2,3]triazolo[4,5-d]pyrimidine,
- 15 7-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine,
- 7-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidine,
- 20 4-methoxy-3-{4-[3-(2-methylphenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]piperazin-1-yl}benzonitrile,
- 3-(2-fluorophenyl)-7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine,
- 3-(2-fluorophenyl)-7-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidine,
- 25 3-fluoro-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}benzamide,

- trans-4-{7-[4-(2-methoxyphenyl)piperazin-1-yl]-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl}cyclohexanecarboxamide,
- methyl 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)piperazin-1-yl]benzoate,
- 5 N-(2-hydroxyethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)piperazin-1-yl]benzamide,
- 4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(4-fluorophenyl)-1H-
- 10 pyrazolo[3,4-d]pyrimidine,
- methyl 3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzoate,
- 4-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzamide,
- 15 4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 2-{4-[1-(3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(3-methylphenyl)-1H-pyrazolo[3,4-
- 20 d]pyrimidine,
- 4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 2-{4-[1-(4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 25 1-(3-bromophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,

- 2-{4-[1-(3-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 1-(3-bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 5 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[3-(1H-pyrazol-5-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine,
- 3'-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}biphenyl-3-carboxamide,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[3-(thiophen-3-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidine,
- 10 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(2-methylphenyl)-4-{4-[2-(methylsulfonyl)phenyl]piperazin-1-yl}-1H-pyrazolo[3,4-d]pyrimidine,
- 15 4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 2-{4-[1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(2-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 20 4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 25 3-(3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}phenyl)propanamidem,

- 3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzonitrile,
- 1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-b]pyridine,
- 5 4-[4-(5-chloro-2-methoxyphenyl)piperazin-1-yl]-1-(2-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine,
- 1-(2-fluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-b]pyridine,
- 4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine,
- 10 b]pyridine,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-b]pyridine,
- 1-(2,4-dichlorobenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(2,4-dichlorobenzyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 15 pyrazolo[3,4-d]pyrimidine,
- 2-{4-[1-(2,4-dichlorobenzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 1-cyclopentyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 20 2-[4-(1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol,
- 1-cyclopentyl-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(2,4-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 25 2-{4-[1-(2,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,

- 1-(2,4-difluorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(2-bromophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 5 2-{4-[1-(2-bromophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 1-(2-bromophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 2'-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}biphenyl-3-carboxamide,
- 10 1-(2-chlorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 2-{4-[1-(2-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenol,
- 15 1-(2-chlorophenyl)-4-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(3-chloro-2-fluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(3-chloro-2-fluorophenyl)-4-[4-(5-fluoro-2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 20 1-(2-fluorobenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 25 1-(cyclopentylmethyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,

- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(2-nitrobenzyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidine,
- 5 methyl 3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}methyl)benzoate,
- [3-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}methyl)phenyl](morpholin-4-yl)methanone,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[2-(morpholin-4-ylsulfonyl)benzyl]-1H-pyrazolo[3,4-d]pyrimidine,
- 10 1-(2,6-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(3-chlorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 15 1-(2-fluoro-4-methylphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(thiophen-2-yl)-1H-pyrazolo[3,4-d]pyrimidine,
- 3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-
- 20 N,N-dimethylaniline,
- 1-(2-methoxyphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}benzonitrile,
- 25 2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-N,N-dimethylaniline,

- 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}aniline,
- 5 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidine,
- 4-{4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}aniline,
- 1-(2,5-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 10 1-(2-ethylphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(3,5-difluorophenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 15 4-[4-(2-methoxyphenyl)piperazin-1-yl]-1-[2-(propan-2-yloxy)phenyl]-1H-pyrazolo[3,4-d]pyrimidine,
- 1-(5-fluoro-2-methoxyphenyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 4-[4-(2,5-dimethoxyphenyl)piperazin-1-yl]-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine,
- 20 3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzonitrile,
- N-{3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}acetamide,
- N-(3-fluorobenzyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 25 4-methoxy-N-[3-(morpholin-4-yl)propyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,

