



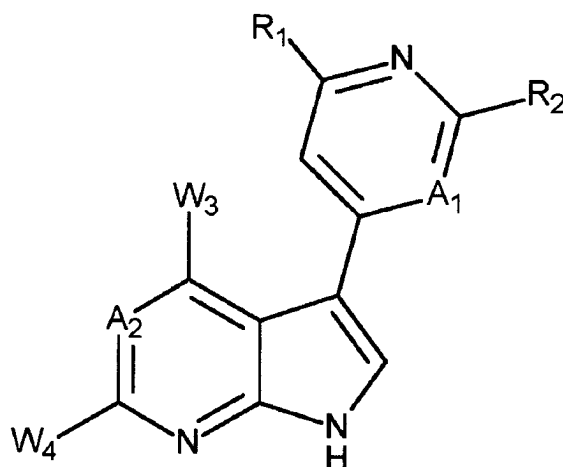
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(54) Title: NEW PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES AS DUAL DYRK1/CLK1 INHIBITORS



(I)

(57) Abstract: (Formula I) Compounds of formula (I) useful for the treatment of cancer, neurodegenerative disorders and metabolic disorders.

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NEW PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES AS DUAL DYRK1/CLK1 INHIBITORS

5 The present invention relates to new pyrrolo[2,3-*d*]pyrimidine derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are new and have very valuable pharmacological characteristics in the field of oncology.

The present invention relates to the use of dual DYRK1 / CLK1 inhibitors in the treatment of cancer, neurodegenerative disorders and metabolic disorders.

10 In cancer, the dual-specificity tyrosine-phosphorylation-regulated kinases DYRK1A and DYRK1B have been demonstrated to control several pathways that enhance cancer cell proliferation, migration and metastasis, induce resistance to cell death and repress responses to conventional and targeted anti-cancer therapies [Abbassi *et al*, Pharmacol Ther. 2015;151:87-98; Ionescu *et al*, Mini Rev Med Chem. 2012;12(13):1315-29; Friedman *et al*, J Cell Biochem. 2007;102(2):274-9; Yoshida *et al*, Biochem Pharmacol. 15 2008;76(11):1389-94]. Reported substrates of DYRK1A that are involved in this regulation of cancer progression and resistance to therapy include the transcription factors GIL1, STAT3 and FOXO1 [Mao *et al*, J Biol Chem. 2002;277(38):35156-61; Matsuo *et al*, J Immunol Methods 2001;247:141-51; Woods *et al*, Biochem J. 2001;355(Pt 3):597-607].

20 DYRK1A is also believed to stabilise cancer-associated tyrosine kinase receptors such as EGFR and FGFR *via* interaction with the protein Sprouty2 [Ferron *et al*, Cell Stem Cell. 2010;7(3):367-79; Aranda *et al*, Mol Cell Biol. 2008;28(19):5899-911]. DYRK1A, and also DYRK1B, have been shown to be required for the induction of cell quiescence in response to treatment of cancer cells by chemotherapeutic agents and targeted therapies.

25 This is important since it is known that quiescent cancer cells are relatively insensitive to most anti-cancer drugs and radiation [Ewton *et al*, Mol Cancer Ther. 2011;10(11):2104-14; Jin *et al*, J Biol Chem. 2009;284(34):22916-25]. For example, DYRK1A activates the DREAM multisubunit protein complex, which maintains cells in quiescence and protects against apoptosis [Litovchick *et al*, Genes Dev. 2011;25(8):801-13]. DYRK1B has been

demonstrated to prevent cell-cycle exit in response to chemotherapy *via* phosphorylation of Cyclin D1 [Zou *et al*, J Biol Chem. 2004;279(26):27790-8]. DYRK1B has also been shown to protect against chemotherapy through a reduction in reactive oxygen species content [Hu *et al*, Genes Cancer. 2010;1(8):803-811].

5 It is thus clear that the use of DYRK1A / DYRK1B inhibitors would constitute a novel anti-cancer treatment in a wide variety of cancers when used either alone or in combination with conventional therapy, radiation or targeted therapies as a strategy to combat resistance.

10 The role of DYRK1A in neurological disorders is well established. DYRK1A is associated with neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases, as well as with Down's syndrome, mental retardation and motor defects and [Abbassi *et al*, Pharmacol Ther. 2015;151:87-98; Beker *et al*, CNS Neurol Disord Drug Targets. 2014;13(1):26-33; Dierssen, Nat Rev Neurosci. 2012 Dec;13(12):844-58]. DYRK1A has been identified as a major kinase phosphorylating the microtubule-associated protein TAU, leading to the formation of neurotoxic neurofibrillary tangles and
15 neurodegeneration as seen in Alzheimer's [Azorsa *et al*, BMC Genomics. 2010;11:25]. DYRK1A also alters the splicing of TAU pre-mRNA leading to an imbalance between TAU isoforms which is sufficient to cause neurodegeneration and dementia [Liu *et al*, Mol Neurodegener. 2008;3:8]. It is not surprising, therefore, that DYRK1A is believed to be
20 causally involved in the development of Alzheimer-like neurodegenerative diseases in Down Syndrome patients, where three copies of the *DYRK1A* gene are present on chromosome 21. In these individuals, increased DYRK1A activity also causes premature neuronal differentiation and a decrease in mature neurones [Hämmerle *et al*, Development. 2011;138(12):2543-54].

25 It is thus clear that the use of DYRK1A inhibitors would offer a novel therapeutic approach for the treatment of neurodegenerative disorders, in particular Alzheimer's disease, as well as for other neurological conditions such as Down's syndrome.

The CDC2-like kinase (CLK) family contains four isoforms (CLK1-4) which are important in regulating the function of the spliceosome complex [Fedorov *et al*, Chem Biol.
30 2011;18(1):67-76]. This complex, comprised of small nuclear RNAs (snRNA) and a large number of associated proteins, regulates the splicing of pre-mRNAs to give mature protein-encoding mRNAs. CLK1 is known to regulate the activity of the spliceosome *via*

phosphorylation of the constituent serine–arginine-rich (SR) proteins [Bullock *et al*, Structure. 2009;17(3):352-62]. By controlling the activity of the spliceosome in this way, many genes are able express more than one mRNA leading to diversity in the translated proteins. The alternative protein isoforms transcribed from the same gene will often have different activities and physiological functions. Deregulation of alternative splicing has been linked to cancer, where a number of cancer-related proteins are known to be alternatively spliced [Druillennec *et al*, J Nucleic Acids. 2012;2012:639062]. An example of an alternatively spliced protein in cancer is Cyclin D1, important for the progression of cancer cells through the cell cycle [Wang *et al*, Cancer Res. 2008;68(14):5628-38].

It is thus clear that the use of CLK1 inhibitors would constitute a novel anti-cancer treatment in a wide variety of cancers when used either alone or in combination with conventional therapy, radiation or targeted therapies.

Alternative splicing regulated by CLK1 has also been described to play a role in neurodegenerative diseases, including Alzheimer's and Parkinson's, *via* phosphorylation of the SR proteins of the spliceosome [Jain *et al*, Curr Drug Targets. 2014;15(5):539-50]. In the case of Alzheimer's, CLK1 is known to regulate the alternative splicing of the microtubule-associated protein TAU leading to an imbalance between TAU isoforms which is sufficient to cause neurodegeneration and dementia [Liu *et al*, Mol Neurodegener. 2008;3:8].

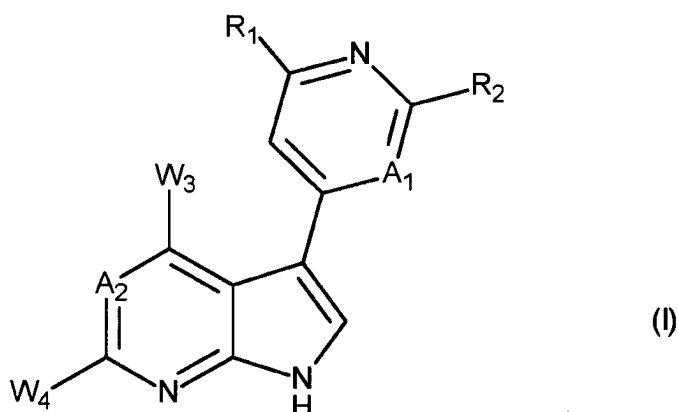
It is thus clear that the use of CLK1 inhibitors would offer a novel therapeutic approach for the treatment of neurodegenerative disorders, in particular Alzheimer's disease, as well as for other neurological conditions such as Parkinson's.

In the treatment of both cancer and neurological disease, there is thus undoubtedly an urgent need for compounds which potently inhibit the DYRK1 and CLK1 kinases whilst not affecting other closely-related kinases. The DYRK1 and CLK1 kinases are members of the CMGC group, which includes the CDK and the GSK kinases, the chronic inhibition of which is believed to be a cause of toxicity to the patient. For example, common toxicities observed in the clinic with CDK inhibition are similar to those observed with conventional cytotoxic therapy, and include hematologic toxicity (leukopenia and thrombocytopenia), gastrointestinal toxicity (nausea and diarrhea), and fatigue [Kumar *et al*, Blood. 2015;125(3):443-8]. The present invention describes a new class of DYRK1 / CLK1

inhibitors which are highly selective for DYRK1 and CLK1 over these other kinases and which would thus be suitable for use in the treatment of these pathologies.

Diabetes type 1 and type 2 both involve deficiency of functional pancreatic insulin-producing beta cells. Restoring functional beta-cell mass is thus an important therapeutic goal for these diseases which affect 380 million people worldwide. Recent studies have shown that DYRK1A inhibition promotes human beta-cell proliferation in vitro and in vivo and, following prolonged treatment, can increase glucose-dependent insulin secretion [Dirice *et al*, Diabetes. 2016;65(6):1660-71; Wang *et al*, Nat Med. 2015;21(4):383-8]. These observations clearly suggest that the use of potent and selective DYRK1A inhibitors would offer a novel therapeutic approach for the treatment and/or prevention of metabolic disorders including diabetes and obesity.

The present invention relates more especially to compounds of formula (I):



wherein:

- ◆ R₁ and R₂, each independently of the other, represent a hydrogen atom, a halogen atom, -NR₅R₅' or a linear or branched (C₁-C₆)alkyl group,
- ◆ W₃ represents a linear or branched (C₁-C₆)alkoxy, -O-(C₀-C₆)alkylene-Cy₁, -O-(C₀-C₆)alkylene-Cy₁-Cy₂, -NR_aR_b, -NR_a-(C₀-C₆)alkylene-Cy₁, -NR_a-(C₀-C₆)alkylene-Cy₁-Cy₂, -NR_a-(C₀-C₆)alkylene-Cy₁-O-(C₁-C₆)alkylene-Cy₂, -Cy₁, -Cy₁-(C₀-C₆)alkylene-Cy₂, -Cy₁-O-(C₀-C₆)alkylene-Cy₂, -(C₁-C₆)alkylene-Cy₁, -(C₂-C₆)alkenylene-Cy₁, -(C₂-C₆)alkynylene-Cy₁, -(C₁-C₆)alkylene-O-Cy₁, it

being understood that the alkylene moieties defined hereinbefore may be linear or branched,

- ◆ W₄ represents a cyano group, a cycloalkyl group, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group optionally substituted by a cycloalkyl group,
- ◆ R₅ and R₅', each independently of the others, represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- ◆ R_a and R_b, each independently of the other, represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- ◆ A₁ and A₂, each independently of the other, represent CH or a nitrogen atom,
- ◆ Cy₁, Cy₂ and Cy₃, independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group,

wherein:

- "aryl" means a phenyl, naphthyl, biphenyl or indenyl group,
- "heteroaryl" means any mono- or bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 4 hetero atoms selected from oxygen, sulphur and nitrogen,
- "cycloalkyl" means any mono- or bi-cyclic, non-aromatic, carbocyclic group containing from 3 to 11 ring members, which may include fused, bridged or spiro ring systems,
- "heterocycloalkyl" means any mono- or bi-cyclic, non-aromatic, condensed or spiro group composed of from 3 to 10 ring members and containing from 1 to 3 hetero atoms or groups selected from oxygen, sulphur, SO, SO₂ and nitrogen, which may include fused, bridged or spiro ring systems,
- “-(C₀-C₆)alkylene-“ refers either to a covalent bond (-C₀alkylene-) or to an alkylene group containing 1, 2, 3, 4, 5 or 6 carbon atoms,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene to be substituted by from 1 to 4 groups selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₂-C₆)alkenyl group, linear or branched (C₂-C₆)alkynyl group, linear or branched

(C₁-C₆)alkoxy optionally substituted by -NR_cR_d or by from 1 to 3 halogen atoms, linear or branched (C₁-C₆)alkyl-S-, hydroxy, oxo (or *N*-oxide where appropriate), nitro, cyano, -C(O)-OR_c, -C(O)-R_c, -O-C(O)-R_d, -C(O)-NR_cR_d, -NR_c-C(O)-R_d, -NR_cR_d, linear or branched (C₁-C₆)polyhaloalkyl, or halogen, it being understood that R_c and R_d independently of one another represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,

to their enantiomers and diastereoisomers, and to addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid etc.

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, *tert*-butylamine etc.

Advantageously, R₁ represents a hydrogen and R₂ a -NH₂ group.

In one embodiment of the invention, A₁ represents a CH group.

In another embodiment of the invention, A₁ represents a nitrogen atom.

In a preferred embodiment of the invention, A₂ represents a nitrogen atom.

Alternatively, A₂ represents a CH group. When A₂ represents a CH group, A₁ represents preferably a CH group.

In another embodiment of the invention, W₃ represents a linear or branched (C₁-C₆)alkoxy, -O-(C₀-C₆)alkylene-Cy₁, -O-(C₀-C₆)alkylene-Cy₁-Cy₂, -NR_a-(C₁-C₆)alkylene-Cy₁-Cy₂,

-NR_a-(C₀-C₆)alkylene-Cy₁-O-(C₁-C₆)alkylene-Cy₂, -Cy₁-O-(C₀-C₆)alkylene-Cy₂,
 -(C₁-C₆)alkylene-Cy₁, -(C₂-C₆)alkenylene-Cy₁, -(C₂-C₆)alkynylene-Cy₁, -(C₁-C₆)alkylene-
 O-Cy₁, it being understood that the alkylene moieties defined hereinbefore may be linear
 or branched.

5 Alternatively, W₃ represents a Cy₁ group selected from: 1,3-benzodioxolyl, 1*H*-indolyl, phenyl, pyridinyl, 2,3-dihydro-1,4-benzodioxinyl, 1-benzothiophenyl, 1-benzofuranyl, 3,4-dihydronaphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, 3,4-dihydro-2*H*-1,4-benzoxazinyl, wherein the preceding groups are optionally substituted according to the definition mentioned previously.

10 In an other embodiment, W₃ represents: (i) a -NR_a-Cy₁ group, wherein Cy₁ represents a group selected from: phenyl, 2,3-dihydro-1*H*-indene and 1,2,3,4-tetrahydronaphthalene, wherein the preceding groups are optionally substituted according to the definition mentioned previously; or (ii) a -NR_a-(C₁-C₆)alkylene-Cy₁ group, wherein Cy₁ represents a
 15 group selected from: phenyl, pyridinyl, furanyl, thiophenyl, 1*H*-pyrazolyl, 1,3-thiazolyl, 1,2-oxazolyl, cyclohexyl, cyclopropyl and 1*H*-indolyl, wherein the preceding groups are optionally substituted according to the definition mentioned previously.

In a specific embodiment, W₃ represents a -phenylene-(C₀-C₆)alkylene-Cy₂.

More preferably, W₃ represents -O-(C₁-C₆)alkylene-Cy₁ or -NR_a-(C₁-C₆)alkylene-Cy₁, wherein Cy₁ is a phenyl or a pyridinyl group, these latter group being optionally
 20 substituted by one or two groups selected from methoxy, methyl or halogen.

Preferred W₄ groups are as follows: methyl ; propan-2-yl ; prop-1-en-2-yl ; ethenyl ; cyano ; ethynyl ; cyclopropyl ; cyclopropylethynyl. Methyl group is even more preferred.

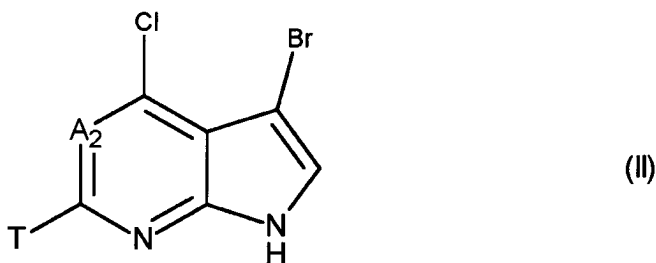
Preferred compounds according to the invention are included in the following group:

25 - 5-(2-aminopyridin-4-yl)-*N*-(2-methoxybenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

- 4-[2-methyl-4-(thiophen-3-ylmethoxy)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine,
- 5-(2-aminopyridin-4-yl)-*N*-(2,6-dichlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5 - 5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyridin-4-yl)-2-methyl-*N*-(2-methylbenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyridin-4-yl)-*N*-(2-chloro-6-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 10 - 5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(3-methylpyridin-2-yl)methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyridin-4-yl)-*N*-[(3-fluoropyridin-2-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 15 - 5-(2-aminopyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

their enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

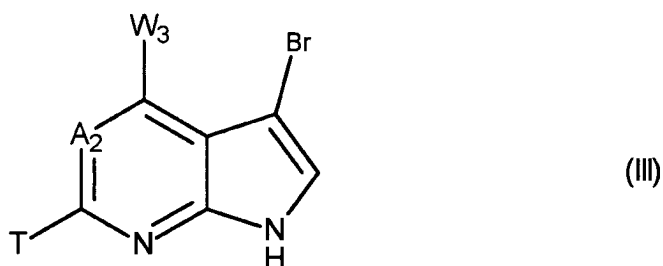
20 The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (II):



wherein T represents a halogen atom, a methane-sulfanyl group, a cycloalkyl group or a linear or branched (C₁-C₆)alkyl group, and A₂ is as defined in formula (I),

which compound is subjected to a nucleophilic substitution in the presence of an appropriate alcohol or amine derivative, or subjected to coupling with an appropriate boronic acid derivative,

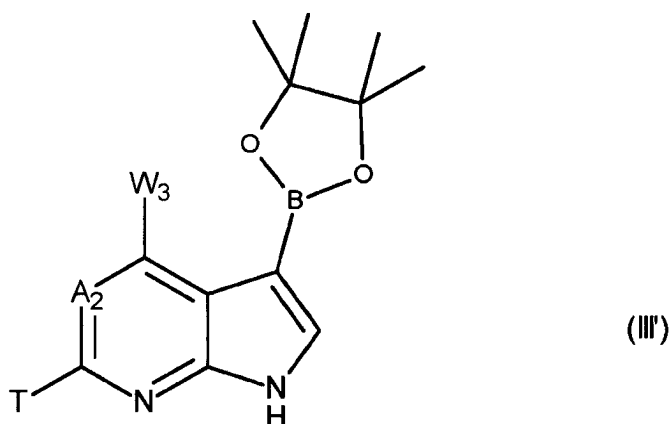
to yield the compound of formula (III) :



wherein T is as defined previously, A₂ and W₃ are as defined in formula (I),

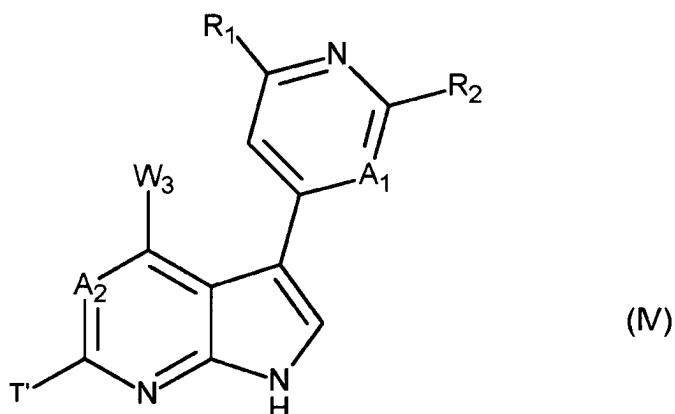
which compound of formula (III) is either :

- (i) converted into its methanesulfonyl derivative when T represents a methanesulfonyl group, then reacted with NaCN and further subjected to coupling with an appropriate boronic acid derivative,
- (ii) or directly subjected to coupling with an appropriate boronic acid derivative,
- (iii) or subjected to coupling with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane to yield :



which compound of formula (III') is further reacted with the appropriate halide,

to yield compound of formula (IV) :



wherein T' represents a halogen atom, a cyano group, a cycloalkyl group or a linear or branched (C₁-C₆)alkyl group, and A₁, A₂, R₁, R₂ and W₃ are as defined in formula (I),

which compound of formula (IV):

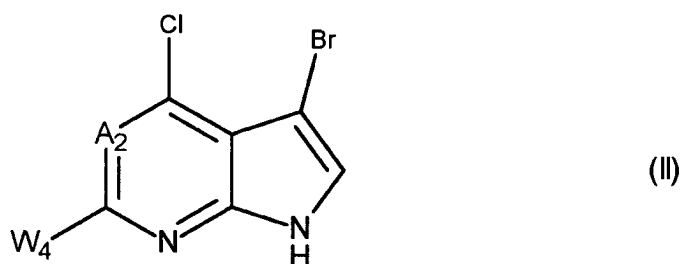
- 5 - may be subjected to coupling with an appropriate alkynyl (or alkenyl) boronic acid derivative or alkynyl (or alkenyl) (trifluoro)borate derivative salt, when T' represents a halogen atom,

to yield the compounds of formula (I),

- 10 which compound of formula (I) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

- it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino...) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.
- 15

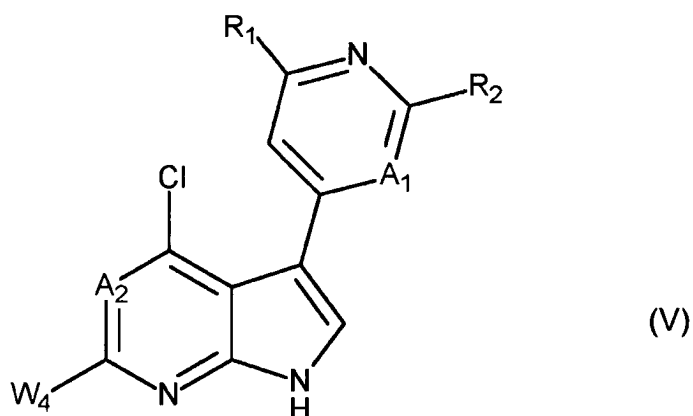
The invention relates also to an alternative process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (II):



wherein W_4 and A_2 are as defined in formula (I),

which compound of formula (II) is subjected to coupling with an appropriate boronic acid derivative,

5 to yield compound of formula (V):



wherein A_1 , A_2 , R_1 , R_2 , and W_4 are as defined in formula (I),

which compound of formula (V) is either subjected to a nucleophilic substitution, or subjected to a coupling reaction with an appropriate boronic acid derivative, or subjected to a coupling with a compound of formula $\equiv R_3$, wherein R_3 represents a hydrogen or Cy_1 ,

10 to yield the compounds of formula (I),

which compound of formula (I) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically

acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino...) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.

The compound of formula (II), the alcohol and amino derivatives, the boronic acid derivatives, the borate salt derivatives and $\text{B}(\text{OR})_3$ mentioned above are either commercially available or can be obtained by the person skilled in the art using conventional chemical reactions described in the literature.

Pharmacological study of the compounds of the invention has shown that they are powerful DYRK1/CLK1 inhibitors which are highly selective for DYRK1 and CLK1 over other kinases such as CDK9.

More especially, the compounds according to the invention will be useful in the treatment of chemo- or radio-resistant cancers.

Among the cancer treatments envisaged there may be mentioned, without implying any limitation, haematological cancer (lymphoma and leukemia) and solid tumors including carcinoma, sarcoma, or blastoma. There may be mentioned more preferably acute megakaryoblastic leukaemia (AMKL), acute lymphoblastic leukaemia (ALL), ovarian cancer, pancreatic cancer, gastrointestinal stromal tumours (GIST), osteosarcoma (OS), colorectal carcinoma (CRC), neuroblastoma and glioblastoma.

In another embodiment, the compounds of the invention will be useful in the treatment of neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases, as well as with Down's syndrome, mental retardation and motor defects.

Alternatively, the compounds of the invention could be used in the treatment and/or prevention of metabolic disorders including diabetes and obesity.

The present invention relates also to pharmaceutical compositions comprising at least one compound of formula (I) in combination with one or more pharmaceutically acceptable excipients.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral, nasal, per- or trans-cutaneous, rectal, perlingual, ocular or respiratory administration, especially tablets or dragées, sublingual tablets, sachets, paquets, capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels, and drinkable or injectable ampoules.

The dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the therapeutic indication, or of any associated treatments, and ranges from 0.01 mg to 5 g per 24 hours in one or more administrations.

Furthermore, the present invention relates also to the combination of a compound of formula (I) with an anticancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors, signaling pathway inhibitors, phosphatase inhibitors, apoptosis inducers and antibodies, and also to pharmaceutical compositions comprising that type of association and their use in the manufacture of medicaments for use in the treatment of cancer.

The combination of a compound of formula (I) with an anticancer agent may be administered simultaneously or sequentially. The administration route is preferably the oral route, and the corresponding pharmaceutical compositions may allow the instantaneous or delayed release of the active ingredients. The compounds of the combination may moreover be administered in the form of two separate pharmaceutical compositions, each containing one of the active ingredients, or in the form of a single pharmaceutical composition, in which the active ingredients are in admixture.

The compounds of the invention may also be used in association with radiotherapy in the treatment of cancer.

List of abbreviations

	Abbreviation	Name
	Ac	acetyl
	aq.	Aqueous
5	Bn	benzyl
	Boc	<i>tert</i> -butyloxycarbonyl protecting group
	dppf	1,1'-bis(diphenylphosphino)ferrocene
	DCM	dichloromethane
	DEAD	diethyl azodicarboxylate
10	DIBAL	diisobutylaluminium hydride
	DMAP	4-diméthylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
	dtbpf	1,1'-bis(di- <i>tert</i> -butylphosphino)ferrocene
15	eq.	equivalent
	Et	ethyl
	IPA	isopropanol
	HPLC-MS	liquid chromatography–mass spectrometry
	LiHMDS	lithium bis(trimethylsilyl)amide
20	mCBPA	<i>meta</i> -chloroperoxybenzoic acid
	Me	methyl
	NBS	<i>N</i> -bromosuccinimide
	ⁿ Bu	<i>n</i> -butyl
	ⁿ BuPAd ₂	<i>n</i> -butyldiademantylphosphine
25	Pd/C	palladium on carbon
	Ph	phenyl
	PPh ₃	triphenylphosphine
	pTSA	<i>para</i> -toluenesulfonic acid
	RT	retention time
30	sat.	saturated

SEM	[2-(trimethylsilyl)ethoxy]methyl
^t Bu	<i>tert</i> -butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

5 General Procedures

All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying. Flash chromatography was performed with pre- packed silica gel cartridges (Strata SI-1 ; 61Å, Phenomenex, Cheshire UK or 1ST Flash II, 54Å, Argonaut, Hengoed, UK) or
10 by automated flash chromatography using a Combiflash R_f apparatus (Teledyne Isco Inc.) using RediSep R_f preppacked silica columns (Teledyne Isco Inc.) or SilaSep pre-packed columns (Silicycle Inc.). Thin layer chromatography was conducted with 5 x 10 cm plates coated with Merck Type 60 F₂₅₄ silica gel.

The compounds of the present invention were characterized by high performance liquid
15 chromatography-mass spectroscopy (HPLC-MS) on either an Agilent HP1200 Rapid Resolution Mass detector 6140 multimode source *M/z* range 150 to 1000 amu or an Agilent HP1100 Mass detector 1946D ESI source *M/z* range 150 to 1000 amu. The conditions and methods listed below are identical for both machines.

Column for 7.5 min run: GeminiNX, 5 µm, C18, 30 x 2.1 mm (Phenomenex) or Zorbax
20 Eclipse Plus, 3.5 µm, C18, 30 x 2.1 mm (Agilent). Temperature: 35 °C.

Column for 3.75 min run: GeminiNX, 5µm, C18, 30 x 2.1 mm (Phenomenex) or Zorbax Eclipse Plus, 3.5 µm, C18, 30 x 2.1 mm (Agilent). Temperature: 35 °C.

Column for 1.9 min run: Kinetex, 2.5 µm, C18, 50 x 2.1 mm (Phenomenex) or Accucore, 2.6 µm, C18, 50 x 2.1 mm.

25 Temperature: 55 °C.

Mobile Phase: A - H₂O + 10 mmol / ammonium formate + 0.08% (v/v) formic acid at pH ca 3.5.

B - 95% Acetonitrile + 5% A + 0.08% (v/v) formic acid.

Injection Volume: 1 µL

30 Method A "Short" method gradient table, either positive (pos) or positive and negative (pos / neg) ionisation

Time (min)	Solvent A (%)	Solvent B (%)	Flow (mL/min)
0	95	5	1
0.25	95	5	1
2.50	5	95	1
2.55	5	95	1.7
3.60	5	95	1.7
3.65	5	95	1
3.70	95	5	1
3.75	95	5	1

Method B "Super Short" method gradient table, either positive (pos) or positive and negative (pos / neg) ionisation

Time (min)	Solvent A (%)	Solvent B (%)	Flow (mL/min)
0	95	5	1.3
0.12	95	5	1.3
1.30	5	95	1.3
1.35	5	95	1.6
1.85	5	95	1.6
1.90	5	95	1.3
1.95	95	5	1.3

Detection: UV detection at 230, 254 and 270 nm.

The compounds of the present invention were also characterized by Nuclear Magnetic Resonance (NMR). Analysis was performed with a Bruker DPX-400 spectrometer and proton NMR spectra were measured at 400 MHz. The spectral reference was the known chemical shift of the solvent. Proton NMR data is reported as follows: chemical shift (δ) in ppm, followed by the multiplicity, where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dm = doublet of multiplets, ddd = doublet of double doublets, td = triplet of doublets, qd = quartet of doublets and br = broad, and finally the integration.

Some compounds of the invention were purified by preparative HPLC. These were performed on a Waters FractionLynx MS autopurification system, with a Gemini® 5 μm C18(2), 100 mm $\times$ 20 mm i.d. column from Phenomenex, running at a flow rate of 20 $\text{cm}^3\text{min}^{-1}$ with UV diode array detection (210–400 nm) and mass-directed collection.

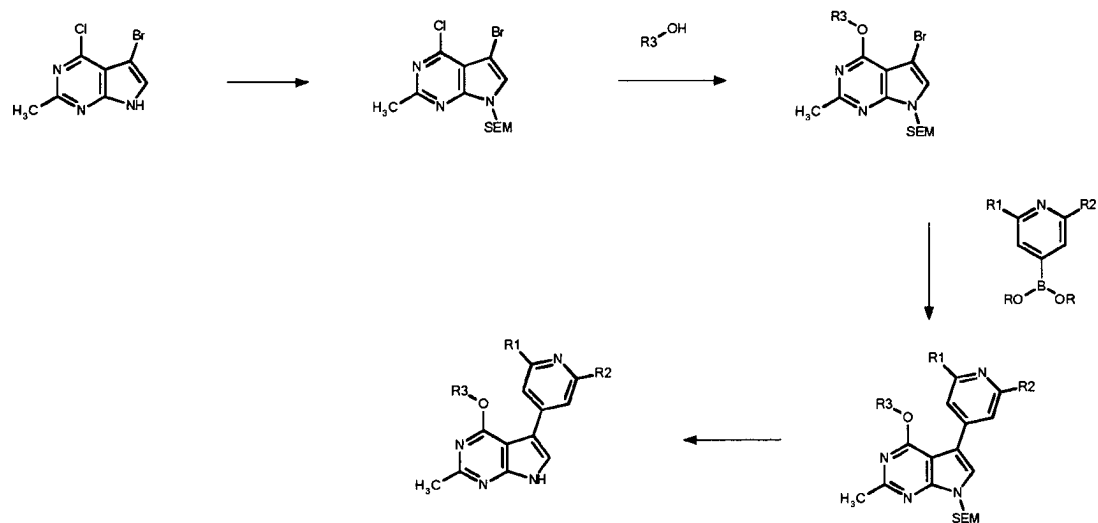
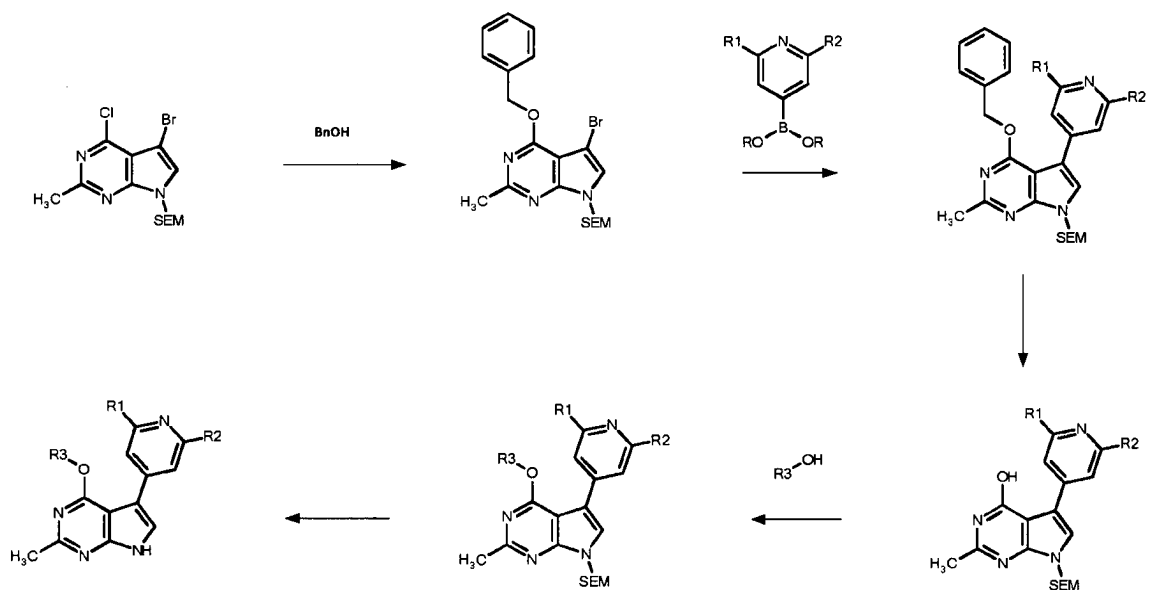
5 At pH 4: solvent A = 10 mM ammonium acetate in HPLC grade water + 0.08% v/v formic acid. Solvent B = 95% v/v HPLC grade acetonitrile + 5% v/v solvent A + 0.08% v/v formic acid.

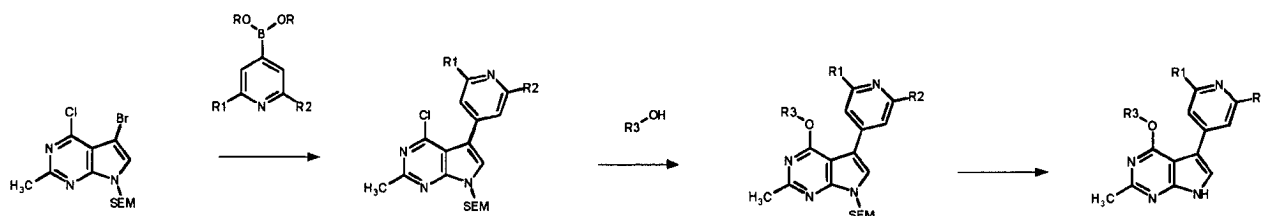
10 At pH 9: solvent A = 10 mM ammonium acetate in HPLC grade water + 0.08% v/v ammonia solution. Solvent B = 95% v/v HPLC grade acetonitrile + 5% v/v solvent A + 0.08% v/v ammonia solution.

The mass spectrometer was a Waters Micromass ZQ2000 spectrometer, operating in positive or negative ion electrospray ionisation modes, with a molecular weight scan range of 150 to 1000.

15 Some compounds of the present invention were characterised using an Agilent 1290 Infinity II series instrument connected to an Agilent TOF 6230 single quadrupole with an ESI source. High resolution mass spectra were recorded in positive-negative switching mode ionization unless otherwise stated. UV detection was by diode array detector at 230, 254 and 270 nm. Column: Thermo Accucore 2.6 μm C18, 50x2 mm, at 55 °C column temperature. Buffer A: Water /10 mM ammonium formate / 0.04% (v/v) formic acid
20 pH=3.5. Buffer B: Acetonitrile / 5.3 % (v/v) A / 0.04% (v/v) formic. (Injection volume: 1 μL).

The following Preparations and Examples illustrate the invention without limiting it in any way.

General Procedure I**General Procedure II**

General Procedure III

In General Procedures I, II and III :

- R₁ and R₂ are as defined in formula (I),

- R₃ represents a linear or branched (C₁-C₆)alkyl group, -(C₀-C₆)alkylene-Cy₁,
 5 -(C₀-C₆)alkylene-Cy₁-Cy₂, it being understood that Cy₁ and Cy₂, independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group.

Example 1: 4-methoxy-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine

Step 1: 5-bromo-4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-
 10 d]pyrimidine (**Preparation 1**)

To a solution of 5-bromo-4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (1 g, 4.06 mmol) in DMF (30 mL) was added NaH (60% in mineral oil, 1 eq) at 0 °C under N₂. The reaction mixture was stirred for 30 min before adding SEM-Cl (1.1 eq) at 0 °C and allowed to warm to room temperature overnight under N₂. The reaction mixture was diluted with diethyl ether (100 mL), washed with brine (4 x 50 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (1.18 g, 3.13 mmol, 77%) as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.12 (s, 1H), 5.65 (s, 2H), 3.67–3.57 (m, 2H), 2.74 (s, 3H), 0.98–0.87 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.59 min; *m/z* = RT = 1.59 min; *m/z* = 377 [M+H]⁺

Step 2: 5-bromo-4-methoxy-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (Preparation 2)

To a suspension of NaH (60% in mineral oil, 2 eq) in THF (10 mL) was added MeOH (1.3 eq) dropwise at 0 °C under N₂. Stirred for 10 min before adding a solution of the compound obtained in Step 1 (0.5 g, 1.3 mmol) in THF (3 mL). The reaction mixture was stirred at 0 °C for 30 min and allowed to warm to room temperature over 1 hour. The reaction mixture was diluted with sat. aq. NH₄Cl solution (20 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo* to give the product (0.494 g, 1.3 mmol, 100%) as a clear oil. The compound was used without further purification.

¹H NMR (399 MHz, DMSO-d₆) δ 7.75 (s, 1H), 5.59 (s, 2H), 4.12 (s, 3H), 3.64–3.55 (m, 2H), 2.65 (s, 3H), 0.97 – 0.87 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.53 min; *m/z* = 374 [M+H]⁺

Step 3: 4-methoxy-2-methyl-5-(pyridin-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (Preparation 3)

The compound obtained in Step 2 and (pyridin-4-yl)boronic acid (1.5 eq) were dissolved in THF/water (6:1, 5 mL) under N₂. Potassium carbonate (3 eq) and Pd(dtbpf)Cl₂ (10% wt) were added and the resulting mixture was degassed under N₂ for 5 minutes. The reaction mixture was heated at 120 °C on a CEM microwave reactor for 1 hour. The reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.11 g, 0.30 mmol, 44%) as an oil.

¹H NMR (399 MHz, DMSO-d₆) δ 8.67–8.61 (m, 2H), 8.11 (s, 1H), 7.83–7.77 (m, 2H), 5.68 (s, 2H), 4.13 (s, 3H), 3.70 – 3.61 (m, 2H), 2.68 (s, 3H), 0.99 – 0.88 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 1.37 min; *m/z* = 371 [M+H]⁺

Step 4: 4-methoxy-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine (Preparation 4)

To a solution of the compound obtained in Step 3 (0.11 g, 0.3 mmol) in THF (3 mL) was added ethylenediamine (5 eq) followed by TBAF (1M solution in THF, 5 eq). The reaction

was heated at 120 °C on a CEM microwave reactor for 1 hour. The reaction mixture was diluted with water (10 mL) and EtOAc (10 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was then triturated with EtOAc to give the product (15 mg, 0.06 mmol, 21%) as a white solid.

5 ¹H NMR (399 MHz, DMSO-d₆) δ 12.33 (s, 1H), 8.58 – 8.50 (m, 2H), 7.85 (s, 1H), 7.78 – 7.72 (m, 2H), 4.05 (s, 3H), 2.57 (s, 3H).

LC/MS (method A): RT = 1.49 min; *m/z* = 241 [M+H]⁺

Example 6: 2-methyl-5-(2-methylpyridin-4-yl)-4-[(3*R*)-piperidin-3-ylmethoxy]-7*H*-pyrrolo[2,3-*d*]pyrimidine

10 *Step 1: 4-(benzyloxy)-5-bromo-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidine*

Starting from 5-bromo-4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidine (**Example 1, Step 1**) (5 g, 13.27 mmol) and benzyl alcohol (1.3 eq) following procedure described in **Preparation 2**, the desired product (5.4 g, 12 mmol, 15 91%) was obtained as a light yellow oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.77 (s, 1H), 7.68 – 7.60 (m, 2H), 7.54 – 7.45 (m, 2H), 7.47 – 7.38 (m, 1H), 5.67 (s, 2H), 5.60 (s, 2H), 3.65 – 3.55 (m, 2H), 2.67 (s, 3H), 0.97 – 0.87 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 3.04 min; *m/z* = 450 [M+H]⁺

20 *Step 2: 4-(benzyloxy)-2-methyl-5-(2-methylpyridin-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidine*

Starting from the compound obtained in Step 1 (2 g, 4.46 mmol) and (2-methylpyridin-4-yl)boronic acid (1.2 eq) following procedure described in **Preparation 3**. The residue was purified via flash chromatography using EtOAc and isohexane as eluent 25 to give the product (1.311 g, 2.8 mmol, 64%) as a brown oil.

¹H NMR (399 MHz, DMSO-d₆) δ 8.36 (dd, 1H), 8.08 (s, 1H), 7.66 – 7.40 (m, 7H), 5.67 (s, 2H), 5.63 (s, 2H), 3.69 – 3.60 (m, 2H), 2.71 (s, 3H), 2.31 (s, 3H), 0.99 – 0.90 (m, 2H), 0.00 (s, 9H).

Step 3: 2-methyl-5-(2-methylpyridin-4-yl)-7-([2-(trimethylsilyl)ethoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (**Preparation 5**)

A suspension of the compound obtained in Step 2 (1.311 g, 2.8 mmol) and Pd/C (10% in wt) in EtOH (40 mL) was agitated under H₂ at room temperature for 2h. The suspension was filtered through a plug of celite and concentrated *in vacuo*. The residue was triturated with isohexane to give the product (0.886 g, 2.39 mmol, 84%) as an off-white solid

¹H NMR (399 MHz, DMSO-d₆) δ 12.14 (s, 1H), 8.47 – 8.40 (m, 1H), 8.01 – 7.91 (m, 3H), 5.54 (s, 2H), 3.62 (dd, 2H), 2.53 (s, 3H), 2.43 (s, 3H), 0.92 (dd, 2H), 0.00 (s, 9H).

Step 4: tert-butyl (3R)-3-([2-methyl-5-(2-methylpyridin-4-yl)-7-([2-(trimethylsilyl)ethoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]oxy)methyl)piperidine-1-carboxylate (**Preparation 6**)

To a solution of the compound obtained in Step 3 (100 mg, 0.27 mmol) and tert-butyl (3R)-3-(hydroxymethyl)piperidine-1-carboxylate (1.5 eq) in THF (5 mL) was added PPh₃ (1.5 eq) at room temperature under N₂. The reaction mixture was allowed to stir at room temperature for 10 minutes and then cooled in an ice-bath before adding DEAD (1.5 eq). The ice-bath was removed and the reaction mixture allowed to stir for 2 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue purified via flash chromatography using EtOAc and isohexane as eluent to give the product (122 mg, 0.214 mmol, 80%) as a clear oil.

¹H NMR (399 MHz, DMSO-d₆) δ 8.51 (d, 1H), 8.08 (s, 1H), 7.72 (s, 1H), 7.61 (d, 1H), 5.67 (s, 2H), 4.51 (dd, 1H), 4.40 (dd, 1H), 3.68 – 3.59 (m, 2H), 3.43 (s, 9H), 2.66 (s, 3H), 2.56 (s, 3H), 1.88 (d, 1H), 1.69 (s, 1H), 1.47 – 1.19 (m, 7H), 0.99 – 0.87 (m, 2H), 0.00 (s, 9H).

Step 5: 2-methyl-5-(2-methylpyridin-4-yl)-4-[(3R)-piperidin-3-ylmethoxy]-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 7**)

To a solution of the compound obtained in Step 4 (78 mg, 0.137 mmol) in DCM (5 mL) was added TFA (3 mL) under N₂ at room temperature and stirred for 3 hours. The reaction mixture was loaded directly into a scx-2 column (10 g), washed with MeOH and DCM and eluted with 1N NH₃ solution in MeOH. The fractions were concentrated *in vacuo* and the

residue was purified via flash chromatography using 2N NH₃ solution in MeOH and DCM as eluent to give the desired product (18 mg, 0.024 mmol, 17%) as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.24 (s, 1H), 8.38 (d, 1H), 7.80 (s, 1H), 7.66 (d, 1H), 7.54 (dd, 1H), 4.30 (qd, 2H), 3.05 – 2.96 (m, 1H), 2.84 (dt, 1H), 2.54 (s, 3H), 2.51 (s, 3H), 2.47 – 2.36 (m, 1H), 2.32 (dd, 1H), 1.97 – 1.86 (m, 1H), 1.79 (dd, 1H), 1.62 – 1.49 (m, 1H), 1.46 – 1.02 (m, 3H).

LC/MS (method A): RT = 1.35 min; *m/z* = 338 [M+H]⁺

Example 20: 4-[2-methyl-4-(1-phenylethoxy)-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine

*Step 1: 4-(4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine*

Starting from 5-bromo-4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-*d*]pyrimidine (0.91 g, 2.42 mmol) and 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.257 g, 0.659 mmol, 27%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.02 (t, 2H), 6.74 – 6.63 (m, 2H), 6.08 (s, 2H), 5.72 (s, 2H), 3.66 (dd, 2H), 2.76 (s, 3H), 0.99 – 0.88 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 2.16 min; *m/z* = 390 [M+H]⁺

*Step 2: 4-[2-methyl-4-(1-phenylethoxy)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine*

Starting from the compound obtained in Step 1 (100 mg, 0.25 mmol) and 1-phenylethan-1-ol (1.3 eq) following procedure described in **Preparation 2**, the product (107 mg, 0.224 mmol, 90%) was obtained as an oil.

LC/MS (method B): RT = 1.38 min; *m/z* = 476 [M+H]⁺

Step 3: 4-[2-methyl-4-(1-phenylethoxy)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine
 Starting from the compound obtained in Step 2 (107 mg, 0.224 mmol) following procedure described in **Preparation 4**, the desired product (40 mg, 0.115 mmol) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.22 (s, 1H), 7.96 (d, 1H), 7.67 (s, 1H), 7.59 – 7.51 (m, 2H), 7.47 – 7.38 (m, 2H), 7.40 – 7.31 (m, 1H), 6.99 – 6.88 (m, 2H), 6.54 (q, 1H), 5.86 (s, 2H), 2.6 (s, 3H), 1.76 (d, 3H).

LC/MS (method B): RT = 1.09 min; *m/z* = 346 [M+H]⁺

Examples 1-28 in the following **Table 1** were prepared by methods outlined in **General Procedure I-III** using appropriate commercially available boronate esters and alcohols. The compounds of **Example 1, 6, 20** are also included.