- 4-methoxy-N-(2-phenylethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-phenyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 5 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(piperidin-1-yl)ethyl]benzamide,
- 4-methoxy-N-(4-phenylbutyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(2-methoxybenzyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 10 4-methoxy-N-(3-methoxybenzyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-(2-fluorobenzyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 15 N-(4-fluorobenzyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(2,2,2-trifluoroethyl)benzamide,
- N-benzyl-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 20 4-methoxy-N-[2-(4-methoxyphenyl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(thiophen-2-ylmethyl)benzamide,
- 25 N-ethyl-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,

- 4-methoxy-N-methyl-N-phenyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-[3-(dimethylamino)propyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 5 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[3-(trifluoromethyl)benzyl]benzamide,
- 4-methoxy-N-[2-(3-methoxyphenyl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-
- 10 (pyridin-4-yl)benzamide,
- N-(4-carbamoylphenyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-(cyclopropylmethyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 15 4-methoxy-N-[2-(morpholin-4-yl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyridin-2-yl)ethyl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-
- 20 [2-(pyrrolidin-1-yl)ethyl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(4-sulfamoylbenzyl)benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-2-ylmethyl)benzamide,
- 25 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-3-ylmethyl)benzamide,

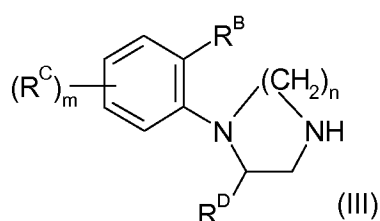
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(pyridin-4-ylmethyl)benzamide,
- 4-methoxy-N-(naphthalen-1-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 5 4-methoxy-N-(naphthalen-2-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(3-methoxyphenyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(4-methoxyphenyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 10 4-methoxy-N-(4-methoxyphenyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-benzyl-4-methoxy-N-methyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-(4-fluorophenyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 15 4-methoxy-N-(2-methylpropyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(4-methoxybenzyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-methyl-N-(2-phenylethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 20 {4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}(4-phenylpiperazin-1-yl)methanone,
- 4-methoxy-N-(3-phenylpropyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 25 methyl N-{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoyl}-beta-alaninate,

- methyl 4-({4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzoyl}amino)butanoate,
- 4-methoxy-N,N-bis(2-methoxyethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 5 [4-(3-methoxyphenyl)piperazin-1-yl]{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanone,
- [4-(4-methoxyphenyl)piperazin-1-yl]{4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}methanone,
- N-(2,2-dimethylpropyl)-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-
- 10 4-yl)piperazin-1-yl]benzamide,
- N-[4-(diethylamino)butyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- N-[4-(dimethylamino)butyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 15 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(thiophen-2-yl)ethyl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyridin-4-yl)ethyl]benzamide,
- 4-methoxy-N-(3-methoxypropyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-
- 20 yl)piperazin-1-yl]benzamide,
- N-[2-(4-fluorophenyl)ethyl]-4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(2-methoxyethyl)-N-methyl-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 25 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-[2-(pyridin-3-yl)ethyl]benzamide,

- 4-methoxy-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-[(1-methyl-1H-pyrazol-5-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 5 4-methoxy-N-(1-methyl-1H-pyrazol-3-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-[2-(4-methylpiperazin-1-yl)ethyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(1-methyl-1H-pyrazol-4-yl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 10 d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-[(5-methylpyrazin-2-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-N-(thiophen-3-ylmethyl)benzamide,
- 15 4-methoxy-N-[(1-methyl-1H-imidazol-5-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 4-methoxy-N-(2-phenoxyethyl)-3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzamide,
- 20 N-(4-methoxyphenyl)-4-({4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}methyl)benzamide,
- 1-(2-bromo-5-methoxybenzyl)-4-[4-(2-methoxyphenyl)piperazin-1-yl]-1H-pyrazolo[3,4-d]pyrimidine,
- 25 3-[4-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenol,
- 6-[4-(2-methoxyphenyl)piperazin-1-yl]-9-phenyl-9H-purine,
- 6-[4-(2-methoxyphenyl)piperazin-1-yl]-8-methyl-9-phenyl-9H-purine,

6-[4-(2-methoxyphenyl)-1,4-diazepan-1-yl]-8-methyl-9-phenyl-9H-purine,
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
of same.

- 5 13. A method of preparing a compound of general formula (I) according to any
one of claims 1 to 12,
in which method an intermediate of general formula (III) :

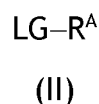


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in which R^B , R^C , R^D , m , and n are as defined in any one of claims 1 to 12;

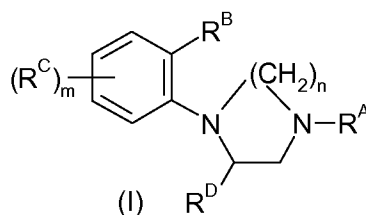
is allowed to react with a compound of general formula (II) :

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in which R^A is as defined in any one of claims 1 to 12, and LG is a leaving group;

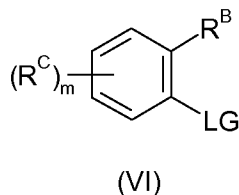
thus providing a compound of general formula (I) :



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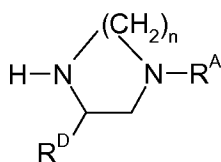
in which R^A , R^B , R^C , R^D , m , and n are as defined in any one of claims 1 to 12.

14. A method of preparing a compound of general formula (I) according to any one of claims 1 to 12, in which method an intermediate of general formula (VI) :



5 in which R^B , R^C and m are as defined in any one of claims 1 to 12, and LG is a leaving group;

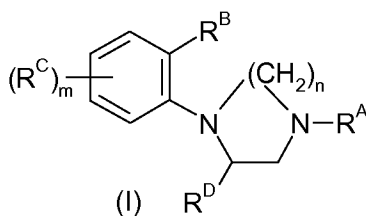
is allowed to react with a compound of general formula (V) :



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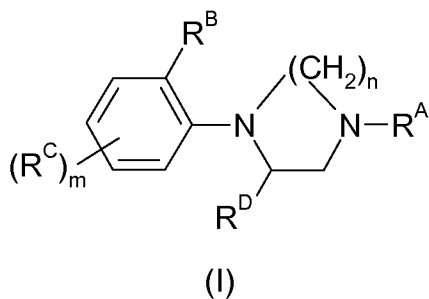
in which R^A , R^D and n are as defined in any one of claims 1 to 12;

thus providing a compound of general formula (I) :



15 in which R^A , R^B , R^C , R^D , m , and n are as defined in any one of claims 1 to 12.

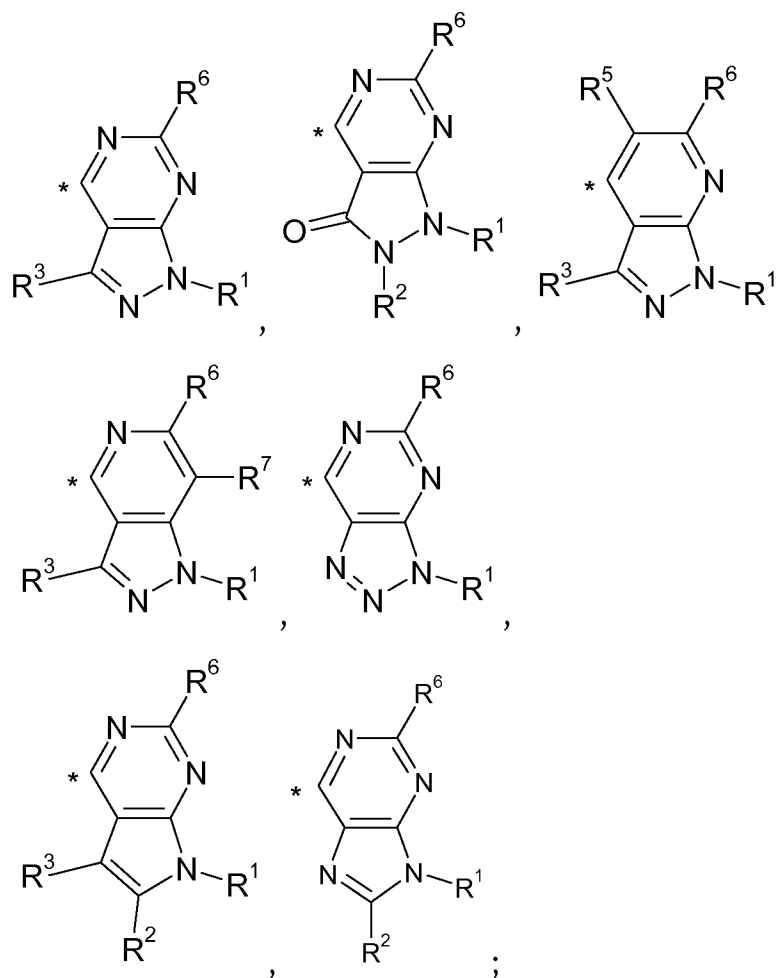
15. A compound of formula (I) :