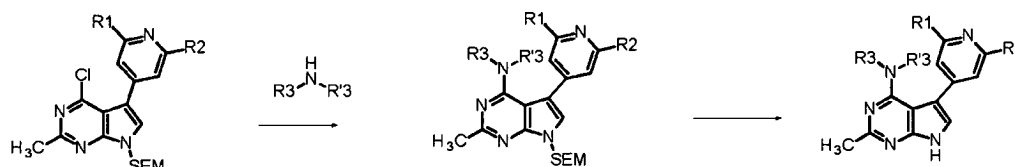
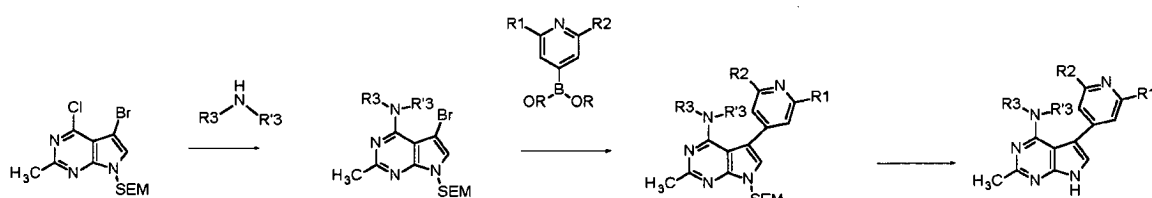
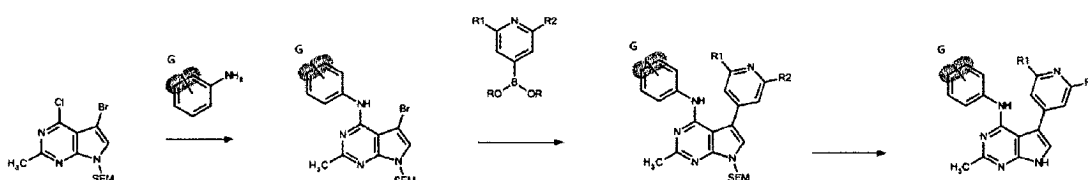
Table 1: HRMS (TOF, ESI) data

Example	Structure	Mol Formula	Calcd Exact Mass	Found <i>m/z</i>	Adduct
1	4-methoxy-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine	C ₁₃ H ₁₂ N ₄ O	240.1011	241.1082	[M + H] ⁺
2	4-(4-methoxy-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-amine	C ₁₃ H ₁₃ N ₅ O	255.1120	256.1196	[M + H] ⁺
3	5-(2-fluoropyridin-4-yl)-4-methoxy-2-methyl-7H-pyrrolo[2,3-d]pyrimidine	C ₁₃ H ₁₁ F N ₄ O	258.0917	259.0996	[M + H] ⁺
4	4-methoxy-2-methyl-5-(2-methylpyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine	C ₁₄ H ₁₄ N ₄ O	254.1168	255.1238	[M + H] ⁺

5	2-methyl-5-(2-methylpyridin-4-yl)-4-(thiophen-3-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₈ H ₁₆ N ₄ O S	336.1045	337.1129	[M + H] ⁺
6	2-methyl-5-(2-methylpyridin-4-yl)-4-[(3 <i>R</i>)-piperidin-3-ylmethoxy]-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₉ H ₂₃ N ₅ O	337.1903	338.1982	[M + H] ⁺
7	4-(cyclopropylmethoxy)-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₆ H ₁₆ N ₄ O	280.1324	281.1400	[M + H] ⁺
8	4-(2-cyclopropylethoxy)-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₇ H ₁₈ N ₄ O	294.1481	293.1409	[M - H] ⁻
9	4-[2-(1 <i>H</i> -indol-3-yl)ethoxy]-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₂₂ H ₁₉ N ₅ O	369.1590	370.1657	[M + H] ⁺
10	2-methyl-4-(2-phenylethoxy)-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₂₀ H ₁₈ N ₄ O	330.1481	331.1547	[M + H] ⁺
11	4-(benzyloxy)-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₉ H ₁₆ N ₄ O	316.1324	317.1391	[M + H] ⁺
12	2-methyl-5-(pyridin-4-yl)-4-[2-(pyrrolidin-1-yl)ethoxy]-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₈ H ₂₁ N ₅ O	323.1746	324.1818	[M + H] ⁺
13	2-methyl-4-[2-(piperidin-1-yl)ethoxy]-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C ₁₉ H ₂₃ N ₅ O	337.1903	338.1975	[M + H] ⁺

14	2-methyl-5-(pyridin-4-yl)-4-(tetrahydrofuran-2-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C17 H18 N4 O2	310.1430	311.1508	[M + H] ⁺
15	4-(cyclopentylmethoxy)-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C18 H20 N4 O	308.1637	309.1711	[M + H] ⁺
16	2-methyl-4-[(5-methyl-1,2-oxazol-3-yl)methoxy]-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidine	C17 H15 N5 O2	321.1226	322.1299	[M + H] ⁺
17	4-[2-methyl-4-(thiophen-3-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C17 H15 N5 O S	337.0997	338.1068	[M + H] ⁺
18	4-[2-methyl-4-(1,3-thiazol-5-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C16 H14 N6 O S	338.0950	339.1025	[M + H] ⁺
19	4-[2-methyl-4-(thiophen-2-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C17 H15 N5 O S	337.0997	338.1072	[M + H] ⁺
20	4-[2-methyl-4-(1-phenylethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H19 N5 O	345.1590	346.1654	[M + H] ⁺
21	4-{2-methyl-4-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C18 H18 N6 O S	366.1263	367.1343	[M + H] ⁺
22	4-[2-methyl-4-(pyridin-3-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C18 H16 N6 O	332.1386	333.1453	[M + H] ⁺

23	4-[2-methyl-4-(pyridin-4-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C18 H16 N6 O	332.1386	333.1452	[M + H] ⁺
24	4-(4-([5-(4-fluorophenyl)-1,2-oxazol-3-yl]methoxy)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C22 H17 F N6 O2	416.1397	417.1459	[M + H] ⁺
25	4-([5-(2-aminopyridin-4-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-yl]oxy)methylbenzonitrile	C20 H16 N6 O	356.1386	357.1464	[M + H] ⁺
26	4-{4-[(4-methoxybenzyl)oxy]-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C20 H19 N5 O2	361.1539	360.1463	[M - H] ⁻
27	4-(2-methyl-4-{[4-(propan-2-yl)benzyl]oxy}-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C22 H23 N5 O	373.1903	374.1972	[M + H] ⁺
28	4-[2-methyl-4-(1,3-thiazol-4-ylmethoxy)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C16 H14 N6 O S	338.0950	339.1019	[M + H] ⁺

General Procedure IV**General Procedure V****General Procedure VI**

In General Procedures IV, V and VI:

- R₁ and R₂ are as defined in formula (I),
- R₃ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, -(C₀-C₆)alkylene-Cy₁, -(C₀-C₆)alkylene-Cy₁-Cy₂, -(C₀-C₆)alkylene-Cy₁-O-(C₁-C₆)alkylene-Cy₂, it being understood that Cy₁ and Cy₂, independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or a heteroaryl group,
- and R'₃ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,
- or R₃ and R'₃ form with the nitrogen atom carrying them a heterocycloalkyl or an heteroaryl,

- G represents a group selected from the list of substituents defined in formula (I), it being understood that the phenyl may be substituted by from 1 to 4 independent G groups.

Example 30: 4-[2-methyl-4-(pyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine

5 *Step 1: 4-[2-methyl-4-(pyrrolidin-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine (Preparation 8)*

To a solution of 4-(4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-amine (**Example 20, Step 1**) (50 mg, 0.128 mmol) in THF (3 mL) was added pyrrolidine (3 eq). The reaction mixture was heated at 90
10 °C on a CEM microwave reactor for 1 hour (reaction monitored by LC-MS). The reaction mixture was diluted with DCM (10 mL) and water (10 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo* to give the desired product (58 mg, >100%). Purity estimated around 90% by LCMS. The compound was used without further purification.

15 LC/MS (method A): RT = 2.08 min; *m/z* = 425 [M+H]⁺

Step 2: 4-[2-methyl-4-(pyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine
Starting from the compound obtained in Step 1 (58 mg) following procedure described in **Preparation 4**, the desired product (23 mg, 0.078 mmol, 61% over two steps) was obtained as a white solid.

20 ¹H NMR (DMSO-d₆) δ: 11.71 (s, 1H), 7.86 (d, 1H), 7.17 (d, 1H), 6.56 – 6.44 (m, 2H), 5.89 (s, 2H), 3.31 (m, 4H), 2.41 (s, 3H), 1.72 – 1.63 (m, 4H)

Example 32: 5-(2-aminopyridin-4-yl)-N-benzyl-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

25 *Step 1: N-benzyl-5-bromo-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-amine*

Starting from 5-bromo-4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (**Example 1, Step 1**) (1 g, 2.65 mmol) and phenylmethanamine

(4 eq) following procedure described in **Preparation 8**. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (1.08 g, 2.41 mmol, 91%) as a clear oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.55 (s, 1H), 7.49 – 7.26 (m, 5H), 7.04 (t, 1H), 5.51 (s, 2H), 4.85 (d, 2H), 3.62 – 3.53 (m, 2H), 2.47 (s, 3H), 0.99 – 0.85 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 2.95 min; *m/z* = 449 [M+H]⁺

Step 2: 5-(2-aminopyridin-4-yl)-N-benzyl-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 1 (0.702 g, 1.57 mmol) and 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.335 g, 0.727 mmol, 46%) was obtained as a light brown oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.97 (dd, 1H), 7.50 – 7.34 (m, 5H), 7.35 – 7.26 (m, 1H), 6.65 – 6.56 (m, 2H), 6.09 (t, 1H), 6.06 (s, 2H), 5.58 (s, 2H), 4.77 (d, 2H), 3.67 – 3.58 (m, 2H), 2.51 (s, 3H), 0.98 – 0.84 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 2.33 min; *m/z* = 461 [M+H]⁺

Step 3: 5-(2-aminopyridin-4-yl)-N-benzyl-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 2 (0.335 g, 0.727 mmol) following procedure described in **Preparation 4**, the desired product (51 mg, 0.154 mmol, 21%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 11.73 (s, 1H), 7.89 (d, 1H), 7.42 – 7.28 (m, 4H), 7.29 – 7.19 (m, 2H), 6.60 – 6.49 (m, 2H), 5.92 (d, 3H), 4.70 (d, 2H), 2.42 (s, 3H).

LC/MS (method A): RT = 1.65 min; *m/z* = 331 [M+H]⁺

Example 52: 5-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Step 1: 5-bromo-N-[(2,6-difluorophenyl)methyl]-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from 5-bromo-4-chloro-2-methyl-7- $\{[2-(\text{trimethylsilyl})\text{ethoxy}]\text{methyl}\}$ -7H-pyrrolo[2,3-d]pyrimidine (**Example 1, Step 1**) (1.2 g, 3.19 mmol) and (2,6-difluorophenyl)methanamine (4 eq) following procedure described in **Preparation 8**. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the desired product as a clear oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.56 (s, 1H), 7.46 (tt, 1H), 7.24 – 7.11 (m, 2H), 6.81 (t, 1H), 5.51 (s, 2H), 4.92 (d, 2H), 3.62 – 3.53 (m, 2H), 2.49 (s, 3H), 0.97 – 0.85 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 2.96 min; m/z = 485 [M+H]⁺

Step 2: 5-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-2-methyl-7- $\{[2-(\text{trimethylsilyl})\text{ethoxy}]\text{methyl}\}$ -7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 1 (1 g, 2.07 mmol) and 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.422 g, 0.849 mmol, 41%) was obtained as a light brown oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.99 (dd, 1H), 7.52 – 7.39 (m, 2H), 7.22 – 7.11 (m, 2H), 6.61 – 6.53 (m, 2H), 6.05 (d, 3H), 5.57 (s, 2H), 4.85 (d, 2H), 3.66 – 3.57 (m, 2H), 2.53 (s, 3H), 1.00 – 0.86 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.32 min; m/z = 497 [M+H]⁺

Step 3: 5-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 2 (0.422 g, 0.849 mmol) following procedure described in **Preparation 4**, the product (0.104 g, 0.284 mmol, 33%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 11.74 (s, 1H), 7.90 (d, 1H), 7.37 (tt, 1H), 7.24 (d, 1H), 7.09 (t, 2H), 6.54 – 6.45 (m, 2H), 5.93 (s, 2H), 5.85 (t, 1H), 4.77 (d, 2H), 2.43 (s, 3H).

LC/MS (method B): RT = 0.96 min; m/z = 367 [M+H]⁺

Example 129: 5-(2-aminopyridin-4-yl)-2-methyl-N-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Step 1: 5-bromo-2-methyl-N-phenyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Preparation 9)

To a solution of 5-bromo-4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (**Example 1, Step 1**) (0.2 g, 0.53 mmol) in DMF (2 mL) was added aniline (1.2 eq) followed by *t*-BuOK (2 eq) at room temperature under N₂. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.109 g, 0.251 mmol, 47%) as a clear oil.

LC/MS (method B): RT = 1.68 min; *m/z* = 433 [M+H]⁺

Step 2: tert-butyl N-{4-[2-methyl-4-(phenylamino)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-yl}carbamate

Starting from the compound obtained in Step 1 (0.109 g, 0.251 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.2 eq) following procedure described in **Preparation 3**, the product (0.118 g, 0.215 mmol, 86%) was obtained as clear oil.

LC/MS (method B): RT = 1.68 min; *m/z* = 547 [M+H]⁺

Step 3: 5-(2-aminopyridin-4-yl)-2-methyl-N-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 2 (0.118 g, 0.215 mmol) following procedure described in **Preparation 7**, the desired product (37 mg, 0.117 mmol, 54%) was obtained as a pale yellow solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.00 (d, 1H), 8.00 (d, 1H), 7.72 – 7.65 (m, 3H), 7.45 (d, 1H), 7.35 – 7.28 (m, 2H), 7.00 (m, 1H), 6.71 (dd, 1H), 6.63 (d, 1H), 6.25 (s, 2H), 2.53 (s, 3H).

LC/MS (method B): RT = 0.87 min; *m/z* = 317 [M+H]⁺

Examples 29-146 in the following **Table 2** were prepared by methods outlined in **General Procedure IV-VI** using appropriate commercially available boronate esters and amines. The compounds of **Example 30, 32, 129** are also included.

Table 2: HRMS (TOF, ESI) data

Example	Structure	Mol Formula	Calcd Exact Mass	Found m/z	Adduct
29	5-(2-aminopyridin-4-yl)- <i>N,N</i> ,2-trimethyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₄ H ₁₆ N ₆	268.1436	269.1519	[M + H] ⁺
30	4-[2-methyl-4-(pyrrolidin-1-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₆ H ₁₈ N ₆	294.1593	295.1672	[M + H] ⁺
31	4-{4-[3-(dimethylamino)pyrrolidin-1-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₈ H ₂₃ N ₇	337.2015	338.2085	[M + H] ⁺
32	5-(2-aminopyridin-4-yl)- <i>N</i> -benzyl-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₈ N ₆	330.1593	331.1661	[M + H] ⁺

33	4-[2-methyl-4-(4-methylpiperazin-1-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C17 H21 N7	323.1858	324.1932	[M + H] ⁺
34	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(pyridin-3-ylmethyl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C18 H17 N7	331.1545	332.1612	[M + H] ⁺
35	5-(2-aminopyridin-4-yl)- <i>N</i> -(furan-3-ylmethyl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C17 H16 N6 O	320.1386	321.1466	[M + H] ⁺
36	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(thiophen-3-ylmethyl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C17 H16 N6 S	336.1157	337.1231	[M + H] ⁺
37	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(thiophen-2-ylmethyl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C17 H16 N6 S	336.1157	337.1222	[M + H] ⁺

38	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[(1-methyl-1 <i>H</i> -pyrazol-5-yl)methyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C17 H18 N8	334.1654	335.1722	[M + H] ⁺
39	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(1,3-thiazol-2-ylmethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C16 H15 N7 S	337.1110	338.1179	[M + H] ⁺
40	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(1,3-thiazol-4-ylmethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C16 H15 N7 S	337.1110	338.1189	[M + H] ⁺
41	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(1,3-thiazol-5-ylmethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C16 H15 N7 S	337.1110	338.1179	[M + H] ⁺
42	<i>N</i> -benzyl-2-methyl-5-(pyridin-4-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H17 N5	315.1484	316.1547	[M + H] ⁺

43	<i>N</i> -benzyl-2-methyl-5-(2-methylpyridin-4-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₉ N ₅	329.1640	330.1709	[M + H] ⁺
44	2-methyl-5-(pyridin-4-yl)- <i>N</i> -(thiophen-3-ylmethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₇ H ₁₅ N ₅ S	321.1048	322.1121	[M + H] ⁺
45	2-methyl-5-(2-methylpyridin-4-yl)- <i>N</i> -(thiophen-3-ylmethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₇ N ₅ S	335.1205	336.1283	[M + H] ⁺
46	2-methyl- <i>N</i> -[(5-methyl-1,2-oxazol-3-yl)methyl]-5-(pyridin-4-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₇ H ₁₆ N ₆ O	320.1386	321.1450	[M + H] ⁺
47	2-methyl- <i>N</i> -[(5-methyl-1,2-oxazol-3-yl)methyl]-5-(2-methylpyridin-4-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₈ N ₆ O	334.1542	335.1613	[M + H] ⁺

48	5-(2-aminopyridin-4-yl)- <i>N</i> -(cyclohexylmethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₂₄ N ₆	336.2062	337.2134	[M + H] ⁺
49	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(1-phenylethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₂₀ N ₆	344.1749	345.1814	[M + H] ⁺
50	5-(2-aminopyridin-4-yl)- <i>N</i> -(3-fluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₇ F N ₆	348.1499	349.1567	[M + H] ⁺
51	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-fluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₇ F N ₆	348.1499	347.1430	[M - H] ⁻
52	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ F ₂ N ₆	366.1405	365.1341	[M - H] ⁻

53	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(pyridin-2-ylmethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₇ N ₇	331.1545	330.1471	[M - H] ⁻
54	5-(2-aminopyridin-4-yl)- <i>N</i> -(4-fluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₇ F N ₆	348.1499	347.1416	[M - H] ⁻
55	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-methoxybenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₂₀ N ₆ O	360.1699	359.1611	[M - H] ⁻
56	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(2-methylbenzyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₂₀ N ₆	344.1749	343.1675	[M - H] ⁻
57	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-chlorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₇ Cl N ₆	364.1203	363.1139	[M - H] ⁻

58	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-chloro-6-methylbenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₉ Cl N ₆	378.1360	377.1292	[M - H] ⁻
59	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[(5-methyl-1,2-oxazol-3-yl)methyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₇ H ₁₇ N ₇ O	335.1495	334.1417	[M - H] ⁻
60	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[(3-methylpyridin-2-yl)methyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₉ N ₇	345.1702	344.1630	[M - H] ⁻
61	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-dichlorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ Cl ₂ N ₆	398.0813	397.0746	[M - H] ⁻
62	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-chloro-6-fluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ Cl F N ₆	382.1109	381.1045	[M - H] ⁻

63	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,4-difluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H16 F2 N6	366.1405	365.1323	[M - H] ⁻
64	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[2-(trifluoromethyl)benzyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H17 F3 N6	398.1467	397.1402	[M - H] ⁻
65	5-(2-aminopyridin-4-yl)- <i>N</i> -(cyclopropylmethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C16 H18 N6	294.1593	293.1535	[M - H] ⁻
66	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[1-(pyridin-2-yl)ethyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H19 N7	345.1702	344.1636	[M - H] ⁻
67	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[(1 <i>S</i>)-1-phenylethyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H20 N6	344.1749	343.1688	[M - H] ⁻

68	5-(2-aminopyridin-4-yl)-2-methyl-N-[(1 <i>R</i>)-1-phenylethyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₂₀ N ₆	344.1749	343.1680	[M - H] ⁻
69	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-fluoro-6-methoxybenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₉ F N ₆ O	378.1604	377.1534	[M - H] ⁻
70	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-fluoro-6-methylbenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₉ F N ₆	362.1655	361.1593	[M - H] ⁻
71	5-(2-aminopyridin-4-yl)- <i>N</i> -[(3-fluoropyridin-2-yl)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₆ F N ₇	349.1451	348.1370	[M - H] ⁻
72	5-(2-aminopyridin-4-yl)- <i>N</i> -(1 <i>H</i> -indol-6-ylmethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₁₉ N ₇	369.1702	368.1629	[M - H] ⁻

73	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(2,3,5-trifluorobenzyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H15 F3 N6	384.1310	383.1246	[M - H] ⁻
74	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,3-difluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H16 F2 N6	366.1405	365.1328	[M - H] ⁻
75	5-(2-aminopyridin-4-yl)- <i>N</i> -[4-fluoro-2-(trifluoromethyl)benzyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H16 F4 N6	416.1373	415.1297	[M - H] ⁻
76	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>R</i>)-2,3-dihydro-1 <i>H</i> -inden-1-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C21 H20 N6	356.1749	355.1685	[M - H] ⁻
77	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>S</i>)-2,3-dihydro-1 <i>H</i> -inden-1-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C21 H20 N6	356.1749	355.1677	[M - H] ⁻

78	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -{[3-(trifluoromethyl)pyridin-2-yl]methyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ F ₃ N ₇	399.1419	398.1370	[M - H] ⁻
79	5-(2-aminopyridin-4-yl)- <i>N</i> -(2-ethoxybenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₂₂ N ₆ O	374.1855	373.1783	[M - H] ⁻
80	5-(2-aminopyridin-4-yl)- <i>N</i> -[2-methoxy-6-(trifluoromethyl)benzyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₁₉ F ₃ N ₆ O	428.1572	427.1491	[M - H] ⁻
81	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,3-dichlorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ Cl ₂ N ₆	398.0813	397.0744	[M - H] ⁻
82	5-(2-aminopyridin-4-yl)- <i>N</i> -[1-(2,6-difluorophenyl)ethyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₈ F ₂ N ₆	380.1561	379.1500	[M - H] ⁻

83	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>R</i> ,2 <i>R</i> ,4 <i>S</i>)-bicyclo[2.2.1]hept-2-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H22 N6	334.1906	333.1845	[M - H] ⁻
84	5-(2-aminopyridin-4-yl)- <i>N</i> -(4-fluoro-2-methoxybenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H19 F N6 O	378.1604	377.1540	[M - H] ⁻
85	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>R</i>)-1-(2-methoxyphenyl)ethyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C21 H22 N6 O	374.1855	373.1791	[M - H] ⁻
86	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>R</i>)-1-(2-fluorophenyl)ethyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H19 F N6	362.1655	361.1593	[M - H] ⁻
87	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -{[5-(pyridin-2-yl)thiophen-2-yl]methyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C22 H19 N7 S	413.1423	412.1358	[M - H] ⁻

88	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[(3-phenyl-1,2-oxazol-5-yl)methyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₂ H ₁₉ N ₇ O	397.1651	396.1584	[M - H] ⁻
89	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[2-(trifluoromethoxy)benzyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₇ F ₃ N ₆ O	414.1416	413.1342	[M - H] ⁻
90	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>R</i> ,2 <i>R</i>)-2-(benzyloxy)cyclohexyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₉ N ₇ O	428.2325	427.2252	[M - H] ⁻
91	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[(1 <i>R</i>)-1,2,3,4-tetrahydronaphthalen-1-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₂ H ₂₂ N ₆	370.1906	369.1829	[M - H] ⁻
92	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,5-dichlorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ Cl ₂ N ₆	398.0813	397.0746	[M - H] ⁻

93	5-(2-aminopyridin-4-yl)- <i>N</i> -cyclohexyl-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C18 H22 N6	322.1906	321.1830	[M - H] ⁻
94	5-(2-aminopyridin-4-yl)- <i>N</i> -(3-chloro-2-methylbenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H19 Cl N6	378.1360	377.1288	[M - H] ⁻
95	5-(2-aminopyridin-4-yl)- <i>N</i> -[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C18 H19 N7 O	349.1651	348.1587	[M - H] ⁻
96	4-[4-(3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C21 H20 N6	356.1749	355.1680	[M - H] ⁻
97	4-[2-methyl-4-(3-methylpiperidin-1-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C18 H22 N6	322.1906	323.1978	[M - H] ⁺

98	5-(2-aminopyridin-4-yl)- <i>N</i> -[(3-methoxypyridin-2-yl)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₉ N ₇ O	361.1651	362.1728	[M - H] ⁺
99	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,3-dihydro-1 <i>H</i> -inden-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₂₀ N ₆	356.1749	357.1823	[M + H] ⁺
100	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -(3,3,3-trifluoropropyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₅ H ₁₅ F ₃ N ₆	336.1310	335.1250	[M - H] ⁻
101	4-[4-(3-azaspiro[5.5]undec-3-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₂₂ H ₂₈ N ₆	376.2375	375.2309	[M - H] ⁻
102	4-[2-methyl-4-(8-methyl-2-azaspiro[4.5]dec-2-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₂₂ H ₂₈ N ₆	376.2375	377.2441	[M - H] ⁺

103	4-[2-methyl-4-(2-phenylazetidin-1-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C21 H20 N6	356.1749	357.1821	[M - H] ⁺
104	4-[2-methyl-4-(octahydroisoquinolin-2(1 <i>H</i>)-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C21 H26 N6	362.2219	363.2285	[M - H] ⁺
105	4-{2-methyl-4-[4-(trifluoromethyl)piperidin-1-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C18 H19 F3 N6	376.1623	375.1563	[M - H] ⁺
106	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>S</i>)-1-(2-methoxyphenyl)ethyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C21 H22 N6 O	374.1855	375.1920	[M - H] ⁺
107	4-{2-methyl-4-[2-(trifluoromethyl)pyrrolidin-1-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C17 H17 F3 N6	362.1467	363.1528	[M - H] ⁺

108	4-[4-(6,7-dihydrothieno[3,2- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C19 H18 N6 S	362.1314	363.1393	[M - H] ⁺
109	4-[4-(2-azaspiro[3.5]non-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H24 N6	348.2062	347.1993	[M - H] ⁻
110	4-{2-methyl-4-[(4 <i>aR</i> ,8 <i>aR</i>)-octahydroisoquinolin-2(1 <i>H</i>)-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C21 H26 N6	362.2219	361.2154	[M - H] ⁻
111	4-{2-methyl-4-[(4 <i>aR</i> ,8 <i>aS</i>)-octahydroisoquinolin-2(1 <i>H</i>)-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C21 H26 N6	362.2219	361.2145	[M - H] ⁻
112	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,3-dihydro-1-benzofuran-3-ylmethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C21 H20 N6 O	372.1699	373.1761	[M - H] ⁺

113	5-(2-aminopyridin-4-yl)- <i>N</i> -[1-(3-methoxypyridin-2-yl)ethyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H21 N7 O	375.1808	376.1876	[M - H] ⁺
114	4-[4-(3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C21 H21 N7	371.1858	370.1786	[M - H] ⁻
115	4-{4-[(2,6-difluorobenzyl)amino]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridine-2,6-diamine	C19 H17 F2 N7	381.1513	382.1556	[M - H] ⁺
116	4-{4-[(2-fluoro-6-methoxybenzyl)amino]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridine-2,6-diamine	C20 H20 F N7 O	393.1713	394.1774	[M - H] ⁺
117	4-(4-{[(1 <i>S</i>)-1-(2-methoxyphenyl)ethyl]amino}-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridine-2,6-diamine	C21 H23 N7 O	389.1964	390.2023	[M - H] ⁺

118	4-{4-[(1 <i>R</i>)-2,3-dihydro-1 <i>H</i> -inden-1-ylamino]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridine-2,6-diamine	C21 H21 N7	371.1858	372.1936	[M - H] ⁺
119	5-(2-aminopyridin-4-yl)- <i>N</i> -[(3,5-difluoropyridin-4-yl)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C18 H15 F2 N7	367.1357	368.1421	[M - H] ⁺
120	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)- <i>N</i> ,2-dimethyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H18 F2 N6	380.1561	381.1629	[M - H] ⁺
121	5-(2-aminopyridin-4-yl)- <i>N</i> -[1-(3-fluoropyridin-2-yl)propyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C20 H20 F N7	377.1764	378.1836	[M - H] ⁺
122	5-(2-aminopyridin-4-yl)- <i>N</i> -[(1 <i>S</i>)-1-(3-fluoropyridin-2-yl)ethyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C19 H18 F N7	363.1608	364.1636	[M - H] ⁺

123	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,2-difluoro-2-phenylethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₈ F ₂ N ₆	380.1561	381.1635	[M - H] ⁺
124	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[2-(pyridin-2-yl)ethyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₉ N ₇	345.1702	346.1767	[M - H] ⁺
125	4-{4-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethylmorpholin-4-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine + 4-{4-[(2 <i>S</i> ,6 <i>R</i>)-2,6-dimethylmorpholin-4-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₈ H ₂₂ N ₆ O	338.1855	339.1931	[M - H] ⁺
126	4-{4-[(2 <i>R</i> ,6 <i>S</i>)-2,6-dimethylmorpholin-4-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridine-2,6-diamine + 4-{4-[(2 <i>S</i> ,6 <i>R</i>)-2,6-dimethylmorpholin-4-yl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridine-2,6-diamine	C ₁₈ H ₂₃ N ₇ O	353.1964	354.2044	[M - H] ⁺
127	5-(2-aminopyridin-4-yl)- <i>N</i> -(1,3-benzodioxol-4-ylmethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₈ N ₆ O ₂	374.1491	375.1494	[M - H] ⁺

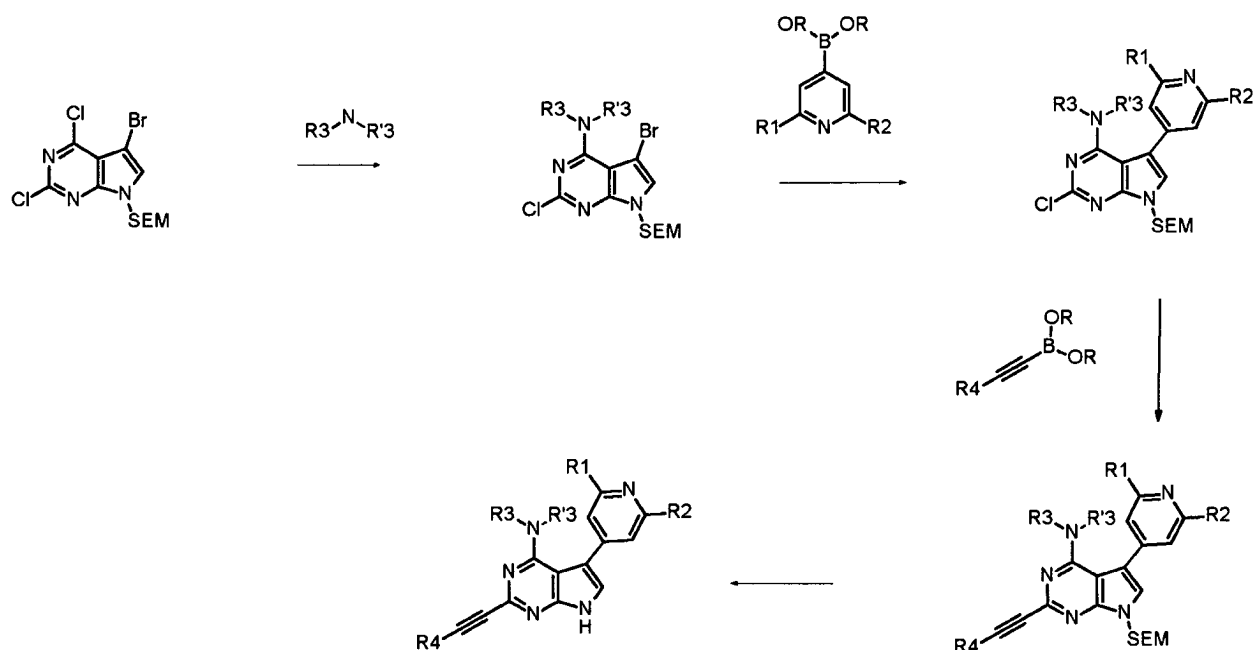
128	4-{4-[(1,3-benzodioxol-4-ylmethyl)amino]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridine-2,6-diamine	C ₂₀ H ₁₉ N ₇ O ₂	389.1600	390.1593	[M - H] ⁺
129	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -phenyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₆ N ₆	316.1436	317.1458	[M - H] ⁺
130	5-(2-aminopyridin-4-yl)-2-methyl- <i>N</i> -[2-(trifluoromethyl)phenyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₅ F ₃ N ₆	384.1310	385.1326	[M - H] ⁺
131	4-(2-methyl-4-{[2-(trifluoromethyl)phenyl]amino}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridine-2,6-diamine	C ₁₉ H ₁₆ F ₃ N ₇	399.1419	400.1434	[M - H] ⁺
132	5-(2-aminopyridin-4-yl)- <i>N</i> -(1,3-benzodioxol-5-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₆ N ₆ O ₂	360.1335	361.1332	[M - H] ⁺

133	4-[4-(4-methoxypiperidin-1-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₈ H ₂₂ N ₆ O	338.1855	339.1871	[M - H] ⁺
134	4-[2-methyl-4-(morpholin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₆ H ₁₈ N ₆ O	310.1542	311.1565	[M - H] ⁺
135	4-[4-(5,6-dihydroimidazo[1,2- <i>a</i>]pyrazin-7(8 <i>H</i>)-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₈ H ₁₈ N ₈	346.1654	347.1663	[M - H] ⁺
136	4-[4-(7,8-dihydropyrido[3,4- <i>b</i>]pyrazin-6(5 <i>H</i>)-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₉ H ₁₈ N ₈	358.1654	359.1659	[M - H] ⁺
137	4-[2-methyl-4-(2-methylmorpholin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₇ H ₂₀ N ₆ O	324.1699	323.1544	[M - H] ⁺

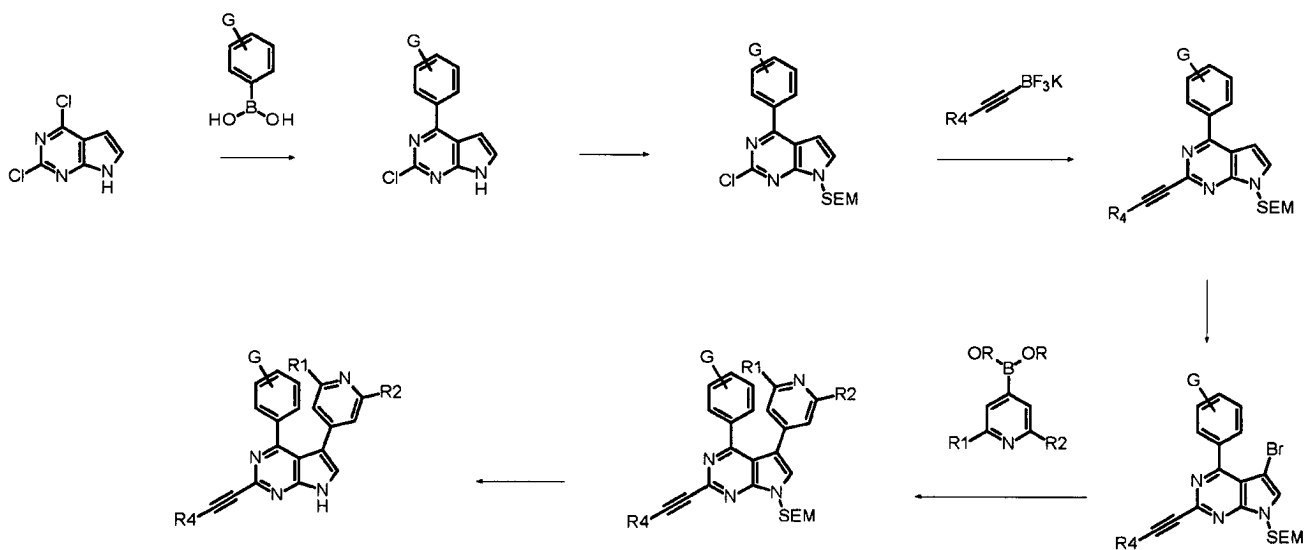
138	4-[4-(3-methoxypiperidin-1-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₈ H ₂₂ N ₆ O	338.1855	339.1855	[M - H] ⁺
139	4-[4-(4-methoxypiperidin-1-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C ₁₈ H ₂₃ N ₇ O	353.1964	354.1972	[M - H] ⁺
140	4-[2-methyl-4-(morpholin-4-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C ₁₆ H ₁₉ N ₇ O	325.1651	326.1724	[M - H] ⁺
141	4-[4-(5,6-dihydroimidazo[1,2- <i>a</i>]pyrazin-7(8 <i>H</i>)-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C ₁₈ H ₁₉ N ₉	361.1763	362.1764	[M - H] ⁺
142	4-[4-(7,8-dihydropyrido[3,4- <i>b</i>]pyrazin-6(5 <i>H</i>)-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C ₁₉ H ₁₉ N ₉	373.1763	374.1760	[M - H] ⁺

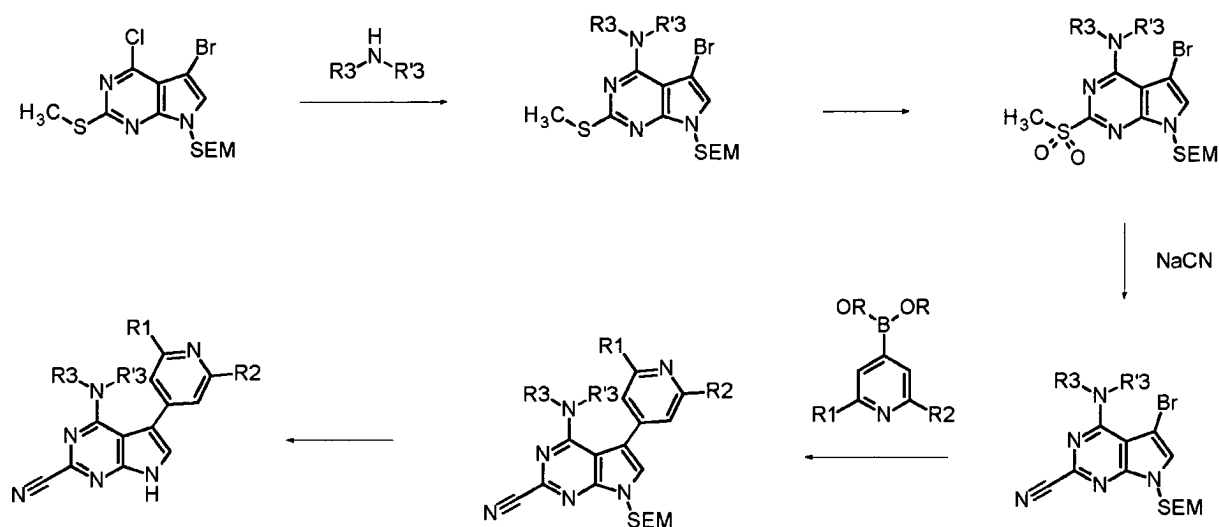
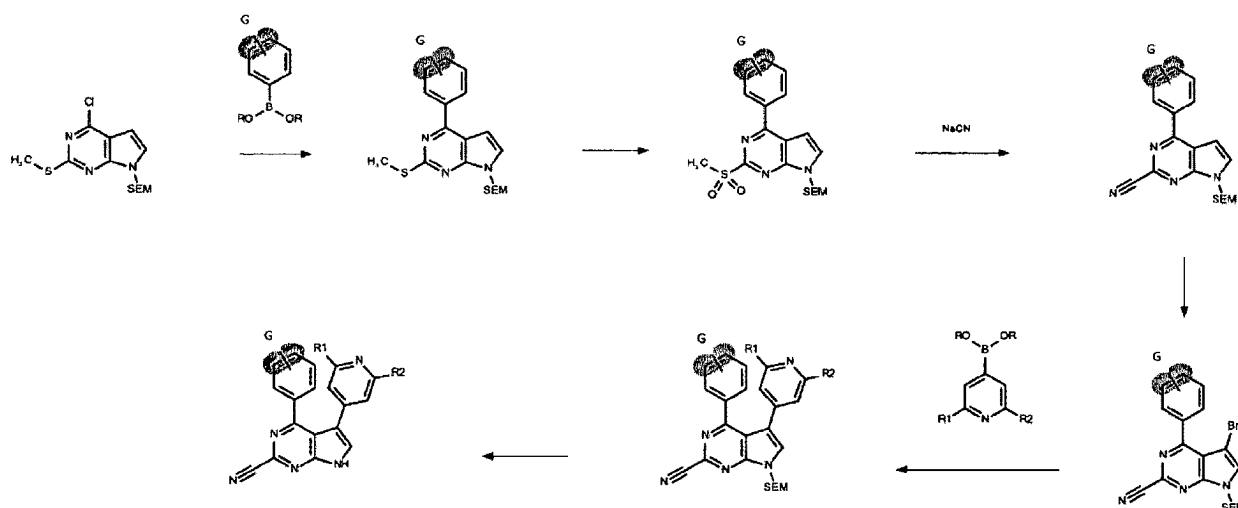
143	4-[2-methyl-4-(2-methylmorpholin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C17 H21 N7 O	339.1808	340.1845	[M - H] ⁺
144	4-[4-(3-methoxypiperidin-1-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C18 H23 N7 O	353.1964	354.1978	[M - H] ⁺
145	<i>N</i> -[2-methoxy-6-(trifluoromethyl)benzyl]-2-methyl-5-(pyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C21 H18 F3 N5 O	413.1463	414.1468	[M - H] ⁺
146	<i>N</i> -[2-methoxy-6-(trifluoromethyl)benzyl]-2-methyl-5-(2-methylpyridin-4-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C22 H20 F3 N5 O	427.1620	428.1633	[M - H] ⁺

General Procedure VII



General Procedure VIII



General Procedure IX**General Procedure X**

In General Procedures VII, VIII, IX and X:

- R_1 and R_2 are as defined in formula (I),

- R₃ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, -(C₀-C₆)alkylene-Cy₁, -(C₀-C₆)alkylene-Cy₁-Cy₂, -(C₀-C₆)alkylene-Cy₁-O-(C₁-C₆)alkylene-Cy₂, it being understood that Cy₁ and Cy₂, independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group,

and R'₃ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group, or R₃ and R'₃ form with the nitrogen atom carrying them a heterocycloalkyl or an heteroaryl,

- R₄ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group or a cycloalkyl group,

- G represents a group selected from the list of substituents defined in formula (I), it being understood that the phenyl may be substituted by from 1 to 4 independent G groups.

Example 148: 5-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-2-ethynyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Step 1: 5-bromo-2-chloro-N-[(2,6-difluorophenyl)methyl]-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from 5-bromo-2,4-dichloro-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidine (prepared following procedure described in WO2007/104944) (1 g, 2.52 mmol) and (2,6-difluorophenyl)methanamine (2 eq) following procedure described in **Preparation 8**. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (1.25 g, 2.48 mmol, 98%) as a clear oil.

LC/MS (method B): RT = 3.0 min; *m/z* = 505 [M+H]⁺

Step 2: tert-butyl N-[4-(2-chloro-4-[(2,6-difluorophenyl)methyl]amino)-7-[[2-(trimethylsilyl)ethoxy]methyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-yl]carbamate

Starting from the compound obtained in Step 1 (1.25 g, 2.48 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.2 eq) following procedure described in **Preparation 3**, the desired product (1.063 g, 1.72 mmol, 69%) was obtained as an off-white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 9.93 (s, 1H), 8.30 (d, 1H), 7.95 (d, 1H), 7.76 (s, 1H), 7.44 (tt, 1H), 7.19 – 7.06 (m, 3H), 6.78 (t, 1H), 5.57 (s, 2H), 4.82 (d, 2H), 3.67 – 3.57 (m, 2H), 1.54 (s, 9H), 0.98 – 0.84 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.71 min; *m/z* = 617 [M+H]⁺

5 *Step 3: 4-{2-[2-(tert-butyldimethylsilyl)ethynyl]-4-[(2,6-difluorophenyl)methyl]amino}-7-[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-2-amine*
(**Preparation 10**)

The compound obtained in Step 2 (0.5 g, 0.81 mmol) and *tert*-butyldimethyl[2-(tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl]silane (1.2 eq) were dissolved in 1,4-dioxane (10 mL) under N₂. 2M Na₂CO₃ aq. solution (1 mL) and tetrakis(triphenylphosphine)palladium (0.08 mmol) were added and the resulting mixture was degassed under N₂ for 5 minutes. The reaction mixture was heated at 160 °C on a CEM microwave reactor for 1 hour. The reaction mixture was filtered through a plug of celite. The filtrate was diluted with water (10 mL) and EtOAc (50 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.379 g) as a yellow oil. Purity estimated around 50% by LCMS. The compound was used without further purification.

LC/MS (method A): RT = 2.84 min; *m/z* = 621 [M+H]⁺

20 *Step 4: 5-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-2-ethynyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine*

Starting from the compound obtained in Step 3 (0.379 g) following procedure described in **Preparation 4**, the desired product (13 mg, 0.003 mmol) was obtained as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 12.19 (s, 1H), 7.97 (d, 1H), 7.54 – 7.41 (m, 2H), 7.19 (q, 2H), 6.62 – 6.54 (m, 2H), 6.09 (t, 1H), 6.03 (s, 2H), 4.86 (d, 2H), 4.06 (s, 1H).

LC/MS (method B): RT = 0.99 min; *m/z* = 377 [M+H]⁺

Example 153: 4-[4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine

Step 1: 4-(1,3-benzodioxol-5-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidine

Starting from 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (1 g, 5.32 mmol) and (1,3-benzodioxol-5-yl)boronic acid (1.05 eq) following procedure described in **Preparation 3**, the desired product (1.45 g, 3.84 mmol) was obtained as a pale yellow solid. Purity estimated around 70% by LCMS. The compound was used without further purification.

LC/MS (method B): RT = 1.2 min; m/z = 274 [M+H]⁺

Step 2: 4-(1,3-benzodioxol-5-yl)-2-chloro-7-([2-(trimethylsilyl)ethoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidine

Starting from the compound obtained in Step 1 (1.45 g, 3.84 mmol) following procedure described in **Preparation 1**, the desired product (1.005 g, 2.49 mmol, 65%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 7.92 (d, 1H), 7.85 (dd, 1H), 7.73 (d, 1H), 7.21 (d, 1H), 7.12 (d, 1H), 6.25 (s, 2H), 5.68 (s, 2H), 3.73 – 3.53 (m, 2H), 0.99 – 0.83 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.57 min; m/z = 404 [M+H]⁺

Step 3: 4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7-([2-(trimethylsilyl)ethoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidine

Starting from the compound obtained in Step 2 (0.45 g, 1.11 mmol) and potassium (2-cyclopropyl-ethyn-1-yl)-trifluoroborate (prepared from *Org. Lett.*, **2010**, *12*, 3272-3275) (1.4 eq) following procedure described in **Preparation 10**, the desired product (0.22 g, 0.512 mmol, 46%) was obtained as a red oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.95 (dd, 1H), 7.89 – 7.77 (m, 1H), 7.73 (dd, 1H), 7.26 – 7.03 (m, 2H), 6.27 – 6.18 (m, 2H), 5.71 (s, 2H), 3.74 – 3.58 (m, 2H), 1.50 (m, 1H), 1.01 – 0.83 (m, 6H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.61 min; m/z = 434 [M+H]⁺

Step 4: 4-(1,3-benzodioxol-5-yl)-5-bromo-2-(cyclopropylethynyl)-7-([2-(trimethylsilyl)ethoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 11**)

To a solution of the compound obtained in Step 3 (0.22 g, 0.512 mmol) in DMF (10 mL) was added NBS (1.05 eq) 0 °C under N₂ and the reaction was allowed to warm to room temperature over 3 hours. The reaction mixture was diluted with water (20 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.147 g, 0.286 mmol, 56%) as a brown oil.

¹H NMR (399 MHz, DMSO-d₆) δ 8.13 (s, 1H), 7.32 – 7.22 (m, 2H), 7.13 (d, 1H), 6.20 (s, 2H), 5.66 (s, 2H), 3.67 – 3.58 (m, 2H), 1.69 (tt, 1H), 1.04 – 0.99 (m, 2H), 0.95 – 0.86 (m, 4H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.64 min; *m/z* = 512 [M+H]⁺

Step 5: *tert*-butyl N-{4-[4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7-([2-(trimethylsilyl)ethoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-yl}carbamate

Starting from the compound obtained in Step 4 (0.110 g, 0.21 mmol) and *tert*-butyl N-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**, the desired product (96 mg, 0.153 mmol, 71%) was obtained as an off-white solid.

LC/MS (method B): RT = 1.63 min; *m/z* = 626 [M+H]⁺

Step 6: 4-[4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine

Starting from the compound obtained in Step 5 (96 mg, 0.153 mmol) following procedure described in **Preparation 7**, the desired product (34 mg, 0.083 mmol, 54%) was obtained as an off-white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.51 (s, 1H), 7.83 (s, 1H), 7.61 (d, 1H), 6.96 (d, 1H), 6.88 – 6.80 (m, 1H), 6.74 (d, 1H), 6.15 (t, 1H), 6.02 (s, 2H), 6.04 – 5.98 (m, 1H), 5.68 (s, 2H), 1.63 (tt, 1H), 1.07 – 0.90 (m, 2H), 0.91 – 0.79 (m, 2H).

LC/MS (method B): RT = 0.99 min; *m/z* = 396 [M+H]⁺

Example 157: 5-(2-aminopyridin-4-yl)-4-[(2,6-difluorobenzyl)amino]-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

Step 1: 5-bromo-N-[(2,6-difluorophenyl)methyl]-2-(methanesulfonyl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-amine

5 Starting from 5-bromo-4-chloro-2-(methanesulfonyl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (prepared following procedure described in WO2007/104944) (0.77 g, 1.88 mmol) and 2,6-difluorobenzylamine (3 eq) following procedure described in **Preparation 8**, the desired product (0.856 g, 1.66 mmol, 88%) was obtained as a pale yellow oil.

10 ¹H NMR (399 MHz, DMSO-d₆) δ 7.49 (m, 2H), 7.18 (t, 2H), 6.97 (s, 1H), 5.49 (s, 2H), 4.94 (d, 2H), 3.58 (m, 2H), 2.55 (s, 3H), 0.98 – 0.87 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.7 min; *m/z* = 515 [M+H]⁺

Step 2: 5-bromo-N-[(2,6-difluorophenyl)methyl]-2-methanesulfonyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Preparation 12)

15 To a solution of the compound obtained in Step 1 (0.856 g, 1.66 mmol) in DCM (20 mL) was added mCBPA (2.5 eq) portion wise at 0°C under N₂. The reaction mixture was stirred at the same temperature for 1 hour before allowed to warm to room temperature over 2 hours. The reaction mixture was diluted with sat. aq. NaHCO₃ (20 mL) solution and DCM (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and
20 concentrated *in vacuo* to give the product (0.831 g, 1.51 mmol, 92%) as a yellow oil. The compound was used without further purification.

LC/MS (method B): RT = 1.53 min; *m/z* = 549 [M+H]⁺

Step 3: 5-bromo-4-{[(2,6-difluorophenyl)methyl]amino}-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile (Preparation 13)

25 To a solution of the compound obtained in Step 2 (0.660 g, 1.11 mmol) in DMF (15 mL) was added sodium cyanide (2.5 eq) under N₂ at room temperature. The reaction mixture was heated at 90 °C for 2 hours. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via

flash chromatography using EtOAc and isohexane as eluent to give the product (0.453 g, 0.916 mmol, 76%) as a clear oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.97 (s, 1H), 7.55 – 7.41 (m, 2H), 7.19 (t, 2H), 5.58 (s, 2H), 4.93 (d, 2H), 3.63 – 3.53 (m, 2H), 0.99 – 0.83 (m, 2H), 0.00 (s, 9H).

5 LC/MS (method A): RT = 2.94 min; *m/z* = 496 [M+H]⁺

Step 4: tert-butyl N-[4-(2-cyano-4-[(2,6-difluorophenyl)methyl]amino)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-yl]carbamate

Starting from the compound obtained in Step 3 (0.225 g, 0.46 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following
10 procedure described in **Preparation 3**, the desired product (0.135 g, 1.51 mmol, 49%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 9.96 (s, 1H), 8.32 (d, 1H), 8.03 (s, 1H), 7.97 (d, 1H), 7.45 (t, 1H), 7.19 – 7.08 (m, 3H), 6.94 (t, 1H), 5.67 (s, 2H), 4.84 (d, 2H), 3.63 (t, 2H), 0.99 – 0.85 (m, 2H), 0.00 (s, 9H).

15 LC/MS (method A): RT = 2.98 min; *m/z* = 608 [M+H]⁺

Step 5: 5-(2-aminopyridin-4-yl)-4-[(2,6-difluorobenzyl)amino]-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

Starting from the compound obtained in Step 4 (0.135 g, 1.51 mmol) following procedure described in **Preparation 7**, the desired product (17 mg, 0.04 mmol) was obtained as a
20 white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.56 (s, 1H), 7.92 (d, 1H), 7.64 (s, 1H), 7.40 (tt, 1H), 7.11 (t, 2H), 6.54 – 6.43 (m, 3H), 5.98 (s, 2H), 4.77 (d, 2H).

LC/MS (method B): RT = 1.03 min; *m/z* = 378 [M+H]⁺

Example 158: 4-(1,3-benzodioxol-5-yl)-5-(2,6-diaminopyridin-4-yl)-7H-pyrrolo[2,3-
25 *d*]pyrimidine-2-carbonitrile

Step 1: 4-(1,3-benzodioxol-5-yl)-2-(methylsulfanyl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine

Starting from 4-chloro-2-(methylsulfanyl)-7-{{2-(trimethylsilyl)ethoxy}methyl}-7H-pyrrolo[2,3-d]pyrimidine (prepared following procedure described in WO2007/104944) (0.411 g, 1.25 mmol) and (1,3-benzodioxol-5-yl)boronic acid (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.462 g, 1.11 mmol, 89%) was obtained as a pale yellow oil.

¹H NMR (399 MHz, DMSO-d₆) δ 7.84 (dd, 1H), 7.78 – 7.69 (m, 2H), 7.20 (d, 1H), 6.99 (d, 1H), 6.24 (s, 2H), 5.68 (s, 2H), 3.68 (m, 2H), 2.71 (s, 3H), 1.00 – 0.86 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.63 min; *m/z* = 416 [M+H]⁺

Step 2: 4-(1,3-benzodioxol-5-yl)-2-methanesulfonyl-7-{{2-(trimethylsilyl)ethoxy}methyl}-7H-pyrrolo[2,3-d]pyrimidine

Starting from the compound obtained in Step 1 (0.462 g, 1.11 mmol) following procedure described in **Preparation 12**, the desired product (0.475 g, 1.06 mmol, 95%) was obtained as a pale orange oil.

¹H NMR (399 MHz, DMSO-d₆) δ 8.19 (d, 1H), 8.01 – 7.92 (m, 2H), 7.86 (d, 1H), 7.29 (d, 1H), 6.27 (s, 2H), 5.81 (s, 2H), 3.73 – 3.61 (m, 2H), 3.57 (s, 3H), 1.01 – 0.92 (m, 2H), 0.00 (s, 9H).

LC/MS (method A): RT = 2.7 min; *m/z* = 448 [M+H]⁺

Step 3: 4-(1,3-benzodioxol-5-yl)-7-{{2-(trimethylsilyl)ethoxy}methyl}-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

Starting from the compound obtained in Step 2 (0.260 g, 0.58 mmol) following procedure described in **Preparation 13**, the desired product (0.200 g, 0.51 mmol, 87%) was obtained as a dark oil.

LC/MS (method A): RT = 2.84 min; *m/z* = 395 [M+H]⁺

Step 4: 4-(1,3-benzodioxol-5-yl)-5-bromo-7-{{2-(trimethylsilyl)ethoxy}methyl}-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

Starting from the compound obtained in Step 3 (0.200 g, 0.51 mmol) following procedure described in **Preparation 11**, the desired product (0.183 g, 0.386 mmol, 76%) was obtained as a pale yellow solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.45 (s, 1H), 7.40 – 7.28 (m, 2H), 7.17 (d, 1H), 6.22 (s, 2H), 5.74 (s, 2H), 3.71 – 3.57 (m, 2H), 0.97 – 0.89 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.59 min; *m/z* = 473 [M+H]⁺

Step 5: *tert*-butyl *N*-[6-(*tert*-butoxycarbonylamino)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]carbamate (**Preparation 14**)

(4-bromo-6-*tert*-butoxycarbonylamino-pyridin-2-yl)-carbamicacid *tert*-butyl ester (prepared following procedure described in *J. Org. Chem.* **2004**, 69, 543-548) (10 g, 25.27 mmol), bis(pinacolato)diboron (1.5 eq), Pd(OAc)₂ (0.05 eq), 1,1'-bis(diphenylphosphino)ferrocene (0.05 eq) and KOAc (3 eq) were dissolved in 1,4-dioxane (160 mL) under N₂ at room temperature. The reaction mixture was stirred at 80 °C overnight under N₂. The reaction mixture was cooled to room temperature, filtered through celite and washed with warm 1,4-dioxane. Solvent was removed *in vacuo*. The residue was purified via flash chromatography using EtOAc and DCM as eluent to give the product (7.099 g, 16.3 mmol, 63%) as an off-white solid.

¹H NMR (399 MHz, CDCl₃) δ 8.16 (brs, 2H), 7.92 (s, 2H), 1.54 (s, 18H), 1.34 (s, 12H).

Step 6: 4-(1,3-benzodioxol-5-yl)-5-(2,6-diaminopyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidine-2-carbonitrile

The procedure described in **Preparation 3** was applied starting from the compound obtained in Step 4 (0.183 g, 0.386 mmol) and the compound obtained in Step 5 (1.1 eq).

The crude reaction mixture was concentrated *in vacuo* and the residue dissolved in DCM (2mL) and TFA (1.5 mL) following procedure described in **Preparation 7**, the desired product (8.4 mg, 0.022 mmol, 6%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 13.07 (s, 1H), 8.02 (s, 1H), 7.09 – 6.97 (m, 2H), 6.79 (d, 1H), 6.04 (s, 2H), 5.32 (s, 2H), 5.21 (s, 4H).

LC/MS (method B): RT = 0.92 min; *m/z* = 372 [M+H]⁺

Examples 147-158 in the following **Table 3** were prepared by methods outlined in **General Procedure VII-X** using appropriate commercially available boronate esters and amines. The compounds of **Example 148, 153, 157, 158** are also included.

Table 3: HRMS (TOF, ESI) data

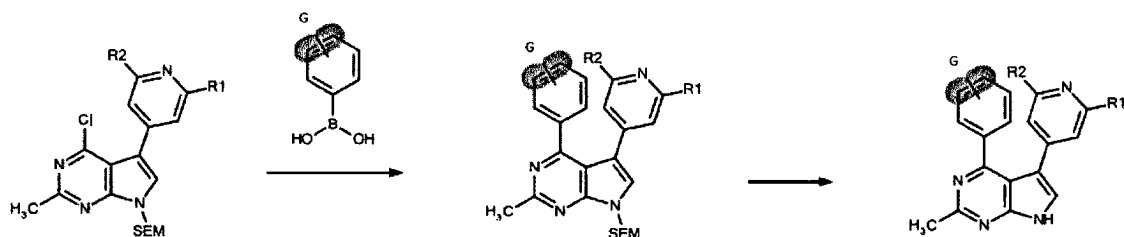
Example	Structure	Mol Formula	Calcd Exact Mass	Found m/z	Adduct
147	5-(2-aminopyridin-4-yl)-2-cyclopropyl- <i>N</i> -(2,6-difluorobenzyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₁₈ F ₂ N ₆	392.1561	391.1494	[M - H] ⁺
148	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-ethynyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₄ F ₂ N ₆	376.1248	375.1193	[M - H] ⁺
149	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-(prop-1-en-2-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₁₈ F ₂ N ₆	392.1561	391.1479	[M - H] ⁺
150	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-(propan-2-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₁ H ₂₀ F ₂ N ₆	394.1718	393.1650	[M - H] ⁺
151	5-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-ethenyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₂₀ H ₁₆ F ₂ N ₆	378.1405	377.1342	[M - H] ⁺

152	5-(2-aminopyridin-4-yl)-2-(cyclopropylethynyl)-N-(2,6-difluorobenzyl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C23 H18 F2 N6	416.1561	417.1618	[M - H] ⁺
153	4-[4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C23 H17 N5 O2	395.1382	396.1383	[M - H] ⁺
154	4-[4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C23 H18 N6 O2	410.1491	411.1546	[M - H] ⁺
155	4-[4-(1,3-benzodioxol-5-yl)-2-ethynyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C20 H14 N6 O2	370.1178	371.1182	[M - H] ⁺
156	4-[4-(1,3-benzodioxol-5-yl)-2-ethynyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H13 N5 O2	355.1069	356.1108	[M - H] ⁺

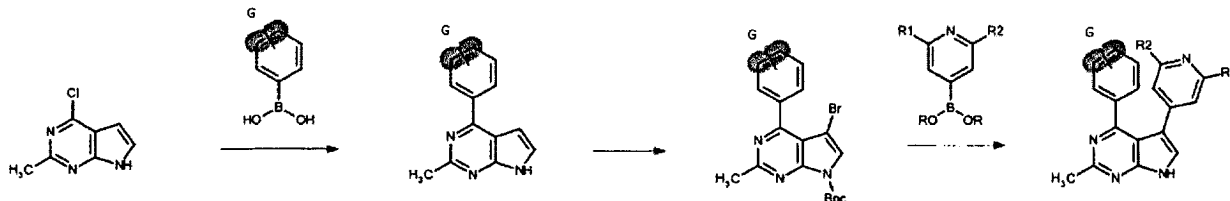
157	5-(2-aminopyridin-4-yl)-4-[(2,6-difluorobenzyl)amino]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidine-2-carbonitrile	C ₁₉ H ₁₃ F ₂ N ₇	377.1200	378.1242	[M - H] ⁺
158	4-(1,3-benzodioxol-5-yl)-5-(2,6-diaminopyridin-4-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidine-2-carbonitrile	C ₁₉ H ₁₃ N ₇ O ₂	371.1131	370.1036	[M - H] ⁻

Example 150 was prepared from **Example 149** using method described in **Preparation 5**.

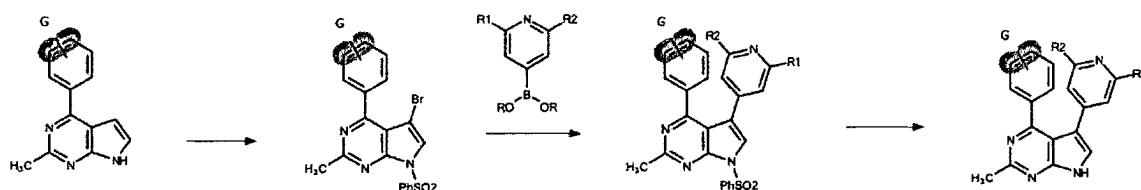
General Procedure XI



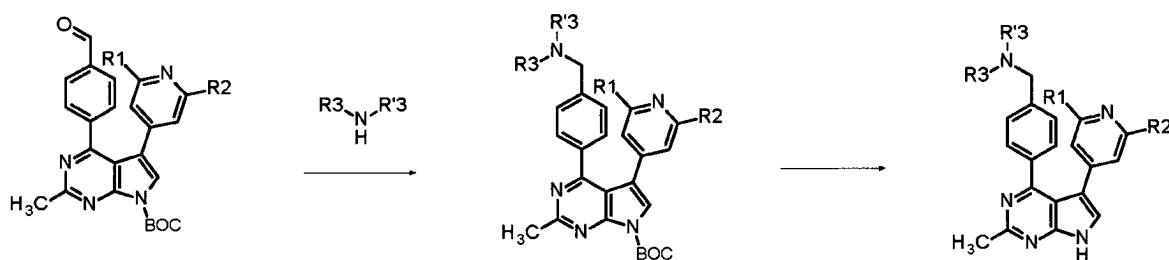
General Procedure XII



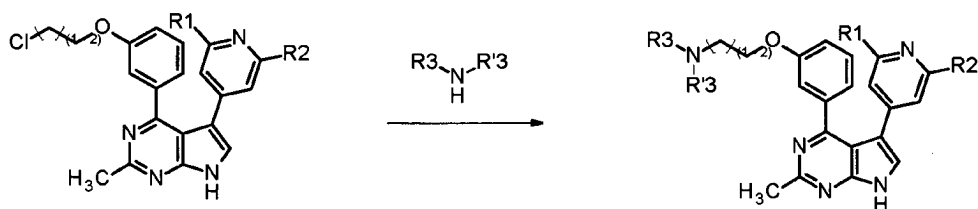
General Procedure XIII



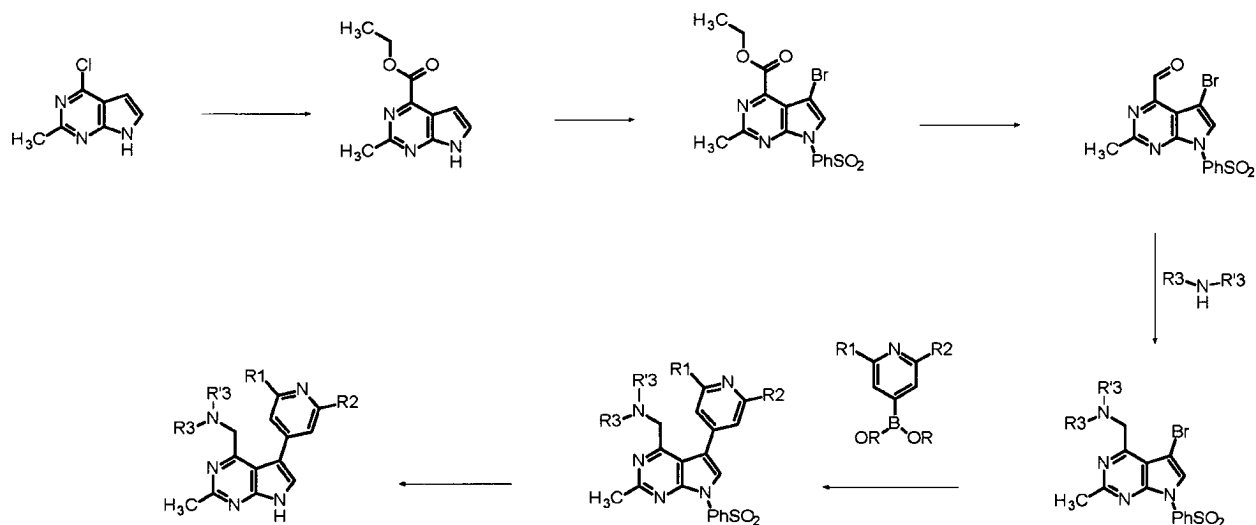
General Procedure XIV



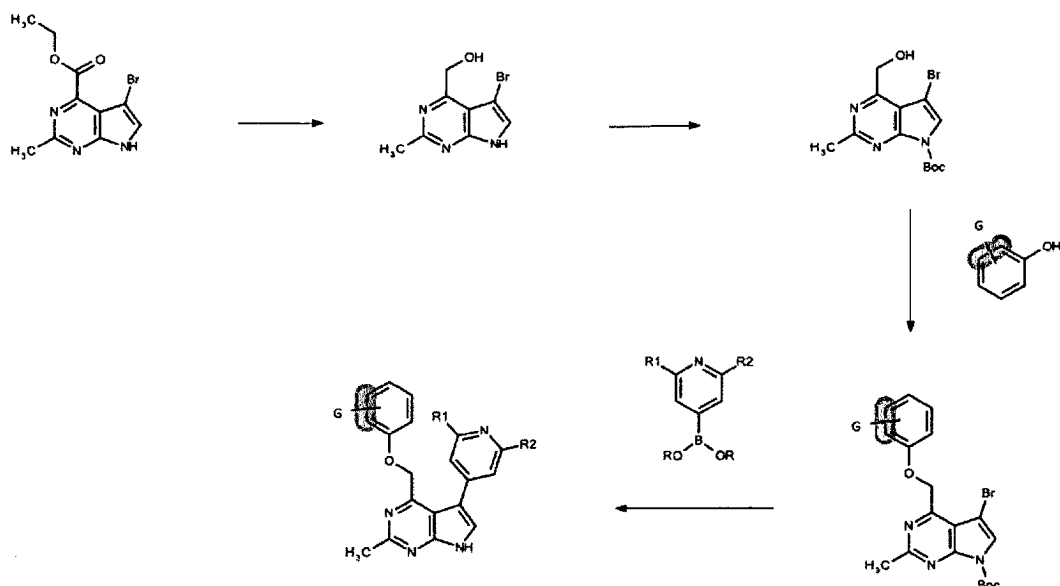
General Procedure XV



General Procedure XVI



General Procedure XVII



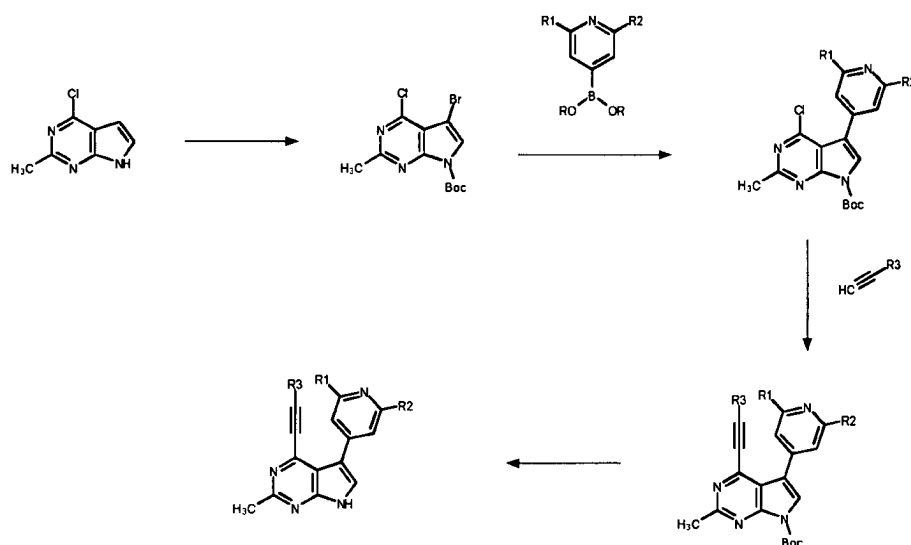
In General Procedures XI to XVII:

- R_1 and R_2 are as defined in formula (I),

- 5 - R_3 represents a hydrogen atom, a linear or branched (C_1-C_6) alkyl group, $-(C_0-C_6)$ alkylene- Cy_1 , $-(C_0-C_6)$ alkylene- Cy_1-Cy_2 , $-(C_0-C_6)$ alkylene- $Cy_1-O-(C_1-C_6)$ alkylene- Cy_2 , it being understood that Cy_1 and Cy_2 , independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group, and R'_3 represents a hydrogen atom or a linear or branched (C_1-C_6) alkyl group,
- 10 or R_3 and R'_3 form with the nitrogen atom carrying them a heterocycloalkyl or an heteroaryl,

- G represents a group selected from the list of substituents defined in formula (I), it being understood that the phenyl may be substituted by from 1 to 4 independent G groups.

General Procedure XVIII



wherein R₃ represents a hydrogen, a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group.

Example 162: 4-[4-(3-fluoro-5-methoxyphenyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine

Step 1: tert-butyl N-{4-[4-(3-fluoro-5-methoxyphenyl)-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-yl}carbamate

Starting from *tert-butyl N*-[4-(4-chloro-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-yl]carbamate (prepared following the procedure described in **Example 20**, *Step 1* using *tert-butyl N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate) (100 mg, 0.2 mmol) and (3-fluoro-5-methoxyphenyl)boronic acid (1.1 eq) following procedure described in **Preparation 3**, the desired product (104 mg, 0.179 mmol, 88%) was obtained as an off-white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 9.69 (s, 1H), 8.15 (s, 1H), 8.06 (d, 1H), 7.52 (s, 1H), 6.94 – 6.79 (m, 2H), 6.72 (dd, 1H), 6.66 (dd, 1H), 5.77 (s, 2H), 3.70 (dd, 2H), 3.5 (s, 3H), 2.82 (s, 3H), 1.49 (s, 9H), 1.00 – 0.81 (m, 2H), 0.00 (s, 9H).

LC/MS (method B): RT = 1.66 min; *m/z* = 580 [M+H]⁺

Step 2: 4-[4-(3-fluoro-5-methoxyphenyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine (Preparation 15)

To a solution of the compound obtained in Step 1 (104 mg, 0.179 mmol) in DCM (2 mL) was added boron trifluoride diethyl etherate (2 eq) drop wise at 0 °C under N₂ and the reaction mixture was allowed to warm to room temperature over 4 hours. The reaction mixture was diluted with sat. aq. NaHCO₃ (20 mL) solution and DCM (20 mL). The organic layer was separated and concentrated *in vacuo*. The residue was dissolved in MeCN (2 mL), ammonium hydroxide solution (28% ammonia in water, 2 mL) was added and the mixture stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was triturated with diethyl ether to give the product (8.7 mg, 0.024 mmol, 14%) as a pale yellow powder.

¹H NMR (399 MHz, DMSO-d₆) δ 12.39 (s, 1H), 7.74 (s, 1H), 7.59 (d, 1H), 6.89 (ddd, 1H), 6.81 (dt, 1H), 6.66 (dd, 1H), 6.20 – 6.14 (m, 1H), 5.99 (dd, 1H), 5.68 (s, 2H), 3.51 (s, 3H), 2.72 (s, 3H).

LC/MS (method B): RT = 0.9 min; *m/z* = 350 [M+H]⁺

Example 164: 4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine

Step 1: 4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (Preparation 16)

4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (0.511 g, 3.05 mmol) and (2,2-difluoro-1,3-benzodioxol-5-yl)boronic acid (1.02 eq) were dissolved in THF/water (10:1, 10 mL) under N₂. Cesium carbonate (2 eq) and Pd(dppf)Cl₂ (10% wt) were added and the resulting mixture was degassed under N₂ for 5 minutes. The reaction mixture was heated at 140 °C on a CEM microwave reactor for 1 hour. The mixture was diluted with water (150 mL) and the resulting precipitated was collected by filtration to give the product (0.88 g, 3.04 mmol, 99%) as an off-white solid.

LC/MS (method B): RT = 1.27 min; *m/z* = 290 [M+H]⁺

Step 2: tert-butyl 5-bromo-4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (Preparation 17)

To a solution of the compound obtained in Step 1 (0.88 g, 3.04 mmol) in DMF (15 mL) was added NBS (1.1 eq) portion wise at 0 °C under N₂ and the reaction mixture was allowed to warm to room temperature over 2 hours (reaction monitored by LCMS). Di-*tert*-butyl dicarbonate (1.2 eq), DMAP (0.01 eq) and trimethylamine (2 eq) were added to the mixture and stirred overnight under N₂ at room temperature. The reaction mixture was diluted with water (50 mL) and EtOAc (50 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.681 g, 1.45 mmol, 48%) as a pale yellow oil.

¹H NMR (399 MHz, DMSO-d₆) δ 8.05 (s, 1H), 7.72 (d, 1H), 7.59 (d, 1H), 7.50 (dd, 1H), 2.75 (s, 3H), 1.64 (s, 9H).

LC/MS (method B): RT = 1.6 min; *m/z* = 470 [M+H]⁺

Step 3: 4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine (Preparation 18)

The compound obtained in Step 2 (0.681 g, 1.45 mmol) and *tert*-butyl N-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) were dissolved in THF/water (3:1, 20 ml) under N₂. Potassium carbonate (3 eq) and Pd(dtbpf)Cl₂ (10% wt) were added and the resulting mixture was degassed under N₂ for 5 minutes. The reaction mixture was heated at 65 °C overnight under N₂, cooled to room temperature and diluted with water (10 mL) and DCM (50 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the desired coupled compound. The compound was dissolved in 2 M HCl solution in MeOH (4 mL) and heated at 90 °C on a CEM microwave reactor for 1 hour. The reaction mixture was concentrated *in vacuo* and diluted with 10% IPA in DCM (20 ml), washed with sat. aq. NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent to give, after trituration with diethyl ether, the product (99 mg, 0.26 mmol, 26%) as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.39 (s, 1H), 7.74 (s, 1H), 7.58 (d, 1H), 7.36 (d, 1H), 7.27 (d, 1H), 7.19 (dd, 1H), 6.07 (t, 1H), 6.00 (dd, 1H), 5.68 (s, 2H), 2.72 (s, 3H).

LC/MS (method B): RT = 0.96 min; *m/z* = 382 [M+H]⁺

Example 168: 4-{2-methyl-4-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-2-amine

Step 1: 7-(benzenesulfonyl)-5-bromo-2-methyl-4-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine (Preparation 19)

To a solution of 2-methyl-4-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidine (prepared following the procedure described in **Example 164, Step 1** using 3-(trifluoromethyl)phenyl]boronic acid) (186 mg, 0.67 mmol) in DMF (5 mL) was added NBS (1.1 eq) at 0 °C under N₂ and the reaction was allowed to warm to room temperature over 2 hours. The reaction mixture was cooled to 0 °C, NaH (60% in mineral oil, 1.4 eq) was added and stirred for 5 minutes before adding benzenesulfonyl chloride (1.1 eq) under N₂. The reaction mixture was allowed to warm to room temperature overnight, diluted with water (20 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (201 mg) as a brown oil. Purity estimated around 70% by LCMS. The compound was used without further purification.

LC/MS (method B): RT = 1.57 min; *m/z* = 496 [M+H]⁺

Step 2: 4-[7-(benzenesulfonyl)-2-methyl-4-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine

Starting from the compound obtained in Step 1 (201 mg) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**, the desired product (106 mg, 0.177 mmol, 26% over two steps) was obtained as a yellow oil.

LC/MS (method B): RT = 1.22 min; *m/z* = 510 [M+H]⁺

Step 3: 4-{2-methyl-4-[3-(trifluoromethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-2-amine (Preparation 20)

To a solution of the compound obtained in Step 2 (106 mg, 0.177 mmol) in MeOH (5 mL) was added K₂CO₃ (5 eq) and the resulting suspension was stirred at room temperature

overnight. The suspension was filtered, concentrated *in vacuo* and the residue was purified via flash chromatography using MeOH and DCM as eluent to give the product (10 mg, 0.027 mmol, 15%) as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.42 (s, 1H), 7.87 – 7.79 (m, 1H), 7.74 (d, 2H), 7.56 (s, 2H), 7.61 – 7.47 (m, 1H), 6.17 – 6.11 (m, 1H), 5.90 (dd, 1H), 5.64 (s, 2H), 2.74 (s, 3H).

LC/MS (method B): RT = 0.94 min; *m/z* = 370 [M+H]⁺

Example 169: 4-(2-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine

*Step 1: tert-butyl 5-(2-{[(tert-butoxy)carbonyl]amino}pyridin-4-yl)-2-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-7H-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (Preparation 21)*

To a solution of *tert*-butyl 5-(2-{[(*tert*-butoxy)carbonyl]amino}pyridin-4-yl)-4-(4-formylphenyl)-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (prepared following the procedure described in **Example 164** using (4-formylphenyl)boronic acid) (200 mg, 0.38 mmol) in MeOH (5 mL) was added 1-methylpiperazine (2 eq) followed by sodium cyanoborohydride (1.5 eq) at room temperature under N₂. The reaction mixture was stirred overnight. Then, it was diluted with sat aq. NaHCO₃ solution (10 mL) and DCM (10 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent to give the product (86 mg, 0.14 mmol, 37%) as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 9.67 (s, 1H), 8.02 – 7.93 (m, 2H), 7.34 (s, 1H), 7.23 (d, 2H), 7.06 (d, 2H), 6.75 (dd, 1H), 3.44 (s, 2H), 2.78 (s, 3H), 2.5 – 2.2 (m, 8H), 2.18 (s, 3H), 1.67 (s, 9H), 1.44 (s, 9H).

LC/MS (method B): RT = 1.26 min; *m/z* = 614 [M+H]⁺

*Step 2: 4-(2-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine (Preparation 22)*

The compound obtained in Step 1 (86 mg, 0.14 mmol) was dissolved in 2 M HCl in MeOH solution (4 mL) and heated at 80 °C on a CEM microwave reactor for 1 hour. The mixture

was concentrated *in vacuo* and the residue was triturated with diethyl ether to give the product (58 mg, 0.119 mmol) as an HCl salt.

¹H NMR (399 MHz, DMSO-d₆) δ 13.71 (brs, 1H), 13.23 (brs, 1H), 11.91 (brs, 1H), 8.25 (d, 1H), 7.77 (m, 4H), 7.56 (d, 2H), 6.48 (dd, 1H), 6.39 (d, 1H), 4.7 – 3.2 (m, 13H), 2.81 (s, 3H).

LC/MS (method B): RT = 0.7 min; *m/z* = 414 [M+H]⁺

Example 174: 4-(2-methyl-4-{3-[3-(morpholin-4-yl)propoxy]phenyl}-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine (*Preparation 23*)

To a solution of 4-{4-[3-(3-chloropropoxy)phenyl]-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine (prepared following the procedure described in **Example 168** using 2-[3-(3-chloropropoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*US2007/0004675*)) (50 mg, 0.13 mmol) in MeCN (2 mL) was added NaI (4 eq), K₂CO₃ (6 eq) and morpholine (4 eq). The reaction mixture was heated at 150 °C on a CEM microwave reactor for 30 minutes. The reaction mixture was diluted with 10% MeOH in DCM (5 mL), filtered through a phase separator column and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent to give, after trituration with MeCN, the product (30 mg, 0.067 mmol, 53%) as an off-white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.33 (s, 1H), 7.70 (s, 1H), 7.51 (d, 1H), 7.21 (t, 1H), 7.12 (dt, 1H), 6.95 – 6.87 (m, 1H), 6.85 – 6.79 (m, 1H), 6.19 (d, 1H), 5.91 (dd, 1H), 5.63 (s, 2H), 3.67 (t, 2H), 3.55 (t, 4H), 2.71 (s, 3H), 2.36 (s, 6H), 1.81 – 1.72 (m, 2H).

LC/MS (method B): RT = 0.617 min; *m/z* = 445 [M+H]⁺

Example 178: 4-[4-(2,3-dihydro-1H-indol-1-ylmethyl)-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine

*Step 1: ethyl 2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine-4-carboxylate (Preparation 24)*

4-chloro-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine (4 g, 23.87 mmol), sodium acetate (2 eq), Pd(OAc)₂ (0.07 eq) and 1,1'-bis(diphenylphosphino)ferrocene (0.07 eq) in ethanol (140 mL) were combined in a Parr reaction bottle under N₂. The system was purged three times with carbon monoxide and pressurized to 28 psi. The reactor was warmed to 70 °C and

shaken overnight in a Parr shaker hydrogenator apparatus. The reactor was cooled to room temperature, carbon monoxide removed by vacuum and the reaction mixture was filtered through a plug of celite. The filtrate was concentrated *in vacuo* and the residue was triturated with water and diethyl ether to give the product (3.811 g, 18.58 mmol, 78%) as a pale brown solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.24 (s, 1H), 7.69 (d, 1H), 6.81 (d, 1H), 4.43 (q, 2H), 2.71 (s, 3H), 1.39 (t, 3H).

LC/MS (method B): RT = 0.92 min; *m/z* = 206 [M+H]⁺

Step 2: ethyl 7-(benzenesulfonyl)-5-bromo-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-4-carboxylate

Starting from the compound obtained in Step 1 (1.83 g, 3.8 mmol) following procedure described in **Preparation 19**, the desired product (1.63 g, 3.8 mmol, 60%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.36 (s, 1H), 8.25 – 8.17 (m, 2H), 7.85 – 7.74 (m, 1H), 7.74 – 7.64 (m, 2H), 4.44 (q, 2H), 2.75 (s, 3H), 1.34 (t, 3H).

LC/MS (method B): RT = 1.41 min; *m/z* = 423 [M+H]⁺

Step 3: 7-(benzenesulfonyl)-5-bromo-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde (Preparation 25)

To a solution of the compound obtained in Step 2 (0.5 g, 1.18 mmol) in THF (13 mL) was added DIBAL (1M in THF solution, 3 eq) at -78 °C under N₂. The reaction mixture was stirred at the same temperature for 1 hour and allowed to warm to room temperature over 2 hours. Cooled to -78 °C, the mixture was quenched with water (1 mL) and 2N NaOH solution (0.5 mL) and allowed to warm to room temperature. MgSO₄ was added to the mixture, filtered through a plug of celite and concentrated *in vacuo* to give the product (1.2 g, >100%). The compound was used without further purification.

LC/MS (method B): RT = 1.31 min; *m/z* = 413, [M+H]⁺ not found

Step 4: 1-{[7-(benzenesulfonyl)-5-bromo-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]methyl}-2,3-dihydro-1H-indole

Starting from the compound obtained in Step 3 (1.2 g) and indoline (1.2 eq) following procedure described in **Preparation 21**, the desired product (0.193 g, 0.399 mmol, 34% over two steps) was obtained as a white solid.

LC/MS (method B): RT = 1.57 min; m/z = 482 $[M+H]^+$

5 *Step 5: 4-[7-(benzenesulfonyl)-4-(2,3-dihydro-1H-indol-1-ylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine*

Starting from the compound obtained in Step 4 (0.193 g, 0.399 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.133 g, 0.267 mmol, 67%)
10 was obtained as a white solid.

^1H NMR (399 MHz, DMSO- d_6) δ 8.28 – 8.20 (m, 2H), 7.96 – 7.88 (m, 2H), 7.83 – 7.74 (m, 1H), 7.75 – 7.64 (m, 2H), 6.93 (dd, 1H), 6.79 (td, 1H), 6.70 (dd, 1H), 6.56 (dd, 1H), 6.50 (td, 1H), 6.09 – 5.99 (m, 3H), 4.36 (s, 2H), 3.03 (t, 2H), 2.69 (d, 5H).

LC/MS (method B): RT = 1.16 min; m/z = 497 $[M+H]^+$

15 *Step 6: 4-[4-(2,3-dihydro-1H-indol-1-ylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridin-2-amine*

Starting from the compound obtained in Step 5 (0.133 g, 0.267 mmol) following procedure described in **Preparation 20**, the product (41 mg, 0.114 mmol, 43%) was obtained as an off-white solid.

20 ^1H NMR (399 MHz, DMSO- d_6) δ 12.18 (d, 1H), 7.89 (d, 1H), 7.54 (d, 1H), 6.94 (dd, 1H), 6.81 (td, 1H), 6.65 (dd, 1H), 6.57 – 6.45 (m, 2H), 6.17 (d, 1H), 5.92 (s, 2H), 4.45 (s, 2H), 3.10 (t, 2H), 2.71 (t, 2H), 2.64 (s, 3H).

LC/MS (method B): RT = 0.89 min; m/z = 357 $[M+H]^+$

25 **Example 193: 4-(2-methyl-4-{[2-(trifluoromethyl)phenoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)pyridin-2-amine**

Step 1: {5-bromo-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl}methanol (Preparation 26)

To a solution of ethyl 5-bromo-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-4-carboxylate (prepared following the procedure described in **Example 153**, Step 4 starting from ethyl

2-methyl-7H-pyrrolo[2,3-d]pyrimidine-4-carboxylate (**Preparation 24**) (0.500 g, 1.76 mmol) in THF (10 mL) was added LiBH₄ (2 eq) portion wise at 0 °C under N₂. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with sat. aq. NaHCO₃ (10 mL) solution and EtOAc (10 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent to give the product (0.237 g, 0.98 mmol, 56%) as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.29 (s, 1H), 7.67 (s, 1H), 5.23 (t, 1H), 4.96 (d, 2H), 2.65 (s, 3H).

LC/MS (method B): RT = 0.51 min; *m/z* = 243 [M+H]⁺

Step 2: tert-butyl 5-bromo-4-(hydroxymethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate

To a solution of the compound obtained in Step 1 (0.237 g, 0.98 mmol) was added di-tert-butyl dicarbonate (1.2 eq), DMAP (0.01 eq) and trimethylamine (2 eq) following procedure described in **Preparation 17**. The desired product (0.345 g, >100%) was obtained as a white solid. Purity estimated around 70% by LC-MS. The compound was used without further purification.

LC/MS (method B): RT = 1.23 min; *m/z* = 342 [M+H]⁺

Step 3: tert-butyl 5-bromo-2-methyl-4-([2-(trifluoromethyl)phenoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate

Starting from the compound obtained in Step 2 (0.345 g) and 2-(trifluoromethyl)phenol (1.1 eq) following procedure described in **Preparation 6**, the desired product (0.63 g, >100%) was obtained as a yellow oil. Purity estimated around 45% by LC-MS. The compound was used without further purification.

LC/MS (method B): RT = 1.58 min; *m/z* = 485 [M+H]⁺

Step 4: tert-butyl 5-(2-([(tert-butoxy)carbonyl]amino)pyridin-4-yl)-2-methyl-4-([2-(trifluoromethyl)phenoxy]methyl)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate

Starting from the compound obtained in Step 3 (0.63 g) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following

procedure described in **Preparation 18**, the desired product (62 mg, 0.155 mmol) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.34 (s, 1H), 7.67 (s, 1H), 7.62 – 7.53 (m, 3H), 7.22 (d, 1H), 7.09 (t, 1H), 6.63 (dd, 1H), 6.51 (t, 1H), 5.75 (d, 2H), 5.31 (s, 2H), 2.66 (s, 3H).

5 LC/MS (method B): RT = 0.99 min; *m/z* = 400 [M+H]⁺

Example 198: 4-[4-(cyclopropylethynyl)-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine

*Step 1: tert-butyl 5-bromo-4-chloro-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate*

Starting from 4-chloro-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine (10.53 g, 59.67 mmol) following procedure described in **Preparation 17**, the product (14.43 g, 41.63 mmol, 93%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.11 (s, 1H), 2.69 (s, 3H), 1.62 (s, 9H).

*Step 2: tert-butyl 5-(2-{{(tert-butoxy)carbonyl}amino}pyridin-4-yl)-4-chloro-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate*

15 Starting from the compound obtained in Step 1 (1 g, 2.89 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**, the desired product (1.059 g, 2.3 mmol, 80%) was obtained as a pale yellow solid.

20 ¹H NMR (399 MHz, DMSO-d₆) δ 9.89 (s, 1H), 8.31 (dd, 1H), 8.02 (s, 1H), 7.97 (t, 1H), 7.20 (dd, 1H), 2.71 (s, 3H), 1.64 (s, 9H), 1.48 (s, 9H).

LC/MS (method B): RT = 1.49 min; *m/z* = 460 [M+H]⁺

*Step 3: tert-butyl 5-(2-{{(tert-butoxy)carbonyl}amino}pyridin-4-yl)-4-(cyclopropylethynyl)-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (Preparation 27)*

25 To a solution of the compound obtained in Step 2 (100 mg, 0.22 mmol) in Et₃N (4 ml) and THF (1 mL) was added ethynylcyclopropane (3 eq) and CuI (0.3 eq) at room temperature. The solution was purged with N₂ for 5 minutes before adding Pd(PPh₃)₂Cl₂ (0.3 eq) and the reaction mixture was stirred at 80 °C for 5 hours on a CEM microwave reactor. The reaction mixture cooled to room temperature and concentrated *in vacuo*. The residue was

purified via flash chromatography using MeOH and DCM as eluent to give the product (70 mg, 0.143 mmol, 66%) as a white solid.

LC/MS (method B): RT = 1.51 min; m/z = 490 $[M+H]^+$

Step 4: 4-[4-(cyclopropylethynyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyridine-2-amine

Starting from the compound obtained in Step 3 (70 mg, 0.143 mmol) following procedure described in **Preparation 7**, the desired product (32 mg, 0.11 mmol, 77%) was obtained as a white solid.

^1H NMR (399 MHz, DMSO- d_6) δ 12.27 (s, 1H), 7.91 (d, 1H), 7.67 (d, 1H), 6.67 (dd, 1H), 6.59 (t, 1H), 5.91 (s, 2H), 2.60 (s, 3H), 1.50 (tt, 1H), 0.85 (m, 2H), 0.66 (m, 2H).

LC/MS (method B): RT = 0.76 min; m/z = 290 $[M+H]^+$

Examples 159-204 in the following **Table 4** were prepared by methods outlined in **General Procedure XI-XVIII** using appropriate commercially available boronate ester, alcohol, amines and ethynyl. The compounds of **Example 162, 164, 168, 169, 174, 178, 193, 198** are also included.

Table 4: HRMS (TOF, ESI) data

Example	Structure	Mol Formula	Calcd Exact Mass	Found m/z	Adduct
159	4-{2-methyl-4-[(E)-2-phenylethenyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-2-amine	C ₂₀ H ₁₇ N ₅	327.1484	328.1564	$[M - H]^+$

160	4-[2-methyl-4-(2-phenylethyl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H19 N5	329.1640	328.1574	[M - H] ⁻
161	4-[4-(1 <i>H</i> -indol-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H16 N6	340.1436	341.1519	[M - H] ⁺
162	4-[4-(3-fluoro-5-methoxyphenyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C19 H16 F N5 O	349.1339	348.1269	[M - H] ⁻
163	4-(2-methyl-4-phenyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C18 H15 N5	301.1327	302.1396	[M - H] ⁺
164	4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C19 H13 F2 N5 O2	381.1037	380.0972	[M - H] ⁻

165	4-{2-methyl-4-[4-(pyrrolidin-1-ylmethyl)phenyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₂₃ H ₂₄ N ₆	384.2062	385.2135	[M - H] ⁺
166	4-{4-[(2,6-difluorophenoxy)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₉ H ₁₅ F ₂ N ₅ O	367.1245	366.1172	[M - H] ⁻
167	4-[4-(3-methoxyphenyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₉ H ₁₇ N ₅ O	331.1433	330.1369	[M - H] ⁻
168	4-{2-methyl-4-[3-(trifluoromethyl)phenyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₉ H ₁₄ F ₃ N ₅	369.1201	368.1140	[M - H] ⁻
169	4-(2-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C ₂₄ H ₂₇ N ₇	413.2328	412.2268	[M - H] ⁻

170	4-[4-(5-fluoropyridin-3-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C17 H13 F N6	320.1186	319.1112	[M - H] ⁻
171	4-{2-methyl-4-[3-(pyrrolidin-1-yl)phenyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C22 H22 N6	370.1906	369.1839	[M - H] ⁻
172	4-[4-(4-ethoxyphenyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H19 N5 O	345.1590	346.1656	[M + H] ⁺
173	4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H17 N5 O2	359.1382	360.1440	[M + H] ⁺
174	4-(2-methyl-4-{3-[3-(morpholin-4-yl)propoxy]phenyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C25 H28 N6 O2	444.2274	445.2250	[M + H] ⁺

175	4-[5-(2-aminopyridin-4-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-yl]-2-fluorobenzonitrile	C ₁₉ H ₁₃ F N ₆	344.1186	343.1119	[M + H] ⁺
176	4-{4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₇ H ₁₈ F ₂ N ₆	344.1561	343.1486	[M + H] ⁺
177	4-{4-[(3,3-difluoropiperidin-1-yl)methyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₈ H ₂₀ F ₂ N ₆	358.1718	357.1622	[M + H] ⁺
178	4-[4-(2,3-dihydro-1 <i>H</i> -indol-1-ylmethyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₂₁ H ₂₀ N ₆	356.1749	355.1683	[M + H] ⁺
179	4-[4-(1,3-benzodioxol-5-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₉ H ₁₅ N ₅ O ₂	345.1226	344.1127	[M + H] ⁺

180	4-[4-(3,5-difluorophenyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₁₈ H ₁₃ F ₂ N ₅	337.1139	336.1057	[M + H] ⁺
181	4-{2-methyl-4-[3-(trifluoromethoxy)phenyl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₁₉ H ₁₄ F ₃ N ₅ O	385.1150	384.1086	[M + H] ⁺
182	4-[4-(1-benzothiophen-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₂₀ H ₁₅ N ₅ S	357.1048	356.0969	[M + H] ⁺
183	4-[4-(1-benzofuran-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₂₀ H ₁₅ N ₅ O	341.1277	340.1217	[M + H] ⁺
184	4-[2-methyl-4-(5-methyl-1-benzothiophen-2-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C ₂₁ H ₁₇ N ₅ S	371.1205	372.1210	[M + H] ⁺

185	4-[4-(7-chloro-1-benzothiophen-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C20 H14 Cl N5 S	391.0658	392.0712	[M + H] ⁺
186	4-[2-methyl-4-(1-methyl-1 <i>H</i> -indol-2-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C21 H18 N6	354.1593	353.1534	[M + H] ⁺
187	4-[4-(3,4-dihydronaphthalen-2-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C22 H19 N5	353.1640	352.1583	[M + H] ⁺
188	4-[2-methyl-4-(1,2,3,4-tetrahydronaphthalen-2-yl)-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C22 H21 N5	355.1797	354.1732	[M + H] ⁺
189	4-{2-methyl-4-[(2 <i>S</i>)-1,2,3,4-tetrahydronaphthalen-2-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C22 H21 N5	355.1797	354.1716	[M + H] ⁺

190	4-{2-methyl-4-[(2 <i>R</i>)-1,2,3,4-tetrahydronaphthalen-2-yl]-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C22 H21 N5	355.1797	354.1728	[M + H] ⁺
191	4-[4-(7-fluoro-1,3-benzodioxol-5-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C19 H14 F N5 O2	363.1132	362.1022	[M + H] ⁺
192	4-[4-(1,3-benzodioxol-5-yl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C19 H16 N6 O2	360.1335	361.1420	[M + H] ⁺
193	4-(2-methyl-4-{[2-(trifluoromethyl)phenoxy]methyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C20 H16 F3 N5 O	399.1307	398.1246	[M + H] ⁺
194	4-{4-[(2-fluorophenyl)ethynyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C20 H14 F N5	343.1233	342.1116	[M + H] ⁺

195	4-[2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C22 H21 N5	355.1797	356.1805	[M + H] ⁺
196	4-[4-(cyclopropylethynyl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridine-2,6-diamine	C17 H16 N6	304.1436	305.1458	[M + H] ⁺
197	4-{4-[(2-methoxyphenyl)ethynyl]-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C21 H17 N5 O	355.1433	356.1442	[M + H] ⁺
198	4-[4-(cyclopropylethynyl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyridin-2-amine	C17 H15 N5	289.1327	288.1228	[M + H] ⁺
199	4-(2-methyl-4-{3-[3-(piperidin-1-yl)propoxy]phenyl}-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C26 H30 N6 O	442.2481	443.2474	[M + H] ⁺

200	4-(2-methyl-4-{3-[3-(4-methylpiperazin-1-yl)propoxy]phenyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C ₂₆ H ₃₁ N ₇ O	457.2590	456.2477	[M + H] ⁺
201	4-{4-[3-(2-chloroethoxy)phenyl]-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-2-amine	C ₂₀ H ₁₈ Cl N ₅ O	379.1200	378.1140	[M + H] ⁺
202	4-(2-methyl-4-{3-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C ₂₄ H ₂₆ N ₆ O	414.2168	415.2165	[M + H] ⁺
203	4-(4-{3-[2-(dimethylamino)ethoxy]phenyl}-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C ₂₂ H ₂₄ N ₆ O	388.2012	389.1996	[M + H] ⁺
204	4-(2-methyl-4-{3-[2-(morpholin-4-yl)ethoxy]phenyl}-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)pyridin-2-amine	C ₂₄ H ₂₆ N ₆ O ₂	430.2117	431.2096	[M + H] ⁺

Example 160 was prepared from **Example 159** using method described in **Preparation 5**.

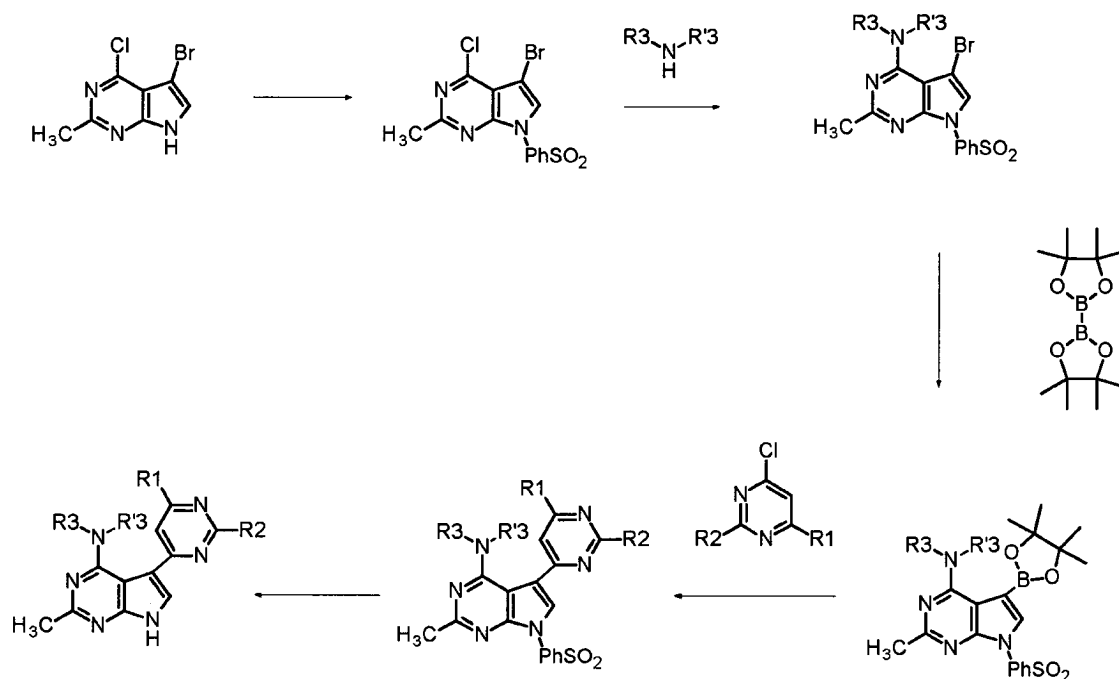
Example 188 was prepared from **Example 187** using method described in **Preparation 5**.

Example 189 and 190 were prepared from **Example 188** by preparative HPLC with a

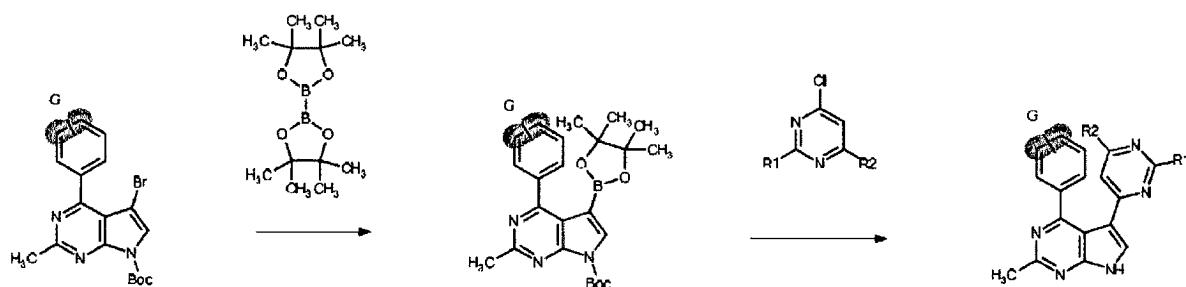
5 chiral stationary phase. **Example 191** was prepared from 2-(7-fluoro-1,3-benzodioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane prepared from

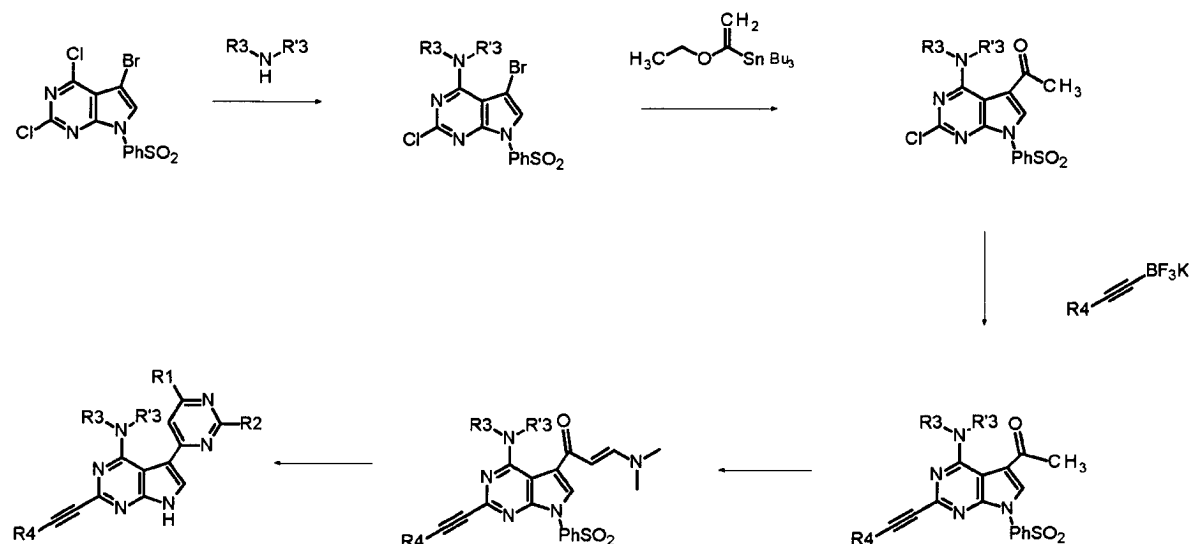
6-bromo-4-fluoro-1,3-benzodioxole following the procedure described in **Preparation 14**.
 ^1H NMR (399 MHz, Chloroform- d) δ 7.18 (d, 1H), 7.08 (s, 1H), 6.05 (s, 2H), 1.35 (s, 12H).