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in which :

R^A is selected from the group consisting of:



wherein * indicates the point of attachment of said groups with the rest of the molecule;

10 R^B represents a hydrogen atom or a -OH, -SH, -NH₂, C₁-C₃-alkoxy-, HO-C₁-C₃-alkyl-, HO-C₂-C₃-alkoxy-, halo-C₁-C₃-alkyl-, halo-C₁-C₃-alkoxy-, -S-(C₁-C₃-alkyl), -S-(halo-C₁-C₃-alkyl), -N(H)(C₁-C₃-alkyl), -N(C₁-C₃-alkyl)(C₁-C₃-alkyl) or a H₂N-C₁-C₃-alkyl- group;

15 each

R^C independently represents a halogen atom, or a -CN, -OH, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, $R^{8a}(R^{8b})N$ -C₁-C₆-alkyl-, HO-C₁-C₆-alkyl-,

- C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 aryl-, heteroaryl-, 3- to 10-membered heterocycloalkyl-,
 4- to 10-membered heterocycloalkenyl-, C₃-C₇-cycloalkyl-,
 -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸, -N(R^{8a})R^{8b}, -NO₂,
 5 -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b}, -N(R^{8c})C(=O)N(R^{8a})R^{8b},
 -N(R^{8c})C(=O)C(=O)N(R^{8a})R^{8b},
 -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸, -N(R^{8c})S(=O)₂R⁸, -OR⁸,
 -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸, -S(=O)R⁸, -S(=O)₂R⁸,
 -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or -S(=O)(=NR^{8c})R⁸ group;
 10 or
 when two R^C groups are present ortho to each other on the phenyl-
 group, said two R^C groups together form a bridge :
 O(CH₂)₂O, *O(CH₂)O*, *O(CF₂)O*, *CH₂C(R^{8a})(R^{8b})O*, *C(=O)N(R^{8a})CH₂*,
 N(R^{8a})C(=O)CH₂O, *NHC(=O)NH* or *(CH₂)_t*; wherein each * represents
 15 the point of attachment to said phenyl- group;
- R^D represents a hydrogen atom or a methyl- group;
- R¹ represents a hydrogen atom or a C₁-C₆-alkyl-, C₂-C₆-alkenyl-,
 20 C₂-C₆-alkynyl-, C₁-C₆-alkoxy-, C₁-C₆-alkoxy-C₁-C₆-alkyl-,
 C₃-C₇-cycloalkyl-, -(CH₂)_p-C₃-C₇-cycloalkyl,
 C₄-C₈-cycloalkenyl-, -(CH₂)_p-C₄-C₈-cycloalkenyl,
 3- to 10-membered heterocycloalkyl-,
 -(CH₂)_p-(3- to 10-membered heterocycloalkyl),
 25 4- to 10-membered heterocycloalkenyl-,
 -(CH₂)_p-(4- to 10-membered heterocycloalkenyl),
 aryl-, -(CH₂)_p-aryl, heteroaryl- or -(CH₂)_p-heteroaryl group,
 wherein said group is optionally substituted, identically or differently,
 with 1, 2, 3, 4 or 5 R⁹ groups ;

30

- R^2 represents a hydrogen atom or a C_1 - C_6 -alkyl-, trifluoromethyl- or C_3 - C_7 -cycloalkyl- group ;
- R^3 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-,
 5 halo- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$,
 $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$,
 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-OR^8$,
 $-O(C=O)R^8$ or $-O(C=O)N(R^{8a})R^{8b}$ group ;
- 10 wherein said C_1 - C_3 -alkyl- group is optionally substituted with a group
 selected from: $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$,
 $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$,
 $-OR^8$, $-O(C=O)R^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ and
 $-S(=O)(=NR^{8c})R^8$;
- 15 R^5 represents a hydrogen atom or a C_1 - C_6 -alkyl-, trifluoromethyl- or
 C_3 - C_7 -cycloalkyl- group;
- R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl-, C_1 - C_3 -alkoxy-,
 20 halo- C_1 - C_3 -alkyl-, halo- C_1 - C_3 -alkoxy-, HO- C_1 - C_3 -alkyl-, $-C(=O)R^8$,
 $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$, $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$,
 $-N(R^{8c})C(=O)R^8$, $-N(H)C(=O)N(R^{8a})R^{8b}$, $-N(R^{8c})C(=O)N(R^{8a})R^{8b}$,
 $-N(H)C(=O)OR^8$, $-N(R^{8c})C(=O)OR^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$, $-OR^8$ or
 $-O(C=O)R^8$ group ;
- 25 wherein said C_1 - C_3 -alkyl- group is optionally substituted with a group
 selected from: $-C(=O)R^8$, $-C(=O)N(H)R^{8a}$, $-C(=O)N(R^{8a})R^{8b}$, $-C(=O)O-R^8$,
 $-N(R^{8a})R^{8b}$, $-N(H)C(=O)R^8$, $-N(R^{8c})C(=O)R^8$, $-N(H)S(=O)_2R^8$, $-N(R^{8c})S(=O)_2R^8$,
 $-OR^8$, $-O(C=O)R^8$, $-S(=O)_2R^8$, $-S(=O)_2N(H)R^8$, $-S(=O)_2N(R^{8a})R^{8b}$ and
 $-S(=O)(=NR^{8c})R^8$;

30

R⁷ represents a hydrogen atom or a C₁-C₆-alkyl-, trifluoromethyl- or C₃-C₇-cycloalkyl- group;

R⁸, R^{8a}, R^{8b}, R^{8c}

5 represent, independently from each other, a hydrogen atom, or a C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-, (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-, heteroaryl-, aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-C₁-C₆-alkyl- or
 10 (aryl)-(3- to 10-membered heterocycloalkyl)- group;
 said C₁-C₆-alkyl-, C₃-C₇-cycloalkyl-, (C₃-C₇-cycloalkyl)-(C₁-C₆-alkyl)-, 3- to 10-membered heterocycloalkyl-,
 (3- to 10-membered heterocycloalkyl)-(C₁-C₆-alkyl)-, aryl-,
 aryl-C₁-C₆-alkyl-, (aryl)-O-(C₁-C₆-alkyl)-, heteroaryl-,
 15 heteroaryl-C₁-C₆-alkyl-, (aryl)-(3- to 10-membered heterocycloalkyl)-
 group being optionally substituted one or more times, identically or differently, with R¹⁰; or

R^{8a} and R^{8b}, together with the nitrogen atom they are attached to, form a

20 4- to 7-membered heterocycloalkyl- group, which is optionally substituted once with C₁-C₃-alkyl-, C₃-C₇-cycloalkyl- or a phenyl- group, the phenyl- group being optionally substituted 1, 2 or 3 times, identically or differently, with halogen, C₁-C₃-alkyl- or C₁-C₃-alkoxy;