General Procedure XIX



General Procedure XX



General Procedure XXI**In General Procedures XIX, XX and XXI:**

- R_1 and R_2 are as defined in formula (I),

- R_3 represents a hydrogen atom, a linear or branched (C_1-C_6) alkyl group, $-(C_0-C_6)$ alkylene- Cy_1 , $-(C_0-C_6)$ alkylene- Cy_1-Cy_2 , $-(C_0-C_6)$ alkylene- $Cy_1-O-(C_1-C_6)$ alkylene- Cy_2 , it being understood that Cy_1 and Cy_2 , independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group,

and R'_3 represents a hydrogen atom or a linear or branched (C_1-C_6) alkyl group,

or R_3 and R'_3 form with the nitrogen atom carrying them a heterocycloalkyl or an heteroaryl,

- R_4 represents a hydrogen atom, a linear or branched (C_1-C_6) alkyl group or a cycloalkyl group,

- G represents a group selected from the list of substituents defined in formula (I), it being understood that the phenyl may be substituted by from 1 to 4 independent G groups.

Example 206: 5-(2-aminopyrimidin-4-yl)-N-(2,6-difluorobenzyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Step 1: 7-(benzenesulfonyl)-5-bromo-4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine

Starting from 4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (1 g, 4.06 mmol) following procedure described in **Preparation 19**, the desired product (1.264 g, 3.27 mmol, 81%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.31 (s, 1H), 8.24 – 8.16 (m, 2H), 7.85 – 7.78 (m, 1H), 7.73 – 7.65 (m, 2H), 2.69 (s, 3H).

LC/MS (method B): RT = 1.46 min; *m/z* = 387 [M+H]⁺

Step 2: 7-(benzenesulfonyl)-5-bromo-N-[(2,6-difluorophenyl)methyl]-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 1 (1.2 g, 3.10 mmol) and (2,6-difluorophenyl)methanamine (2 eq) following procedure described in **Preparation 8**, the desired product (1.410 g, 2.86 mmol, 92%) was obtained as a white solid.

LC/MS (method B): RT = 1.52 min; *m/z* = 493 [M+H]⁺

Step 3: 7-(benzenesulfonyl)-N-[(2,6-difluorophenyl)methyl]-2-methyl-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (Preparation 28)

To a solution of the compound obtained in Step 2 (1 g, 2.03 mmol) in THF (5 mL) was added bis(pinacolato)diboron (1.2 eq), KOAc (3 eq) and PdCl₂(PPh₃)₂ (10% wt). The resulting mixture was degassed under N₂ for 5 minutes before heated at 140 °C on a CEM microwave reactor for 1 hour. The reaction mixture was filtered through a plug of celite, washed with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and conc. *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the desired product (0.675 g, 1.25 mmol, 62%) as a white solid.

LC/MS (method B): RT = 1.63 min; *m/z* = 541 [M+H]⁺

Step 4: 5-(2-aminopyrimidin-4-yl)-N-(2,6-difluorobenzyl)-2-methyl-7-(benzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 3 (0.915 g, 1.69 mmol) and 4-chloropyrimidin-2-amine (1.5 eq) following procedure described in **Preparation 3**, the product (0.551 g, 1.08 mmol, 64%) was obtained as a pale brown solid.

¹H NMR (399 MHz, DMSO-d₆) δ 10.79 (t, 1H), 8.44 (s, 1H), 8.29 (d, 1H), 8.20 – 8.13 (m, 2H), 7.80 (m, 1H), 7.65 (t, 2H), 7.40 – 7.24 (m, 2H), 7.01 (t, 2H), 6.70 (s, 2H), 4.90 (d, 2H), 2.38 (s, 3H).

LC/MS (method B): RT = 1.41 min; *m/z* = 508 [M+H]⁺

Step 5: 5-(2-aminopyrimidin-4-yl)-N-(2,6-difluorobenzyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 4 (0.551 g, 1.08 mmol) following procedure described in **Preparation 20**, the desired product (0.159 g, 0.432 mmol, 40%) was obtained as a pale orange solid.

¹H NMR (399 MHz, DMSO-d₆) δ 11.97 (s, 1H), 10.63 (s, 1H), 8.14 (d, 1H), 8.04 (s, 1H), 7.33 (m, 1H), 7.12 (d, 1H), 7.06 (q, 2H), 6.35 (s, 2H), 4.91 (d, 2H), 2.36 (s, 3H).

LC/MS (method B): RT = 0.96 min; *m/z* = 368 [M+H]⁺

Example 208: *5-(2-aminopyrimidin-4-yl)-N-(1,3-benzodioxol-4-ylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine*

Step 1: 7-(benzenesulfonyl)-5-bromo-4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine

Starting from 4-chloro-2-methyl-7H-pyrrolo[2,3-d]pyrimidine (1 g, 4.06 mmol) following procedure described in **Preparation 19**, the desired product (1.264 g, 3.27 mmol, 81%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.31 (s, 1H), 8.24 – 8.16 (m, 2H), 7.85 – 7.78 (m, 1H), 7.73 – 7.65 (m, 2H), 2.69 (s, 3H).

LC/MS (method B): RT = 1.46 min; *m/z* = 387 [M+H]⁺

Step 2: 7-(benzenesulfonyl)-N-(1,3-benzodioxol-4-ylmethyl)-5-bromo-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 1 (0.5 g, 1.29 mmol) and 1,3-benzodioxol-4-ylmethanamine (2 eq) following procedure described in **Preparation 8**, the desired product (0.562 g, 1.12 mmol, 87%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.19 – 8.11 (m, 2H), 7.82 – 7.72 (m, 2H), 7.66 (dd, 2H), 7.10 (t, 1H), 6.86 – 6.71 (m, 3H), 6.03 (s, 2H), 4.69 (d, 2H), 2.41 (s, 3H).

LC/MS (method B): RT = 1.52 min; m/z = 501 [M+H]⁺

Step 3: 7-(benzenesulfonyl)-N-(1,3-benzodioxol-4-ylmethyl)-2-methyl-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (**Preparation 28**)

To a solution of the compound obtained in Step 2 (0.25 g, 0.5 mmol) in THF (5 mL) was added bis(pinacolato)diboron (1.2 eq), KOAc (3 eq) and PdCl₂(PPh₃)₂ (10% wt). The resulting mixture was degassed under N₂ for 5 minutes before heated at 140 °C on a CEM microwave reactor for 1 hour. The reaction mixture was filtered through a plug of celite, washed with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.227 g, 0.414 mmol, 83%) as a white solid.

LC/MS (method B): RT = 1.61 min; m/z = 549 [M+H]⁺

Step 4: 4-[7-(benzenesulfonyl)-4-[(1,3-benzodioxol-4-ylmethyl)amino]-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyrimidin-2-amine

Starting from the compound obtained in Step 3 (227 mg, 0.414 mmol) and 4-chloropyrimidin-2-amine (1.5 eq) following procedure described in **Preparation 3**, the desired product (85 mg, 0.165 mmol, 40%) was obtained as a pale brow solid.

¹H NMR (399 MHz, DMSO-d₆) δ 9.54 (s, 2H), 8.26 – 8.17 (m, 2H), 7.82 – 7.72 (m, 1H), 7.72 – 7.64 (m, 3H), 7.54 (s, 2H), 6.80 – 6.63 (m, 3H), 6.51 (t, 1H), 5.93 (s, 2H), 4.60 (d, 2H), 2.44 (s, 3H).

LC/MS (method B): RT = 1.44 min; m/z = 549 [M+H]⁺

Step 5: 5-(2-aminopyrimidin-4-yl)-N-(1,3-benzodioxol-4-ylmethyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine

Starting from the compound obtained in Step 4 (85 mg, 0.165 mmol) following procedure described in **Preparation 20**, the desired product (25 mg, 0.066 mmol, 40%) was obtained as a pale orange solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.00 (s, 1H), 10.55 (t, 1H), 8.14 (d, 1H), 8.06 (d, 1H), 7.13 (d, 1H), 6.91 – 6.72 (m, 3H), 6.22 (s, 2H), 6.03 (s, 2H), 4.81 (d, 2H), 2.37 (s, 3H).

LC/MS (method B): RT = 0.935 min; m/z = 376 [M+H]⁺

Example 210: 4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyrimidin-2-amine

Step 1: *tert*-butyl 4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate

Starting from *tert*-butyl 5-bromo-4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (see **Example 164**, Step 2) (240 mg, 0.51 mmol) following procedure described in **Preparation 28**, the desired product (75 mg, 0.145 mmol, 28%) was obtained as a white solid.

LC/MS (method B): RT = 1.62 min; m/z = 516 [M+H]⁺

Step 2: 4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyrimidin-2-amine

Starting from the compound obtained in Step 1 (75 mg, 0.145 mmol) and 4-chloropyrimidin-2-amine (1.5 eq) following procedure described in **Preparation 18**, the desired product (7 mg, 0.018 mmol, 13%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.52 (s, 1H), 8.01 – 7.92 (m, 2H), 7.40 (d, 1H), 7.32 (m, 1H), 7.22 (dd, 1H), 6.21 (d, 1H), 6.10 (s, 2H), 2.72 (s, 3H).

LC/MS (method B): RT = 1.02 min; m/z = 383 [M+H]⁺

Example 211: 4-[4-(3,4-dihydroisoquinolin-2(1H)-yl)-2-ethynyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyrimidin-2-amine

Step 1: 2-[7-(benzenesulfonyl)-5-bromo-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,2,3,4-tetrahydroisoquinoline

Starting from 7-(benzenesulfonyl)-5-bromo-2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (prepared following procedure described in WO2007/042299) (0.875 g, 2.15 mmol) and 1,2,3,4-tetrahydroisoquinoline (2.5 eq) following procedure described in **Preparation 8**, the desired product (1.044 g) was obtained as a pale yellow solid (purity around 80% by LC-MS). The compound was used without further purification.

LC/MS (method B): RT = 1.69 min; m/z = 505 [M+H]

Step 2: 1-[7-(benzenesulfonyl)-2-chloro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]ethan-1-one (**Preparation 29**)

The compound obtained in Step 1 (0.52 g, 1.03 mmol), LiCl (2.5 eq), tetrakis(triphenylphosphine)palladium (0.1 eq) and tributyl(1-ethoxyvinyl)tin (1.2 eq) were dissolved in 1,4-dioxane (10 mL) under N₂ at room temperature. The reaction mixture was stirred at 100 °C overnight under N₂. The reaction mixture was cooled to room temperature, 2N HCl (5 mL) solution was added and the reaction mixture stirred for 1 hour. The reaction mixture was diluted with sat. aq. NaHCO₃ (20 mL) solution and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (0.448 g). Purity around 70% by LC-MS. The compound was used without further purification.

LC/MS (method B): RT = 1.55 min; m/z = 467 [M+H]⁺

Step 3: Potassium *tert*-butyldimethyl[2-(trifluoroboranyl)ethynyl]silane (**Preparation 30**)

To a solution of *tert*-butyldimethyl[2-(tetramethyl-1,3,2-dioxaborolan-2-yl)ethynyl]silane (0.973 g, 3.65 mmol) in acetone (15 mL) was added a solution of potassium bifluoride (4 eq) in water (5 mL) at 0 °C and the suspension was allowed to warm to room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was triturated

with warm acetone to give the product (0.705 g, 2.86 mmol) as a white solid which was used without further purification.

¹H NMR (399 MHz, DMSO-d₆) δ 0.89 (s, 9H), 0.00 (s, 6H).

Step 4: 1-[7-(benzenesulfonyl)-2-[2-(*tert*-butyldimethylsilyl)ethynyl]-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]ethan-1-one

Starting from the compound obtained in Step 2 (0.400 g, 0.86 mmol) and potassium *tert*-butyldimethyl[2-(trifluoroboranyl)ethynyl]silane (1.78 eq) following procedure described in **Preparation 10**, the desired product (0.220 g, 0.35 mmol, 45%) was obtained as yellow oil.

LC/MS (method B): RT = 1.75 min; *m/z* = 571 [M+H]⁺

Step 5: 1-[7-(benzenesulfonyl)-2-[2-(*tert*-butyldimethylsilyl)ethynyl]-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-3-(dimethylamino)prop-2-en-1-one (**Preparation 31**)

To a solution of the compound obtained in Step 4 (0.220 g, 0.35 mmol) in DMF (5 mL) was added *N,N*-dimethylformamide dimethyl acetal (6 eq) at room temperature under N₂. The reaction mixture was stirred at 90 °C for 3 hours. The mixture was cooled to room temperature, diluted with water (20 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using EtOAc and isohexane as eluent to give the product (84 mg, 0.134 mmol, 35%) as a yellow oil.

LC/MS (method B): RT = 1.69 min; *m/z* = 626 [M+H]⁺

Step 6: 4-[4-(3,4-dihydroisoquinolin-2(1H)-yl)-2-ethynyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]pyrimidin-2-amine (**Preparation 32**)

To a solution of the compound obtained in Step 5 (84 mg, 0.134 mmol) in THF (3 mL) was added TBAF (1M in THF solution, 1.1 eq) at 0 °C under N₂. The reaction mixture was allowed to warm to room temperature over 1 hour. The mixture was diluted with DCM (10 mL), washed with sat. aq. NaHCO₃ solution, dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in butan-1-ol (3 mL), guanidine carbonate (1.5 eq) and sodium methoxide (4 eq) were added and the reaction mixture was stirred at 130 °C on a CEM

microwave reactor for 30 minutes. The mixture was poured into water (10 mL) and DCM (10 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel, eluting with 10% MeOH in DCM followed by preparative HPLC at pH = 4 to afford the product (1.4 mg, 0.004 mmol, 3%) as a yellow solid.

¹H NMR (399 MHz, DMSO-*d*₆) δ 12.39 (s, 1H), 8.13 (d, 1H), 7.77 (s, 1H), 7.18 – 7.06 (m, 3H), 7.02 – 6.94 (m, 1H), 6.75 (d, 1H), 6.54 (s, 2H), 4.56 (s, 2H), 4.05 (s, 1H), 3.64 (t, 2H), 2.76 (t, 2H).

LC/MS (method B): RT = 1.13 min; *m/z* = 368 [M+H]⁺

Examples 205-212 in the following **Table 5** were prepared by methods outlined in **General Procedure XIX, XXI** using appropriate commercially available boronate ester, amines and ethynyl. The compounds of **Example 208, 210, 211** are also included.

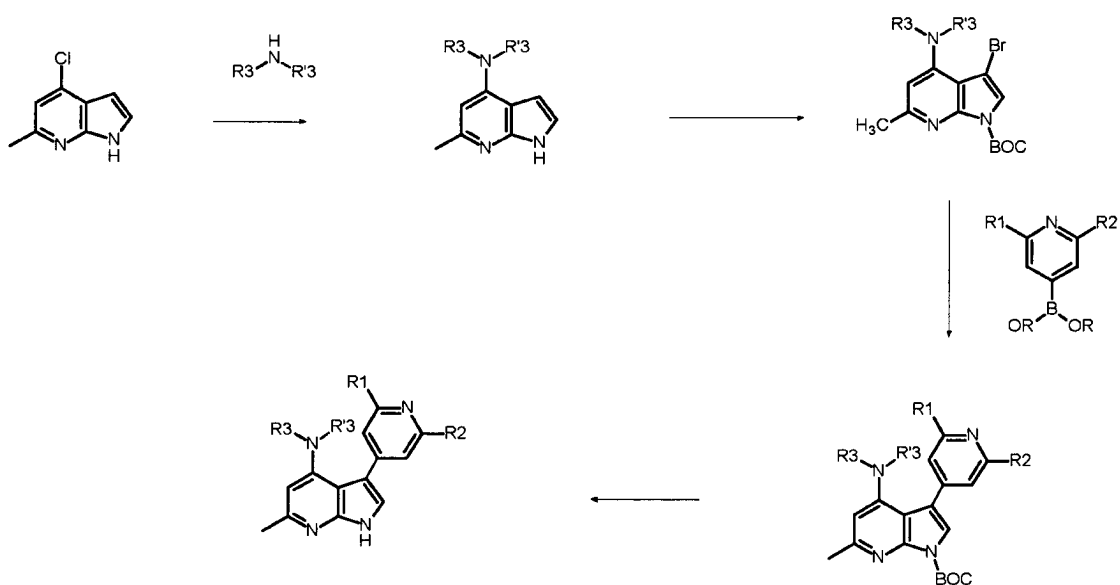
Table 5: HRMS (TOF, ESI) data

Example	Structure	Mol Formula	Calcd Exact Mass	Found <i>m/z</i>	Adduct
205	5-(2-amino-6-methylpyrimidin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₇ F ₂ N ₇	381.1513	382.1569	[M + H] ⁺
206	5-(2-aminopyrimidin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₅ F ₂ N ₇	367.1357	368.1413	[M + H] ⁺

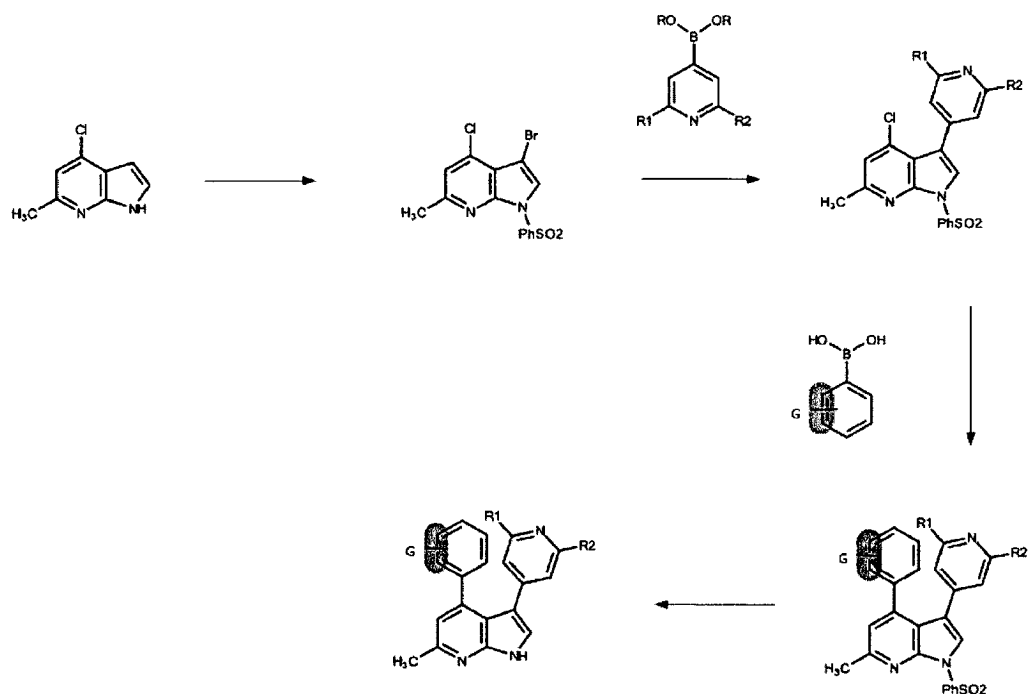
207	4-[4-(1-benzothiophen-2-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyrimidin-2-amine	C ₁₉ H ₁₄ N ₆ S	358.1001	359.1020	[M + H] ⁺
208	5-(2-aminopyrimidin-4-yl)- <i>N</i> -(1,3-benzodioxol-4-ylmethyl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₉ H ₁₇ N ₇ O ₂	375.1444	374.1375	[M + H] ⁺
209	4-[4-(1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyrimidin-2-amine	C ₁₈ H ₁₄ N ₆ O ₂	346.1178	347.1190	[M + H] ⁺
210	4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyrimidin-2-amine	C ₁₈ H ₁₂ F ₂ N ₆ O ₂	382.0990	381.0912	[M + H] ⁺
211	4-[4-(3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2-ethynyl-7H-pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]pyrimidin-2-amine	C ₂₁ H ₁₇ N ₇	367.1545	366.1442	[M + H] ⁺

212	5-(6-aminopyrimidin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-2-methyl-7 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-4-amine	C ₁₈ H ₁₅ F ₂ N ₇	367.1357	368.1376	[M + H] ⁺
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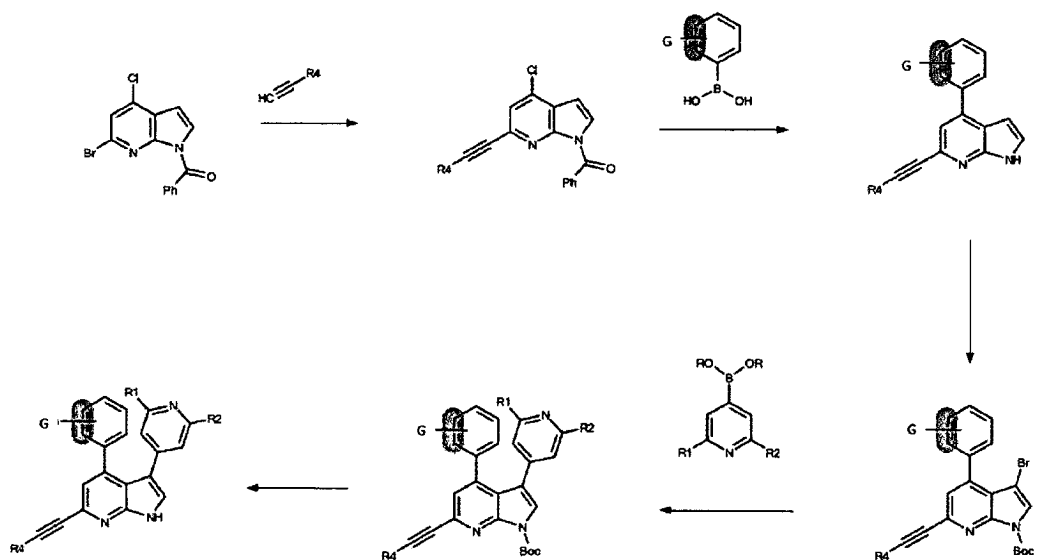
General Procedure XXII

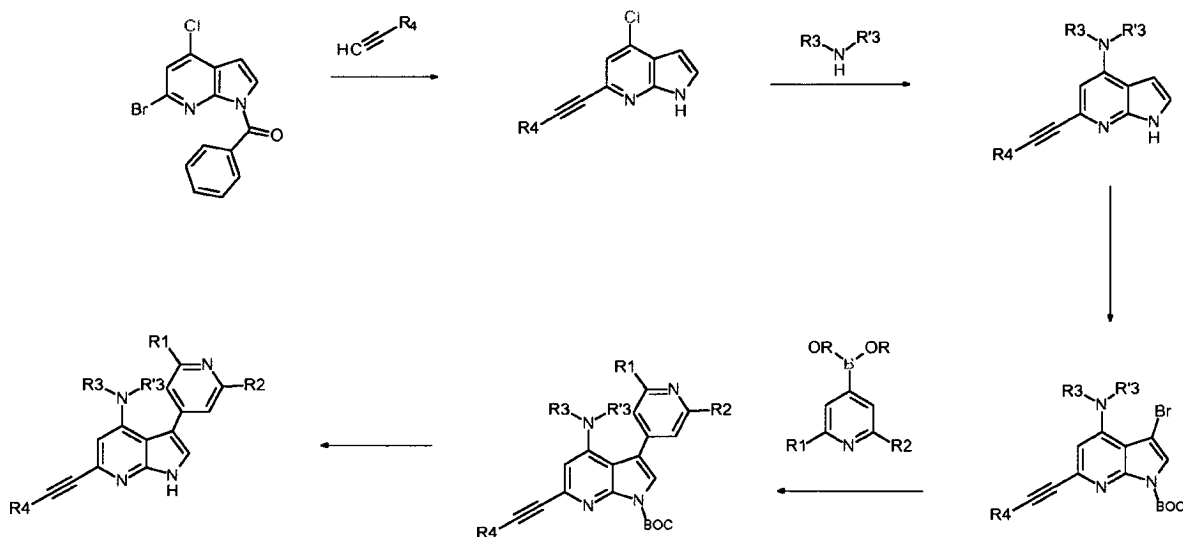
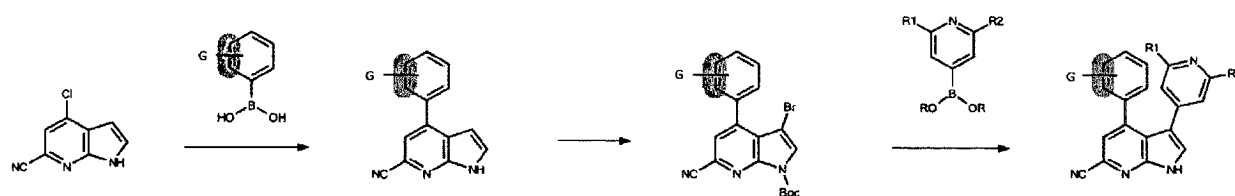


General Procedure XXIII



General Procedure XXIV



General Procedure XXV**General procedure XXVI****In General Procedures XXII to XXIV:**

- R_1 and R_2 are as defined in formula (I),

- R_3 represents a hydrogen atom, a linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group, $-(\text{C}_0\text{-C}_6)\text{alkylene-Cy}_1$, $-(\text{C}_0\text{-C}_6)\text{alkylene-Cy}_1\text{-Cy}_2$, $-(\text{C}_0\text{-C}_6)\text{alkylene-Cy}_1\text{-O-(C}_1\text{-C}_6)\text{alkylene-Cy}_2$, it being understood that Cy_1 and Cy_2 , independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or an heteroaryl group,

and R'_3 represents a hydrogen atom or a linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group,

or R_3 and R'_3 form with the nitrogen atom carrying them a heterocycloalkyl or an heteroaryl,

- R_4 represents a hydrogen atom, a linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group or a cycloalkyl group,

- G represents a group selected from the list of substituents defined in formula (I), it being understood that the phenyl may be substituted by from 1 to 4 independent G groups.

Example 213: 3-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-4-amine

5 **Step 1: N-[(2,6-difluorophenyl)methyl]-6-methyl-1H-pyrrolo[2,3-b]pyridin-4-amine (Preparation 33)**

To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine (0.5 g, 3 mmol) in MeCN (15 mL) was added 2,6-difluorobenzylamine (2 eq) and pTSA.H₂O (2 eq) under N₂ at room temperature. The reaction mixture was heated at 150 °C in a CEM microwave reactor
10 for 4 hours. The mixture was diluted with sat. aq. NaHCO₃ (20 mL) solution and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent to give the product (0.521 g, 1.90 mmol, 63%) as yellow solid.

¹H NMR (399 MHz, DMSO-d₆) δ 10.96 (s, 1H), 7.43 (tt, 1H), 7.20 – 7.08 (m, 2H), 6.95
15 (d, 1H), 6.77 (t, 1H), 6.53 (d, 1H), 6.15 (s, 1H), 4.44 (d, 2H), 2.35 (s, 3H).

LC/MS (method A): RT = 1.82 min; *m/z* = 274 [M+H]⁺

Step 2: tert-butyl 3-bromo-4-[(2,6-difluorophenyl)methyl]amino}-6-methyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

Starting from the compound obtained in Step 1 (0.415 g, 1.51 mmol) following procedure
20 described in **Preparation 17**, the desired product (0.280 g, 0.61 mmol, 40%) was obtained as a solid.

¹H NMR (399 MHz, Chloroform-d) δ 7.36 (s, 1H), 7.33 – 7.23 (m, 1H), 6.95 (t, 2H), 6.46 (s, 1H), 6.20 (d, 1H), 4.57 (d, 2H), 2.59 (s, 3H), 1.65 (s, 10H).

LC/MS (method A): RT = 2.53 min; *m/z* = 452 [M+H]⁺

25 **Step 3: tert-butyl 3-(2-aminopyridin-4-yl)-4-[(2,6-difluorophenyl)methyl]amino}-6-methyl-1H-pyrrolo[2,3-b]pyridine-1-carboxylate**

Starting from the compound obtained in Step 2 (0.280 g, 0.61 mmol) and *tert*-butyl N-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.4 eq) following

procedure described in **Preparation 3**, the desired product (0.154 g, 0.33 mmol, 53%) was obtained as an off-white solid.

LC/MS (method B): RT = 0.99 min; m/z = 466 $[M+H]^+$

5 *Step 4: 3-(2-aminopyridin-4-yl)-N-(2,6-difluorobenzyl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-4-amine*

Starting from the compound obtained in Step 3 (0.154 g, 0.33 mmol) following procedure described in **Preparation 7**, the product (0.110 g, 0.30 mmol, 91%) was obtained as a white solid.

10 ^1H NMR (399 MHz, DMSO- d_6) δ 11.43 (s, 1H), 7.85 (d, 1H), 7.42 (tt, 1H), 7.20 – 7.07 (m, 3H), 6.51 – 6.43 (m, 2H), 6.29 (s, 1H), 5.89 (s, 2H), 5.23 (t, 1H), 4.49 (d, 2H), 2.39 (s, 3H).

LC/MS (method A): RT = 1.58 min; m/z 366 $[M+H]^+$

Example 214: 4-[4-(5-fluoropyridin-3-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]pyridin-2-amine

15 *Step 1: 1-(benzenesulfonyl)-3-bromo-4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine*

Starting from 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine (0.713 g, 4.27 mmol) following procedure described in **Preparation 19**, the desired product (0.493 g, 1.28 mmol, 30%) was obtained as a white solid.

20 ^1H NMR (399 MHz, DMSO- d_6) δ 8.21 – 8.13 (m, 3H), 7.81 – 7.72 (m, 1H), 7.70 – 7.62 (m, 2H), 7.41 (s, 1H), 2.56 (s, 3H).

LC/MS (method B): RT = 1.52 min; m/z = 386 $[M+H]^+$

Step 2: 4-[1-(benzenesulfonyl)-4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]pyridin-2-amine

25 Starting from the compound obtained in Step 1 (0.493 g, 1.28 mmol) and 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (1.4 eq) following procedure described in **Preparation 3**, the desired product (0.200 g, 0.501 mmol, 39%) was obtained as a pale yellow solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.27 – 8.17 (m, 2H), 8.00 – 7.91 (m, 2H), 7.81 – 7.63 (m, 3H), 7.38 (s, 1H), 6.64 (dd, 1H), 6.57 (d, 1H), 5.99 (s, 2H), 2.57 (s, 3H).

LC/MS (method B): RT = 1.13 min; *m/z* = 399 [M+H]⁺

Step 3: 4-[1-(benzenesulfonyl)-4-(5-fluoropyridin-3-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]pyridin-2-amine

Starting from the compound obtained in Step 2 (0.133 g, 0.33 mmol) and (5-fluoropyridin-3-yl)boronic acid (1.1 eq) following procedure described in **Preparation 3**, the product (97 mg, 0.211 mmol, 63%) was obtained as a pale brown solid.

¹H NMR (399 MHz, DMSO-d₆) δ 8.48 (d, 1H), 8.31 – 8.23 (m, 2H), 8.19 (t, 1H), 7.97 (s, 1H), 7.82 – 7.73 (m, 1H), 7.73 – 7.63 (m, 2H), 7.62 – 7.44 (m, 4H), 7.33 (s, 1H), 6.16 (m, 1H), 5.89 (dd, 1H), 5.77 (s, 2H), 2.65 (s, 3H).

LC/MS (method B): RT = 1.1 min; *m/z* = 460 [M+H]⁺

Step 4: 4-[4-(5-fluoropyridin-3-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl]pyridin-2-amine

Starting from the compound obtained in Step 3 (97 mg, 0.211 mmol) following procedure described in **Preparation 20**, the desired product (20 mg, 0.06 mmol, 30%) was obtained as a white solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.06 (s, 1H), 8.49 (d, 1H), 8.26 (d, 1H), 7.63 (s, 1H), 7.56 – 7.46 (m, 2H), 7.10 (s, 1H), 6.08 (d, 1H), 5.87 (dd, 1H), 5.62 (s, 2H), 2.61 (s, 3H).

LC/MS (method A): RT = 1.67 min; *m/z* = 320 [M+H]⁺

Example 215: 4-[6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]pyridin-2-amine

Step 1: 1-benzoyl-4-chloro-6-(cyclopropylethynyl)-1H-pyrrolo[2,3-b]pyridine

Starting from 1-benzoyl-6-bromo-4-chloro-1H-pyrrolo[2,3-b]pyridine (prepared following procedure described on WO2009/087225) (1.12 g, 3.72 mmol) and ethynylcyclopropane (3 eq) following procedure described in **Preparation 27**, the desired product (1.053 g, 3.28 mmol, 88%) was obtained as a pale brown solid.

LC/MS (method B): RT = 1.52 min; *m/z* = 321 [M+H]⁺

Step 2: 6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-pyrrolo[2,3-b]pyridine

Starting from the compound obtained in Step 1 (0.5 g, 1.56 mmol) and (2,3-dihydro-1,4-benzodioxin-6-yl)boronic acid (1.2 eq) following procedure described in **Preparation 3**, the desired product (0.234 g, 0.74 mmol, 47%) was obtained as a brown solid.

LC/MS (method B): RT = 1.35 min; m/z = 316 $[M+H]^+$

Step 3: tert-butyl 3-bromo-6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

Starting from the compound obtained in Step 2 (0.234 g, 0.74 mmol) following procedure described in **Preparation 17**, the desired product (0.326 g, 0.658 mmol, 89%) was obtained as a pale yellow solid.

LC/MS (method B): RT = 1.7 min; m/z = 497 $[M+H]^+$

Step 4: tert-butyl 3-(2-((tert-butoxy)carbonyl)amino)pyridin-4-yl)-6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

Starting from the compound obtained in Step 3 (0.326 g, 0.658 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.211 g, 0.347 mmol, 53%) was obtained as a pale yellow solid.

LC/MS (method A): RT = 3.05 min; m/z = 609 $[M+H]^+$

Step 5: 4-[6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-pyrrolo[2,3-b]pyridin-3-yl]pyridin-2-amine

Starting from the compound obtained in Step 4 (0.211 g, 0.347 mmol) following procedure described in **Preparation 7**, the desired product (54 mg, 0.132 mmol, 38%) was obtained as a white solid.

^1H NMR (399 MHz, DMSO- d_6) δ 12.08 (s, 1H), 7.72 (s, 1H), 7.50 (d, 1H), 7.07 (s, 1H), 6.73 – 6.60 (m, 3H), 6.05 (m, 1H), 5.89 (dd, 1H), 5.52 (s, 2H), 4.20 (ddd, 4H), 1.60 (tt, 1H), 0.98 – 0.87 (m, 2H), 0.87 – 0.76 (m, 2H).

LC/MS (method A): RT = 2.16; m/z = 409 $[M+H]^+$

Example 216: 3-(2-aminopyridin-4-yl)-6-(cyclopropylethynyl)-N-(2,6-difluorobenzyl)-1H-pyrrolo[2,3-b]pyridin-4-amine

Step 1: 4-chloro-6-(cyclopropylethynyl)-1H-pyrrolo[2,3-b]pyridine (Preparation 34)

5 To a solution of 1-benzoyl-6-bromo-4-chloro-1H-pyrrolo[2,3-b]pyridine (prepared following procedure described in WO2009/087225) (1.52 g, 4.54 mmol) in Et₃N (15 ml) and THF (3 mL) was added ethynylcyclopropane (3 eq) and CuI (0.3 eq) at room temperature. The solution was purged with N₂ for 5 minutes before adding Pd(PPh₃)₂Cl₂ (0.3 eq) and the reaction mixture was stirred at room temperature overnight. Water (1 mL)
10 was added to the reaction mixture and heated at 80 °C on CEM microwave reactor for 1 hour. The mixture was diluted with water (20 mL) and DCM (20 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent followed by trituration with isohexane to give the product (0.652 g, 3 mmol, 66%) as an off-white
15 solid.

¹H NMR (399 MHz, DMSO-d₆) δ 12.04 (s, 1H), 7.65 (d, 1H), 7.24 (s, 1H), 6.50 (d, 1H), 1.59 (tt, 1H), 1.01 – 0.85 (m, 2H), 0.89 – 0.72 (m, 2H).

LC/MS (method B): RT = 1.31 min; m/z = 217 $[M+H]^+$

Step 2: 6-(cyclopropylethynyl)-N-[(2,6-difluorophenyl)methyl]-1H-pyrrolo[2,3-b]pyridin-4-amine (Preparation 35)

20 The compound obtained in Step 1 (0.3 g, 1.38 mmol), 2,6-difluorobenzylamine (1.2 eq), BrettPhos (0.01 eq) and BrettPhos precatalyst (0.01 eq) were added into a microwave vial. The vial was sealed with a teflon screw-cap, then evacuated and backfilled with N₂. LiHMDS (1M solution in THF, 2 eq) was added at room temperature under N₂. The
25 reaction mixture was heated at 65 °C in a CEM microwave reactor for 4 hours. The reaction mixture was quenched with 1N HCl (2 mL) solution and diluted with DCM (50 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified via flash chromatography using MeOH and DCM as eluent to give the product (0.429 g, 1.32 mmol, 96%) as a pale brown solid.

¹H NMR (399 MHz, DMSO-d₆) δ 11.13 (t, 1H), 7.43 (tt, 1H), 7.20 – 7.06 (m, 3H), 6.94 (t, 1H), 6.59 (dd, 1H), 6.33 (s, 1H), 4.44 (d, 2H), 1.53 (tt, 1H), 0.96 – 0.81 (m, 2H), 0.80 – 0.66 (m, 2H).

LC/MS (method B): RT = 1.12 min; *m/z* = 324 [M+H]⁺

5 *Step 3: tert-butyl 3-bromo-6-(cyclopropylethynyl)-4-[(2,6-difluorophenyl)methyl]amino}-1H-pyrrolo[2,3-b]pyridine-1-carboxylate*

Starting from the compound obtained in Step 2 (0.429 g, 1.32 mmol) following procedure described in **Preparation 17**, the desired product (0.463 g, 0.921 mmol, 69%) was obtained as an off-white solid.

10 ¹H NMR (399 MHz, Chloroform-d) δ 7.42 (s, 1H), 7.29 (m, 1H), 7.01 – 6.92 (m, 2H), 6.69 (s, 1H), 6.19 (t, 1H), 4.56 (d, 2H), 1.64 (s, 9H), 1.50 (m, 1H), 1.00 – 0.86 (m, 4H).

LC/MS (method B): RT = 1.61 min; *m/z* = 502 [M+H]⁺

Step 4: tert-butyl 3-(2-[(tert-butoxy)carbonyl]amino)pyridin-4-yl)-6-(cyclopropylethynyl)-4-[(2,6-difluorophenyl)methyl]amino}-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

15 Starting from the compound obtained in Step 3 (0.463 g, 0.921 mmol) and *tert*-butyl *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**, the desired product (0.233 g, 0.378 mmol, 41%) was obtained as a pale yellow solid.

20 ¹H NMR (399 MHz, Chloroform-d) δ 8.25 – 8.19 (m, 1H), 8.06 (d, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.27 – 7.21 (m, 1H), 7.02 (dd, 1H), 6.95 – 6.85 (m, 2H), 6.72 (s, 1H), 4.86 (t, 1H), 4.45 (d, 2H), 1.67 (s, 9H), 1.55 (s, 9H), 1.53 – 1.48 (m, 1H), 0.97 – 0.82 (m, 4H).

LC/MS (method B): RT = 1.64 min; *m/z* = 616 [M+H]⁺

Step 5: 3-(2-aminopyridin-4-yl)-6-(cyclopropylethynyl)-N-(2,6-difluorobenzyl)-1H-pyrrolo[2,3-b]pyridin-4-amine

25 Starting from the compound obtained in Step 4 (0.233 g, 0.378 mmol) following procedure described in **Preparation 7**, the desired product (88 mg, 0.211 mmol, 56%) was obtained as a white solid.

^1H NMR (399 MHz, DMSO- d_6) δ 11.61 (s, 1H), 7.85 (d, 1H), 7.48 – 7.36 (m, 1H), 7.32 (s, 1H), 7.14 (t, 2H), 6.50 – 6.42 (m, 3H), 5.91 (s, 2H), 5.31 (t, 1H), 4.48 (d, 2H), 1.56 (tt, 1H), 0.91 (m, 2H), 0.80 – 0.71 (m, 2H).

LC/MS (method B): RT = 1.09 min; m/z = 416 $[\text{M}+\text{H}]^+$

5 **Example 223: 3-(2-aminopyridin-4-yl)-4-(1,3-benzodioxol-5-yl)-1H-pyrrolo[2,3-*b*]pyridine-6-carbonitrile**

*Step 1: 4-(1,3-benzodioxol-5-yl)-1H-pyrrolo[2,3-*b*]pyridine-6-carbonitrile*

Starting from 4-chloro-1H-pyrrolo[2,3-*b*]pyridine-6-carbonitrile (prepared from *Synthesis*,
2008, (2), 201-204) (100 mg, 0.56 mmol) and (1,3-benzodioxol-5-yl)boronic acid (1.1 eq)
10 following procedure described in **Preparation 3**, the desired product (84 mg, 0.32 mmol, 57%) was obtained as a yellow solid.

^1H NMR (399 MHz, DMSO- d_6) δ 12.38 (s, 1H), 7.93 – 7.82 (m, 1H), 7.75 (s, 1H), 7.43 – 7.31 (m, 2H), 7.12 (d, 1H), 6.78 (dd, 1H), 6.14 (s, 2H).

LC/MS (method B): RT = 1.23 min; m/z = 264 $[\text{M}+\text{H}]^+$

15 *Step 2: tert-butyl 4-(1,3-benzodioxol-5-yl)-3-bromo-6-cyano-1H-pyrrolo[2,3-*b*]pyridine-1-carboxylate*

Starting from the compound obtained in Step 1 (0.289 g, 1.1 mmol) following procedure described in **Preparation 17**, the desired product (0.373 g, 0.84 mmol, 77%) was obtained as a yellow solid.

20 ^1H NMR (399 MHz, DMSO- d_6) δ 8.33 (s, 1H), 7.87 (s, 1H), 7.14 – 7.04 (m, 2H), 6.98 (dd, 1H), 6.14 (s, 2H), 1.64 (s, 9H).

*Step 3: 3-(2-aminopyridin-4-yl)-4-(1,3-benzodioxol-5-yl)-1H-pyrrolo[2,3-*b*]pyridine-6-carbonitrile*

Starting from the compound obtained in Step 2 (0.180 g, 0.41 mmol) and *tert*-butyl
25 *N*-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]carbamate (1.1 eq) following procedure described in **Preparation 3**. The crude reaction mixture was concentrated *in vacuo* and the residue dissolved in DCM (2mL) and TFA (1.5 mL) following procedure described in **Preparation 7**. The crude reaction mixture was concentrated *in vacuo* and the

residue was triturated with MeOH to give the product (49 mg, 0.137 mmol, 34%) as a TFA salt.

¹H NMR (399 MHz, DMSO-d₆) δ 13.10 (d, 2H), 8.38 (d, 1H), 7.79 (s, 1H), 7.67 (t, 3H), 6.98 (d, 1H), 6.85 (d, 1H), 6.71 (dd, 1H), 6.49 – 6.30 (m, 2H), 6.05 (s, 2H).

5 LC/MS (method B): RT = 0.97 min; *m/z* = 356 [M+H]⁺

Examples 213-225 in the following **Table 6** were prepared by methods outlined in **General Procedure XXII-XXVI** using appropriate commercially available boronate ester, amines and ethynyl. The compounds of Example **213**, **214**, **215**, **216**, **223** are also included.

Table 6: HRMS (TOF, ESI) data

Example	Structure	Mol Formula	Calcd Exact Mass	Found <i>m/z</i>	Adduct
213	3-(2-aminopyridin-4-yl)- <i>N</i> -(2,6-difluorobenzyl)-6-methyl-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-4-amine	C ₂₀ H ₁₇ F ₂ N ₅	365.1452	366.1514	[M + H] ⁺
214	4-[4-(5-fluoropyridin-3-yl)-6-methyl-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridin-2-amine	C ₁₈ H ₁₄ F N ₅	319.1233	320.1299	[M + H] ⁺
215	4-[6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridin-2-amine	C ₂₅ H ₂₀ N ₄ O ₂	408.1586	409.1618	[M + H] ⁺

216	3-(2-aminopyridin-4-yl)-6-(cyclopropylethynyl)- <i>N</i> -(2,6-difluorobenzyl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-4-amine	C ₂₄ H ₁₉ F ₂ N ₅	415.1609	416.1638	[M + H] ⁺
217	4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-methyl-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridin-2-amine	C ₂₁ H ₁₈ N ₄ O ₂	358.1430	359.1428	[M + H] ⁺
218	4-[4-(1,3-benzodioxol-5-yl)-6-(cyclopropylethynyl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridine-2,6-diamine	C ₂₄ H ₁₉ N ₅ O ₂	409.1539	410.1570	[M + H] ⁺
219	4-[4-(1,3-benzodioxol-5-yl)-6-(cyclopropylethynyl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridin-2-amine	C ₂₄ H ₁₈ N ₄ O ₂	394.1430	395.1430	[[M + H] ⁺
220	4-[4-(1,3-benzodioxol-5-yl)-6-ethynyl-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridin-2-amine	C ₂₁ H ₁₄ N ₄ O ₂	354.1117	355.1120	[M + H] ⁺

221	4-[4-(1,3-benzodioxol-5-yl)-6-ethynyl-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridine-2,6-diamine	C ₂₁ H ₁₅ N ₅ O ₂	369.1226	368.1146	[M + H] ⁺
222	4-[4-(1,3-benzodioxol-5-yl)-6-methyl-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridine-2-amine	C ₂₀ H ₁₆ N ₄ O ₂	344.1273	343.1191	[M + H] ⁺
223	3-(2-aminopyridin-4-yl)-4-(1,3-benzodioxol-5-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine-6-carbonitrile	C ₂₀ H ₁₃ N ₅ O ₂	355.1069	354.1014	[M + H] ⁺
224	4-(1,3-benzodioxol-5-yl)-3-(2,6-diaminopyridin-4-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridine-6-carbonitrile	C ₂₀ H ₁₄ N ₆ O ₂	370.1178	371.1170	[M + H] ⁺
225	4-[6-methyl-4-(4-methyl-3,4-dihydro-2 <i>H</i> -1,4-benzoxazin-6-yl)-1 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyridin-3-yl]pyridine-2-amine	C ₂₂ H ₂₁ N ₅ O	371.1746	372.1738	[M + H] ⁺

PHARMACOLOGICAL STUDY

EXAMPLE A: Kinase TR-FRET assays

Inhibition of the enzymatic activity of human kinases was evaluated in a Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) assay in 384-well reaction plates. In this assay, full-length human kinases from Carma Biosciences – DYRK1A (NM_001396, ref. 04-130; 2.0 ng/μl), DYRK1B (NM_004714, ref. 04-131; 1.2 ng/μl), CLK1 (NM_001162407, ref. 04-126; 0.7 ng/μl), CDK9 (NM_001261, ref. 04-110; 0.9 ng/μl), or GSK3β (NM_001146156, ref. 04-141; 2.0 ng/μl) – were incubated for 40 minutes (DYRK1A and DYRK1B) or 100 minutes (CLK1, CDK9 and GSK3β) at room temperature with ATP (Sigma A2383, 10 μM) and a *ULight*TM-labelled human Myelin Basic Protein (MBP) peptide substrate (Perkin Elmer TRF0109, 100 nM) in a reaction buffer composed of 50 mM HEPES pH7.4, 1 mM EGTA, 10 mM MgCl₂, 2 mM DTT and 0.01% Tween20. Test compounds of the invention were added in reaction buffer at a range of concentrations from 0.1 nM to 30 μM. Following addition of EDTA (Sigma E7889, 10 mM) to stop the reaction, Europium-labelled mouse monoclonal antibody recognizing phospho-Thr232 in MBP (Perkin Elmer TRF0201, 1 nM) was added. After one hour, the reaction plates were read using a fluorescence reader (EnVision®, Perkin Elmer) at 620nm and 665 nm (excitation at 340 nm): when the Europium donor fluorophore is excited by light at 340 nm, an energy transfer (620 nm) to the acceptor occurs, which will then emit light at 665 nm. The activity, and hence inhibition, of DYRK1A kinase activity is thus measured by the relative intensity of the emitted light. The IC₅₀ was calculated from the concentration-activity curve as the concentration of the test compound required for 50% inhibition of kinase activity. The results are presented in Table 1.

EXAMPLE B: Kinase ADP assays

The activity of His-TEV-DYRK1A Kinase domain (aa127-485) was measured using the accumulation of ADP produced during the phosphorylation of the peptide substrate Woodtide (Zinnsser Analytic) using ATP (Sigma Aldrich A7699). The enzyme reaction was conducted in assay buffer (pH 7.4), containing 15 mM Hepes; 20 mM NaCl; 1 mM EGTA; 10 mM MgCl₂; 0.02% Tween20 and 0.1 mg/ml Bovine-γ-globulin. Test compounds of the invention were added in reaction buffer in a range of concentrations for

10 minutes at 30°C in the presence of 20 nM DYRK1A enzyme, 40 µM peptide substrate and 20 µM ATP. Detection reagents (DiscoverX 90-0083), ADP Hunter Plus Reagent A and then ADP Hunter Plus Reagent B were added. After a following 20 minutes incubation at 30°C, ADP Hunter Plus Stop Solution was added. The fluorescence intensity was measured at 590nm. The IC₅₀ was calculated from the concentration-activity curve as the concentration of the test compound required for 50% inhibition of kinase activity. The results are presented in Table 1.

EXAMPLE C: Cellular DYRK1A autophosphorylation assay

On day 0, human U2-OS osteosarcoma cells were seeded in 12-well culture plates (100,000 cells per well) and incubated at 37°C in the presence of 5% CO₂ in 1 ml McCoy's 5A (Modified) medium containing GlutaMAX™ (Gibco 36600), supplemented with 50 units/ml penicillin, 50 µg/ml streptomycin, 10 mM Hepes buffer, pH = 7.4, and 10% foetal calf serum (FCS, Sigma F7524). On day 1, medium was replaced with 500 µl Optimem medium containing GlutaMAX™ (Gibco 51985), 150 ng of a pcDNA3.1 plasmid (Invitrogen) containing a sequence coding for full-length, wild-type human DYRK1A (NM_001396) with an HA tag, 0.3 % lipofectamine (Invitrogen 18324-020), and 0.6 % Plus reagent (Invitrogen Cat N°11514-015). After 5 hours, medium was replaced with 900 µl McCoy's 5A (Modified) medium containing GlutaMAX™ (Gibco 36600). On day 2, cells were exposed to a range of concentrations of the test compounds of the invention for 5 hours. Cells were then washed in phosphate-buffered saline solution and cell lysed in lysis buffer comprised of 150 mM NaCl, 20 mM Tris-HCl pH 7.4, 1% triton X-100, 1 mM EGTA, 1 mM EDTA and protease (1% v/v; 539134; Calbiochem) and phosphatase (1% v/v; 524625; Calbiochem) inhibitor cocktails (50 µl lysis buffer/well). The relative levels of phospho-Ser520-DYRK1A were assayed using either western blotting or the Mesoscale ELISA platform. For analysis by western blot, lysates were diluted into Laemmli sample buffer (Bio-Rad) containing 5% v/v β-mecaptoethanol, heated for 5 min at 95°C, and resolved on Tris-glycine gels or NuPage Bis-Tris gels (Novex; Invitrogen). Biotinylated molecular weight standards (Cell Signaling Technology) were included in all gels. Proteins were transferred to nitrocellulose membranes (Hybond, ECL; Amersham), which were blocked in Tris-buffered saline / 0.1% tween 20 (TBST) containing 5% milk, and probed at 4°C overnight with anti-phospho-Ser520-DYRK1A antibody (Eurogentec SE6974-75;

0.23 $\mu\text{g/ml}$ in 5% BSA) or anti DYRK1A antibody (Abnova H00001859; 0.5 $\mu\text{g/ml}$ in 5% milk). Peroxidase-conjugated secondary antibodies were diluted into 5% milk and applied to membranes for 1h at 20°C. Chemiluminescence detection was performed using the ECL plus western blotting detection kit (Amersham) and was recorded on ECL plus hyperfilm (Amersham). Blots were scanned using the Bio-Rad GS-800 calibrated densitometer and quantitative analysis of western blots was performed using TotalLab software (Amersham). IC₅₀ values for inhibition of phospho-Ser520-DYRK1A were calculated from dose-response curves plotting the ratio between phospho-Ser520-DYRK1A and total DYRK1A signals at each concentration. For analysis by Mesoscale ELISA, lysates were transferred to BSA-blocked ELISA plates with pre-bound anti-HA capture antibodies (Novus biological NB600-364; 15 $\mu\text{g/ml}$) for 1 hour with shaking at RT. Anti-phospho-Ser520-DYRK1A antibody (Eurogentec SE6974-75; 2.3 – 3.0 mg/ml) and anti DYRK1A antibody (Abnova H00001859; 3 $\mu\text{g/ml}$) was then added for 1 hour at RT, followed by addition of Sulfa-TAG anti-rabbit detection antibody (ref MSD R32AB; 1 $\mu\text{g/ml}$) and Sulfa-TAG anti-mouse detection antibody (ref MSD R32-AC-1; 1 $\mu\text{g/ml}$). After a further 1 hour, Read Buffer was added and plates were read on the Sector Imager 2400 (Mesoscale). IC₅₀ values for inhibition of phospho-Ser520-DYRK1A were calculated from dose-response curves. The results showed that the compounds of the invention are powerful inhibitors of cellular DYRK1A Ser520 autophosphorylation. The results are presented in Table 1.

EXAMPLE D: Pharmacodynamic assay in tumor xenografts for inhibition of DYRK1A autophosphorylation

For pharmacodynamics studies of inhibition of DYRK1A autophosphorylation, female SCID mice were injected subcutaneously with RS4;11 human acute lymphoblastic leukemia cells. When tumors reached a size of 200 – 300 mm³, mice were randomized into homogeneous groups of 3 and given a single oral administration of the compounds of the invention at doses of up to 100 mg/kg. At various times after treatment, typically 2 hours and 6 hours, treated and control mice were sacrificed, tumors were excised and proteins were extracted in tissue lysis buffer comprised of 150 mM NaCl, 20 mM Tris-HCl pH 7.4, 1% triton X-100, 1 mM EGTA, 1 mM EDTA and protease (1% v/v; 539134; Calbiochem) and phosphatase (1% v/v; 524625; Calbiochem) inhibitor cocktails. The relative levels of

phospho-Ser520-DYRK1A were assayed using western blotting. For this, lysates were diluted into Laemmli sample buffer (Bio-Rad) containing 5% v/v β -mecaptoethanol, heated for 5 min at 95°C, and resolved on Tris-glycine gels or NuPage Bis-Tris gels (Novex; Invitrogen). Biotinylated molecular weight standards (Cell Signaling Technology) were included in all gels. Proteins were transferred to nitrocellulose membranes (Hybond, ECL; Amersham), which were blocked in Tris-buffered saline / 0.1% tween 20 (TBST) containing 5% milk, and probed at 4°C overnight with anti-phospho-Ser520-DYRK1A antibody (Eurogentec SE6974-75; 0.23 μ g/ml in 5% BSA) or anti DYRK1A antibody (Abnova H00001859; 0.5 μ g/ml in 5% milk). Peroxidase-conjugated secondary antibodies were diluted into 5% milk and applied to membranes for 1h at 20°C. Chemiluminescence detection was performed using the ECL plus western blotting detection kit (Amersham) and was recorded on ECL plus hyperfilm (Amersham). Blots were scanned using the Bio-Rad GS-800 calibrated densitometer and quantitative analysis of western blots was performed using TotalLab software (Amersham). The percentage inhibition of phospho-Ser520-DYRK1A as compared to the control tumors was calculated using the ratio between phospho-Ser520-DYRK1A and total DYRK1A signals at each dose. The results showed that the compounds of the invention are powerful inhibitors of tumor DYRK1A Ser520 autophosphorylation.

EXAMPLE E: Efficacy studies in tumor xenografts

For anti-tumor efficacy studies, female nude NCr nu/nu mice were injected subcutaneously with U87-MG human glioblastoma cells. When tumors reached a size of approximately 150 mm³, mice were randomized into homogeneous groups of 8 and treated orally with the compounds of the invention at doses of up to 200 mg/kg once daily for up to 3 weeks. Anti-tumor efficacy was monitored by at least twice-weekly measurement of tumor sizes using calipers, and body weights were recorded in order to document potential general toxicity. Percentage tumor growth inhibition (TGI) on a given day was calculated using the formula: $(1 - [\text{RTV}(\text{treated}) / \text{RTV}(\text{untreated})]) \times 100$, where RTV = relative tumor volume on the given day *versus* start of treatment. The results showed that the compounds of the invention are powerful inhibitors of tumor growth.

Table 1: IC₅₀ of Dyrk1/Clk1 inhibitor

	IC ₅₀ (μM) Dyrk1A TR-FRET assay	IC ₅₀ (μM) Dyrk1A ADP assay	IC ₅₀ (μM) Dyrk1B TR-FRET assay	IC ₅₀ (μM) Clk1 TR-FRET assay	IC ₅₀ (μM) CDK9 TR-FRET assay	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 1		0,047				
Example 2	0,018	0,023	0,0222		4,41	0,48
Example 3		0,241				
Example 4	0,0253	0,044	0,044		10	
Example 5	0,0094	0,015	0,0005		10	
Example 6		0,07				
Example 7		0,039				
Example 8		0,038				
Example 9		0,06				
Example 10		0,085				
Example 11	0,0173	0,012	0,0132		10	
Example 12		2,041				
Example 13		1,373				
Example 14		0,043				
Example 15	0,0355	0,032	0,0143		10	
Example 16	0,0149	0,011	0,0178	0,0328	10	0,1402
Example 17	0,009	0,006	0,0013	0,0166	1,8543	0,0093
Example 18	0,0151	0,012	0,0003	0,024	10	0,0663
Example 19		0,025				
Example 20	0,0197	0,013				
Example 21	0,0102	0,023	0,0091		3,7762	
Example 22		0,018				
Example 23		0,015				
Example 24		0,066				
Example 25	0,0031	0,012	0,0079	0,0177	10	0,036
Example 26		0,029				
Example 27	0,0444	0,04	0,0522		10	
Example 28		0,011				

	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Clk1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 29		0,062				
Example 30		0,827				
Example 31		1,068				
Example 32	0,0056	0,015	0,0012		10	0,323
Example 33		0,165				
Example 34		0,278				
Example 35	0,0248	0,043	0,0094		10	0,8865
Example 36	0,0091	0,027	0,0062		5,5232	0,4857
Example 37	0,007	0,025	0,0005		10	0,358
Example 38		0,149				
Example 39		0,084				
Example 40		0,051				
Example 41		0,158				
Example 42		0,233				
Example 43		0,278				
Example 44		0,249				
Example 45	0,2005	0,496			30	0,6864
Example 46		0,369				
Example 47		0,372				
Example 48	0,043	0,044			10	0,208
Example 49		0,127				
Example 50		0,045				
Example 51	0,0029	0,013			10	0,126
Example 52	0,0043	0,007	0,0027	0,0167	10	0,0232
Example 53	0,0233	0,021			10	0,2375
Example 54	0,0129	0,032			10	0,5105
Example 55	0,0102	0,009	0,0043	0,0157	1,3025	0,0058
Example 56	0,0114	0,012			2,5354	0,0117
Example 57	0,0026	0,015	0,0098	0,0233	8,0604	0,0497
Example 58	0,0215	0,01	0,0175	0,0245	10	0,0337
Example 59	0,0102	0,042	0,0191		10	0,2587

	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Ctk1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 60	0,003	0,011			10	0,0206
Example 61	0,0062	0,01	0,0029	0,0129	10	0,0115
Example 62	0,0186	0,008	0,0002	0,0162	10	0,021
Example 63	0,0107	0,014			10	0,0408
Example 64	0,0059	0,015	0,0093		10	0,2335
Example 65	0,0709	0,069			30	0,8984
Example 66	0,0107	0,045			10	0,3
Example 67		0,094				
Example 68		0,059				
Example 69	0,0016	0,006	0,0011		0,6478	0,0036
Example 70	0,0025	0,009	0,0015	0,0152	1,5031	0,027
Example 71	0,0051	0,008	0,0074	0,0237	10	0,031
Example 72	0,021	0,013			10	0,3
Example 73	0,0059	0,038			10	0,3
Example 74	0,0012	0,014		0,0184	10	0,1115
Example 75	0,0143	0,037			10	0,3
Example 76	0,0063	0,01	0,0005		10	0,0672
Example 77		0,057				
Example 78	0,0013	0,01	0,0145	0,0293	10	0,0721
Example 79	0,0021	0,008	0,008		10	0,105
Example 80	0,0059	0,004	0,0106		10	0,0156
Example 81	0,0085	0,014	0,0141		10	0,1659
Example 82	0,001	0,045	0,0199		10	
Example 83	0,0006	0,081	0,0404		10	
Example 84		0,006				0,0097
Example 86		0,121				
Example 87		1,939				
Example 88		2,091				
Example 89	0,0492	0,077			30	
Example 90		10				

	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Clk1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 91		0,038				
Example 92		0,087				
Example 93		0,176				
Example 94	0,0077	0,019	0,0112	0,0378	3	0,1549
Example 95	0,0979	0,066			30	0,5344
Example 96	0,0023	0,009	0,0315	0,0151	3	0,0119
Example 97		0,063				
Example 98		0,022		0,0241		0,1923
Example 99	0,0086	0,029	0,0293	0,0549	3	0,1921
Example 100		0,161				
Example 101		0,034				0,3
Example 102		0,293				
Example 103		0,694				
Example 104	0,0081	0,015	0,0167	0,0225	3	0,1055
Example 105		0,121				
Example 106		0,018		0,0171		0,1769
Example 107		0,666				
Example 108	0,0027	0,009	0,0092	0,0283	3	0,0491
Example 109		0,524				
Example 110		0,048				
Example 111		0,013				
Example 112		0,234				
Example 113		0,114				
Example 114		0,009		0,0162		0,006
Example 115	0,0031	0,005	0,0094	0,0172	3	0,0185
Example 116		0,005		0,0136		0,0009
Example 117	0,0059	0,01	0,0093	0,0195		0,0377
Example 118		0,011				
Example 119	0,0066	0,02	0,0192	0,0828	3	0,2317
Example 120		0,115				
Example 121		0,066				

	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Clik1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 122		0,05				
Example 123		0,071		0,0615		0,3
Example 124		0,296				
Example 125	0,053	0,073			3,72	
Example 126		0,418				
Example 127		0,011				0,0169
Example 128		0,009				0,0093
Example 129		0,072				
Example 130		0,26				
Example 131		0,6				
Example 132	0,0338	0,122			30	
Example 133		0,269				
Example 134		0,848				
Example 135		0,091				
Example 136		0,169				
Example 137		0,336				
Example 138		0,407				
Example 139		0,883				
Example 140		1,223				
Example 141		0,417				
Example 142		0,512				
Example 143		1,057				
Example 144		0,545				
Example 145		0,042				0,4706
Example 146		0,172				
Example 147		0,17				
Example 148	0,0042	0,007	0,0144	0,0303	10	0,0335
Example 149		0,734				
Example 150	0,0034	0,74			1,1651	
Example 151		0,028				
Example 152		0,012				0,0101

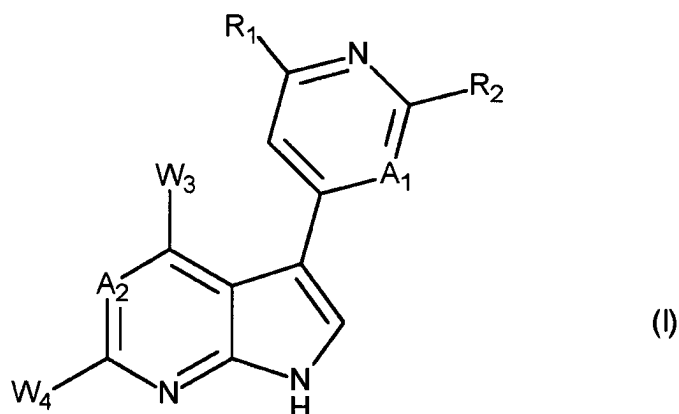
	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Clk1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 153		0,011				0,0146
Example 154		0,013				0,053
Example 155		0,024				0,3
Example 156		0,029				
Example 157		0,26				
Example 158	0,0655	0,15			30	
Example 159		0,012				0,0187
Example 160		0,184				
Example 161	0,0091	0,028	0,0252	0,1222	3	0,1501
Example 162		0,014				
Example 163		0,026		0,1041		0,1974
Example 164		0,015				0,0883
Example 165		0,301				
Example 166		0,025		0,2476		0,1179
Example 167		0,015		0,042		0,0444
Example 168		0,01				
Example 169		0,216				
Example 170		1,824				0,3
Example 171		0,033				
Example 172		0,037				
Example 173	0,0045	0,013	0,0051	0,0334	3	0,0497
Example 174		0,07				
Example 175		0,146				
Example 176		0,196				
Example 177		0,532				
Example 178	0,0052	0,013	0,0141	0,1795	3	0,0782
Example 179	0,0031	0,014	0,0115	0,0425	10	0,0365
Example 180		0,079				
Example 181		0,019				0,15
Example 182		0,013				0,0142
Example 183		0,006				0,029

	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Ctk1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 184		0,012				0,0319
Example 185	0,0048	0,011	0,0158	0,0631	10	0,012
Example 186	0,0053	0,017	0,0211	0,0927	10	0,0855
Example 187	0,003	0,013	0,0081	0,0649	11,639	0,0342
Example 188		0,07				
Example 189		0,062				0,3
Example 190		0,419				
Example 191		0,006				0,0443
Example 192		0,008				0,048
Example 193		0,116				
Example 194		0,007				0,017
Example 195		0,008				0,0071
Example 196		0,023				0,1715
Example 197		0,009				
Example 198		0,017				0,1193
Example 199		0,148				
Example 200		0,027				
Example 201		0,012				
Example 202		0,144				
Example 203		0,155				
Example 204		0,089				
Example 205		0,055				
Example 206	0,0071	0,008	0,0133	0,0238	10	0,0015
Example 207	0,0049	0,01	0,0181	0,0545	7,8293	0,0694
Example 208		0,01				0,0041
Example 209		0,032				0,1571
Example 210		0,05				0,3
Example 211		0,027				
Example 212		0,009				
Example 213	0,0026	0,008	0,0092	0,0172	3	0,057
Example 214		0,242				

	IC ₅₀ (μM) Dyrk1A TR-FRET assays	IC ₅₀ (μM) Dyrk1A ADP assays	IC ₅₀ (μM) Dyrk1B TR-FRET assays	IC ₅₀ (μM) Cdk1 TR-FRET assays	IC ₅₀ (μM) CDK9 TR-FRET assays	IC ₅₀ (μM) P-Ser520- Dyrk1A -Cell assay
Example 215		0,019				0,1032
Example 216	0,0145	0,021	0,0219	0,1212	10	0,0807
Example 217	0,0027	0,01	0,0077	0,0261	10	0,0385
Example 218		0,015				0,0289
Example 219		0,019				0,0325
Example 220		0,034				0,1933
Example 221		0,016				0,1323
Example 222		0,008				0,0442
Example 223		0,043				0,3
Example 224		0,03				0,2249
Example 225		0,037				

EXAMPLE F: Pharmaceutical composition: Tablets

	1000 tablets containing a dose of 5 mg of a compound selected from Examples 1 to 225	5 g
	Wheat starch	20 g
	Maize starch.....	20 g
5	Lactose	30 g
	Magnesium stearate	2 g
	Silica.....	1 g
	Hydroxypropylcellulose	2 g

CLAIMS**1.** Compound of formula (I):

wherein:

- ◆ R_1 and R_2 , each independently of the other, represent a hydrogen atom, a halogen atom, $-NR_5R_5'$ or a linear or branched (C_1-C_6) alkyl group,
- ◆ W_3 represents a linear or branched (C_1-C_6) alkoxy, $-O-(C_0-C_6)$ alkylene- Cy_1 , $-O-(C_0-C_6)$ alkylene- Cy_1-Cy_2 , $-NR_aR_b$, $-NR_a-(C_0-C_6)$ alkylene- Cy_1 , $-NR_a-(C_0-C_6)$ alkylene- Cy_1-Cy_2 , $-NR_a-(C_0-C_6)$ alkylene- $Cy_1-O-(C_1-C_6)$ alkylene- Cy_2 , $-Cy_1$, $-Cy_1-(C_0-C_6)$ alkylene- Cy_2 , $-Cy_1-O-(C_0-C_6)$ alkylene- Cy_2 , $-(C_1-C_6)$ alkylene- Cy_1 , $-(C_2-C_6)$ alkenylene- Cy_1 , $-(C_2-C_6)$ alkynylene- Cy_1 , $-(C_1-C_6)$ alkylene- $O-Cy_1$, it being understood that the alkylene moieties defined hereinbefore may be linear or branched,
- ◆ W_4 represents a cyano group, a cycloalkyl group, a linear or branched (C_1-C_6) alkyl group, a linear or branched (C_2-C_6) alkenyl group, a linear or branched (C_2-C_6) alkynyl group optionally substituted by a cycloalkyl group,
- ◆ R_5 and R_5' , each independently of the others, represent a hydrogen atom or a linear or branched (C_1-C_6) alkyl group,
- ◆ R_a and R_b , each independently of the other, represent a hydrogen atom or a linear or branched (C_1-C_6) alkyl group,
- ◆ A_1 and A_2 , each independently of the other, represent CH or a nitrogen atom,
- ◆ Cy_1 , Cy_2 and Cy_3 , independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl or a heteroaryl group,

wherein:

- "aryl" means a phenyl, naphthyl, biphenyl or indenyl group,
- "heteroaryl" means any mono- or bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 4 hetero atoms selected from oxygen, sulphur and nitrogen,
- "cycloalkyl" means any mono- or bi-cyclic, non-aromatic, carbocyclic group containing from 3 to 11 ring members, which may include fused, bridged or spiro ring systems,
- "heterocycloalkyl" means any mono- or bi-cyclic, non-aromatic, condensed or spiro group composed of from 3 to 10 ring members and containing from 1 to 3 hetero atoms or groups selected from oxygen, sulphur, SO, SO₂ and nitrogen, which may include fused, bridged or spiro ring systems,
- "(C₀-C₆)alkylene-" refers either to a covalent bond (-C₀alkylene-) or to an alkylene group containing 1, 2, 3, 4, 5 or 6 carbon atoms,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined and the alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene to be substituted by from 1 to 4 groups selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₂-C₆)alkenyl group, linear or branched (C₂-C₆)alkynyl group, linear or branched (C₁-C₆)alkoxy optionally substituted by -NR_cR_d or by from 1 to 3 halogen atoms, linear or branched (C₁-C₆)alkyl-S-, hydroxy, oxo (or *N*-oxide where appropriate), nitro, cyano, -C(O)-OR_c, -C(O)-R_c, -O-C(O)-R_d, -C(O)-NR_cR_d, -NR_c-C(O)-R_d, -NR_cR_d, linear or branched (C₁-C₆)polyhaloalkyl, or halogen, it being understood that R_c and R_d independently of one another represent a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,

to their enantiomers and diastereoisomers, and to addition salts thereof with a pharmaceutically acceptable acid or base.

2. Compound of formula (I) according to claim 1, wherein R₁ represents a hydrogen and R₂ a -NH₂ group.

3. Compound of formula (I) according to claim 1 or 2, wherein A₁ represents a CH group.

4. Compound of formula (I) according to claim 1 or 2, wherein A₁ represents a nitrogen atom.

5. Compound of formula (I) according to one of claims 1 to 3, wherein A₂ represents a nitrogen atom.

6. Compound of formula (I) according to one of claims 1 to 3, wherein A₂ represents a CH group.

7. Compound of formula (I) according to claim 6, wherein A₂ represents a CH group and A₁ represents a CH group.

8. Compound of formula (I) according to one of claims 1 to 7, wherein W₃ represents a linear or branched (C₁-C₆)alkoxy, -O-(C₀-C₆)alkylene-Cy₁, -O-(C₀-C₆)alkylene-Cy₁-Cy₂, -NR_a-(C₁-C₆)alkylene-Cy₁-Cy₂, -NR_a-(C₀-C₆)alkylene-Cy₁-O-(C₁-C₆)alkylene-Cy₂, -Cy₁-O-(C₀-C₆)alkylene-Cy₂, -(C₁-C₆)alkylene-Cy₁, -(C₂-C₆)alkenylene-Cy₁, -(C₂-C₆)alkynylene-Cy₁, -(C₁-C₆)alkylene-O-Cy₁, it being understood that the alkylene moieties defined hereinbefore may be linear or branched.

9. Compound of formula (I) according to one of claims 1 to 7, wherein W₃ represents a Cy₁ group selected from: 1,3-benzodioxolyl, 1*H*-indolyl, phenyl, pyridinyl, 2,3-dihydro-1,4-benzodioxinyl, 1-benzothiophenyl, 1-benzofuranyl, 3,4-dihydronaphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, 3,4-dihydro-2*H*-1,4-benzoxazinyl, wherein the preceding groups are optionally substituted according to the definition of claim 1.

10. Compound of formula (I) according to one of claims 1 to 7, wherein W₃ represents:
(i) a -NR_a-Cy₁ group, wherein Cy₁ represents a group selected from: phenyl, 2,3-dihydro-1*H*-indene and 1,2,3,4-tetrahydronaphthalene, wherein the preceding groups are optionally

substituted according to the definition of claim 1; or (ii) a $-NR_a-(C_1-C_6)alkylene-Cy_1$ group, wherein Cy_1 represents a group selected from: phenyl, pyridinyl, furanyl, thiophenyl, 1*H*-pyrazolyl, 1,3-thiazolyl, 1,2-oxazolyl, cyclohexyl, cyclopropyl and 1*H*-indolyl, wherein the preceding groups are optionally substituted according to the definition of claim 1.

11. Compound of formula (I) according to one of claims 1 to 7, wherein W_3 represents a $-phenylene-(C_0-C_6)alkylene-Cy_2$.

12. Compound of formula (I) according to one of claims 1 to 7, wherein W_3 represents $-O-(C_1-C_6)alkylene-Cy_1$ or $-NR_a-(C_1-C_6)alkylene-Cy_1$, wherein Cy_1 is a phenyl or a pyridinyl group, these latter group being optionally substituted by one or two groups selected from methoxy, methyl or halogen.

13. Compound of formula (I) according to one of claims 1 to 12, wherein W_4 groups are as follows: methyl ; propan-2-yl ; prop-1-en-2-yl ; ethenyl ; cyano ; ethynyl ; cyclopropyl ; cyclopropylethynyl.

14. Compound of formula (I) according to claim 13, wherein W_4 is a methyl group.

15. Compound of formula (I) according to claim 1, selected from the following group:

- 5-(2-aminopyridin-4-yl)-*N*-(2-methoxybenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 4-[2-methyl-4-(thiophen-3-ylmethoxy)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine,
- 5-(2-aminopyridin-4-yl)-*N*-(2,6-dichlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyridin-4-yl)-2-methyl-*N*-(2-methylbenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

- 5-(2-aminopyridin-4-yl)-*N*-(2-chloro-6-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(3-methylpyridin-2-yl)methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5 - 5-(2-aminopyridin-4-yl)-*N*-[(3-fluoropyridin-2-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,
- 5-(2-aminopyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine,

10 its enantiomers and diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

16. Compound of formula (I) according to claim 1 which is 5-(2-aminopyridin-4-yl)-*N*-(2,6-dichlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

17. Compound of formula (I) according to claim 1 which is 5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

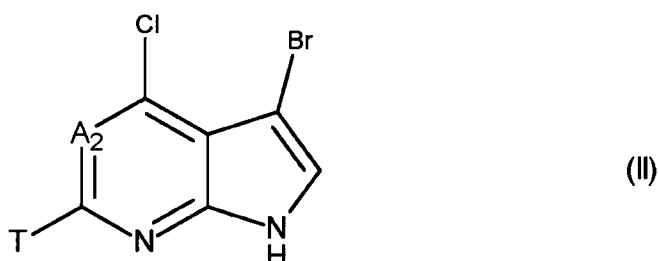
15 **18.** Compound of formula (I) according to claim 1 which is 5-(2-aminopyridin-4-yl)-*N*-(2-chloro-6-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

19. Compound of formula (I) according to claim 1 which is 5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(3-methylpyridin-2-yl)methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

20 **20.** Compound of formula (I) according to claim 1 which is 5-(2-aminopyridin-4-yl)-*N*-[(3-fluoropyridin-2-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

21. Compound of formula (I) according to claim 1 which is 5-(2-aminopyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

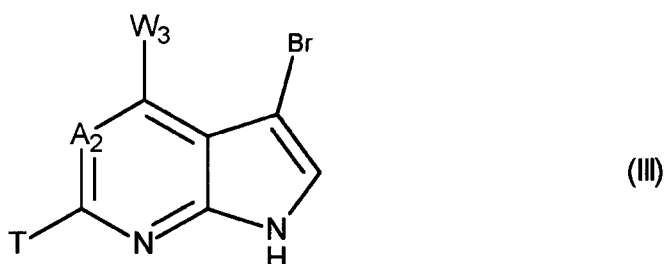
22. Process for the preparation of compounds of formula (I) according to claim 1, which process is characterised in that there is used as starting material the compound of formula (II):



5 wherein T represents a halogen atom, a methane-sulfanyl group, a cycloalkyl group or a linear or branched (C₁-C₆)alkyl group, and A₂ is as defined in formula (I),

which compound is subjected to a nucleophilic substitution in the presence of an appropriate alcohol or amine derivative, or subjected to coupling with an appropriate boronic acid derivative,

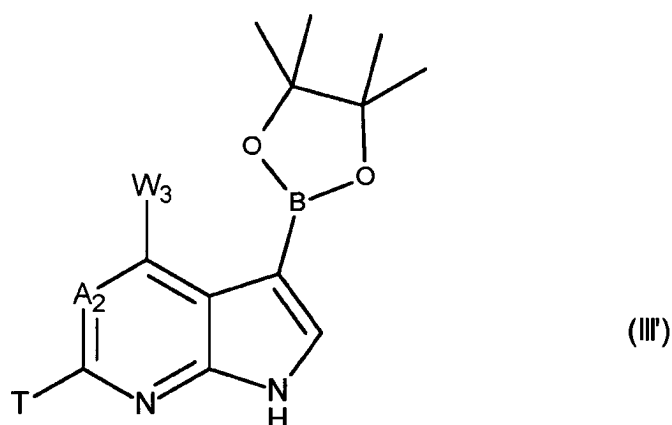
10 to yield the compound of formula (III) :



wherein T is as defined previously, A₂ and W₃ are as defined in formula (I),

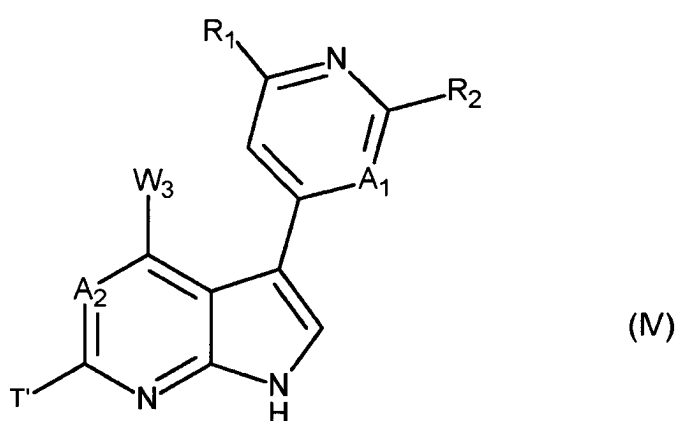
which compound of formula (III) is either :

- 15 (ii) converted into its methanesulfonyl derivative when T represents a methanesulfanyl group, then reacted with NaCN and further subjected to coupling with an appropriate boronic acid derivative,
- (iv) or directly subjected to coupling with an appropriate boronic acid derivative,
- (v) or subjected to coupling with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane to yield :



which compound of formula (III') is further reacted with the appropriate halide,

to yield compound of formula (IV) :



- 5 wherein T' represents represents a halogen atom, a cyano group, a cycloalkyl group or a linear or branched (C₁-C₆)alkyl group, and A₁, A₂, R₁, R₂ and W₃ are as defined in formula (I),

which compound of formula (IV):

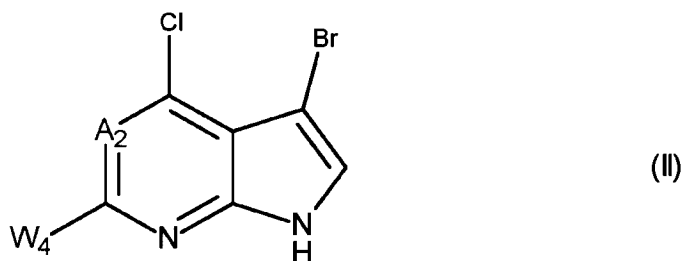
- may be subjected to coupling with an appropriate alkynyl (or alkenyl) boronic acid
 10 derivative or alkynyl (or alkenyl) (trifluoro)borate derivative salt, when T' represents a halogen atom,

to yield the compounds of formula (I),

which compound of formula (I) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

5 it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino...) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.

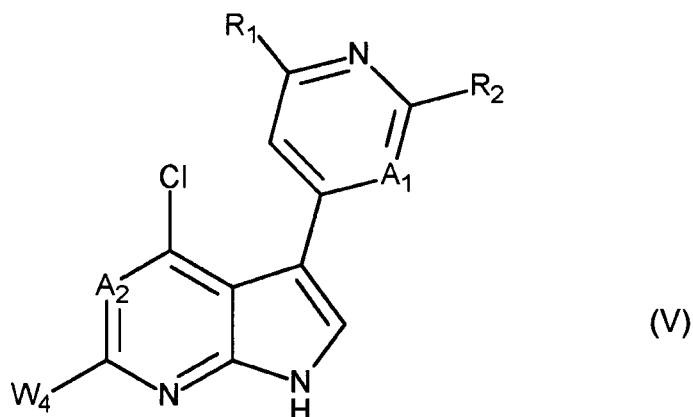
10 **23.** Process for the preparation of compounds of formula (I) according to claim 1, which process is characterised in that there is used as starting material the compound of formula (II):



wherein W₄ and A₂ are as defined in formula (I),

15 which compound of formula (II) is subjected to coupling with an appropriate boronic acid derivative,

to yield compound of formula (V):



wherein A₁, A₂, R₁, R₂, and W₄ are as defined in formula (I),

which compound of formula (V) is either subjected to a nucleophilic substitution, or subjected to a coupling reaction with an appropriate boronic acid derivative, or subjected to a coupling with a compound of formula $\equiv\text{---R}_3$, wherein R₃ represents a hydrogen or Cy₁,

to yield the compounds of formula (I),

which compound of formula (I) may be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

it being understood that, at any time considered appropriate in the course of the above-described process, certain groups (hydroxy, amino...) of the reagents or intermediates of synthesis may be protected and then deprotected according to the requirements of synthesis.

24. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 21, or an addition salt thereof with a pharmaceutically acceptable acid or base, in combination with one or more pharmaceutically acceptable excipients.

25. Pharmaceutical composition according to claim 24 for use in the treatment of cancer, neurodegenerative disorders or metabolic disorders.

26. Pharmaceutical composition according to claim 25, wherein the cancer is selected from acute megakaryoblastic leukaemia (AMKL), acute lymphoblastic leukaemia (ALL), ovarian cancer, pancreatic cancer, gastrointestinal stromal tumours (GIST), osteosarcoma (OS), colorectal carcinoma (CRC), neuroblastoma and glioblastoma.

27. Pharmaceutical composition according to claim 25, wherein the neurodegenerative disorders are selected from Alzheimer's, Parkinson's and Huntington's diseases, Down's syndrome, mental retardation and motor defects.

28. Use of a pharmaceutical composition according to claim 24 in the manufacture of a medicament intended for the treatment of cancer, neurodegenerative disorders or metabolic disorders.

29. Use according to claim 28, wherein the cancer is selected from acute megakaryoblastic leukaemia (AMKL), acute lymphoblastic leukaemia (ALL), ovarian cancer, pancreatic cancer, gastrointestinal stromal tumours (GIST), osteosarcoma (OS), colorectal carcinoma (CRC), neuroblastoma and glioblastoma.

30. Use according to claim 28, wherein the neurodegenerative disorders are selected from Alzheimer's, Parkinson's and Huntington's diseases, Down's syndrome, mental retardation and motor defects.

31. Compound of formula (I) according to one of claims 1 to 21, or an addition salt thereof with a pharmaceutically acceptable acid or base, for use in the treatment of cancer, neurodegenerative disorders or metabolic disorders.

32. Use of a compound of formula (I) according to one of claims 1 to 21, or an addition salt thereof with a pharmaceutically acceptable acid or base, in the manufacture of a

medicament intended for the treatment of cancer, neurodegenerative disorders or metabolic disorders.

33. Combination of a compound of formula (I) according to any one of claims 1 to 21 with an anticancer agent selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors, signaling pathway inhibitors, phosphatase inhibitors, apoptosis inducers and antibodies.

34. Pharmaceutical composition comprising a combination according to claim 33 in combination with one or more pharmaceutically acceptable excipients.

35. Combination according to claim 33 for use in the treatment of cancer.

36. Use of a combination according to claim 33 in the manufacture of a medicament for use in the treatment of cancer.

37. Compound of formula (I) according to any one of claims 1 to 21 for use in in the treatment of cancer necessitating radiotherapy.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/073403

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 C07D487/04 A61P35/00 A61P25/16 A61P25/28 A61K31/437 A61K31/519 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, 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 2014/001973 A1 (PFIZER [US]) 3 January 2014 (2014-01-03) page 18, line 19 - page 20, line 15; claim 1 -----	1-37
X	WO 2015/092592 A1 (PFIZER [US]) 25 June 2015 (2015-06-25) page 13, line 13 - page 15, line 9; claim 1 -----	1-37
X	EP 2 125 803 A1 (CENTRE NAT RECH SCIENT [FR]; UNIV PARIS CURIE [FR]; UNIV CLAUDE BERNAR) 2 December 2009 (2009-12-02) paragraph [0190]; claims 1, 11, 12 -----	1-37
☐ 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 20 October 2016		Date of mailing of the international search report 31/10/2016
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Miniejew, Catherine

INTERNATIONAL SEARCH REPORT

Information on patent family members

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		DO P2014000303 A	15-03-2015
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D·沃姆斯利 A·科斯基

权利要求书6页 说明书80页

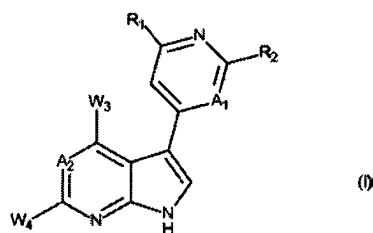
(54)发明名称

作为双重DYRK1/CLK1抑制剂的新的吡咯并

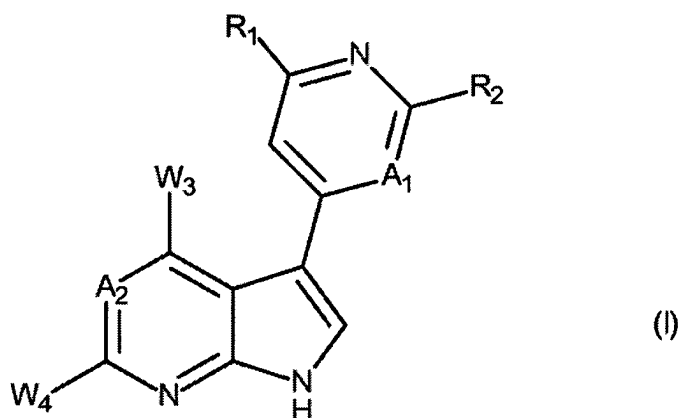
[2,3-d]嘧啶衍生物

(57)摘要

用于治疗癌症、神经退行性疾病和代谢性疾病的式(I)化合物。



1. 式 (I) 的化合物、其对映体和非对映体以及其与可药用酸或碱的加成盐：



其中：

◆R₁和R₂彼此独立地代表氢原子、卤原子、-NR₅R₅' 或直链或支链的 (C₁-C₆) 烷基，

◆W₃代表直链或支链的 (C₁-C₆) 烷氧基、-O- (C₀-C₆) 亚烷基-Cy₁、-O- (C₀-C₆) 亚烷基-Cy₁-Cy₂、-NR_aR_b、-NR_a- (C₀-C₆) 亚烷基-Cy₁、-NR_a- (C₀-C₆) 亚烷基-Cy₁-Cy₂、-NR_a- (C₀-C₆) 亚烷基-Cy₁-O- (C₁-C₆) 亚烷基-Cy₂、-Cy₁、-Cy₁- (C₀-C₆) 亚烷基-Cy₂、-Cy₁-O- (C₀-C₆) 亚烷基-Cy₂、- (C₁-C₆) 亚烷基-Cy₁、- (C₂-C₆) 亚烯基-Cy₁、- (C₂-C₆) 亚炔基-Cy₁、- (C₁-C₆) 亚烷基-O-Cy₁，应当理解的是，以上所定义的亚烷基部分可以是直链或支链的，

◆W₄代表氰基、环烷基、直链或支链的 (C₁-C₆) 烷基、直链或支链的 (C₂-C₆) 烯基、任选地被环烷基取代的直链或支链的 (C₂-C₆) 炔基，

◆R₅和R₅' 彼此独立地代表氢原子或直链或支链的 (C₁-C₆) 烷基，

◆R_a和R_b彼此独立地代表氢原子或直链或支链的 (C₁-C₆) 烷基，

◆A₁和A₂彼此独立地代表CH或氮原子，

◆Cy₁、Cy₂和Cy₃彼此独立地代表环烷基、杂环烷基、芳基或杂芳基，其中：

-“芳基”是指苯基、萘基、联苯基或茚基，

-“杂芳基”是指由5至10个环成员组成的任意单环或双环基团，其具有至少1个芳香族部分并且包含1至4个选自氧、硫和氮的杂原子，

-“环烷基”是指包含3至11个环成员的任意单环或双环非芳香族碳环基团，其可包括稠环、桥环或螺环系统，

-“杂环烷基”是指由3至10个环成员组成的并且包含1至3个选自氧、硫、S₀、S₀₂和氮的杂原子的任意单环或双环非芳香族的稠合或螺环基团，其可包括稠环、桥环或螺环系统，

-“- (C₀-C₆) 亚烷基-”是指共价键 (-C₀亚烷基-) 或含有1、2、3、4、5或6个碳原子的亚烷基，

所定义的芳基、杂芳基、环烷基和杂环烷基以及烷基、烯基、炔基、亚烷基、亚烯基、亚炔基可以被1至4个选自直链或支链的 (C₁-C₆) 烷基、直链或支链的 (C₂-C₆) 烯基、直链或支链的 (C₂-C₆) 炔基、任选地被-NR_cR_d或被1至3个卤原子取代的直链或支链的 (C₁-C₆) 烷氧基、直链或支链的 (C₁-C₆) 烷基-S-、羟基、氧代 (或在适当情况下的N-氧化物)、硝基、氰基、-C (O) -OR_c、-C (O) -R_c、-O-C (O) -R_d、-C (O) -NR_cR_d、-NR_c-C (O) -R_d、-NR_cR_d、直链或支链的 (C₁-C₆) 多卤代烷基或卤素的基团取代，应当理解的是，R_c和R_d彼此独立地代表氢原子或直链或支链的 (C₁-

C₆) 烷基。

2. 根据权利要求1的式(I)化合物,其中R₁代表氢并且R₂代表-NH₂基团。

3. 根据权利要求1或2的式(I)化合物,其中A₁代表CH基团。

4. 根据权利要求1或2的式(I)化合物,其中A₁代表氮原子。

5. 根据权利要求1至3之一的式(I)化合物,其中A₂代表氮原子。

6. 根据权利要求1至3之一的式(I)化合物,其中A₂代表CH基团。

7. 根据权利要求6的式(I)化合物,其中A₂代表CH基团并且A₁代表CH基团。

8. 根据权利要求1至7之一的式(I)化合物,其中W₃代表直链或支链的(C₁-C₆) 烷氧基、-O-(C₀-C₆) 亚烷基-Cy₁、-O-(C₀-C₆) 亚烷基-Cy₁-Cy₂、-NR_a-(C₁-C₆) 亚烷基-Cy₁-Cy₂、-NR_a-(C₀-C₆) 亚烷基-Cy₁-O-(C₁-C₆) 亚烷基-Cy₂、-Cy₁-O-(C₀-C₆) 亚烷基-Cy₂、-(C₁-C₆) 亚烷基-Cy₁、-(C₂-C₆) 亚烯基-Cy₁、-(C₂-C₆) 亚炔基-Cy₁、-(C₁-C₆) 亚烷基-O-Cy₁,应当理解的是,以上所定义的亚烷基部分可以是直链或支链的。

9. 根据权利要求1至7之一的式(I)化合物,其中W₃代表Cy₁基团,其选自:1,3-苯并二氧杂环戊烯基、1H-吡啶基、苯基、吡啶基、2,3-二氢-1,4-苯并二𫔇英基、1-苯并噻吩基、1-苯并呋喃基、3,4-二氢萘基、1,2,3,4-四氢萘基、3,4-二氢-2H-1,4-苯并𫔇嗪基,其中前述基团任选地按照权利要求1的定义被取代。

10. 根据权利要求1至7之一的式(I)化合物,其中W₃代表:(i) -NR_a-Cy₁基团,其中Cy₁代表选自下列的基团:苯基、2,3-二氢-1H-茚和1,2,3,4-四氢萘,其中前述基团任选地按照权利要求1的定义被取代;或(ii) -NR_a-(C₁-C₆) 亚烷基-Cy₁基团,其中Cy₁代表选自下列的基团:苯基、吡啶基、呋喃基、噻吩基、1H-吡啶基、1,3-噻唑基、1,2-𫔇唑基、环己基、环丙基和1H-吡啶基,其中前述基团任选地按照权利要求1的定义被取代。

11. 根据权利要求1至7之一的式(I)化合物,其中W₃代表-亚苯基-(C₀-C₆) 亚烷基-Cy₂。

12. 根据权利要求1至7之一的式(I)化合物,其中W₃代表-O-(C₁-C₆) 亚烷基-Cy₁或-NR_a-(C₁-C₆) 亚烷基-Cy₁,其中Cy₁是苯基或吡啶基,后述基团任选地被一个或两个选自甲氧基、甲基或卤素的基团取代。

13. 根据权利要求1至12之一的式(I)化合物,其中W₄基团是如下基团:甲基;丙-2-基;丙-1-烯-2-基;乙烯基;氰基;乙炔基;环丙基;环丙基乙炔基。

14. 根据权利要求13的式(I)化合物,其中W₄是甲基。

15. 根据权利要求1的式(I)化合物,选自:

-5-(2-氨基吡啶-4-基)-N-(2-甲氧基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

-4-[2-甲基-4-(噻吩-3-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺,

-5-(2-氨基吡啶-4-基)-N-(2,6-二氯苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

-5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

-5-(2-氨基吡啶-4-基)-2-甲基-N-(2-甲基苄基)-7H-吡咯并[2,3-d]嘧啶-4-胺,

-5-(2-氨基吡啶-4-基)-N-(2-氯-6-氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

-5-(2-氨基吡啶-4-基)-2-甲基-N-[(3-甲基吡啶-2-基)甲基]-7H-吡咯并[2,3-d]嘧啶-4-胺,

-5-(2-氨基吡啶-4-基)-N-[(3-氟吡啶-2-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

-5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺，
其对映体和非对映体以及其与可药用酸或碱的加成盐。

16. 根据权利要求1的式(I)化合物，所述化合物是5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺。

17. 根据权利要求1的式(I)化合物，所述化合物是5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺。

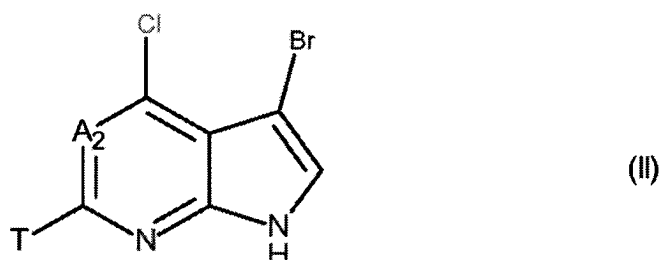
18. 根据权利要求1的式(I)化合物，所述化合物是5-(2-氨基吡啶-4-基)-N-(2-氯-6-氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺。

19. 根据权利要求1的式(I)化合物，所述化合物是5-(2-氨基吡啶-4-基)-2-甲基-N-[(3-甲基吡啶-2-基)甲基]-7H-吡咯并[2,3-d]嘧啶-4-胺。

20. 根据权利要求1的式(I)化合物，所述化合物是5-(2-氨基吡啶-4-基)-N-[(3-氟吡啶-2-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺。

21. 根据权利要求1的式(I)化合物，所述化合物是5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺。

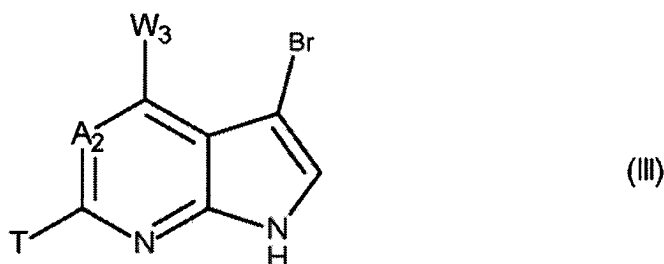
22. 制备根据权利要求1的式(I)化合物的方法，该方法的特征在于将式(II)的化合物用作原料



其中T代表卤原子、甲硫基、环烷基或直链或支链的(C₁-C₆)烷基，并且A₂如式(I)中所定义，

将该化合物在适宜的醇或胺衍生物的存在下进行亲核取代反应，或与适宜的硼酸衍生物进行偶联，

以生成式(III)的化合物：



其中T如前所定义，A₂和W₃如式(I)中所定义，

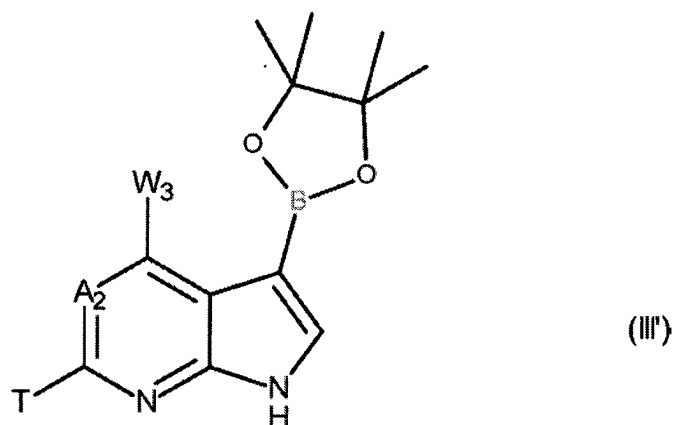
将式(III)的化合物：

(i) 当T代表甲硫基时，将其转化成甲磺酰基衍生物，然后与NaCN反应并进一步与适宜的硼酸衍生物进行偶联，

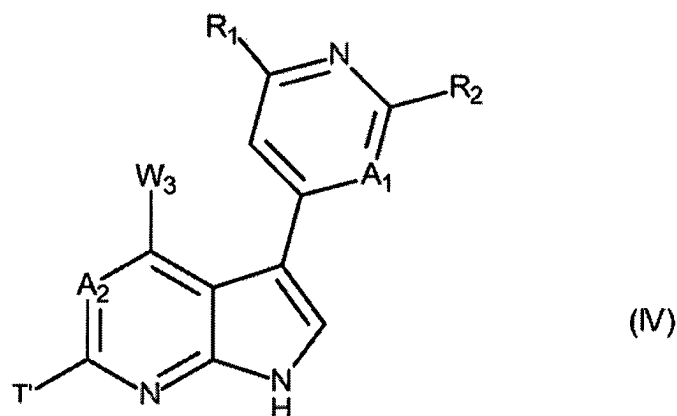
(ii) 或者直接与适宜的硼酸衍生物进行偶联，

(iii) 或者与4,4,4',4'',5,5,5',5''-八甲基-2,2'-双-1,3,2-二氧硼戊环进行偶联以

生成:



将该式 (III') 的化合物进一步与适宜的卤化物进行反应，以生成式 (IV) 的化合物:



其中 T' 代表卤原子、氰基、环烷基或直链或支链的 (C₁-C₆) 烷基, 并且 A₁、A₂、R₁、R₂ 和 W₃ 如式 (I) 中所定义,

当 T' 代表卤原子时, 所述式 (IV) 的化合物:

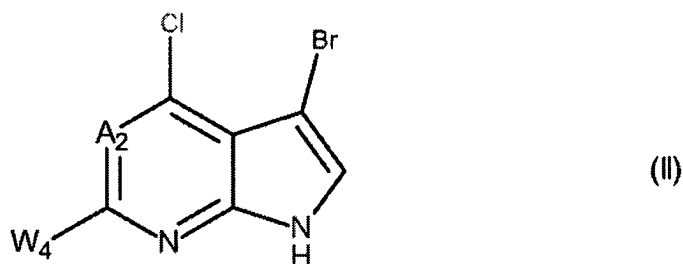
- 可以与适宜的炔基 (或烯基) 硼酸衍生物或炔基 (或烯基) (三氟) 硼酸酯衍生物盐进行偶联,

以生成式 (I) 的化合物,

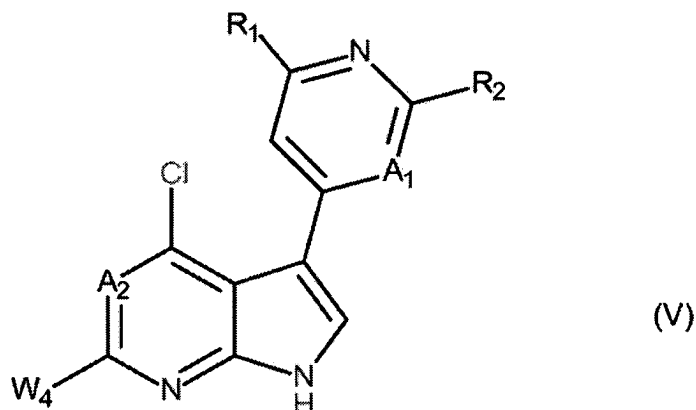
所述式 (I) 的化合物可以根据常规的分离技术进行纯化, 如果需要, 将其转化成其与药用酸或碱的加成盐, 并且任选地根据常规分离技术将其分离成其异构体,

应当理解, 在上述方法过程中被认为适合的任意时间, 试剂或合成中间体的一些基团 (羟基、氨基...) 可以根据合成的需要进行保护然后脱保护。

23. 制备根据权利要求 1 的式 (I) 化合物的方法, 该方法的特征在于将式 (II) 的化合物用作原料:



其中W₄和A₂如式(I)中所定义，
将式(II)的化合物与适宜的硼酸衍生物进行偶联，
以生成式(V)的化合物：



其中A₁、A₂、R₁、R₂和W₄如式(I)中所定义，
将该式(V)的化合物进行亲核取代反应，或与适宜的硼酸衍生物进行偶联反应，或与式
 ---R_3 的化合物进行偶联，其中R₃代表氢或Cy₁，
以生成式(I)的化合物，

所述式(I)的化合物可以根据常规的分离技术进行纯化，如果需要，将其转化成其与可药用酸或碱的加成盐，并且任选地根据常规分离技术将其分离成其异构体，

应当理解，在上述方法过程中被认为适合的任意时间，试剂或合成中间体的一些基团(羟基、氨基…)可以根据合成的需要进行保护然后脱保护。

24. 包含根据权利要求1至21任意一项的式(I)化合物或其与可药用酸或碱的加成盐以及一种或多种可药用赋形剂的药物组合物。

25. 用于治疗癌症、神经退行性疾病或代谢性疾病的根据权利要求24的药物组合物。

26. 根据权利要求25的药物组合物，其中的癌症选自急性巨核细胞白血病(AMKL)、急性淋巴细胞白血病(ALL)、卵巢癌、胰腺癌、胃肠道间质瘤(GIST)、骨肉瘤(OS)、结直肠癌(CRC)、神经母细胞瘤和胶质母细胞瘤。

27. 根据权利要求25的药物组合物，其中的神经退行性疾病选自阿尔茨海默氏症、帕金森氏症和亨廷顿病、唐氏综合症、精神发育迟滞和运动缺陷。

28. 根据权利要求24的药物组合物在制备用于治疗癌症、神经退行性疾病或代谢性疾病的药物中的用途。

29. 根据权利要求28的用途，其中的癌症选自急性巨核细胞白血病(AMKL)、急性淋巴细胞白血病(ALL)、卵巢癌、胰腺癌、胃肠道间质瘤(GIST)、骨肉瘤(OS)、结直肠癌(CRC)、神经母细胞瘤和胶质母细胞瘤。

30. 根据权利要求28的用途, 其中的神经退行性疾病选自阿尔茨海默氏症、帕金森氏症和亨廷顿病、唐氏综合症、精神发育迟滞和运动缺陷。

31. 用于治疗癌症、神经退行性疾病或代谢性疾病的根据权利要求1至21之一的式(I)化合物或其与可药用酸或碱的加成盐。

32. 根据权利要求1至21之一的式(I)化合物或其与可药用酸或碱的加成盐在制备用于治疗癌症、神经退行性疾病或代谢性疾病的药物中的用途。

33. 根据权利要求1至21任意一项的式(I)化合物与选自基因毒物、有丝分裂抑制剂、抗代谢药、蛋白酶体抑制剂、激酶抑制剂、信号通路抑制剂、磷酸酶抑制剂、细胞凋亡诱导剂和抗体的抗癌药的组合。

34. 包含根据权利要求33的组合以及一种或多种可药用赋形剂的药物组合物。

35. 用于治疗癌症的根据权利要求33的组合。

36. 根据权利要求33的组合在制备用于治疗癌症的药物中的用途。

37. 用于治疗需要放疗的癌症的根据权利要求1至21任意一项的式(I)化合物。

作为双重DYRK1/CLK1抑制剂的新的吡咯并[2,3-d]嘧啶衍生物

[0001] 本发明涉及新的吡咯并[2,3-d]嘧啶衍生物、其制备方法以及含有它们的药物组合物。

[0002] 本发明的化合物是新的且在肿瘤学领域具有非常有价值的药理学特性。

[0003] 本发明涉及双重DYRK1/CLK1抑制剂在治疗癌症、神经退行性疾病和代谢性疾病中的用途。

[0004] 在癌症中,双特异性酪氨酸磷酸化调节激酶DYRK1A和DYRK1B已被证实控制着多种途径,这些途径可以增强癌细胞增殖、迁移和转移,诱导对细胞死亡的抗性和抑制对常规和靶向抗癌疗法的反应[Abbassi等人,Pharmacol Ther.2015;151:87-98;Ionescu等人,Mini Rev Med Chem.2012;12(13):1315-29;Friedman等人,J Cell Biochem.2007;102(2):274-9;Yoshida等人,Biochem Pharmacol.2008;76(11):1389-94]。已报道的参与调节癌症进展和对治疗的耐受性的DYRK1A的底物包括转录因子GLI1、STAT3和FOXO1[Mao等人,J Biol Chem.2002;277(38):35156-61;Matsuo等人,J Immunol Methods 2001;247:141-51;Woods等人,Biochem J.2001;355(Pt 3):597-607]。据信DYRK1A还可以通过与蛋白Sprout2相互作用而稳定癌症相关性酪氨酸激酶受体如EGFR和FGFR[Ferron等人,Cell Stem Cell.2010;7(3):367-79;Aranda等人,Mol Cell Biol.2008;28(19):5899-911]。已证实DYRK1A和DYRK1B是在针对通过化疗药和靶向疗法治疗癌细胞的响应中诱导细胞休眠所需的。这很重要,因为已知休眠的癌细胞对大多数抗癌药物和辐射相对不敏感[Ewton等人,Mol Cancer Ther.2011;10(11):2104-14;Jin等人,J Biol Chem.2009;284(34):22916-25]。例如,DYRK1A激活DREAM多亚基蛋白复合物,该复合物维持细胞处于休眠状态并阻止细胞凋亡[Litovchick等人,Genes Dev.2011;25(8):801-13]。已证实DYRK1B可以通过磷酸化细胞周期蛋白D1阻止因响应于化疗而退出细胞周期[Zou等人,J Biol Chem.2004;279(26):27790-8]。还证实DYRK1B可以通过降低活性氧物质含量来对抗化疗[Hu等人,Genes Cancer.2010;1(8):803-811]。

[0005] 由此可见,DYRK1A/DYRK1B抑制剂的使用将构成对各种癌症的新的抗癌治疗,无论是单独使用还是作为对抗抗药性的一种策略与常规疗法、放射疗法或靶向疗法联合使用。

[0006] DYRK1A在神经障碍中的作用是公认的。DYRK1A与神经退行性疾病如阿尔茨海默氏症、帕金森氏症和亨廷顿氏症,以及唐氏综合征、精神发育迟滞和运动缺陷有关[Abbassi等人,Pharmacol Ther.2015;151:87-98;Beker等人,CNS Neurol Disord Drug Targets.2014;13(1):26-33;Dierssen,Nat Rev Neurosci.2012Dec;13(12):844-58]。DYRK1A已被确定为是磷酸化微管相关蛋白TAU的一个主要激酶,导致阿尔茨海默氏症中所观察到的神经毒性神经原纤维缠结的形成和神经变性[Azorsa等人,BMC Genomics.2010;11:25]。DYRK1A还改变TAU pre-mRNA的剪接,导致足以引起神经变性和痴呆的TAU蛋白异构体之间的不平衡[Liu等人,Mol Neurodegener.2008;3:8]。因此,确信DYRK1A与唐氏综合征患者(该疾病患者的21号染色体上存在三份DYRK1A基因)中阿尔茨海默氏症样疾病的出现存在因果关系是合乎情理的。在这些个体中,增加的DYRK1A活性还造成过早的神经细胞分化

和成熟神经元的减少[Hämmerle等人,Development.2011;138(12):2543-54]。

[0007] 由此可见,DYRK1A抑制剂的使用将为神经退行性疾病、特别是阿尔茨海默氏症以及其他神经病症例如唐氏综合症的治疗提供新的治疗途径。

[0008] CDC2-样激酶(CLK)家族包含四个亚型(CLK1-4),它们在调节剪接体复合物的功能中是非常重要的[Fedorov等人,Chem Biol.2011;18(1):67-76]。该复合物由核小RNA(snRNA)和大量的相关蛋白组成,调节pre-mRNA的剪接以产生成熟的蛋白编码mRNA。已知CLK1通过磷酸化组成型丝氨酸-精氨酸富含(SR)蛋白来调节剪接体的活性[Bullock等人,结构式.2009;17(3):352-62]。通过以这种方式控制剪接体的活性,许多基因都能表达一种以上的mRNA,导致翻译蛋白质的多样性。转录自同一基因的替代蛋白亚型通常具有不同的活性和生理功能。选择性剪接的调控异常与癌症是相关联的,其中一些与癌症相关的蛋白质被认为是选择性剪接的[Druillennec等人,J Nucleic Acids.2012;2012:639062]。一个在癌症中选择性剪接的蛋白质的例子是细胞周期蛋白D1,其对于癌细胞通过细胞周期的进展是非常重要的[Wang等人,Cancer Res.2008;68(14):5628-38]。

[0009] 由此可见,CLK1抑制剂的使用将构成对各种癌症的新的抗癌治疗,无论是单独使用还是与常规疗法、放射疗法或靶向疗法联合使用。

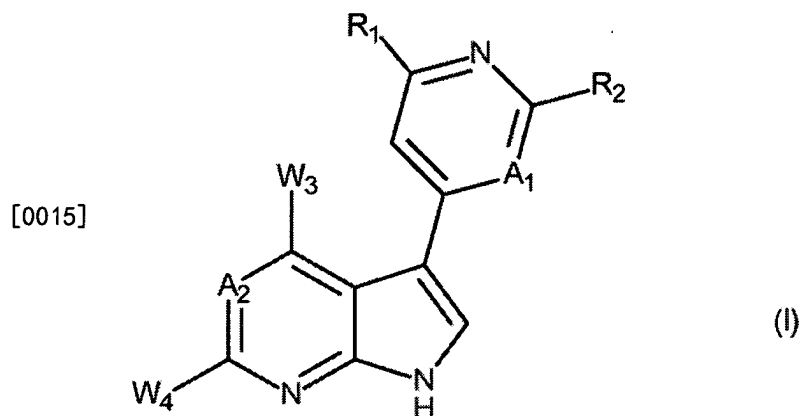
[0010] 还有记载表明,由CLK1调节的选择性剪接通过磷酸化剪接体的SR蛋白在包括阿尔茨海默氏症和帕金森氏症在内的神经退行性疾病中起作用[Jain等人,Curr Drug Targets.2014;15(5):539-50]。在阿尔茨海默氏症的情况下,已知CLK1调节微管相关蛋白TAU的选择性剪接,导致足以引起神经变性和痴呆的TAU蛋白异构体之间的不平衡[Liu等人,Mol Neurodegener.2008;3:8]。

[0011] 由此可见,CLK1抑制剂的使用将为神经退行性疾病、特别是阿尔茨海默氏症以及其他神经病症例如帕金森氏症的治疗提供新的治疗途径。

[0012] 因此,在癌症和神经系统疾病的治疗中,毫无疑问地迫切需要能有效抑制DYRK1和CLK1激酶而不影响其它密切相关的激酶的化合物。DYRK1和CLK1激酶是CMGC组的成员,该组包括CDK和GSK激酶,对它的慢性抑制被认为是对病人产生毒性的原因。例如,在临床中观察到的CDK抑制的常见毒性反应与传统的细胞毒疗法中所观察到的类似,包括血液学毒性(白细胞及血小板减少)、胃肠道毒性(恶心和腹泻)以及疲劳[Kumar等人,Blood.2015;125(3):443-8]。本发明描述了一类新的DYRK1/CLK1抑制剂,相对于其它激酶,该抑制剂对DYRK1和CLK1具有高度选择性,因此适用于治疗这些疾病。

[0013] 1型糖尿病和2型糖尿病都涉及生产胰岛素的功能性胰腺β细胞的缺乏。因此,恢复功能性β细胞量是这些影响全世界3亿8000万人的疾病的一个重要治疗目标。最近的研究表明,抑制DYRK1A促进在体外和体内的人类β细胞增殖,并且在长时间的治疗后,可以增加葡萄糖依赖性胰岛素分泌[Dirice等人,Diabetes.2016;65(6):1660-71;Wang等人,Nat Med.2015;21(4):383-8]。这些结果清楚地表明,强的选择性DYRK1A抑制剂的使用将为包括糖尿病和肥胖在内的代谢性疾病的治疗和/或预防提供新的治疗途径。

[0014] 本发明尤其涉及式(I)的化合物、其对映体和非对映体以及其与可药用酸或碱的加成盐:



[0016] 其中：

[0017] ◆R₁和R₂彼此独立地代表氢原子、卤原子、-NR₅R₅' 或直链或支链的(C₁-C₆)烷基，

[0018] ◆W₃代表直链或支链的(C₁-C₆)烷氧基、-O-(C₀-C₆)亚烷基-Cy₁、-O-(C₀-C₆)亚烷基-Cy₁-Cy₂、-NR_aR_b、-NR_a-(C₀-C₆)亚烷基-Cy₁、-NR_a-(C₀-C₆)亚烷基-Cy₁-Cy₂、-NR_a-(C₀-C₆)亚烷基-Cy₁-O-(C₁-C₆)亚烷基-Cy₂、-Cy₁、-Cy₁-(C₀-C₆)亚烷基-Cy₂、-Cy₁-O-(C₀-C₆)亚烷基-Cy₂、-(C₁-C₆)亚烷基-Cy₁、-(C₂-C₆)亚烯基-Cy₁、-(C₂-C₆)亚炔基-Cy₁、-(C₁-C₆)亚烷基-O-Cy₁，应当理解的是，以上所定义的亚烷基部分可以是直链或支链的，

[0019] ◆W₄代表氰基、环烷基、直链或支链的(C₁-C₆)烷基、直链或支链的(C₂-C₆)烯基、任选地被环烷基取代的直链或支链的(C₂-C₆)炔基，

[0020] ◆R₅和R₅' 彼此独立地代表氢原子或直链或支链的(C₁-C₆)烷基，

[0021] ◆R_a和R_b彼此独立地代表氢原子或直链或支链的(C₁-C₆)烷基，

[0022] ◆A₁和A₂彼此独立地代表CH或氮原子，

[0023] ◆Cy₁、Cy₂和Cy₃彼此独立地代表环烷基、杂环烷基、芳基或杂芳基，其中：

[0024] -“芳基”是指苯基、萘基、联苯基或茚基，

[0025] -“杂芳基”是指由5至10个环成员组成的任意单环或双环基团，其具有至少1个芳香族部分并且包含1至4个选自氧、硫和氮的杂原子，

[0026] -“环烷基”是指包含3至11个环成员的任意单环或双环非芳香族碳环基团，其可包括稠环、桥环或螺环系统，

[0027] -“杂环烷基”是指由3至10个环成员组成的并且包含1至3个选自氧、硫、S₀、S₀₂和氮的杂原子的任意单环或双环非芳香族的稠合或螺环基团，其可包括稠环、桥环或螺环系统，

[0028] -“- (C₀-C₆) 亚烷基-”是指共价键(-C₀亚烷基-)或含有1、2、3、4、5或6个碳原子的亚烷基，

[0029] 所定义的芳基、杂芳基、环烷基和杂环烷基以及烷基、烯基、炔基、亚烷基、亚烯基、亚炔基可以被1至4个选自直链或支链的(C₁-C₆)烷基、直链或支链的(C₂-C₆)烯基、直链或支链的(C₂-C₆)炔基、任选地被-NR_cR_d或被1至3个卤原子取代的直链或支链的(C₁-C₆)烷氧基、直链或支链的(C₁-C₆)烷基-S-、羟基、氧代(或在适当情况下的N-氧化物)、硝基、氰基、-C(O)-OR_c、-C(O)-R_c、-O-C(O)-R_d、-C(O)-NR_cR_d、-NR_c-C(O)-R_d、-NR_cR_d、直链或支链的(C₁-C₆)多卤代烷基或卤素的基团取代，应当理解的是，R_c和R_d彼此独立地代表氢原子或直链或支链的(C₁-C₆)烷基。

[0030] 在可药用酸中,可以提及但不限于盐酸、氢溴酸、硫酸、磷酸、乙酸、三氟乙酸、乳酸、丙酮酸、丙二酸、琥珀酸、戊二酸、富马酸、酒石酸、马来酸、柠檬酸、抗坏血酸、草酸、甲磺酸、樟脑酸等。

[0031] 在可药用碱中,可以提及但不限于氢氧化钠、氢氧化钾、三乙胺、叔丁基胺等。

[0032] 有利地是, R_1 代表氢并且 R_2 代表 $-NH_2$ 基团。

[0033] 在本发明的一个实施方案中, A_1 代表CH基团。

[0034] 在本发明的另一个实施方案中, A_1 代表氮原子。

[0035] 在本发明的一个优选的实施方案中, A_2 代表氮原子。

[0036] 或者, A_2 代表CH基团。当 A_2 代表CH基团时, A_1 优选代表CH基团。

[0037] 在本发明的另一个实施方案中, W_3 代表直链或支链的 (C_1-C_6) 烷氧基、 $-O-(C_0-C_6)$ 亚烷基- Cy_1 、 $-O-(C_0-C_6)$ 亚烷基- Cy_1-Cy_2 、 $-NR_a-(C_1-C_6)$ 亚烷基- Cy_1-Cy_2 、 $-NR_a-(C_0-C_6)$ 亚烷基- $Cy_1-O-(C_1-C_6)$ 亚烷基- Cy_2 、 $-Cy_1-O-(C_0-C_6)$ 亚烷基- Cy_2 、 $-(C_1-C_6)$ 亚烷基- Cy_1 、 $-(C_2-C_6)$ 亚烯基- Cy_1 、 $-(C_2-C_6)$ 亚炔基- Cy_1 、 $-(C_1-C_6)$ 亚烷基- $O-Cy_1$,应当理解的是,以上所定义的亚烷基部分可以是直链或支链的。

[0038] 或者, W_3 代表 Cy_1 基团,其选自:1,3-苯并二氧杂环戊烯基、1H-吡啶基、苯基、吡啶基、2,3-二氢-1,4-苯并二噁英基、1-苯并噻吩基、1-苯并呋喃基、3,4-二氢萘基、1,2,3,4-四氢萘基、3,4-二氢-2H-1,4-苯并噻嗪基,其中前述基团任选地按照之前描述的定义被取代。

[0039] 在另一个实施方案中, W_3 代表:(i) $-NR_a-Cy_1$ 基团,其中 Cy_1 代表选自下列的基团:苯基、2,3-二氢-1H-茛和1,2,3,4-四氢萘,其中前述基团任选地按照之前描述的定义被取代;或(ii) $-NR_a-(C_1-C_6)$ 亚烷基- Cy_1 基团,其中 Cy_1 代表选自下列的基团:苯基、吡啶基、呋喃基、噻吩基、1H-吡啶基、1,3-噻唑基、1,2-噻唑基、环己基、环丙基和1H-吡啶基,其中前述基团任选地按照之前描述的定义被取代。

[0040] 在一个具体的实施方案中, W_3 代表-亚苯基- (C_0-C_6) 亚烷基- Cy_2 。

[0041] 更优选地, W_3 代表 $-O-(C_1-C_6)$ 亚烷基- Cy_1 或 $-NR_a-(C_1-C_6)$ 亚烷基- Cy_1 ,其中 Cy_1 是苯基或吡啶基,后述基团任选地被一个或两个选自甲氧基、甲基或卤素的基团取代。

[0042] 优选的 W_4 基团是如下基团:甲基;丙-2-基;丙-1-烯-2-基;乙烯基;氰基;乙炔基;环丙基;环丙基乙炔基。更优选甲基。

[0043] 优选的本发明化合物包括在以下组中:

[0044] -5-(2-氨基吡啶-4-基)-N-(2-甲氧基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0045] -4-[2-甲基-4-(噻吩-3-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺,

[0046] -5-(2-氨基吡啶-4-基)-N-(2,6-二氯苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0047] -5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0048] -5-(2-氨基吡啶-4-基)-2-甲基-N-(2-甲氧基苄基)-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0049] -5-(2-氨基吡啶-4-基)-N-(2-氯-6-氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-

胺,

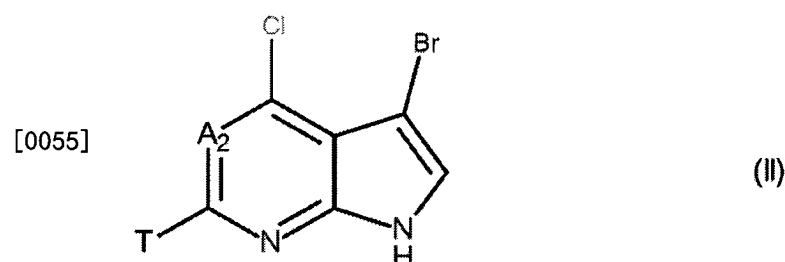
[0050] -5-(2-氨基吡啶-4-基)-2-甲基-N-[(3-甲基吡啶-2-基)甲基]-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0051] -5-(2-氨基吡啶-4-基)-N-[(3-氟吡啶-2-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0052] -5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺,

[0053] 其对映体和非对映体以及其与可药用酸或碱的加成盐。

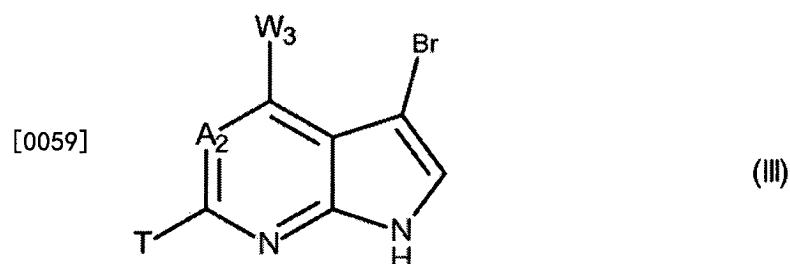
[0054] 本发明还涉及用于制备式(I)化合物的方法,该方法的特征在于将式(II)的化合物用作原料



[0056] 其中T代表卤原子、甲硫基、环烷基或直链或支链的(C₁-C₆)烷基,并且A₂如式(I)中所定义,

[0057] 将该化合物在适宜的醇或胺衍生物的存在下进行亲核取代反应,或与适宜的硼酸衍生物进行偶联,

[0058] 以生成式(III)的化合物:



[0060] 其中T如前所定义,A₂和W₃如式(I)中所定义,

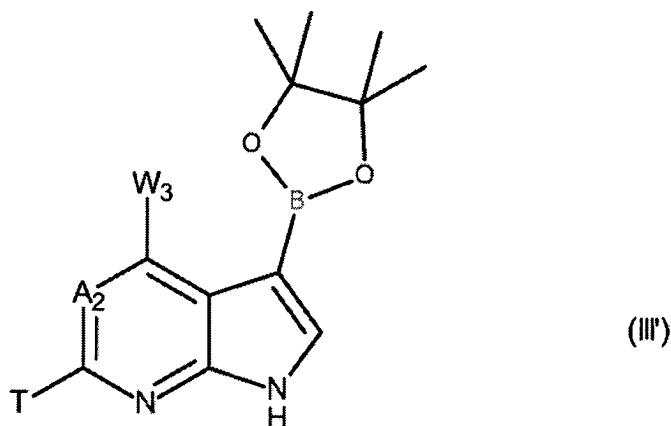
[0061] 将式(III)的化合物:

[0062] (i) 当T代表甲硫基时,将其转化成甲磺酰基衍生物,然后与NaCN反应并进一步与适宜的硼酸衍生物进行偶联,

[0063] (ii) 或者直接与适宜的硼酸衍生物进行偶联,

[0064] (iii) 或者与4,4,4',4',5,5,5',5'-八甲基-2,2'-双-1,3,2-二氧硼戊环进行偶联以生成:

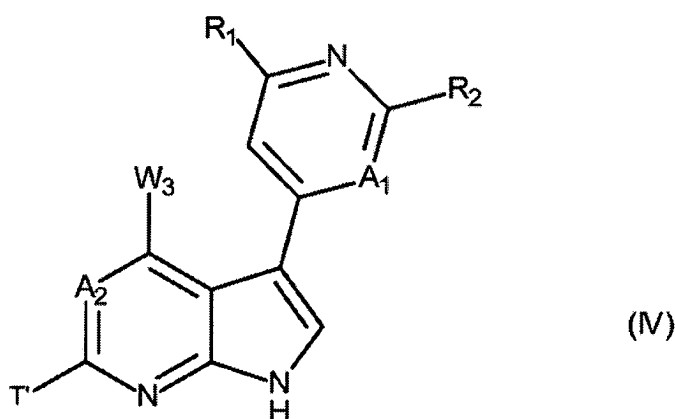
[0065]



[0066] 将该式 (III') 的化合物进一步与适宜的卤化物进行反应,

[0067] 以生成式 (IV) 的化合物:

[0068]

[0069] 其中T' 代表卤原子、氰基、环烷基或直链或支链的(C₁-C₆) 烷基,并且A₁、A₂、R₁、R₂和W₃如式(I)中所定义,

[0070] 当T' 代表卤原子时,所述式(IV)的化合物:

[0071] -可以与适宜的炔基(或烯基)硼酸衍生物或炔基(或烯基)(三氟)硼酸酯衍生物盐进行偶联,

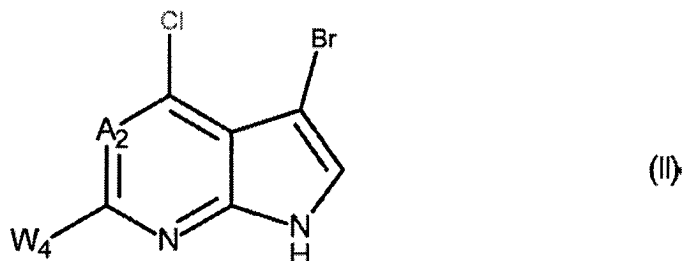
[0072] 以生成式(I)的化合物,

[0073] 所述式(I)的化合物可以根据常规的分离技术进行纯化,如果需要,将其转化成其与可药用酸或碱的加成盐,并且任选地根据常规分离技术将其分离成其异构体,

[0074] 应当理解,在上述方法过程中被认为适合的任意时间,试剂或合成中间体的一些基团(羟基、氨基…)可以根据合成的需要进行保护然后脱保护。

[0075] 本发明还涉及用于制备式(I)化合物的另一种方法,该方法的特征在于将式(II)的化合物用作原料:

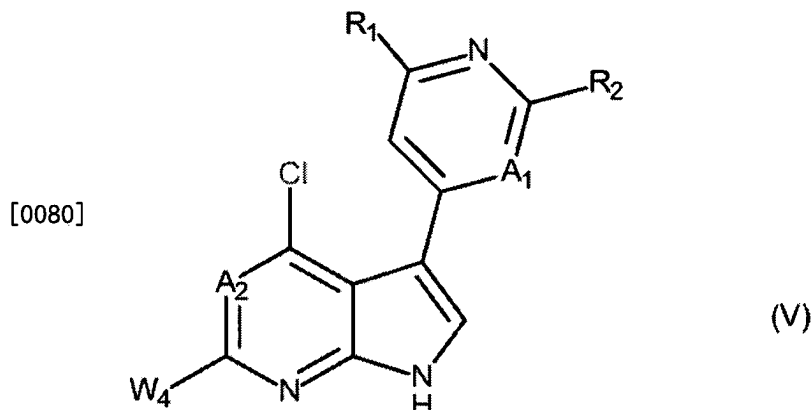
[0076]



[0077] 其中W₄和A₂如式(I)中所定义,

[0078] 将式(II)的化合物与适宜的硼酸衍生物进行偶联,

[0079] 以生成式(V)的化合物:



[0081] 其中A₁、A₂、R₁、R₂和W₄如式(I)中所定义,

[0082] 将该式(V)的化合物进行亲核取代反应,或与适宜的硼酸衍生物进行偶联反应,或与式 ---R_3 的化合物进行偶联,其中R₃代表氢或Cy₁,以生成式(I)的化合物,

[0083] 所述式(I)的化合物可以根据常规的分离技术进行纯化,如果需要,将其转化成其与可药用酸或碱的加成盐,并且任选地根据常规分离技术将其分离成其异构体,

[0084] 应当理解,在上述方法过程中被认为适合的任意时间,试剂或合成中间体的一些基团(羟基、氨基...)可以根据合成的需要进行保护然后脱保护。

[0085] 以上提到的式(II)的化合物、醇和氨基衍生物、硼酸衍生物、硼酸酯盐衍生物和 ---R_3 可以购买到或者可以由本领域技术人员使用文献中记载的常规化学反应制得。

[0086] 本发明化合物的药理学研究已经证实它们是强的DYRK1/CLK1抑制剂,相对于其它激酶例如CDK9,它们对DYRK1和CLK1具有高度选择性。

[0087] 更具体地,本发明的化合物可用于治疗化疗或放疗抗性的癌症。

[0088] 在关注的癌症治疗中,可以提及但不限于血液系统癌症(淋巴瘤和白血病)和实体肿瘤,包括癌、肉瘤或母细胞瘤。可以提到的更优选的是急性巨核细胞白血病(AMKL)、急性淋巴细胞白血病(ALL)、卵巢癌、胰腺癌、胃肠道间质瘤(GIST)、骨肉瘤(OS)、结直肠癌(CRC)、神经母细胞瘤和胶质母细胞瘤。

[0089] 在另一个实施方案中,本发明的化合物可用于治疗诸如阿尔茨海默氏症、帕金森氏症和亨廷顿病等神经退行性疾病,以及唐氏综合症、精神发育迟滞和运动缺陷。

[0090] 另外,本发明的化合物可用于代谢性疾病、包括糖尿病和肥胖的治疗和/或预防。

[0091] 本发明还涉及药物组合物,其包含至少一种式(I)的化合物与一种或多种可药用赋形剂的组合。

[0092] 在本发明的药物组合物中,更具体地可以提及适合于口服、胃肠外、鼻、经皮或透皮、直肠、经舌、眼部或呼吸道施用的那些,尤其是片剂或糖衣丸、舌下片、小药囊(sachets)、药包(paquets)、胶囊、舌下给药剂型(glossettes)、锭剂、栓剂、霜剂、软膏剂、皮肤凝胶和可饮用或可注射安瓿。

[0093] 剂量可以根据患者的性别、年龄和体重、施用途经、治疗适应症或任意相关治疗的

性质的不同而改变,且范围在0.01mg—5g/24小时内,分一次或多次施用。

[0094] 此外,本发明还涉及式(I)化合物与选自基因毒物、有丝分裂抑制剂、抗代谢药、蛋白酶体抑制剂、激酶抑制剂、信号通路抑制剂、磷酸酶抑制剂、细胞凋亡诱导剂和抗体的抗癌药的组合,并且还涉及包含该类组合的药物组合物及其在制备用于治疗癌症的药物中的用途。

[0095] 式(I)化合物与抗癌剂的组合可以同时或顺序施用。施用途优选口服途径,并且相应的药物组合物可以瞬间或延迟释放活性成分。组合中的化合物可以以各自含有一种活性成分的两种独立的药物组合物的形式施用,或者以其中的活性成分以混合物存在的单一药物组合物的形式施用。

[0096] 本发明的化合物还可以与放疗组合用于治疗癌症。

[0097] 缩写列表

[0098]	缩写	名称
[0099]	Ac	乙酰基
[0100]	aq.	含水的
[0101]	Bn	苄基
[0102]	Boc	叔丁氧基羰基保护基
[0103]	dppf	1,1'-双(二苯基膦)二茂铁
[0104]	DCM	二氯甲烷
[0105]	DEAD	偶氮二甲酸二乙酯
[0106]	DIBAL	二异丁基氢化铝
[0107]	DMAP	4-二甲基氨基吡啶
[0108]	DMF	N,N-二甲基甲酰胺
[0109]	DMSO	二甲基亚砷
[0110]	dtbpf	1,1'-双(二叔丁基膦)二茂铁
[0111]	eq.	当量
[0112]	Et	乙基
[0113]	IPA	异丙醇
[0114]	HPLC-MS	液相色谱-质谱
[0115]	LiHMDS	二(三甲基硅基)氨基锂
[0116]	mCBPA	间氯过氧苯甲酸
[0117]	Me	甲基
[0118]	NBS	N-溴琥珀酰亚胺
[0119]	ⁿ Bu	正丁基
[0120]	ⁿ BuPAd ₂	正丁基二金刚烷基膦
[0121]	Pd/C	钯碳
[0122]	Ph	苯基
[0123]	PPh ₃	三苯基膦
[0124]	pTSA	对甲苯磺酸
[0125]	RT	保留时间

- [0126] sat. 饱和的
 [0127] SEM [2-(三甲基硅烷基)乙氧基]甲基
 [0128] ^tBu 叔丁基
 [0129] TFA 三氟乙酸
 [0130] THF 四氢呋喃

[0131] 通用方法

[0132] 所有得自商品来源的试剂不经进一步纯化直接使用。无水溶剂得自商品来源并且不经进一步干燥直接使用。快速色谱用预填充硅胶短柱 (Strata SI-1; **61Å**, Phenomenex, Cheshire UK 或 IST Flash II, **54Å**, Argonaut, Hengoed, UK) 进行, 或通过自动快速色谱用 Combiflash R_f 装置 (Teledyne Isco Inc.) 用 RediSep R_f 预填充硅胶柱 (Teledyne Isco Inc.) 或 SilaSep 预填充柱 (Silicycle Inc.) 进行。薄层色谱用涂敷 Merck 60F₂₅₄ 型硅胶的 5x 10cm 板进行。

[0133] 本发明的化合物通过高效液相色谱-质谱 (HPLC-MS) 在 Agilent HP1200 快速分辨质谱检测器 6140 多模源 M/z 范围 150 至 1000 amu 或 Agilent HP1100 质谱检测器 1946D ESI 源 M/z 范围 150 至 1000 amu 上进行表征。下面列出的条件和方法对这两种机器是相同的。

[0134] 运行时间为 7.5 分钟的柱: GeminiNX, 5μm, C18, 30x 2.1mm (Phenomenex) 或 Zorbax Eclipse Plus, 3.5μm, C18, 30x 2.1mm (Agilent)。温度: 35℃。

[0135] 运行时间为 3.75 分钟的柱: GeminiNX, 5μm, C18, 30x 2.1mm (Phenomenex) 或 Zorbax Eclipse Plus, 3.5μm, C18, 30x 2.1mm (Agilent)。温度: 35℃。

[0136] 运行时间为 1.9 分钟的柱: Kinetex, 2.5μm, C18, 50x 2.1mm (Phenomenex) 或 Accucore, 2.6μm, C18, 50x 2.1mm。温度: 55℃。

[0137] 流动相: A-H₂O+10mmol/甲酸铵+0.08% (v/v) 甲酸, pH 约 3.5。

[0138] B-95% 乙腈+5%A+0.08% (v/v) 甲酸。

[0139] 注射体积: 1μL

[0140] 方法 A“短”法梯度表, 正 (pos) 或正和负 (pos/neg) 电离

[0141]

时间 (min)	溶剂 A (%)	溶剂 B (%)	流速 (mL/min)
0	95	5	1
0.25	95	5	1
2.50	5	95	1
2.55	5	95	1.7
3.60	5	95	1.7
3.65	5	95	1
3.70	95	5	1
3.75	95	5	1

[0142] 方法 B“超短”法梯度表, 正 (pos) 或正和负 (pos/neg) 电离

[0143]

时间 (min)	溶剂 A (%)	溶剂 B (%)	流速 (mL/min)
0	95	5	1.3

0.12	95	5	1.3
1.30	5	95	1.3
1.35	5	95	1.6
1.85	5	95	1.6
1.90	5	95	1.3
1.95	95	5	1.3

[0144] 检测:在230、254和270nm UV检测。

[0145] 还通过核磁共振(NMR)对本发明的化合物进行了表征。分析用Bruker DPX-400波谱仪进行,在400MHz测定质子NMR。光谱对照是已知的溶剂化学位移。质子核磁共振数据报告如下:以ppm为单位的化学位移(δ),在其之后是裂分多重性,其中s=单峰,d=二重峰,t=三重峰,q=四重峰,quint=五重峰,m=多重峰,dd=双二重峰,dt=双三重峰,dm=双多重峰,ddd=双双二重峰,td=三二重峰,qd=四二重峰,br=宽峰,最后是积分值。

[0146] 某些本发明的化合物通过制备型HPLC纯化。所述纯化在Waters FractionLynx MS自动纯化系统上进行,使用来自Phenomenex的**Gemini**[®]5 μ m C18(2),100mm $\times$ 20mm i.d.柱,运行流速20cm³min⁻¹,UV二极管阵列检测(210-400nm),并根据质量进行收集。

[0147] 在pH 4条件下:溶剂A=10mM乙酸铵在HPLC级水中的溶液+0.08%v/v甲酸。溶剂B=95%v/v HPLC级乙腈+5%v/v溶剂A+0.08%v/v甲酸。

[0148] 在pH 9条件下:溶剂A=10mM乙酸铵在HPLC级水中的溶液+0.08%v/v氨溶液。溶剂B=95%v/v HPLC级乙腈+5%v/v溶剂A+0.08%v/v氨溶液。

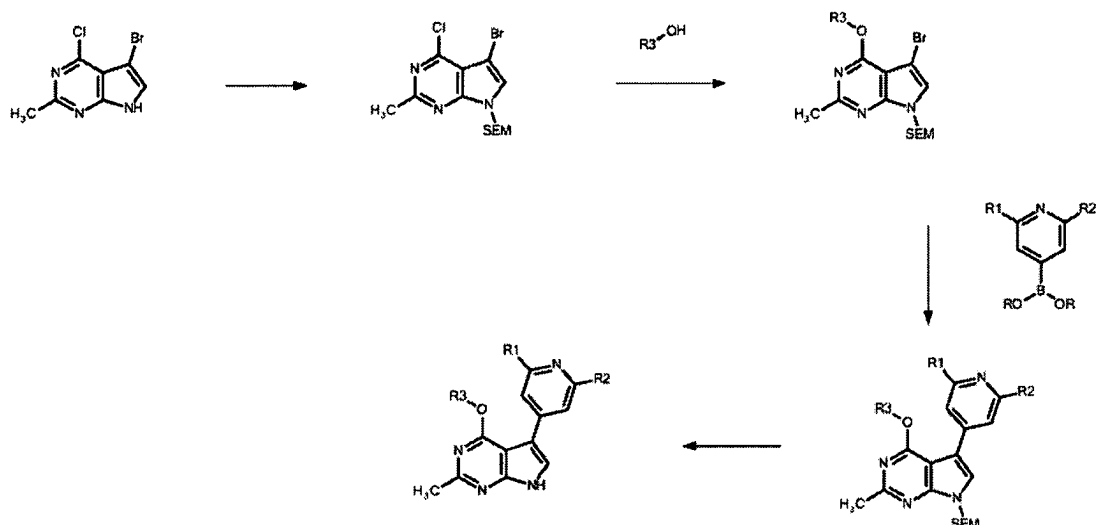
[0149] 质谱仪为Waters Micromass ZQ2000波谱仪,正或负离子电喷雾电离模式操作,分子量的扫描范围为150到1000。

[0150] 某些本发明的化合物用连接到带有ESI源的Agilent TOF 6230单四极杆的Agilent 1290 Infinity II系列仪器进行表征。除非另有说明,以正负切换模式电离记录高分辨率质谱。紫外检测采用二极管阵列检测器,波长为230、254和270nm。柱:Thermo Accucore 2.6 μ m C18,50 $\times$ 2mm,柱温55 $^{\circ}$ C。缓冲液A:水/10mM甲酸铵/0.04%(v/v)甲酸,pH=3.5。缓冲液B:乙腈/5.3%(v/v)A/0.04%(v/v)甲酸(注射体积:1 μ L)。

[0151] 以下制备例和实施例举例说明了本发明,但不以任何方式限定本发明。

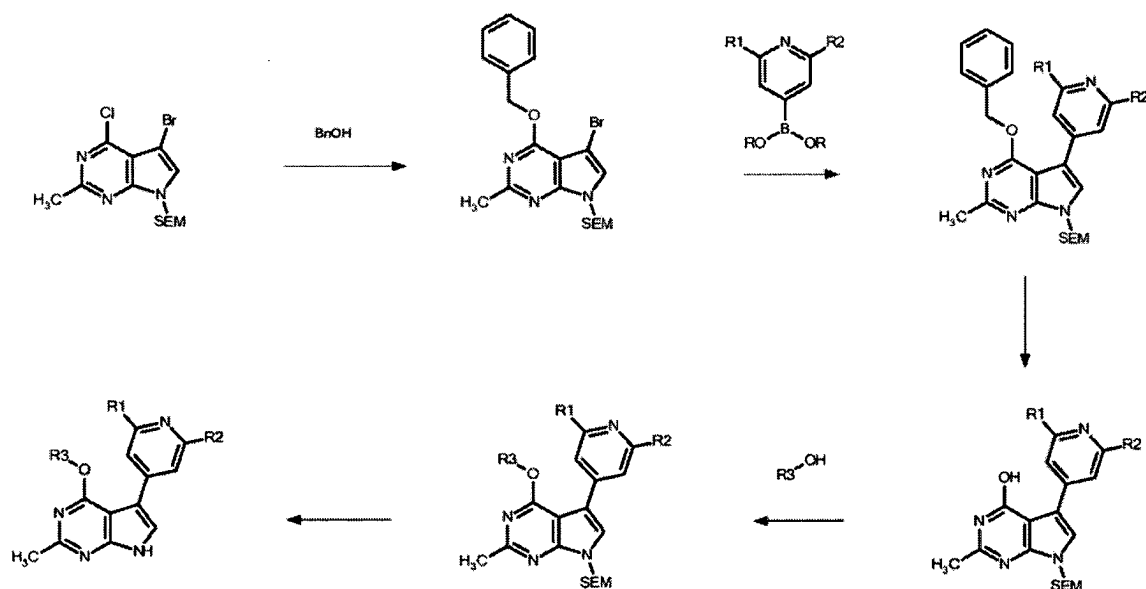
[0152] 通用方法I

[0153]



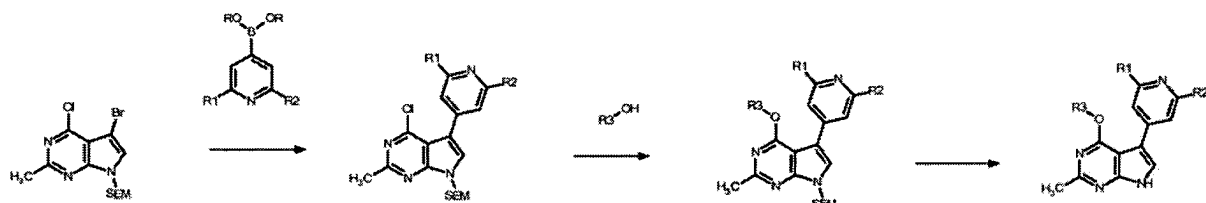
[0154] 通用方法II

[0155]



[0156] 通用方法III

[0157]



[0158] 在通用方法I、II和III中:

[0159] -R₁和R₂如式(I)中所定义,

[0160] -R₃代表直链或支链的(C₁-C₆)烷基、-(C₀-C₆)亚烷基-Cy₁、-(C₀-C₆)亚烷基-Cy₁-Cy₂,应当理解的是,Cy₁和Cy₂彼此独立地代表环烷基、杂环烷基、芳基或杂芳基。

[0161] 实施例1:4-甲氧基-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶

[0162] 步骤1:5-溴-4-氯-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(制备例1)

[0163] 向5-溴-4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶(1g,4.06mmol)的DMF(30mL)溶液中在0℃及氮气氛下加入NaH(60%的矿物油分散液,1eq)。将反应混合物搅拌30分钟,然后在0℃下加入SEM-Cl(1.1eq)并在氮气氛下升温至室温过夜。将反应混合物用乙醚(100mL)稀释,用盐水(4x 50mL)洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到白色固体状产物(1.18g,3.13mmol,77%)。

[0164] ^1H NMR(399MHz,DMSO- d_6) δ 8.12(s,1H),5.65(s,2H),3.67-3.57(m,2H),2.74(s,3H),0.98-0.87(m,2H),0.00(s,9H)。

[0165] LC/MS(方法B):RT=1.59min;m/z=RT=1.59min;m/z=377[M+H] $^+$

[0166] 步骤2:5-溴-4-甲氧基-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(制备例2)

[0167] 向NaH(60%的矿物油分散液,2eq)的THF(10mL)悬浮液中加入步骤1所得到的化合物(0.5g,1.3mmol)的THF(3mL)溶液。将反应混合物于0℃搅拌30分钟,然后在1小时内升温至室温。将反应混合物用饱和氯化铵水溶液(20mL)和EtOAc(20mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩得到澄清油状产物(0.494g,1.3mmol,100%)。该化合物不经进一步纯化直接使用。

[0168] ^1H NMR(399MHz,DMSO- d_6) δ 7.75(s,1H),5.59(s,2H),4.12(s,3H),3.64-3.55(m,2H),2.65(s,3H),0.97-0.87(m,2H),0.00(s,9H)。

[0169] LC/MS(方法B):RT=1.53min;m/z=374[M+H] $^+$

[0170] 步骤3:4-甲氧基-2-甲基-5-(吡啶-4-基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(制备例3)

[0171] 将步骤2中得到的化合物和(吡啶-4-基)硼酸(1.5eq)在氮气氛下溶于THF/水(6:1,5mL)。加入碳酸钾(3eq)和Pd(dtbpf)Cl₂(10%wt)并将形成的混合物在氮气氛下脱气5分钟。将反应混合物在CEM微波反应器上于120℃加热1小时。将反应混合物用水(10mL)和EtOAc(20mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到油状产物(0.11g,0.30mmol,44%)。

[0172] ^1H NMR(399MHz,DMSO- d_6) δ 8.67-8.61(m,2H),8.11(s,1H),7.83-7.77(m,2H),5.68(s,2H),4.13(s,3H),3.70-3.61(m,2H),2.68(s,3H),0.99-0.88(m,2H),0.00(s,9H)。

[0173] LC/MS(方法A):RT=1.37min;m/z=371[M+H] $^+$

[0174] 步骤4:4-甲氧基-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶(制备例4)

[0175] 向步骤3所得到的化合物(0.11g,0.3mmol)的THF(3mL)溶液中加入乙二胺(5eq),然后加入TBAF(1M的THF溶液,5eq)。将反应液在CEM微波反应器上于120℃加热1小时。将反应混合物用水(10mL)和EtOAc(10mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。然后将残余物用EtOAc研磨得到白色固体状产物(15mg,0.06mmol,21%)。

[0176] ^1H NMR(399MHz,DMSO- d_6) δ 12.33(s,1H),8.58-8.50(m,2H),7.85(s,1H),7.78-7.72(m,2H),4.05(s,3H),2.57(s,3H)。

[0177] LC/MS(方法A):RT=1.49min;m/z=241[M+H] $^+$

[0178] 实施例6:2-甲基-5-(2-甲基吡啶-4-基)-4-[(3R)-哌啶-3-基甲氧基]-7H-吡咯并[2,3-d]嘧啶

[0179] 步骤1:4-(苄基氧基)-5-溴-2-甲基-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶

[0180] 从5-溴-4-氯-2-甲基-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶(实施例1,步骤1)(5g,13.27mmol)和苄醇(1.3eq)开始,按照制备例2所述的方法得到浅黄色油状所需产物(5.4g,12mmol,91%)。

[0181] ^1H NMR (399MHz, DMSO- d_6) δ 7.77 (s, 1H), 7.68-7.60 (m, 2H), 7.54-7.45 (m, 2H), 7.47-7.38 (m, 1H), 5.67 (s, 2H), 5.60 (s, 2H), 3.65-3.55 (m, 2H), 2.67 (s, 3H), 0.97-0.87 (m, 2H), 0.00 (s, 9H)。

[0182] LC/MS (方法A): RT=3.04min; m/z=450 [M+H] $^+$

[0183] 步骤2:4-(苄基氧基)-2-甲基-5-(2-甲基吡啶-4-基)-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶

[0184] 从步骤1所得到的化合物(2g,4.46mmol)和(2-甲基吡啶-4-基)硼酸(1.2eq)开始,采用制备例3所述的方法。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到棕色油状产物(1.311g,2.8mmol,64%)。

[0185] ^1H NMR (399MHz, DMSO- d_6) δ 8.36 (dd, 1H), 8.08 (s, 1H), 7.66-7.40 (m, 7H), 5.67 (s, 2H), 5.63 (s, 2H), 3.69-3.60 (m, 2H), 2.71 (s, 3H), 2.31 (s, 3H), 0.99-0.90 (m, 2H), 0.00 (s, 9H)。

[0186] 步骤3:2-甲基-5-(2-甲基吡啶-4-基)-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-4-酚(制备例5)

[0187] 将步骤2所得到的化合物(1.311g,2.8mmol)和Pd/C(10%wt)的EtOH(40mL)悬浮液在 H_2 氛下室温搅拌2小时。将悬浮液用硅藻土塞过滤并真空浓缩。将残余物用异己烷研磨得到米色固体状产物(0.886g,2.39mmol,84%)。