25 R⁹ represents a halogen atom, or a -CN, C₁-C₆-alkoxy-, C₁-C₆-alkyl-, halo-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C₁-C₆-alkyl-, R^{8a}(R^{8b})N-C(=O)(C₁-C₆-alkyl)-, HO-C₁-C₆-alkyl-, C₁-C₆-alkoxy-C₁-C₆-alkyl-, halo-C₁-C₆-alkoxy-C₁-C₆-alkyl-, C₂-C₆-alkenyl-, C₂-C₆-alkynyl-, 3- to 10-membered heterocycloalkyl-, aryl-, heteroaryl-, -C(=O)R⁸, -C(=O)N(H)R^{8a}, -C(=O)N(R^{8a})R^{8b}, -C(=O)O-R⁸,
 30 -N(R^{8a})R^{8b}, -NO₂, -N(H)C(=O)R⁸, -N(R^{8c})C(=O)R⁸, -N(H)C(=O)N(R^{8a})R^{8b},

-N(R^{8c})C(=O)N(R^{8a})R^{8b}, -N(H)C(=O)OR⁸, -N(R^{8c})C(=O)OR⁸, -N(H)S(=O)₂R⁸,
 -N(R^{8c})S(=O)₂R⁸, -OR⁸, -O(C=O)R⁸, -O(C=O)N(R^{8a})R^{8b}, -O(C=O)OR⁸, -SR⁸,
 -S(=O)R⁸, -S(=O)₂R⁸, -S(=O)₂N(H)R⁸, -S(=O)₂N(R^{8a})R^{8b} or
 -S(=O)(=NR^{8c})R⁸ group;

5 wherein the aryl-, heteroaryl- group is optionally substituted, one or more times, identically or differently, with R^c ;

R¹⁰ represents a halogen atom or a C₁-C₃-alkyl-, halo-C₁-C₃-alkyl-, -CN,
 -C(=O)R¹¹, -C(=O)N(H)R¹¹, -C(=O)N(R^{11a})R^{11b}, -C(=O)O-R¹¹, -N(R^{11a})R^{11b},
 10 -NO₂, -N(H)C(=O)R¹¹, -N(R^{11a})C(=O)R^{11b}, -N(H)C(=O)N(R^{11a})R^{11b},
 -N(R^{11a})C(=O)N(R^{11b})R^{11c}, -N(H)C(=O)OR¹¹, -N(R^{11a})C(=O)OR^{11b},
 -N(H)S(=O)₂R¹¹, -N(R^{11a})S(=O)₂R^{11b}, -OR¹¹, -O(C=O)R¹¹, -O(C=O)N(R^{11a})R^{11b},
 -O(C=O)OR¹¹, -SR¹¹, -S(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(H)R¹¹,
 -S(=O)₂N(R^{11a})R^{11b} or -S(=O)(=NR^{11a})R^{11b} group;

15

R¹¹, R^{11a}, R^{11b}, R^{11c}

represent, independently from each other, a hydrogen atom or a
 C₁-C₆-alkyl- group;

20 m is an integer of 0, 1, 2 or 3 ;

n is an integer of 2 or 3 ;

p is an integer of 1 or 2 ;

t is an integer of 3, 4 or 5 ;

25 or a compound according to any of claims 1 to 12, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for use in the treatment or prophylaxis of a disease.

16. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 15 or a compound according to any one of claims 1 to 12, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, and a
5 pharmaceutically acceptable diluent or carrier.

17. A pharmaceutical combination comprising :
- one or more compounds of formula (I) as defined in claim 15 or one or more compounds according to any one of claims 1 to 12, or a tautomer, an N-oxide,
10 a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same;
and
- one or more agents selected from : a taxane, such as Docetaxel, Paclitaxel, or Taxol; an epothilone, such as Ixabepilone, Patupilone, or Sagopilone;
15 Mitoxantrone; Prednisolone; Dexamethasone; Estramustin; Vinblastin; Vincristin; Doxorubicin; Adriamycin; Idarubicin; Daunorubicin; Bleomycin; Etoposide; Cyclophosphamide; Ifosfamide; Procarbazine; Melphalan; 5-Fluorouracil; Capecitabine; Fludarabine; Cytarabine; Ara-C; 2-Chloro-2'-deoxyadenosine; Thioguanine; an anti-androgen, such as Flutamide,
20 Cyproterone acetate, or Bicalutamide; Bortezomib; a platinum derivative, such as Cisplatin, or Carboplatin; Chlorambucil; Methotrexate; and Rituximab.