[0188] ^1H NMR (399MHz, DMSO- d_6) δ 12.14 (s, 1H), 8.47-8.40 (m, 1H), 8.01-7.91 (m, 3H), 5.54 (s, 2H), 3.62 (dd, 2H), 2.53 (s, 3H), 2.43 (s, 3H), 0.92 (dd, 2H), 0.00 (s, 9H)。

[0189] 步骤4:(3R)-3-([2-甲基-5-(2-甲基吡啶-4-基)-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-4-基]氧基)甲基)哌啶-1-甲酸叔丁酯(制备例6)

[0190] 向步骤3所得到的化合物(100mg,0.27mmol)和(3R)-3-(羟基甲基)哌啶-1-甲酸叔丁酯(1.5eq)的THF(5mL)溶液中在室温及氮气氛下加入 PPh_3 (1.5eq)。将反应混合物在室温下搅拌10分钟然后在冰浴中冷却,然后加入DEAD(1.5eq)。移走冰浴并将反应混合物在室温下搅拌2小时。将反应混合物真空浓缩并将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到澄清油状产物(122mg,0.214mmol,80%)。

[0191] ^1H NMR (399MHz, DMSO- d_6) δ 8.51 (d, 1H), 8.08 (s, 1H), 7.72 (s, 1H), 7.61 (d, 1H), 5.67 (s, 2H), 4.51 (dd, 1H), 4.40 (dd, 1H), 3.68-3.59 (m, 2H), 3.43 (s, 9H), 2.66 (s, 3H), 2.56 (s, 3H), 1.88 (d, 1H), 1.69 (s, 1H), 1.47-1.19 (m, 7H), 0.99-0.87 (m, 2H), 0.00 (s, 9H)。

[0192] 步骤5:2-甲基-5-(2-甲基吡啶-4-基)-4-[(3R)-哌啶-3-基甲氧基]-7H-吡咯并[2,3-d]嘧啶(制备例7)

[0193] 向步骤4得到的化合物(78mg,0.137mmol)的DCM(5mL)溶液中在氮气氛及室温下加

入TFA (3mL) 并搅拌3小时。将反应混合物直接上样到scx-2柱 (10g) 上, 用MeOH和DCM洗涤并用1N NH₃的MeOH溶液洗脱。将级分真空浓缩并将残余物通过快速色谱纯化, 用2N NH₃的MeOH溶液和DCM洗脱得到白色固体状所需产物 (18mg, 0.024mmol, 17%)。

[0194] ¹H NMR (399MHz, DMSO-d₆) δ12.24 (s, 1H), 8.38 (d, 1H), 7.80 (s, 1H), 7.66 (d, 1H), 7.54 (dd, 1H), 4.30 (qd, 2H), 3.05-2.96 (m, 1H), 2.84 (dt, 1H), 2.54 (s, 3H), 2.51 (s, 3H), 2.47-2.36 (m, 1H), 2.32 (dd, 1H), 1.97-1.86 (m, 1H), 1.79 (dd, 1H), 1.62-1.49 (m, 1H), 1.46-1.02 (m, 3H)。

[0195] LC/MS (方法A): RT=1.35min; m/z=338 [M+H]⁺

[0196] 实施例20: 4-[2-甲基-4-(1-苯基乙氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0197] 步骤1: 4-(4-氯-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺

[0198] 从5-溴-4-氯-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶 (0.91g, 2.42mmol) 和4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-胺 (1.1eq) 开始, 按照制备例3所述的方法得到白色固体状所需产物 (0.257g, 0.659mmol, 27%)。

[0199] ¹H NMR (399MHz, DMSO-d₆) δ8.02 (t, 2H), 6.74-6.63 (m, 2H), 6.08 (s, 2H), 5.72 (s, 2H), 3.66 (dd, 2H), 2.76 (s, 3H), 0.99-0.88 (m, 2H), 0.00 (s, 9H)。

[0200] LC/MS (方法A): RT=2.16min; m/z=390 [M+H]⁺

[0201] 步骤2: 4-[2-甲基-4-(1-苯基乙氧基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0202] 从步骤1所得到的化合物 (100mg, 0.25mmol) 和1-苯基乙-1-醇 (1.3eq) 开始, 按照制备例2所述的方法得到油状产物 (107mg, 0.224mmol, 90%)。

[0203] LC/MS (方法B): RT=1.38min; m/z=476 [M+H]⁺

[0204] 步骤3: 4-[2-甲基-4-(1-苯基乙氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0205] 从步骤2所得到的化合物 (107mg, 0.224mmol) 开始, 按照制备例4所述的方法得到白色固体状所需产物 (40mg, 0.115mmol)。

[0206] ¹H NMR (399MHz, DMSO-d₆) δ12.22 (s, 1H), 7.96 (d, 1H), 7.67 (s, 1H), 7.59-7.51 (m, 2H), 7.47-7.38 (m, 2H), 7.40-7.31 (m, 1H), 6.99-6.88 (m, 2H), 6.54 (q, 1H), 5.86 (s, 2H), 2.6 (s, 3H), 1.76 (d, 3H)。

[0207] LC/MS (方法B): RT=1.09min; m/z=346 [M+H]⁺

[0208] 下表1中的实施例1-28通过通用方法I-III所描述的方法用适宜的可购买到的硼酸酯和醇制备。也包括了实施例1、6、20的化合物。表1: HRMS (TOF, ESI) 数据

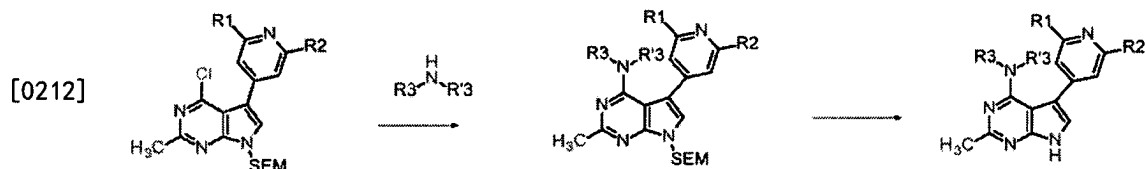
[0209]

实施例	结构式	分子式	计算的精确质量	实测值 m/z	加合物
1	4-甲氧基-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₃ H ₁₂ N ₄ O	240.1011	241.1082	[M+H] ⁺
2	4-(4-甲氧基-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₁₃ H ₁₃ N ₅ O	255.1120	256.1196	[M+H] ⁺
3	5-(2-氟吡啶-4-基)-4-甲氧基-2-甲基-7H-吡咯并[2,3-d]嘧啶	C ₁₃ H ₁₁ FN ₄ O	258.0917	259.0996	[M+H] ⁺
4	4-甲氧基-2-甲基-5-(2-甲基吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₄ H ₁₄ N ₄ O	254.1168	255.1238	[M+H] ⁺
5	2-甲基-5-(2-甲基吡啶-4-基)-4-(噻吩-3-基甲氧基)-7H-吡咯并[2,3-d]嘧啶	C ₁₈ H ₁₆ N ₄ OS	336.1045	337.1129	[M+H] ⁺
6	2-甲基-5-(2-甲基吡啶-4-基)-4-[(3R)-哌啶-3-基甲氧基]-7H-吡咯并[2,3-d]嘧啶	C ₁₉ H ₂₃ N ₅ O	337.1903	338.1982	[M+H] ⁺
7	4-(环丙基甲氧基)-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₆ H ₁₆ N ₄ O	280.1324	281.1400	[M+H] ⁺
8	4-(2-环丙基乙氧基)-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₇ H ₁₈ N ₄ O	294.1481	293.1409	[M-H] ⁻
9	4-[2-(1H-咪唑-3-基)乙氧基]-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₂₂ H ₁₉ N ₅ O	369.1590	370.1657	[M+H] ⁺
10	2-甲基-4-(2-苯基乙氧基)-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₂₀ H ₁₈ N ₄ O	330.1481	331.1547	[M+H] ⁺
11	4-(苄基氧基)-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₉ H ₁₆ N ₄ O	316.1324	317.1391	[M+H] ⁺
12	2-甲基-5-(吡啶-4-基)-4-[2-(吡咯烷-1-基)乙氧基]-7H-吡咯并[2,3-d]嘧啶	C ₁₈ H ₂₁ N ₅ O	323.1746	324.1818	[M+H] ⁺
13	2-甲基-4-[2-(哌啶-1-基)乙氧基]-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₉ H ₂₃ N ₅ O	337.1903	338.1975	[M+H] ⁺
14	2-甲基-5-(吡啶-4-基)-4-(四氢呋喃-2-基甲氧基)-7H-吡咯并[2,3-d]嘧啶	C ₁₇ H ₁₈ N ₄ O ₂	310.1430	311.1508	[M+H] ⁺

[0210]

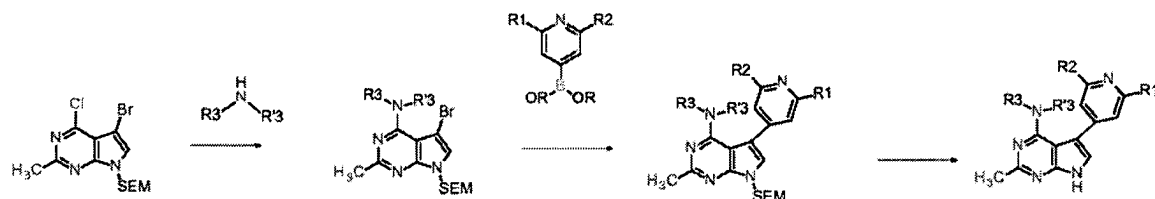
15	4-(环戊基甲氧基)-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₈ H ₂₀ N ₄ O	308.1637	309.1711	[M+H] ⁺
16	2-甲基-4-[(5-甲基-1,2-噁唑-3-基)甲氧基]-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶	C ₁₇ H ₁₅ N ₅ O ₂	321.1226	322.1299	[M+H] ⁺
17	4-[2-甲基-4-(噻吩-3-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₇ H ₁₅ N ₅ OS	337.0997	338.1068	[M+H] ⁺
18	4-[2-甲基-4-(1,3-噻唑-5-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₆ H ₁₄ N ₆ OS	338.0950	339.1025	[M+H] ⁺
19	4-[2-甲基-4-(噻吩-2-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₇ H ₁₅ N ₅ OS	337.0997	338.1072	[M+H] ⁺
20	4-[2-甲基-4-(1-苯基乙氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₀ H ₁₉ N ₅ O	345.1590	346.1654	[M+H] ⁺
21	4-{2-甲基-4-[2-(4-甲基-1,3-噻唑-5-基)乙氧基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₁₈ H ₁₈ N ₆ OS	366.1263	367.1343	[M+H] ⁺
22	4-[2-甲基-4-(吡啶-3-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₈ H ₁₆ N ₆ O	332.1386	333.1453	[M+H] ⁺
23	4-[2-甲基-4-(吡啶-4-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₈ H ₁₆ N ₆ O	332.1386	333.1452	[M+H] ⁺
24	4-(4-{[5-(4-氟苯基)-1,2-噁唑-3-基]甲氧基}-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₂ H ₁₇ FN ₆ O ₂	416.1397	417.1459	[M+H] ⁺
25	4-([5-(2-氨基吡啶-4-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-基]氧基)甲基苄腈	C ₂₀ H ₁₆ N ₆ O	356.1386	357.1464	[M+H] ⁺
26	4-{4-[(4-甲氧基苄基)氧基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₀ H ₁₉ N ₅ O ₂	361.1539	360.1463	[M-H] ⁻
27	4-(2-甲基-4-{[4-(丙-2-基)苄基]氧基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₂ H ₂₃ N ₅ O	373.1903	374.1972	[M+H] ⁺
28	4-[2-甲基-4-(1,3-噻唑-4-基甲氧基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₆ H ₁₄ N ₆ OS	338.0950	339.1019	[M+H] ⁺

[0211] 通用方法IV



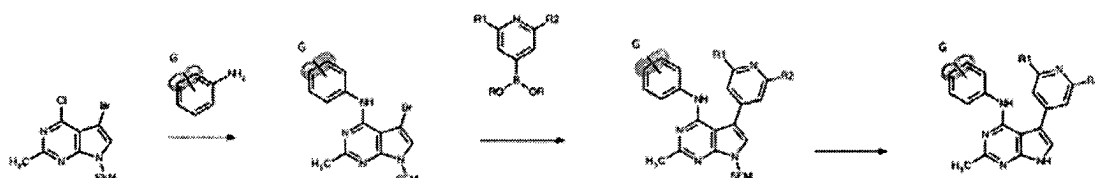
[0213] 通用方法V

[0214]



[0215] 通用方法VI

[0216]



[0217] 在通用方法IV、V和VI中:

[0218] -R₁和R₂如式(I)中所定义,

[0219] -R₃代表氢原子、直链或支链的(C₁-C₆)烷基、-(C₀-C₆)亚烷基-Cy₁、-(C₀-C₆)亚烷基-Cy₁-Cy₂、-(C₀-C₆)亚烷基-Cy₁-O-(C₁-C₆)亚烷基-Cy₂,应当理解的是,Cy₁和Cy₂彼此独立地代表环烷基、杂环烷基、芳基或杂芳基,

[0220] 并且R'₃代表氢原子或直链或支链的(C₁-C₆)烷基,

[0221] 或者R₃和R'₃与携带它们的氮原子形成杂环烷基或杂芳基,

[0222] -G代表选自式(I)中所定义的取代基列表的基团,应当理解的是,苯基可以被1至4个独立的G基团取代。

[0223] **实施例30:** 4-[2-甲基-4-(吡咯烷-1-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0224] 步骤1: 4-[2-甲基-4-(吡咯烷-1-基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺(制备例8)

[0225] 向4-(4-氯-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺(实施例20,步骤1)(50mg, 0.128mmol)的THF(3mL)溶液中加入吡咯烷(3eq)。将反应混合物在CEM微波反应器上于90℃加热1小时(通过LC-MS监测反应)。将反应混合物用DCM(10mL)和水(10mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩得到所需产物(58mg, >100%)。经LCMS估计的纯度约为90%。该化合物不经进一步纯化直接使用。

[0226] LC/MS(方法A): RT=2.08min; m/z=425[M+H]⁺

[0227] 步骤2: 4-[2-甲基-4-(吡咯烷-1-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0228] 从步骤1所得到的化合物(58mg)开始,按照制备例4所述的方法得到白色固体状所

需产物 (23mg, 0.078mmol, 两步的收率为61%)。

[0229] ^1H NMR (DMSO- d_6) δ : 11.71 (s, 1H), 7.86 (d, 1H), 7.17 (d, 1H), 6.56-6.44 (m, 2H), 5.89 (s, 2H), 3.31 (m, 4H), 2.41 (s, 3H), 1.72-1.63 (m, 4H)

[0230] **实施例32**: 5-(2-氨基吡啶-4-基)-N-苄基-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺
步骤1: N-苄基-5-溴-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[0231] 从5-溴-4-氯-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶(实施例1, 步骤1) (1g, 2.65mmol) 和苯基甲胺 (4eq) 开始, 采用制备例8所述的方法。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到澄清油状产物 (1.08g, 2.41mmol, 91%)。

[0232] ^1H NMR (399MHz, DMSO- d_6) δ : 7.55 (s, 1H), 7.49-7.26 (m, 5H), 7.04 (t, 1H), 5.51 (s, 2H), 4.85 (d, 2H), 3.62-3.53 (m, 2H), 2.47 (s, 3H), 0.99-0.85 (m, 2H), 0.00 (s, 9H)。

[0233] LC/MS (方法A): RT=2.95min; m/z=449 [M+H] $^+$

[0234] 步骤2: 5-(2-氨基吡啶-4-基)-N-苄基-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[0235] 从步骤1所得到的化合物 (0.702g, 1.57mmol) 和4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-胺 (1.1eq) 开始, 按照制备例3所述的方法得到浅棕色油状所需产物 (0.335g, 0.727mmol, 46%)。

[0236] ^1H NMR (399MHz, DMSO- d_6) δ : 7.97 (dd, 1H), 7.50-7.34 (m, 5H), 7.35-7.26 (m, 1H), 6.65-6.56 (m, 2H), 6.09 (t, 1H), 6.06 (s, 2H), 5.58 (s, 2H), 4.77 (d, 2H), 3.67-3.58 (m, 2H), 2.51 (s, 3H), 0.98-0.84 (m, 2H), 0.00 (s, 9H)。

[0237] LC/MS (方法A): RT=2.33min; m/z=461 [M+H] $^+$

[0238] 步骤3: 5-(2-氨基吡啶-4-基)-N-苄基-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0239] 从步骤2所得到的化合物 (0.335g, 0.727mmol) 开始, 按照制备例4所述的方法得到白色固体状所需产物 (51mg, 0.154mmol, 21%)。

[0240] ^1H NMR (399MHz, DMSO- d_6) δ : 11.73 (s, 1H), 7.89 (d, 1H), 7.42-7.28 (m, 4H), 7.29-7.19 (m, 2H), 6.60-6.49 (m, 2H), 5.92 (d, 3H), 4.70 (d, 2H), 2.42 (s, 3H)。

[0241] LC/MS (方法A): RT=1.65min; m/z=331 [M+H] $^+$

[0242] **实施例52**: 5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0243] 步骤1: 5-溴-N-[(2,6-二氟苄基)甲基]-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[0244] 从5-溴-4-氯-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶(实施例1, 步骤1) (1.2g, 3.19mmol) 和(2,6-二氟苄基)甲胺 (4eq) 开始, 采用制备例8所述的方法。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到澄清油状所需产物。

[0245] ^1H NMR (399MHz, DMSO- d_6) δ : 7.56 (s, 1H), 7.46 (tt, 1H), 7.24-7.11 (m, 2H), 6.81 (t, 1H), 5.51 (s, 2H), 4.92 (d, 2H), 3.62-3.53 (m, 2H), 2.49 (s, 3H), 0.97-0.85 (m, 2H), 0.00 (s, 9H)。

[0246] LC/MS (方法A): RT=2.96min; m/z=485 [M+H] $^+$

[0247] 步骤2: 5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[0248] 从步骤1所得到的化合物(1g, 2.07mmol)和4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-胺(1.1eq)开始,按照制备例3所述的方法得到浅棕色油状所需产物(0.422g, 0.849mmol, 41%)。

[0249] ^1H NMR (399MHz, DMSO- d_6) δ 7.99 (dd, 1H), 7.52-7.39 (m, 2H), 7.22-7.11 (m, 2H), 6.61-6.53 (m, 2H), 6.05 (d, 3H), 5.57 (s, 2H), 4.85 (d, 2H), 3.66-3.57 (m, 2H), 2.53 (s, 3H), 1.00-0.86 (m, 2H), 0.00 (s, 9H)。

[0250] LC/MS (方法B): RT=1.32min; m/z =497 $[\text{M}+\text{H}]^+$

[0251] 步骤3: 5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0252] 从步骤2所得到的化合物(0.422g, 0.849mmol)开始,按照制备例4所述的方法得到白色固体状产物(0.104g, 0.284mmol, 33%)。

[0253] ^1H NMR (399MHz, DMSO- d_6) δ 11.74 (s, 1H), 7.90 (d, 1H), 7.37 (tt, 1H), 7.24 (d, 1H), 7.09 (t, 2H), 6.54-6.45 (m, 2H), 5.93 (s, 2H), 5.85 (t, 1H), 4.77 (d, 2H), 2.43 (s, 3H)。

[0254] LC/MS (方法B): RT=0.96min; m/z =367 $[\text{M}+\text{H}]^+$

[0255] 实施例129: 5-(2-氨基吡啶-4-基)-2-甲基-N-苄基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0256] 步骤1: 5-溴-2-甲基-N-苄基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺(制备例9)

[0257] 在室温及氮气氛围下,向5-溴-4-氯-2-甲基-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶(实施例1,步骤1)(0.2g, 0.53mmol)的DMF(2mL)溶液中加入苯胺(1.2eq),然后加入t-BuOK(2eq)。将反应混合物在室温下搅拌2小时。将反应混合物用水(10mL)和EtOAc(20mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到澄清油状产物(0.109g, 0.251mmol, 47%)。

[0258] LC/MS (方法B): RT=1.68min; m/z =433 $[\text{M}+\text{H}]^+$

[0259] 步骤2: N-{4-[2-甲基-4-(苄基氨基)-7-([2-(三甲基硅烷基)乙氧基]甲基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-基}氨基甲酸叔丁酯

[0260] 从步骤1所得到的化合物(0.109g, 0.251mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.2eq)开始,按照制备例3所述的方法得到澄清油状产物(0.118g, 0.215mmol, 86%)。

[0261] LC/MS (方法B): RT=1.68min; m/z =547 $[\text{M}+\text{H}]^+$

[0262] 步骤3: 5-(2-氨基吡啶-4-基)-2-甲基-N-苄基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0263] 从步骤2所得到的化合物(0.118g, 0.215mmol)开始,按照制备例7所述的方法得到浅黄色固体状所需产物(37mg, 0.117mmol, 54%)。

[0264] ^1H NMR (399MHz, DMSO- d_6) δ 12.00 (d, 1H), 8.00 (d, 1H), 7.72-7.65 (m, 3H), 7.45 (d, 1H), 7.35-7.28 (m, 2H), 7.00 (m, 1H), 6.71 (dd, 1H), 6.63 (d, 1H), 6.25 (s, 2H), 2.53 (s, 3H)。

[0265] LC/MS (方法B): RT=0.87min; m/z =317 $[\text{M}+\text{H}]^+$

[0266] 下表2中的实施例29-146通过通用方法IV-VI所描述的方法用适宜的可购买到的

硼酸酯和胺制备。也包括了实施例30、32、129的化合物。

[0267] 表2:HRMS (TOF,ESI) 数据

[0268]

实施例	结构式	分子式	计算的精确质量	实测值 m/z	加合物
29	5-(2-氨基吡啶-4-基)-N,N,2-三甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₄ H ₁₆ N ₆	268.1436	269.1519	[M + H] ⁺
30	4-[2-甲基-4-(吡咯烷-1-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₆ H ₁₈ N ₆	294.1593	295.1672	[M + H] ⁺
31	4-{4-[3-(二甲基氨基)吡咯烷-1-基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₁₈ H ₂₃ N ₇	337.2015	338.2085	[M + H] ⁺
32	5-(2-氨基吡啶-4-基)-N-苄基-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₉ H ₁₈ N ₆	330.1593	331.1661	[M + H] ⁺
33	4-[2-甲基-4-(4-甲基哌嗪-1-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₇ H ₂₁ N ₇	323.1858	324.1932	[M + H] ⁺
34	5-(2-氨基吡啶-4-基)-2-甲基-N-(吡啶-3-基甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₈ H ₁₇ N ₇	331.1545	332.1612	[M + H] ⁺
35	5-(2-氨基吡啶-4-基)-N-(呋喃-3-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₇ H ₁₆ N ₆ O	320.1386	321.1466	[M + H] ⁺
36	5-(2-氨基吡啶-4-基)-2-甲基-N-(噻吩-3-基甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₇ H ₁₆ N ₆ S	336.1157	337.1231	[M + H] ⁺
37	5-(2-氨基吡啶-4-基)-2-甲基-N-(噻吩-2-基甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₇ H ₁₆ N ₆ S	336.1157	337.1222	[M + H] ⁺

[0269]

38	5-(2-氨基吡啶-4-基)-2-甲基-N-[(1-甲基-1 <i>H</i> -吡唑-5-基)甲基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₇ H ₁₈ N ₈	334.1654	335.1722	[M + H] ⁺
39	5-(2-氨基吡啶-4-基)-2-甲基-N-(1,3-噻唑-2-基甲基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₆ H ₁₅ N ₇ S	337.1110	338.1179	[M + H] ⁺
40	5-(2-氨基吡啶-4-基)-2-甲基-N-(1,3-噻唑-4-基甲基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₆ H ₁₅ N ₇ S	337.1110	338.1189	[M + H] ⁺
41	5-(2-氨基吡啶-4-基)-2-甲基-N-(1,3-噻唑-5-基甲基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₆ H ₁₅ N ₇ S	337.1110	338.1179	[M + H] ⁺
42	N-苄基-2-甲基-5-(吡啶-4-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₇ N ₅	315.1484	316.1547	[M + H] ⁺
43	N-苄基-2-甲基-5-(2-甲基吡啶-4-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₉ N ₅	329.1640	330.1709	[M + H] ⁺
44	2-甲基-5-(吡啶-4-基)-N-(噻吩-3-基甲基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₇ H ₁₅ N ₅ S	321.1048	322.1121	[M + H] ⁺
45	2-甲基-5-(2-甲基吡啶-4-基)-N-(噻吩-3-基甲基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₈ H ₁₇ N ₅ S	335.1205	336.1283	[M + H] ⁺
46	2-甲基-N-[(5-甲基-1,2-噁唑-3-基)甲基]-5-(吡啶-4-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₇ H ₁₆ N ₆ O	320.1386	321.1450	[M + H] ⁺
47	2-甲基-N-[(5-甲基-1,2-噁唑-3-基)甲基]-5-(2-甲基吡啶-4-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₈ H ₁₈ N ₆ O	334.1542	335.1613	[M + H] ⁺
48	5-(2-氨基吡啶-4-基)-N-(环己基甲基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₂₄ N ₆	336.2062	337.2134	[M + H] ⁺

[0270]

49	5-(2-氨基吡啶-4-基)-2-甲基-N-(1-苯基乙基)-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{20}H_{20}N_6$	344.1749	345.1814	$[M + H]^+$
50	5-(2-氨基吡啶-4-基)-N-(3-氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{17}FN_6$	348.1499	349.1567	$[M + H]^+$
51	5-(2-氨基吡啶-4-基)-N-(2-氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{17}FN_6$	348.1499	347.1430	$[M - H]^-$
52	5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{16}F_2N_6$	366.1405	365.1341	$[M - H]^-$
53	5-(2-氨基吡啶-4-基)-2-甲基-N-(吡啶-2-基甲基)-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{18}H_{17}N_7$	331.1545	330.1471	$[M - H]^-$
54	5-(2-氨基吡啶-4-基)-N-(4-氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{17}FN_6$	348.1499	347.1416	$[M - H]^-$
55	5-(2-氨基吡啶-4-基)-N-(2-甲氧基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{20}H_{20}N_6O$	360.1699	359.1611	$[M - H]^-$
56	5-(2-氨基吡啶-4-基)-2-甲基-N-(2-甲基苄基)-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{20}H_{20}N_6$	344.1749	343.1675	$[M - H]^-$
57	5-(2-氨基吡啶-4-基)-N-(2-氯苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{17}ClN_6$	364.1203	363.1139	$[M - H]^-$
58	5-(2-氨基吡啶-4-基)-N-(2-氯-6-甲基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{20}H_{19}ClN_6$	378.1360	377.1292	$[M - H]^-$

[0271]

59	5-(2-氨基吡啶-4-基)-2-甲基-N-[(5-甲基-1,2-噁唑-3-基)甲基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₇ H ₁₇ N ₇ O	335.1495	334.1417	[M - H] ⁻
60	5-(2-氨基吡啶-4-基)-2-甲基-N-[(3-甲基吡啶-2-基)甲基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₉ N ₇	345.1702	344.1630	[M - H] ⁻
61	5-(2-氨基吡啶-4-基)-N-(2,6-二氯苄基)-2-甲基-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₆ Cl ₂ N ₆	398.0813	397.0746	[M - H] ⁻
62	5-(2-氨基吡啶-4-基)-N-(2-氯-6-氟苄基)-2-甲基-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₆ ClFN ₆	382.1109	381.1045	[M - H] ⁻
63	5-(2-氨基吡啶-4-基)-N-(2,4-二氟苄基)-2-甲基-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₆ F ₂ N ₆	366.1405	365.1323	[M - H] ⁻
64	5-(2-氨基吡啶-4-基)-2-甲基-N-[2-(三氟甲基)苄基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₇ F ₃ N ₆	398.1467	397.1402	[M - H] ⁻
65	5-(2-氨基吡啶-4-基)-N-(环丙基甲基)-2-甲基-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₆ H ₁₈ N ₆	294.1593	293.1535	[M - H] ⁻
66	5-(2-氨基吡啶-4-基)-2-甲基-N-[1-(吡啶-2-基)乙基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₉ N ₇	345.1702	344.1636	[M - H] ⁻
67	5-(2-氨基吡啶-4-基)-2-甲基-N-[(1 <i>S</i>)-1-苯基乙基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₂₀ N ₆	344.1749	343.1688	[M - H] ⁻
68	5-(2-氨基吡啶-4-基)-2-甲基-N-[(1 <i>R</i>)-1-苯基乙基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₂₀ N ₆	344.1749	343.1680	[M - H] ⁻

[0272]

69	5-(2-氨基吡啶-4-基)-N-(2-氟-6-甲氧基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₉ FN ₆ O	378.1604	377.1534	[M - H] ⁻
70	5-(2-氨基吡啶-4-基)-N-(2-氟-6-甲基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₉ FN ₆	362.1655	361.1593	[M - H] ⁻
71	5-(2-氨基吡啶-4-基)-N-[(3-氟吡啶-2-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₈ H ₁₆ FN ₇	349.1451	348.1370	[M - H] ⁻
72	5-(2-氨基吡啶-4-基)-N-(1H-咪唑-6-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₁₉ N ₇	369.1702	368.1629	[M - H] ⁻
73	5-(2-氨基吡啶-4-基)-2-甲基-N-(2,3,5-三氟苄基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₉ H ₁₅ F ₃ N ₆	384.1310	383.1246	[M - H] ⁻
74	5-(2-氨基吡啶-4-基)-N-(2,3-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₉ H ₁₆ F ₂ N ₆	366.1405	365.1328	[M - H] ⁻
75	5-(2-氨基吡啶-4-基)-N-[4-氟-2-(三氟甲基)苄基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₆ F ₄ N ₆	416.1373	415.1297	[M - H] ⁻
76	5-(2-氨基吡啶-4-基)-N-[(1R)-2,3-二氢-1H-茚-1-基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₂₀ N ₆	356.1749	355.1685	[M - H] ⁻
77	5-(2-氨基吡啶-4-基)-N-[(1S)-2,3-二氢-1H-茚-1-基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₂₀ N ₆	356.1749	355.1677	[M - H] ⁻
78	5-(2-氨基吡啶-4-基)-2-甲基-N-{[3-(三氟甲基)吡啶-2-基]甲基}-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₉ H ₁₆ F ₃ N ₇	399.1419	398.1370	[M - H] ⁻

[0273]

79	5-(2-氨基吡啶-4-基)- <i>N</i> -(2-乙氧基苄基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₁ H ₂₂ N ₆ O	374.1855	373.1783	[M - H] ⁻
80	5-(2-氨基吡啶-4-基)- <i>N</i> -[2-甲氧基-6-(三氟甲基)苄基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₁ H ₁₉ F ₃ N ₆ O	428.1572	427.1491	[M - H] ⁻
81	5-(2-氨基吡啶-4-基)- <i>N</i> -(2,3-二氯苄基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₆ Cl ₂ N ₆	398.0813	397.0744	[M - H] ⁻
82	5-(2-氨基吡啶-4-基)- <i>N</i> -[1-(2,6-二氟苯基)乙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₈ F ₂ N ₆	380.1561	379.1500	[M - H] ⁻
83	5-(2-氨基吡啶-4-基)- <i>N</i> -[(1 <i>R</i> ,2 <i>R</i> ,4 <i>S</i>)-二环[2.2.1]庚-2-基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₂₂ N ₆	334.1906	333.1845	[M - H] ⁻
84	5-(2-氨基吡啶-4-基)- <i>N</i> -(4-氟-2-甲氧基苄基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₉ FN ₆ O	378.1604	377.1540	[M - H] ⁻
85	5-(2-氨基吡啶-4-基)- <i>N</i> -[(1 <i>R</i>)-1-(2-甲氧基苯基)乙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₁ H ₂₂ N ₆ O	374.1855	373.1791	[M - H] ⁻
86	5-(2-氨基吡啶-4-基)- <i>N</i> -[(1 <i>R</i>)-1-(2-氟苯基)乙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₉ FN ₆	362.1655	361.1593	[M - H] ⁻
87	5-(2-氨基吡啶-4-基)-2-甲基- <i>N</i> -{[5-(吡啶-2-基)噻吩-2-基]甲基}-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₂ H ₁₉ N ₇ S	413.1423	412.1358	[M - H] ⁻
88	5-(2-氨基吡啶-4-基)-2-甲基- <i>N</i> -[(3-苯基-1,2-噁唑-5-基)甲基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₂ H ₁₉ N ₇ O	397.1651	396.1584	[M - H] ⁻

[0274]

89	5-(2-氨基吡啶-4-基)-2-甲基-N-[2-(三氟甲氧基)苄基]-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₇ F ₃ N ₆ O	414.1416	413.1342	[M - H] ⁻
90	5-(2-氨基吡啶-4-基)-N-[(1R,2R)-2-(苄基氧基)环己基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₈ H ₁₉ N ₇ O	428.2325	427.2252	[M - H] ⁻
91	5-(2-氨基吡啶-4-基)-2-甲基-N-[(1R)-1,2,3,4-四氢萘-1-基]-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₂ H ₂₂ N ₆	370.1906	369.1829	[M - H] ⁻
92	5-(2-氨基吡啶-4-基)-N-(2,5-二氯苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₉ H ₁₆ Cl ₂ N ₆	398.0813	397.0746	[M - H] ⁻
93	5-(2-氨基吡啶-4-基)-N-环己基-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₈ H ₂₂ N ₆	322.1906	321.1830	[M - H] ⁻
94	5-(2-氨基吡啶-4-基)-N-(3-氯-2-甲基苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₉ ClN ₆	378.1360	377.1288	[M - H] ⁻
95	5-(2-氨基吡啶-4-基)-N-[(3,5-二甲基-1,2-噁唑-4-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₈ H ₁₉ N ₇ O	349.1651	348.1587	[M - H] ⁻
96	4-[4-(3,4-二氢异喹啉-2(1H)-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₁ H ₂₀ N ₆	356.1749	355.1680	[M - H] ⁻
97	4-[2-甲基-4-(3-甲基哌啶-1-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₈ H ₂₂ N ₆	322.1906	323.1978	[M - H] ⁺
98	5-(2-氨基吡啶-4-基)-N-[(3-甲氧基吡啶-2-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₁₉ H ₁₉ N ₇ O	361.1651	362.1728	[M - H] ⁺
99	5-(2-氨基吡啶-4-基)-N-(2,3-二氢-1H-茚-2-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₂₀ N ₆	356.1749	357.1823	[M + H] ⁺

[0275]

100	5-(2-氨基吡啶-4-基)-2-甲基- <i>N</i> -(3,3,3-三氟丙基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₅ H ₁₅ F ₃ N ₆	336.1310	335.1250	[M - H] ⁻
101	4-[4-(3-氮杂螺[5.5]十一烷-3-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₂ H ₂₈ N ₆	376.2375	375.2309	[M - H] ⁻
102	4-[2-甲基-4-(8-甲基-2-氮杂螺[4.5]癸烷-2-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₂ H ₂₈ N ₆	376.2375	377.2441	[M - H] ⁺
103	4-[2-甲基-4-(2-苯基氮杂环丁烷-1-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₁ H ₂₀ N ₆	356.1749	357.1821	[M - H] ⁺
104	4-[2-甲基-4-(八氢异喹啉-2(1 <i>H</i>)-基)-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₁ H ₂₆ N ₆	362.2219	363.2285	[M - H] ⁺
105	4-{2-甲基-4-[4-(三氟甲基)哌啶-1-基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₁₈ H ₁₉ F ₃ N ₆	376.1623	375.1563	[M - H] ⁻
106	5-(2-氨基吡啶-4-基)- <i>N</i> -[(1 <i>S</i>)-1-(2-甲氧基苯基)乙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₁ H ₂₂ N ₆ O	374.1855	375.1920	[M - H] ⁺
107	4-{2-甲基-4-[2-(三氟甲基)吡咯烷-1-基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₁₇ H ₁₇ F ₃ N ₆	362.1467	363.1528	[M - H] ⁺
108	4-[4-(6,7-二氢噻吩并[3,2- <i>c</i>]吡啶-5(4 <i>H</i>)-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₁₉ H ₁₈ N ₆ S	362.1314	363.1393	[M - H] ⁺
109	4-[4-(2-氮杂螺[3.5]壬烷-2-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₀ H ₂₄ N ₆	348.2062	347.1993	[M - H] ⁻

[0276]

110	4-{2-甲基-4-[(4a <i>R</i> ,8a <i>R</i>)-八氢异喹啉-2(1 <i>H</i>)-基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₂₁ H ₂₆ N ₆	362.2219	361.2154	[M - H] ⁻
111	4-{2-甲基-4-[(4a <i>R</i> ,8a <i>S</i>)-八氢异喹啉-2(1 <i>H</i>)-基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₂₁ H ₂₆ N ₆	362.2219	361.2145	[M - H] ⁻
112	5-(2-氨基吡啶-4-基)- <i>N</i> -(2,3-二氢-1-苯并呋喃-3-基甲基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₁ H ₂₀ N ₆ O	372.1699	373.1761	[M - H] ⁺
113	5-(2-氨基吡啶-4-基)- <i>N</i> -[1-(3-甲氧基吡啶-2-基)乙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₂₁ N ₇ O	375.1808	376.1876	[M - H] ⁺
114	4-[4-(3,4-二氢异喹啉-2(1 <i>H</i>)-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2,6-二胺	C ₂₁ H ₂₁ N ₇	371.1858	370.1786	[M - H] ⁻
115	4-{4-[(2,6-二氟苄基)氨基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2,6-二胺	C ₁₉ H ₁₇ F ₂ N ₇	381.1513	382.1556	[M - H] ⁺
116	4-{4-[(2-氟-6-甲氧基苄基)氨基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2,6-二胺	C ₂₀ H ₂₀ FN ₇ O	393.1713	394.1774	[M - H] ⁺
117	4-(4-{[(1 <i>S</i>)-1-(2-甲氧基苄基)乙基]氨基}-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基)吡啶-2,6-二胺	C ₂₁ H ₂₃ N ₇ O	389.1964	390.2023	[M - H] ⁺
118	4-{4-[(1 <i>R</i>)-2,3-二氢-1 <i>H</i> -茚-1-基氨基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2,6-二胺	C ₂₁ H ₂₁ N ₇	371.1858	372.1936	[M - H] ⁺
119	5-(2-氨基吡啶-4-基)- <i>N</i> -[(3,5-二氟吡啶-4-基)甲基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₈ H ₁₅ F ₂ N ₇	367.1357	368.1421	[M - H] ⁺

[0277]

120	5-(2-氨基吡啶-4-基)- <i>N</i> -(2,6-二氟苄基)- <i>N</i> ,2-二甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₈ F ₂ N ₆	380.1561	381.1629	[M - H] ⁺
121	5-(2-氨基吡啶-4-基)- <i>N</i> -[1-(3-氟吡啶-2-基)丙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₂₀ FN ₇	377.1764	378.1836	[M - H] ⁺
122	5-(2-氨基吡啶-4-基)- <i>N</i> -[(1 <i>S</i>)-1-(3-氟吡啶-2-基)乙基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₈ FN ₇	363.1608	364.1636	[M - H] ⁺
123	5-(2-氨基吡啶-4-基)- <i>N</i> -(2,2-二氟-2-苯基乙基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₈ F ₂ N ₆	380.1561	381.1635	[M - H] ⁺
124	5-(2-氨基吡啶-4-基)-2-甲基- <i>N</i> -[2-(吡啶-2-基)乙基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₁₉ H ₁₉ N ₇	345.1702	346.1767	[M - H] ⁺
125	4-{4-[(2 <i>R</i> ,6 <i>S</i>)-2,6-二甲基吗啉-4-基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺+ 4-{4-[(2 <i>S</i> ,6 <i>R</i>)-2,6-二甲基吗啉-4-基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₁₈ H ₂₂ N ₆ O	338.1855	339.1931	[M - H] ⁺
126	4-{4-[(2 <i>R</i> ,6 <i>S</i>)-2,6-二甲基吗啉-4-基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2,6-二胺+ 4-{4-[(2 <i>S</i> ,6 <i>R</i>)-2,6-二甲基吗啉-4-基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2,6-二胺	C ₁₈ H ₂₃ N ₇ O	353.1964	354.2044	[M - H] ⁺
127	5-(2-氨基吡啶-4-基)- <i>N</i> -(1,3-苯并二氧杂环戊烯-4-基甲基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	C ₂₀ H ₁₈ N ₆ O ₂	374.1491	375.1494	[M - H] ⁺

[0278]

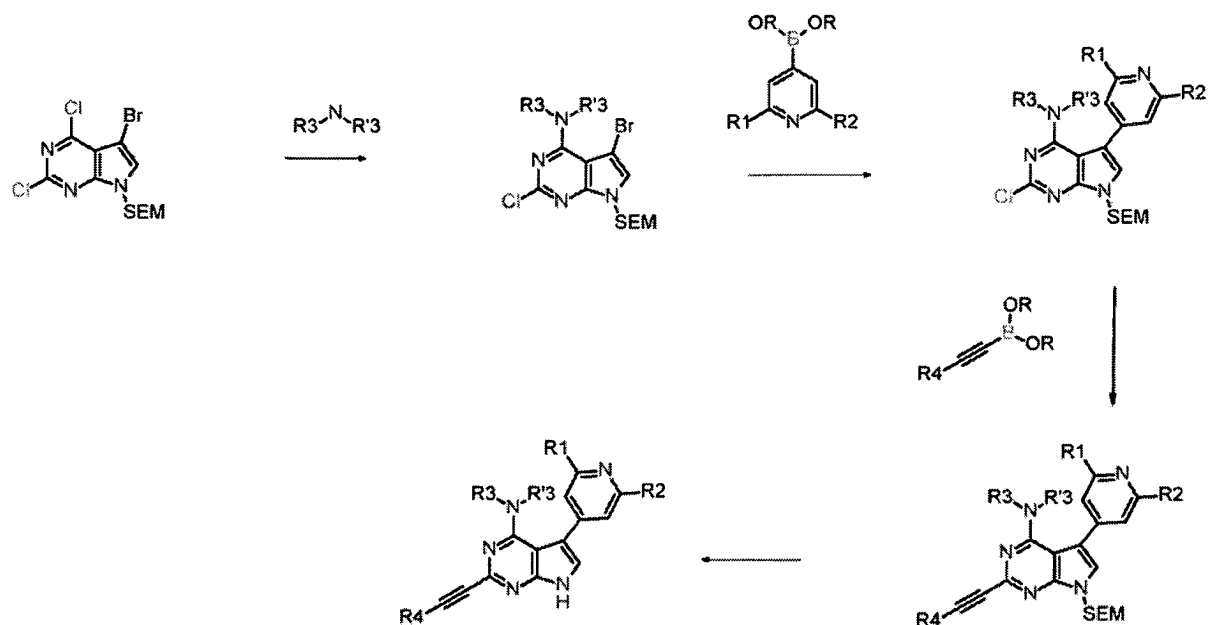
128	4-{4-[(1,3-苯并二氧杂环戊烯-4-基甲基)氨基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2,6-二胺	$C_{20}H_{19}N_7O_2$	389.1600	390.1593	$[M - H]^+$
129	5-(2-氨基吡啶-4-基)-2-甲基-N-苯基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{18}H_{16}N_6$	316.1436	317.1458	$[M - H]^+$
130	5-(2-氨基吡啶-4-基)-2-甲基-N-[2-(三氟甲基)苯基]-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{15}F_3N_6$	384.1310	385.1326	$[M - H]^+$
131	4-(2-甲基-4-{[2-(三氟甲基)苯基]氨基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2,6-二胺	$C_{19}H_{16}F_3N_7$	399.1419	400.1434	$[M - H]^+$
132	5-(2-氨基吡啶-4-基)-N-(1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{19}H_{16}N_6O_2$	360.1335	361.1332	$[M - H]^+$
133	4-[4-(4-甲氧基哌啶-1-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{18}H_{22}N_6O$	338.1855	339.1871	$[M - H]^+$
134	4-[2-甲基-4-(吗啉-4-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{16}H_{18}N_6O$	310.1542	311.1565	$[M - H]^+$
135	4-[4-(5,6-二氢咪唑并[1,2-a]吡嗪-7(8H)-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{18}H_{18}N_8$	346.1654	347.1663	$[M - H]^+$
136	4-[4-(7,8-二氢吡啶并[3,4-b]吡嗪-6(5H)-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{19}H_{18}N_8$	358.1654	359.1659	$[M - H]^+$
137	4-[2-甲基-4-(2-甲基吗啉-4-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{17}H_{20}N_6O$	324.1699	323.1544	$[M - H]^+$
138	4-[4-(3-甲氧基哌啶-1-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{18}H_{22}N_6O$	338.1855	339.1855	$[M - H]^+$

[0279]

139	4-[4-(4-甲氧基哌啶-1-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	$C_{18}H_{23}N_7O$	353.1964	354.1972	$[M - H]^+$
140	4-[2-甲基-4-(吗啉-4-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	$C_{16}H_{19}N_7O$	325.1651	326.1724	$[M - H]^+$
141	4-[4-(5,6-二氢咪唑并[1,2-a]吡嗪-7(8H)-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	$C_{18}H_{19}N_9$	361.1763	362.1764	$[M - H]^+$
142	4-[4-(7,8-二氢吡啶并[3,4-b]吡嗪-6(5H)-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	$C_{19}H_{19}N_9$	373.1763	374.1760	$[M - H]^+$
143	4-[2-甲基-4-(2-甲基吗啉-4-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	$C_{17}H_{21}N_7O$	339.1808	340.1845	$[M - H]^+$
144	4-[4-(3-甲氧基哌啶-1-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	$C_{18}H_{23}N_7O$	353.1964	354.1978	$[M - H]^+$
145	N-[2-甲氧基-6-(三氟甲基)苄基]-2-甲基-5-(吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{21}H_{18}F_3N_5O$	413.1463	414.1468	$[M - H]^+$
146	N-[2-甲氧基-6-(三氟甲基)苄基]-2-甲基-5-(2-甲基吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-4-胺	$C_{22}H_{20}F_3N_5O$	427.1620	428.1633	$[M - H]^+$

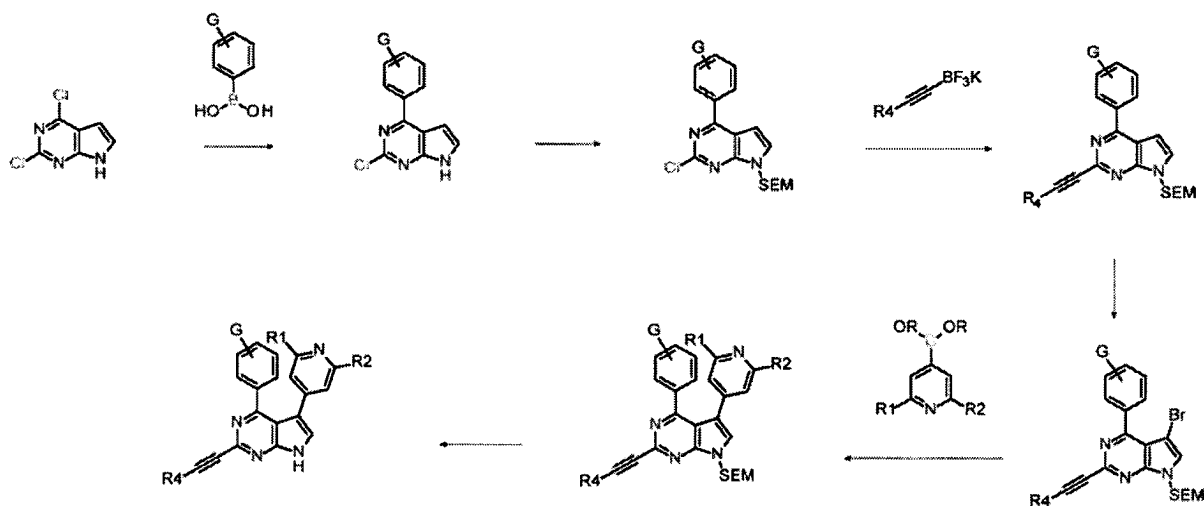
[0280] 通用方法VII

[0281]



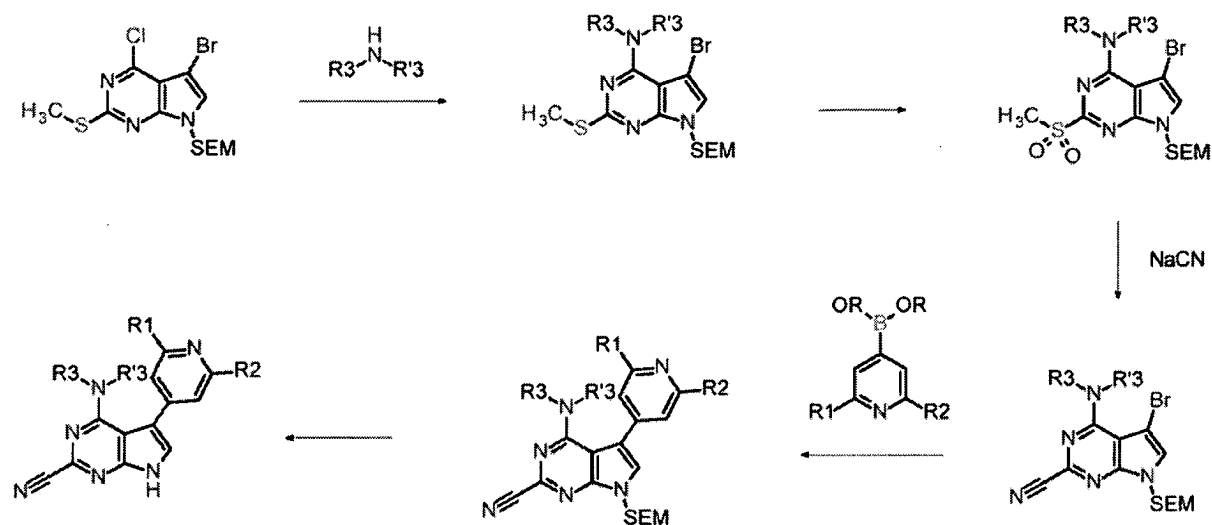
[0282] 通用方法VIII

[0283]