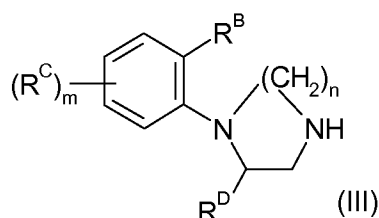
18. Use of a compound as defined in claim 15 or a compound of any one of claims 1 to 12, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt
25 thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

19. Use of a compound as defined in claim 15 or a compound of any one of claims 1 to 12, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt
30 thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture

of same, for the preparation of a medicament for the prophylaxis or treatment of a disease.

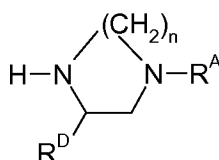
20. Use according to claim 15, 18 or 19, wherein said disease is a disease of uncontrolled cell growth, proliferation and/or survival, an inappropriate cellular immune response, or an inappropriate cellular inflammatory response, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is mediated by GLUT1, more particularly in which the disease of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune response, or inappropriate cellular inflammatory response is a haematological tumour, a solid tumour and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

21. Compounds of general formula (III):



in which R^B , R^C , R^D , m , and n are as defined in any one of claims 1 to 12.

22. Compounds of general formula (V):

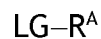


(V)

in which R^A , R^D and n are as defined in any one of claims 1 to 12.

5 **23. Use of a compound**

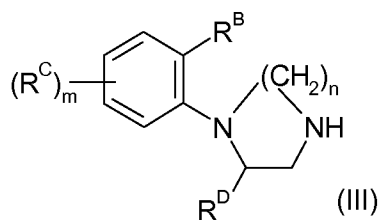
(i) of general formula (II):



(II)

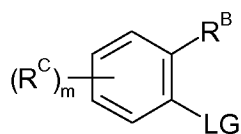
in which R^A is as defined in any one of claims 1 to 12, and LG is a
 10 leaving group;

(ii) of general formula (III):



in which R^B , R^C , R^D , m , and n are as defined in any one of claims 1 to
 15 12;

(iii) of general formula (VI):

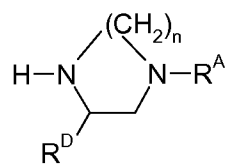


(VI)

in which R^B , R^C and m are as defined in any one of claims 1 to 12, and
 20 LG is a leaving group;

and/or

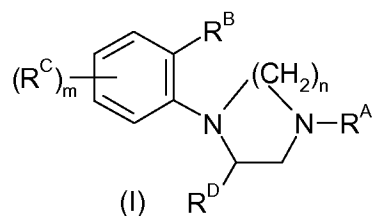
(iv) of general formula (V):



(V)

in which R^A , R^D and n are as defined in any one of claims 1 to 12;

5 for the preparation of compounds of general formula (I):



(I)

in which R^A , R^B , R^C , R^D , m , and n are as defined in any one of claims 1 to 12.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/061618

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/117909 A2 (EXELIXIS INC [US]; ANAND NEEL K [US]; BLAZEY CHARLES M EXELIXIS INC [U]) 15 December 2005 (2005-12-15) claims 1,5,58,61,63,65 page 187; compounds 131,132 page 53, scheme 1 page 83, paragraph 475 page 194; compounds 301-305 page 195; compound 334 paragraph [0241] ----- -/--	1-20,23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 September 2013

Date of mailing of the international search report

17/09/2013

Name and mailing address of the ISA/

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Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/061618

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	QIONG L. ZHOU ET AL: "Akt substrate TBC1D1 regulates GLUT1 expression through the mTOR pathway in 3T3-L1 adipocytes", BIOCHEMICAL JOURNAL, vol. 411, no. 3, 1 May 2008 (2008-05-01), page 647, XP055034722, ISSN: 0264-6021, DOI: 10.1042/BJ20071084 the whole document	1-20,23
A	US 2004/204400 A1 (CHERN JYH-HAUR [TW] ET AL) 14 October 2004 (2004-10-14) claim 32 paragraph [0018] pages 3-4; compounds 4, 7, 9 example 1	1-20,23
A	WO 2004/064721 A2 (TANABE SEIYAKU CO [JP]; TAKAMURO IWAO [JP]; SEKINE YASUO [JP]; TSUBOI) 5 August 2004 (2004-08-05) claims 1,14,18 page 50; examples 135-138	1-20,23
X	US 2005/054651 A1 (NATARAJAN SATEESH K [US] ET AL) 10 March 2005 (2005-03-10) claim 20 paragraphs [0007], [0205], [0225] page 77; example 51	1-19
X	DATABASE PUBCHEM [Online] NCBI; 4 April 2007 (2007-04-04), XP002681526, Database accession no. CID: 16033926 the whole document	1-11, 15-20
A	DATABASE PUBCHEM [Online] NCBI; 28 May 2009 (2009-05-28), XP002681527, Database accession no. CID: 29105802 the whole document	1-20,23
A	DATABASE PUBCHEM [Online] NCBI; 11 July 2005 (2005-07-11), XP002681528, Database accession no. CID: 1421264 the whole document	1-20,23
A	DATABASE PUBCHEM [Online] NCBI; 13 July 2005 (2005-07-13), XP002681530, Database accession no. CID: 1977736 the whole document	1-20,23
	-/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/061618

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE PUBCHEM [Online] NCBI; 4 April 2007 (2007-04-04), XP002681529, Database accession no. CID: 16033894 the whole document	1-11,15, 16,18,19
A	----- WO 2005/051304 A2 (ARRAY BIOPHARMA INC [US]; MITCHELL IAN S [US]; SPENCER KEITH L [US]; S) 9 June 2005 (2005-06-09) page 163, paragraph 604 claim 1	1-20,23
A	----- WO 2009/021169 A2 (LEXICON PHARMACEUTICALS INC [US]; HARRISON BRYCE ALDEN [US]; KIMBALL S) 12 February 2009 (2009-02-12) page 18; example 1b page 12; compound 1b	1-20,23
X	----- WO 2010/106333 A1 (MEDICAL RES COUNCIL TECHNOLOGY [GB]; MCIVER EDWARD GILES [GB]; SMILJAN) 23 September 2010 (2010-09-23) claims 1,26,28,38 page 111; compounds 7,8	1,2,4-6, 8-11,13, 15,16, 18-20,23
X	----- WO 02/079189 A2 (TANABE SEIYAKU CO [JP]; TAKAMURO IWA O [JP]; HOMMA KOICHI [JP]; ISHIDA) 10 October 2002 (2002-10-10) page 65; compound 111 page 372, lines 26-27	1,2,4-6, 8-11,13, 16
X	----- US 2008/119467 A1 (CARREZ CHANTAL [FR] ET AL) 22 May 2008 (2008-05-22) claims 1,33,39 page 10; example 28	1,2,4-6, 8-11,13, 15,16, 18-20,23
X	----- "ZINC04331084 - Compound Summary (CID 7192818)", PUBCHEM; NCBI, 29 July 2006 (2006-07-29), XP002689766, [retrieved on 2006-07-29] the whole document	1,2, 5-11,15, 16
X	----- "ZINC04331092 - Compound Summary (CID 7192825)", PUBCHEM; NCBI, 29 July 2006 (2006-07-29), XP002689767, [retrieved on 2006-07-29] the whole document ----- -/--	1,2, 5-11,15, 16

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/061618

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"ZINC05250434 - Compound Summary (CID 7584351)", PUBCHEM; NCBI, 29 July 2006 (2006-07-29), XP002689768, [retrieved on 2006-07-30] the whole document -----	1,2, 5-11,15, 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/061618

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-20, 23(all partially)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3(completely); 1, 2, 4-20, 23(partially)

compounds of formula I wherein group RA has the first meaning, namely pyrazolo[3,4-d]pyrimidine

2. claims: 1, 2, 4-20, 23(all partially)

compounds of formula I wherein group RA has the remaining meanings

3. claim: 21

intermediary compounds of formula III

4. claim: 22

intermediary compounds of formula V

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/061618

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