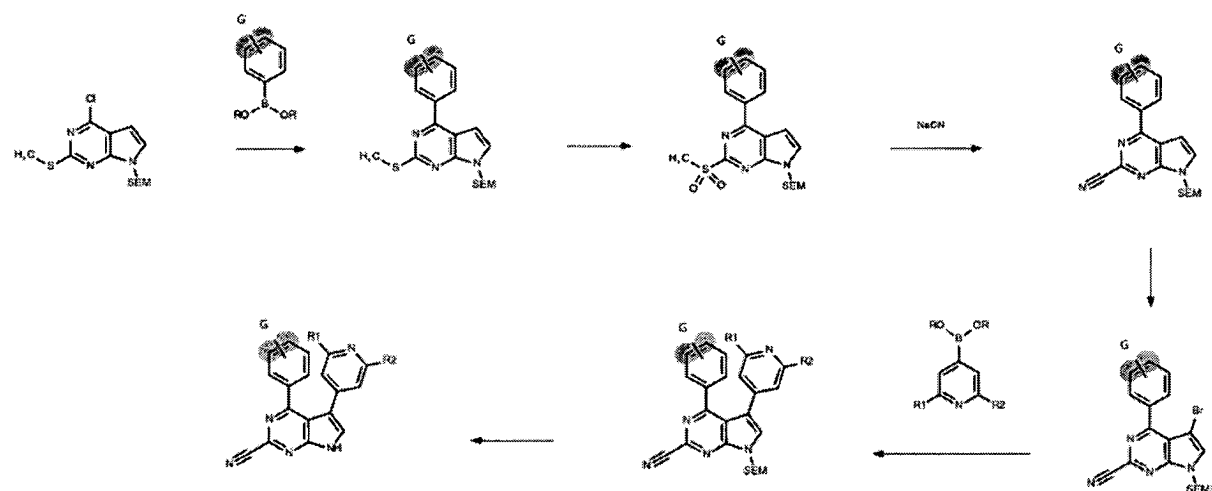
[0284] 通用方法IX

[0285]



[0286] 通用方法X

[0287]



[0288] 在通用方法VII、VIII、IX和X中:

[0289] -R₁和R₂如式(I)中所定义,

[0290] -R₃代表氢原子、直链或支链的(C₁-C₆)烷基、-(C₀-C₆)亚烷基-Cy₁、-(C₀-C₆)亚烷基-Cy₁-Cy₂、-(C₀-C₆)亚烷基-Cy₁-O-(C₁-C₆)亚烷基-Cy₂,应当理解的是,Cy₁和Cy₂彼此独立地代表环烷基、杂环烷基、芳基或杂芳基,

[0291] 并且R'₃代表氢原子或直链或支链的(C₁-C₆)烷基,[0292] 或者R₃和R'₃与携带它们的氮原子形成杂环烷基或杂芳基,[0293] -R₄代表氢原子、直链或支链的(C₁-C₆)烷基或环烷基,

[0294] -G代表选自式(I)中所定义的取代基列表的基团,应当理解的是,苯基可以被1至4个独立的G基团取代。

[0295] 实施例148: 5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-乙炔基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0296] 步骤1: 5-溴-2-氯-N-[(2,6-二氟苄基)甲基]-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-4-胺

[0297] 从5-溴-2,4-二氯-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(按照W02007/104944所述的方法制备)(1g, 2.52mmol)和(2,6-二氟苯基)甲胺(2eq)开始,采用制备例8所述的方法。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到澄清油状产物(1.25g, 2.48mmol, 98%)。

[0298] LC/MS(方法B):RT=3.0min;m/z=505[M+H]⁺

[0299] 步骤2:N-[4-(2-氯-4-{[(2,6-二氟苯基)甲基]氨基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-基]氨基甲酸叔丁酯

[0300] 从步骤1所得到的化合物(1.25g, 2.48mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.2eq)开始,按照制备例3所述的方法得到米色固体状所需产物(1.063g, 1.72mmol, 69%)。

[0301] ¹H NMR (399MHz, DMSO-d₆) δ9.93 (s, 1H), 8.30 (d, 1H), 7.95 (d, 1H), 7.76 (s, 1H), 7.44 (tt, 1H), 7.19-7.06 (m, 3H), 6.78 (t, 1H), 5.57 (s, 2H), 4.82 (d, 2H), 3.67-3.57 (m, 2H), 1.54 (s, 9H), 0.98-0.84 (m, 2H), 0.00 (s, 9H)。

[0302] LC/MS(方法B):RT=1.71min;m/z=617[M+H]⁺

[0303] 步骤3:4-{2-[2-(叔丁基二甲基硅烷基)乙炔基]-4-{[(2,6-二氟苯基)甲基]氨基}-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺(制备例10)

[0304] 将步骤2中得到的化合物(0.5g, 0.81mmol)和叔丁基二甲基[2-(四甲基-1,3,2-二氧硼戊环-2-基)乙炔基]硅烷(1.2eq)在氮气氛下溶于1,4-二恶烷(10mL)。加入2M Na₂CO₃水溶液(1mL)和四(三苯基膦)钯(0.08mmol)并将形成的混合物在氮气氛下脱气5分钟。将反应混合物在CEM微波反应器上于160℃加热1小时。将反应混合物用硅藻土塞过滤。将滤液用水(10mL)和EtOAc(50mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到黄色油状产物(0.379g)。通过LCMS估计的纯度约为50%。该化合物不经进一步纯化直接使用。

[0305] LC/MS(方法A):RT=2.84min;m/z=621[M+H]⁺

[0306] 步骤4:5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-乙炔基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0307] 从步骤3所得到的化合物(0.379g)开始,按照制备例4所述的方法得到白色固体状所需产物(13mg, 0.003mmol)。

[0308] ¹H NMR (400MHz, DMSO-d₆) δ12.19 (s, 1H), 7.97 (d, 1H), 7.54-7.41 (m, 2H), 7.19 (q, 2H), 6.62-6.54 (m, 2H), 6.09 (t, 1H), 6.03 (s, 2H), 4.86 (d, 2H), 4.06 (s, 1H)。

[0309] LC/MS(方法B):RT=0.99min;m/z=377[M+H]⁺

[0310] 实施例153:4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-(环丙基乙炔基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0311] 步骤1:4-(1,3-苯并二氧杂环戊烯-5-基)-2-氯-7H-吡咯并[2,3-d]嘧啶

[0312] 从2,4-二氯-7H-吡咯并[2,3-d]嘧啶(1g, 5.32mmol)和(1,3-苯并二氧杂环戊烯-5-基)硼酸(1.05eq)开始,按照制备例3所述的方法得到浅黄色固体状所需产物(1.45g, 3.84mmol)。通过LCMS估计的纯度约为70%。该化合物不经进一步纯化直接使用。

[0313] LC/MS(方法B):RT=1.2min;m/z=274[M+H]⁺

[0314] 步骤2:4-(1,3-苯并二氧杂环戊烯-5-基)-2-氯-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶

[0315] 从步骤1所得到的化合物(1.45g,3.84mmol)开始,按照制备例1所述的方法得到白色固体状所需产物(1.005g,2.49mmol,65%)。

[0316] ^1H NMR (399MHz, DMSO- d_6) δ 7.92 (d, 1H), 7.85 (dd, 1H), 7.73 (d, 1H), 7.21 (d, 1H), 7.12 (d, 1H), 6.25 (s, 2H), 5.68 (s, 2H), 3.73-3.53 (m, 2H), 0.99-0.83 (m, 2H), 0.00 (s, 9H)。

[0317] LC/MS (方法B): RT=1.57min; m/z=404 [M+H] $^+$

[0318] 步骤3:4-(1,3-苯并二氧杂环戊烯-5-基)-2-(环丙基乙炔基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶

[0319] 从步骤2所得到的化合物(0.45g,1.11mmol)和(2-环丙基-乙炔-1-基)-三氟硼酸钾(按照Org.Lett.,2010,12,3272-3275制备)(1.4eq)开始,按照制备例10所述的方法得到红色油状所需产物(0.22g,0.512mmol,46%)。

[0320] ^1H NMR (399MHz, DMSO- d_6) δ 7.95 (dd, 1H), 7.89-7.77 (m, 1H), 7.73 (dd, 1H), 7.26-7.03 (m, 2H), 6.27-6.18 (m, 2H), 5.71 (s, 2H), 3.74-3.58 (m, 2H), 1.50 (m, 1H), 1.01-0.83 (m, 6H), 0.00 (s, 9H)。

[0321] LC/MS (方法B): RT=1.61min; m/z=434 [M+H] $^+$

[0322] 步骤4:4-(1,3-苯并二氧杂环戊烯-5-基)-5-溴-2-(环丙基乙炔基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(制备例11)

[0323] 向步骤3所得到的化合物(0.22g,0.512mmol)的DMF(10mL)溶液中加入NBS(1.05eq)并将反应液在3小时内升温至室温。将反应混合物用水(20mL)和EtOAc(20mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到棕色油状产物(0.147g,0.286mmol,56%)。

[0324] ^1H NMR (399MHz, DMSO- d_6) δ 8.13 (s, 1H), 7.32-7.22 (m, 2H), 7.13 (d, 1H), 6.20 (s, 2H), 5.66 (s, 2H), 3.67-3.58 (m, 2H), 1.69 (tt, 1H), 1.04-0.99 (m, 2H), 0.95-0.86 (m, 4H), 0.00 (s, 9H)。

[0325] LC/MS (方法B): RT=1.64min; m/z=512 [M+H] $^+$

[0326] 步骤5:N-{4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-(环丙基乙炔基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-基}氨基甲酸叔丁酯

[0327] 从步骤4得到的化合物(0.110g,0.21mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始,按照制备例3所述的方法得到米色固体状所需产物(96mg,0.153mmol,71%)。

[0328] LC/MS (方法B): RT=1.63min; m/z=626 [M+H] $^+$

[0329] 步骤6:4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-(环丙基乙炔基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0330] 从步骤5得到的化合物(96mg,0.153mmol)开始,按照制备例7所述的方法得到米色固体状所需产物(34mg,0.083mmol,54%)。

[0331] ^1H NMR (399MHz, DMSO- d_6) δ 12.51 (s, 1H), 7.83 (s, 1H), 7.61 (d, 1H), 6.96 (d, 1H), 6.88-6.80 (m, 1H), 6.74 (d, 1H), 6.15 (t, 1H), 6.02 (s, 2H), 6.04-5.98 (m, 1H), 5.68 (s, 2H), 1.63 (tt, 1H), 1.07-0.90 (m, 2H), 0.91-0.79 (m, 2H)。

[0332] LC/MS (方法B): RT=0.99min; m/z=396 [M+H]⁺

[0333] 实施例157: 5-(2-氨基吡啶-4-基)-4-[(2,6-二氟苄基)氨基]-7H-吡咯并[2,3-d]嘧啶-2-甲腈

[0334] 步骤1: 5-溴-N-[(2,6-二氟苄基)甲基]-2-(甲硫基)-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-4-胺

[0335] 从5-溴-4-氯-2-(甲硫基)-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶(按照W02007/104944所述的方法制备)(0.77g, 1.88mmol)和2,6-二氟苄基胺(3eq)开始, 采用制备例8所述的方法制得浅黄色油状所需产物(0.856g, 1.66mmol, 88%)。

[0336] ¹H NMR (399MHz, DMSO-d₆) δ 7.49 (m, 2H), 7.18 (t, 2H), 6.97 (s, 1H), 5.49 (s, 2H), 4.94 (d, 2H), 3.58 (m, 2H), 2.55 (s, 3H), 0.98-0.87 (m, 2H), 0.00 (s, 9H)。

[0337] LC/MS (方法B): RT=1.7min; m/z=515 [M+H]⁺

[0338] 步骤2: 5-溴-N-[(2,6-二氟苄基)甲基]-2-甲磺酰基-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-4-胺(制备例12)

[0339] 向步骤1所得到的化合物(0.856g, 1.66mmol)的DCM(20mL)溶液中在0℃及氮气氛下分批加入mCBPA(2.5eq)。将反应混合物在相同的温度下搅拌1小时, 然后在2小时内升温至室温。将反应混合物用饱和碳酸氢钠水溶液(20mL)和DCM(20mL)稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩得到黄色油状产物(0.831g, 1.51mmol, 92%)。该化合物不经进一步纯化直接使用。

[0340] LC/MS (方法B): RT=1.53min; m/z=549 [M+H]⁺

[0341] 步骤3: 5-溴-4-[[[(2,6-二氟苄基)甲基]氨基]-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-2-甲腈(制备例13)

[0342] 向步骤2所得到的化合物(0.660g, 1.11mmol)的DMF(15mL)溶液中在氮气氛及室温下加入氰化钠(2.5eq)。将反应混合物于90℃加热2小时。将反应混合物冷却至室温, 用水(20mL)和EtOAc(20mL)稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到澄清油状产物(0.453g, 0.916mmol, 76%)。

[0343] ¹H NMR (399MHz, DMSO-d₆) δ 7.97 (s, 1H), 7.55-7.41 (m, 2H), 7.19 (t, 2H), 5.58 (s, 2H), 4.93 (d, 2H), 3.63-3.53 (m, 2H), 0.99-0.83 (m, 2H), 0.00 (s, 9H)。

[0344] LC/MS (方法A): RT=2.94min; m/z=496 [M+H]⁺

[0345] 步骤4: N-[4-(2-氰基-4-[[[(2,6-二氟苄基)甲基]氨基]-7-[[2-(三甲基硅烷基)乙氧基]甲基]-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-基]氨基甲酸叔丁酯

[0346] 从步骤3所得到的化合物(0.225g, 0.46mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始, 按照制备例3所述的方法得到白色固体状所需产物(0.135g, 1.51mmol, 49%)。

[0347] ¹H NMR (399MHz, DMSO-d₆) δ 9.96 (s, 1H), 8.32 (d, 1H), 8.03 (s, 1H), 7.97 (d, 1H), 7.45 (t, 1H), 7.19-7.08 (m, 3H), 6.94 (t, 1H), 5.67 (s, 2H), 4.84 (d, 2H), 3.63 (t, 2H), 0.99-0.85 (m, 2H), 0.00 (s, 9H)。

[0348] LC/MS (方法A): RT=2.98min; m/z=608 [M+H]⁺

[0349] 步骤5: 5-(2-氨基吡啶-4-基)-4-[(2,6-二氟苄基)氨基]-7H-吡咯并[2,3-d]嘧

啉-2-甲腈

[0350] 从步骤4得到的化合物(0.135g,1.51mmol)开始,按照制备例7所述的方法得到白色固体状所需产物(17mg,0.04mmol)。

[0351] ^1H NMR (399MHz,DMSO- d_6) δ 12.56 (s,1H),7.92 (d,1H),7.64 (s,1H),7.40 (tt,1H),7.11 (t,2H),6.54-6.43 (m,3H),5.98 (s,2H),4.77 (d,2H)。

[0352] LC/MS (方法B):RT=1.03min;m/z=378[M+H] $^+$

[0353] 实施例158:4-(1,3-苯并二氧杂环戊烯-5-基)-5-(2,6-二氨基吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-2-甲腈

[0354] 步骤1:4-(1,3-苯并二氧杂环戊烯-5-基)-2-(甲硫基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶

[0355] 从4-氯-2-(甲硫基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶(按照W02007/104944所述的方法制备)(0.411g,1.25mmol)和(1,3-苯并二氧杂环戊烯-5-基)硼酸(1.1eq)开始,按照制备例3所述的方法得到浅黄色油状所需产物(0.462g,1.11mmol,89%)。

[0356] ^1H NMR (399MHz,DMSO- d_6) δ 7.84 (dd,1H),7.78-7.69 (m,2H),7.20 (d,1H),6.99 (d,1H),6.24 (s,2H),5.68 (s,2H),3.68 (m,2H),2.71 (s,3H),1.00-0.86 (m,2H),0.00 (s,9H)。

[0357] LC/MS (方法B):RT=1.63min;m/z=416[M+H] $^+$

[0358] 步骤2:4-(1,3-苯并二氧杂环戊烯-5-基)-2-甲磺酰基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶

[0359] 从步骤1所得到的化合物(0.462g,1.11mmol)开始,按照制备例12所述的方法得到浅橙色油状所需产物(0.475g,1.06mmol,95%)。

[0360] ^1H NMR (399MHz,DMSO- d_6) δ 8.19 (d,1H),8.01-7.92 (m,2H),7.86 (d,1H),7.29 (d,1H),6.27 (s,2H),5.81 (s,2H),3.73-3.61 (m,2H),3.57 (s,3H),1.01-0.92 (m,2H),0.00 (s,9H)。

[0361] LC/MS (方法A):RT=2.7min;m/z=448[M+H] $^+$

[0362] 步骤3:4-(1,3-苯并二氧杂环戊烯-5-基)-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-2-甲腈

[0363] 从步骤2所得到的化合物(0.260g,0.58mmol)开始,按照制备例13所述的方法得到黑色油状所需产物(0.200g,0.51mmol,87%)。

[0364] LC/MS (方法A):RT=2.84min;m/z=395[M+H] $^+$

[0365] 步骤4:4-(1,3-苯并二氧杂环戊烯-5-基)-5-溴-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-2-甲腈

[0366] 从步骤3所得到的化合物(0.200g,0.51mmol)开始,按照制备例11所述的方法得到浅黄色固体状所需产物(0.183g,0.386mmol,76%)。

[0367] ^1H NMR (399MHz,DMSO- d_6) δ 8.45 (s,1H),7.40-7.28 (m,2H),7.17 (d,1H),6.22 (s,2H),5.74 (s,2H),3.71-3.57 (m,2H),0.97-0.89 (m,2H),0.00 (s,9H)。

[0368] LC/MS (方法B):RT=1.59min;m/z=473[M+H] $^+$

[0369] 步骤5:N-[6-(叔丁氧基羰基氨基)-4-(4,4,5,5-四甲基-1,3,2-二氧硼戊环-2-基)-2-吡啶基]氨基甲酸叔丁酯(制备例14)

[0370] 将(4-溴-6-叔丁氧基羰基氨基-吡啶-2-基)-氨基甲酸叔丁酯(按照J.Org.Chem.2004,69,543-548所述的方法制备)(10g,25.27mmol)、双(频哪醇合)二硼(1.5eq)、Pd(OAc)₂(0.05eq)、1,1'-双(二苯基膦)二茂铁(0.05eq)和KOAc(3eq)在氮气氛围及室温下溶于1,4-二恶烷(160mL)。将反应混合物在氮气氛围下于80℃搅拌过夜。将反应混合物冷却至室温,用硅藻土过滤并用温热的1,4-二恶烷洗涤。真空除去溶剂。将残余物通过快速色谱纯化,用EtOAc和DCM洗脱得到米色固体状产物(7.099g,16.3mmol,63%)。¹H NMR(399MHz,CDCl₃) δ8.16(brs,2H),7.92(s,2H),1.54(s,18H),1.34(s,12H)。

[0371] 步骤6:4-(1,3-苯并二氧杂环戊烯-5-基)-5-(2,6-二氨基吡啶-4-基)-7H-吡咯并[2,3-d]嘧啶-2-甲腈

[0372] 采用制备例3所述的方法,从步骤4得到的化合物(0.183g,0.386mmol)和步骤5得到的化合物(1.1eq)开始制备。将粗反应混合物真空浓缩并将残余物溶于DCM(2mL)和TFA(1.5mL),按照制备例7所述的方法得到白色固体状所需产物(8.4mg,0.022mmol,6%)。

[0373] ¹H NMR(399MHz,DMSO-d₆) δ13.07(s,1H),8.02(s,1H),7.09-6.97(m,2H),6.79(d,1H),6.04(s,2H),5.32(s,2H),5.21(s,4H)。

[0374] LC/MS(方法B):RT=0.92min;m/z=372[M+H]⁺

[0375] 下表3中的实施例147-158通过通用方法VII-X所描述的方法用适宜的可购买到的硼酸酯和胺制备。也包括了实施例148、153、157、158的化合物。

[0376] 表3:HRMS(TOF,ESI)数据

[0377]

实施例	结构式	分子式	计算的精确质量	实测值 m/z	加合物
147	5-(2-氨基吡啶-4-基)-2-环丙基-N-(2,6-二氟苄基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₁₈ F ₂ N ₆	392.1561	391.1494	[M - H] ⁻
148	5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-乙炔基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₄ F ₂ N ₆	376.1248	375.1193	[M - H] ⁻
149	5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-(丙-1-烯-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₁₈ F ₂ N ₆	392.1561	391.1479	[M - H] ⁻
150	5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-(丙-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₁ H ₂₀ F ₂ N ₆	394.1718	393.1650	[M - H] ⁻
151	5-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-2-乙烯基-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₀ H ₁₆ F ₂ N ₆	378.1405	377.1342	[M - H] ⁻
152	5-(2-氨基吡啶-4-基)-2-(环丙基乙炔基)-N-(2,6-二氟苄基)-7H-吡咯并[2,3-d]嘧啶-4-胺	C ₂₃ H ₁₈ F ₂ N ₆	416.1561	417.1618	[M - H] ⁺
153	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-(环丙基乙炔基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₃ H ₁₇ N ₅ O ₂	395.1382	396.1383	[M - H] ⁺
154	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-(环丙基乙炔基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	C ₂₃ H ₁₈ N ₆ O ₂	410.1491	411.1546	[M - H] ⁺

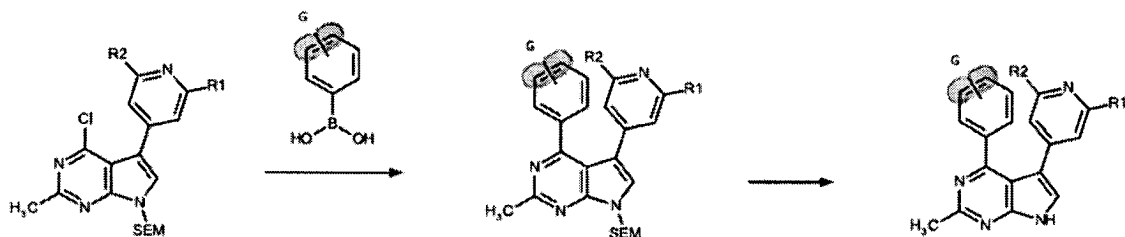
[0378]

155	4-[4-(1,3- 苯并二氧杂环戊烯-5-基)-2-乙炔基-7H-吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2,6-二胺	$C_{20}H_{14}N_6O_2$	370.1178	371.1182	$[M - H]^+$
156	4-[4-(1,3- 苯并二氧杂环戊烯-5-基)-2-乙炔基-7H-吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	$C_{20}H_{13}N_5O_2$	355.1069	356.1108	$[M - H]^+$
157	5-(2-氨基吡啶-4-基)-4-[(2,6-二氟苄基)氨基]-7H-吡咯并[2,3- <i>d</i>]嘧啶-2-甲腈	$C_{19}H_{13}F_2N_7$	377.1200	378.1242	$[M - H]^+$
158	4-(1,3- 苯并二氧杂环戊烯-5-基)-5-(2,6-二氨基吡啶-4-基)-7H-吡咯并[2,3- <i>d</i>]嘧啶-2-甲腈	$C_{19}H_{13}N_7O_2$	371.1131	370.1036	$[M - H]^-$

[0379] 实施例150利用制备例5所述的方法从实施例149制备。

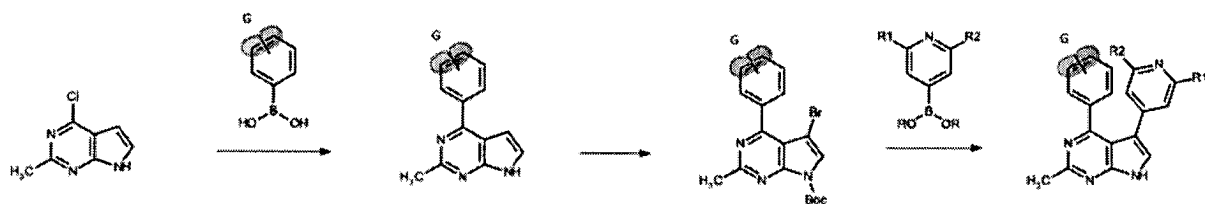
[0380] 通用方法XI

[0381]



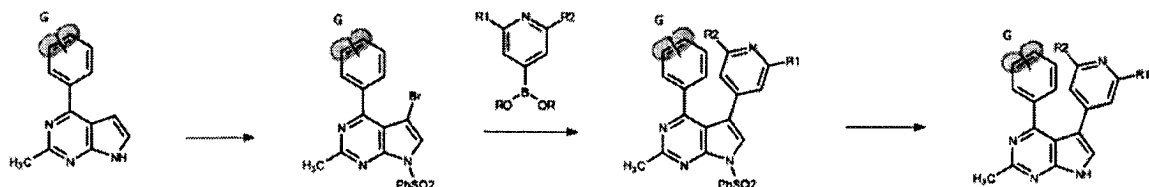
[0382] 通用方法XII

[0383]



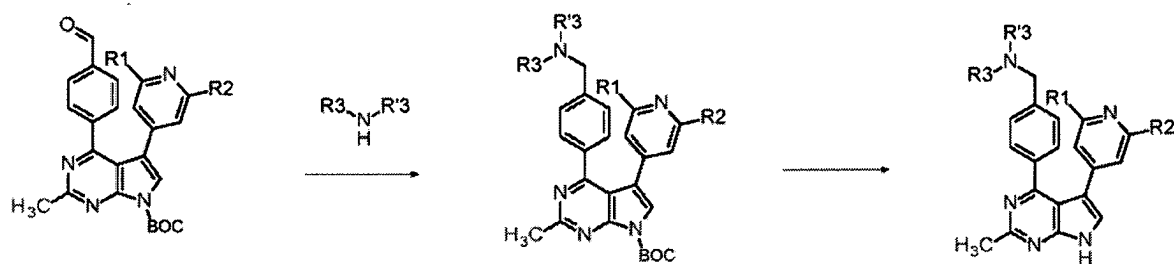
[0384] 通用方法XIII

[0385]

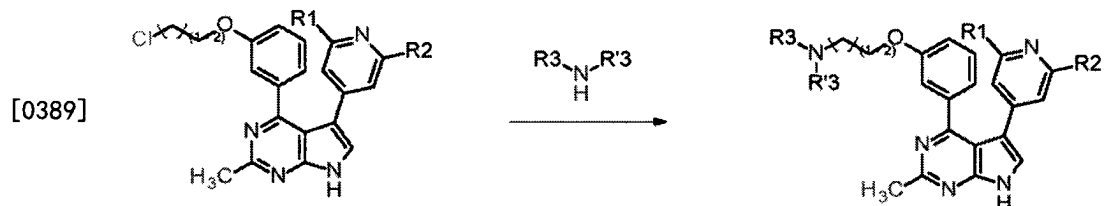


[0386] 通用方法XIV

[0387]



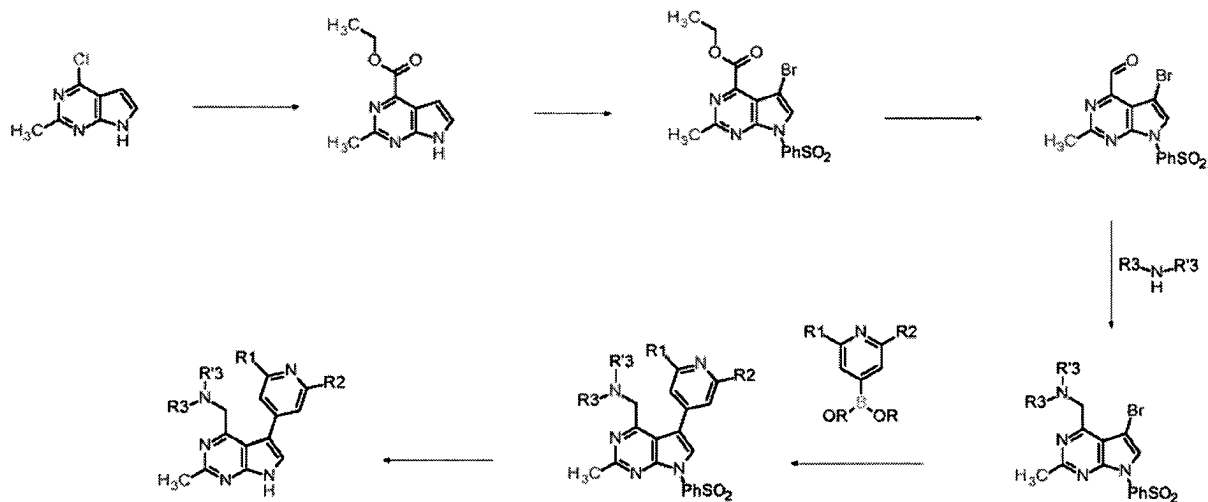
[0388] 通用方法XV



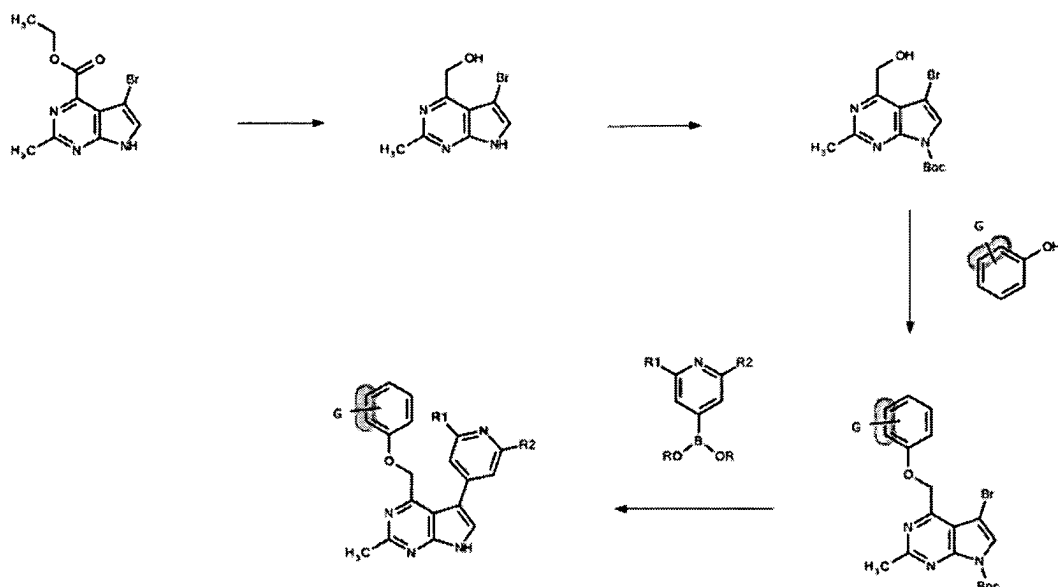
[0389]

[0390] 通用方法XVI

[0391]



[0392] 通用方法XVII



[0394] 在通用方法XI至XVII中:

[0395] -R₁和R₂如式(I)中所定义,

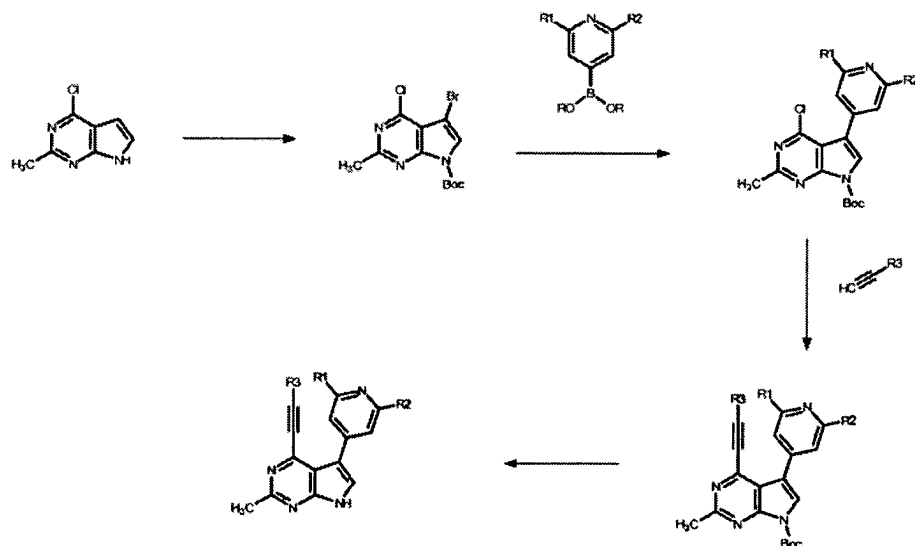
[0396] -R₃代表氢原子、直链或支链的(C₁-C₆)烷基、-(C₀-C₆)亚烷基-Cy₁、-(C₀-C₆)亚烷基-Cy₁-Cy₂、-(C₀-C₆)亚烷基-Cy₁-O-(C₁-C₆)亚烷基-Cy₂,应当理解的是,Cy₁和Cy₂彼此独立地代表环烷基、杂环烷基、芳基或杂芳基,

[0397] 并且R'₃代表氢原子或直链或支链的(C₁-C₆)烷基,

[0398] 或者R₃和R'₃与携带它们的氮原子形成杂环烷基或杂芳基,

[0399] -G代表选自式(I)中所定义的取代基列表的基团,应当理解的是,苯基可以被1至4个独立的G基团取代。

[0400] 通用方法XVIII



[0402] 其中R₃代表氢、环烷基、杂环烷基、芳基或杂芳基。

[0403] 实施例162: 4-[4-(3-氟-5-甲氧基苯基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0404] 步骤1: N-{4-[4-(3-氟-5-甲氧基苯基)-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]

甲基}-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-基]氨基甲酸叔丁酯

[0405] 从N-[4-(4-氯-2-甲基-7-{[2-(三甲基硅烷基)乙氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-基]氨基甲酸叔丁酯(按照实施例20,步骤1中所述的方法用N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯制备)(100mg,0.2mmol)和(3-氟-5-甲氧基苯基)硼酸(1.1eq)开始,按照制备例3所述的方法得到米色固体状所需产物(104mg,0.179mmol,88%)。

[0406] ^1H NMR (399MHz, DMSO- d_6) δ 9.69 (s, 1H), 8.15 (s, 1H), 8.06 (d, 1H), 7.52 (s, 1H), 6.94-6.79 (m, 2H), 6.72 (dd, 1H), 6.66 (dd, 1H), 5.77 (s, 2H), 3.70 (dd, 2H), 3.5 (s, 3H), 2.82 (s, 3H), 1.49 (s, 9H), 1.00-0.81 (m, 2H), 0.00 (s, 9H)。

[0407] LC/MS (方法B): RT=1.66min; m/z=580 [M+H] $^+$

[0408] 步骤2: 4-[4-(3-氟-5-甲氧基苯基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺(制备例15)

[0409] 向步骤1所得到的化合物(104mg,0.179mmol)的DCM(2mL)溶液中在0℃及氮气氛下滴加三氟化硼乙醚合物(2eq)并将反应混合物在4小时内升温至室温。将反应混合物用饱和碳酸氢钠水溶液(20mL)和DCM(20mL)稀释。将有机层分离并真空浓缩。将残余物溶于MeCN(2mL),加入氢氧化铵溶液(28%氨水,2mL)并将混合物在室温下搅拌2小时。将反应混合物真空浓缩并将残余物用乙醚研磨得到浅黄色粉末状产物(8.7mg,0.024mmol,14%)。

[0410] ^1H NMR (399MHz, DMSO- d_6) δ 12.39 (s, 1H), 7.74 (s, 1H), 7.59 (d, 1H), 6.89 (ddd, 1H), 6.81 (dt, 1H), 6.66 (dd, 1H), 6.20-6.14 (m, 1H), 5.99 (dd, 1H), 5.68 (s, 2H), 3.51 (s, 3H), 2.72 (s, 3H)。

[0411] LC/MS (方法B): RT=0.9min; m/z=350 [M+H] $^+$

[0412] 实施例164: 4-[4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0413] 步骤1: 4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶(制备例16)

[0414] 将4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶(0.511g,3.05mmol)和(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)硼酸(1.02eq)在氮气氛下溶于THF/水(10:1,10mL)。加入碳酸铯(2eq)和Pd(dppf)Cl₂(10%wt)并将形成的混合物在氮气氛下脱气5分钟。将反应混合物在CEM微波反应器上于140℃加热1小时。将混合物用水(150mL)稀释并将形成的沉淀通过过滤收集得到米色固体状产物(0.88g,3.04mmol,99%)。

[0415] LC/MS (方法B): RT=1.27min; m/z=290 [M+H] $^+$

[0416] 步骤2: 5-溴-4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯(制备例17)

[0417] 向步骤1所得到的化合物(0.88g,3.04mmol)的DMF(15mL)溶液中在0℃及氮气氛下分批加入NBS(1.1eq)并将反应混合物在2小时内升温至室温(通过LCMS监测反应)。向混合物中加入二碳酸二叔丁酯(1.2eq)、DMAP(0.01eq)和三甲基胺(2eq)并在氮气氛下在室温下搅拌过夜。将反应混合物用水(50mL)和EtOAc(50mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到浅黄色油状产物(0.681g,1.45mmol,48%)。

[0418] ^1H NMR (399MHz, DMSO- d_6) δ 8.05 (s, 1H), 7.72 (d, 1H), 7.59 (d, 1H), 7.50 (dd, 1H), 2.75 (s, 3H), 1.64 (s, 9H)。

[0419] LC/MS (方法B): RT=1.6min; m/z=470 [M+H] $^+$

[0420] 步骤3: 4-[4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺(制备例18)

[0421] 将步骤2中得到的化合物(0.681g, 1.45mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)在氮气氛下溶于THF/水(3:1, 20ml)。加入碳酸钾(3eq)和Pd(dtbpf)Cl₂(10%wt)并将形成的混合物在氮气氛下脱气5分钟。将反应混合物在氮气氛下于65℃加热过夜, 冷却至室温并用水(10mL)和DCM(50mL)稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到所需的偶联化合物。将化合物溶于2M HCl的MeOH溶液(4mL)并在CEM微波反应器上于90℃加热1小时。将反应混合物真空浓缩并用10% IPA的DCM溶液(20mL)稀释, 用饱和碳酸氢钠水溶液洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用MeOH和DCM洗脱, 用乙醚研磨后得到白色固体状产物(99mg, 0.26mmol, 26%)。

[0422] ^1H NMR (399MHz, DMSO- d_6) δ 12.39 (s, 1H), 7.74 (s, 1H), 7.58 (d, 1H), 7.36 (d, 1H), 7.27 (d, 1H), 7.19 (dd, 1H), 6.07 (t, 1H), 6.00 (dd, 1H), 5.68 (s, 2H), 2.72 (s, 3H)。

[0423] LC/MS (方法B): RT=0.96min; m/z=382 [M+H] $^+$

[0424] 实施例168: 4-{2-甲基-4-[3-(三氟甲基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺

[0425] 步骤1: 7-(苯磺酰基)-5-溴-2-甲基-4-[3-(三氟甲基)苯基]-7H-吡咯并[2,3-d]嘧啶(制备例19)

[0426] 向2-甲基-4-[3-(三氟甲基)苯基]-7H-吡咯并[2,3-d]嘧啶(按照实施例164, 步骤1中所述的方法用3-(三氟甲基)苯基]硼酸制备)(186mg, 0.67mmol)的DMF(5mL)溶液中加入在0℃及氮气氛下加入NBS(1.1eq)并将反应液在2小时内升温至室温。将反应混合物冷却至0℃, 加入NaH(60%的矿物油分散液, 1.4eq)并搅拌5分钟, 然后在氮气氛下加入苯磺酰氯(1.1eq)。将反应混合物升温至室温过夜, 用水(20mL)和EtOAc(20mL)稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到(201mg)棕色油状产物。通过LCMS估计的纯度约为70%。该化合物不经进一步纯化直接使用。

[0427] LC/MS (方法B): RT=1.57min; m/z=496 [M+H] $^+$

[0428] 步骤2: 4-[7-(苯磺酰基)-2-甲基-4-[3-(三氟甲基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0429] 从步骤1所得到的化合物(201mg)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始, 按照制备例3所述的方法得到黄色油状所需产物(106mg, 0.177mmol, 两步的收率为26%)。

[0430] LC/MS (方法B): RT=1.22min; m/z=510 [M+H] $^+$

[0431] 步骤3: 4-{2-甲基-4-[3-(三氟甲基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺(制备例20)

[0432] 向步骤2所得到的化合物(106mg, 0.177mmol)的MeOH(5mL)溶液中加入K₂CO₃(5eq)

并将形成的悬浮液在室温下搅拌过夜。将悬浮液过滤,真空浓缩并将残余物通过快速色谱纯化,用MeOH和DCM洗脱得到白色固体状产物(10mg,0.027mmol,15%)。

[0433] ^1H NMR (399MHz, DMSO- d_6) δ 12.42 (s, 1H), 7.87-7.79 (m, 1H), 7.74 (d, 2H), 7.56 (s, 2H), 7.61-7.47 (m, 1H), 6.17-6.11 (m, 1H), 5.90 (dd, 1H), 5.64 (s, 2H), 2.74 (s, 3H)。

[0434] LC/MS (方法B): RT=0.94min; m/z=370 [M+H] $^+$

[0435] 实施例169: 4-(2-甲基-4-{4-[(4-甲基哌嗪-1-基)甲基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺

[0436] 步骤1: 5-(2-{[(叔丁氧基)羰基]氨基}吡啶-4-基)-2-甲基-4-{4-[(4-甲基哌嗪-1-基)甲基]苯基}-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯(制备例21)

[0437] 在室温及氮气氛下,向5-(2-{[(叔丁氧基)羰基]氨基}吡啶-4-基)-4-(4-甲酰基苯基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯(按照实施例164中所述的方法用(4-甲酰基苯基)硼酸制备)(200mg,0.38mmol)的MeOH(5mL)溶液中加入1-甲基哌嗪(2eq),然后加入氰基硼氢化钠(1.5eq)。将反应混合物搅拌过夜。然后将其用饱和NaHCO₃水溶液(10mL)和DCM(10mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用MeOH和DCM洗脱得到白色固体状产物(86mg,0.14mmol,37%)。

[0438] ^1H NMR (399MHz, DMSO- d_6) δ 9.67 (s, 1H), 8.02-7.93 (m, 2H), 7.34 (s, 1H), 7.23 (d, 2H), 7.06 (d, 2H), 6.75 (dd, 1H), 3.44 (s, 2H), 2.78 (s, 3H), 2.5-2.2 (m, 8H), 2.18 (s, 3H), 1.67 (s, 9H), 1.44 (s, 9H)。

[0439] LC/MS (方法B): RT=1.26min; m/z=614 [M+H] $^+$

[0440] 步骤2: 4-(2-甲基-4-{4-[(4-甲基哌嗪-1-基)甲基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺(制备例22)

[0441] 将步骤1中得到的化合物(86mg,0.14mmol)溶于2M HCl的MeOH溶液(4mL)并在CEM微波反应器上于80℃加热1小时。将混合物真空浓缩并将残余物用乙醚研磨得到盐酸盐形式的产物(58mg,0.119mmol)。 ^1H NMR (399MHz, DMSO- d_6) δ 13.71 (brs, 1H), 13.23 (brs, 1H), 11.91 (brs, 1H), 8.25 (d, 1H), 7.77 (m, 4H), 7.56 (d, 2H), 6.48 (dd, 1H), 6.39 (d, 1H), 4.7-3.2 (m, 13H), 2.81 (s, 3H)。

[0442] LC/MS (方法B): RT=0.7min; m/z=414 [M+H] $^+$

[0443] 实施例174: 4-(2-甲基-4-{3-[3-(吗啉-4-基)丙氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺(制备例23)

[0444] 向4-{4-[3-(3-氯丙氧基)苯基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺(按照实施例168中所述的方法用2-[3-(3-氯丙氧基)苯基]-4,4,5,5-四甲基-1,3,2-二氧硼戊环(US2007/0004675)制备)(50mg,0.13mmol)的MeCN(2mL)溶液中加入NaI(4eq)、K₂CO₃(6eq)和吗啉(4eq)。将反应混合物在CEM微波反应器上于150℃加热30分钟。将反应混合物用10%MeOH的DCM溶液(5mL)稀释,用相分离柱过滤并真空浓缩。将残余物通过快速色谱纯化,用MeOH和DCM洗脱,在用MeCN研磨后得到米色固体状产物(30mg,0.067mmol,53%)。

[0445] ^1H NMR (399MHz, DMSO- d_6) δ 12.33 (s, 1H), 7.70 (s, 1H), 7.51 (d, 1H), 7.21 (t, 1H), 7.12 (dt, 1H), 6.95-6.87 (m, 1H), 6.85-6.79 (m, 1H), 6.19 (d, 1H), 5.91 (dd, 1H), 5.63 (s, 2H), 3.67 (t, 2H), 3.55 (t, 4H), 2.71 (s, 3H), 2.36 (s, 6H), 1.81-1.72 (m, 2H)。

[0446] LC/MS (方法B): RT=0.617min; m/z=445 [M+H] $^+$

[0447] 实施例178:4-[4-(2,3-二氢-1H-吡啶-1-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0448] 步骤1:2-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸乙酯(制备例24)

[0449] 将4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶(4g,23.87mmol)、乙酸钠(2eq)、Pd(OAc)₂(0.07eq)和1,1'-双(二苯基膦)二茂铁(0.07eq)在乙醇(140mL)中、在氮气氛下在Parr反应瓶中混合。将体系用一氧化碳净化3次并加压至28psi。将反应器加热至70℃并在Parr振动氢化装置中振摇过夜。将反应器冷却至室温,真空除去一氧化碳并将反应混合物用硅藻土塞过滤。将滤液真空浓缩并将残余物用水和乙醚研磨得到浅棕色固体状产物(3.811g,18.58mmol,78%)。

[0450] ¹H NMR(399MHz,DMSO-d₆) δ12.24(s,1H),7.69(d,1H),6.81(d,1H),4.43(q,2H),2.71(s,3H),1.39(t,3H)。

[0451] LC/MS(方法B):RT=0.92min;m/z=206[M+H]⁺

[0452] 步骤2:7-(苯磺酰基)-5-溴-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸乙酯

[0453] 从步骤1所得到的化合物(1.83g,3.8mmol)开始,按照制备例19所述的方法得到白色固体状所需产物(1.63g,3.8mmol,60%)。

[0454] ¹H NMR(399MHz,DMSO-d₆) δ8.36(s,1H),8.25-8.17(m,2H),7.85-7.74(m,1H),7.74-7.64(m,2H),4.44(q,2H),2.75(s,3H),1.34(t,3H)。

[0455] LC/MS(方法B):RT=1.41min;m/z=423[M+H]⁺

[0456] 步骤3:7-(苯磺酰基)-5-溴-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲醛(制备例25)

[0457] 在-78℃及氮气氛下,向步骤2所得到的化合物(0.5g,1.18mmol)的THF(13mL)溶液中加入DIBAL(1M的THF溶液,3eq)。将反应混合物在相同的温度下搅拌1小时,然后在2小时内升温至室温。冷却至-78℃,将混合物用水(1mL)和2N NaOH溶液(0.5mL)终止反应并使其升温至室温。向混合物中加入MgSO₄,用硅藻土塞过滤并真空浓缩得到产物(1.2g,>100%)。该化合物不经进一步纯化直接使用。

[0458] LC/MS(方法B):RT=1.31min;m/z=413,[M+H]⁺未见

[0459] 步骤4:1-[[7-(苯磺酰基)-5-溴-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-基]甲基]-2,3-二氢-1H-吡啶

[0460] 从步骤3所得到的化合物(1.2g)和二氢吡啶(1.2eq)开始,按照制备例21所述的方法得到白色固体状所需产物(0.193g,0.399mmol,两步的收率为34%)。

[0461] LC/MS(方法B):RT=1.57min;m/z=482[M+H]⁺

[0462] 步骤5:4-[7-(苯磺酰基)-4-(2,3-二氢-1H-吡啶-1-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0463] 从步骤4得到的化合物(0.193g,0.399mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始,按照制备例3所述的方法得到白色固体状所需产物(0.133g,0.267mmol,67%)。

[0464] ¹H NMR(399MHz,DMSO-d₆) δ8.28-8.20(m,2H),7.96-7.88(m,2H),7.83-7.74(m,1H),7.75-7.64(m,2H),6.93(dd,1H),6.79(td,1H),6.70(dd,1H),6.56(dd,1H),6.50(td,1H),6.09-5.99(m,3H),4.36(s,2H),3.03(t,2H),2.69(d,5H)。

[0465] LC/MS(方法B):RT=1.16min;m/z=497[M+H]⁺

[0466] 步骤6: 4-[4-(2,3-二氢-1H-吡啶-1-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0467] 从步骤5得到的化合物(0.133g, 0.267mmol)开始, 按照制备例20所述的方法得到米色固体状产物(41mg, 0.114mmol, 43%)。

[0468] ^1H NMR (399MHz, DMSO- d_6) δ 12.18 (d, 1H), 7.89 (d, 1H), 7.54 (d, 1H), 6.94 (dd, 1H), 6.81 (td, 1H), 6.65 (dd, 1H), 6.57-6.45 (m, 2H), 6.17 (d, 1H), 5.92 (s, 2H), 4.45 (s, 2H), 3.10 (t, 2H), 2.71 (t, 2H), 2.64 (s, 3H)。

[0469] LC/MS (方法B): RT=0.89min; m/z=357 [M+H] $^+$

[0470] 实施例193: 4-(2-甲基-4-{[2-(三氟甲基)苯氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺

[0471] 步骤1: {5-溴-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-基} 甲醇 (制备例26)

[0472] 向5-溴-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸乙酯 (按照实施例153, 步骤4中所述的方法从2-甲基-7H-吡咯并[2,3-d]嘧啶-4-甲酸乙酯 (制备例24) 开始制备) (0.500g, 1.76mmol) 的THF (10mL) 溶液中在0℃及氮气氛围下分批加入LiBH₄ (2eq)。将反应混合物升温至室温过夜。将反应混合物用饱和碳酸氢钠水溶液 (10mL) 和EtOAc (10mL) 稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用MeOH和DCM洗脱得到白色固体状产物 (0.237g, 0.98mmol, 56%)。

[0473] ^1H NMR (399MHz, DMSO- d_6) δ 12.29 (s, 1H), 7.67 (s, 1H), 5.23 (t, 1H), 4.96 (d, 2H), 2.65 (s, 3H)。

[0474] LC/MS (方法B): RT=0.51min; m/z=243 [M+H] $^+$

[0475] 步骤2: 5-溴-4-(羟基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯

[0476] 按照制备例17所述的方法, 向步骤1所得到的化合物 (0.237g, 0.98mmol) 的溶液中加入二碳酸二叔丁酯 (1.2eq)、DMAP (0.01eq) 和三甲基胺 (2eq)。得到白色固体状所需产物 (0.345g, >100%)。通过LC-MS估计的纯度约为70%。该化合物不经进一步纯化直接使用。

[0477] LC/MS (方法B): RT=1.23min; m/z=342 [M+H] $^+$

[0478] 步骤3: 5-溴-2-甲基-4-{[2-(三氟甲基)苯氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯

[0479] 从步骤2所得到的化合物 (0.345g) 和2-(三氟甲基)苯酚 (1.1eq) 开始, 按照制备例6所述的方法得到黄色油状所需产物 (0.63g, >100%)。通过LC-MS估计的纯度约为45%。该化合物不经进一步纯化直接使用。

[0480] LC/MS (方法B): RT=1.58min; m/z=485 [M+H] $^+$

[0481] 步骤4: 5-(2-{[(叔丁氧基)羰基]氨基}吡啶-4-基)-2-甲基-4-{[2-(三氟甲基)苯氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯

[0482] 从步骤3所得到的化合物 (0.63g) 和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯 (1.1eq) 开始, 按照制备例18所述的方法得到白色固体状所需产物 (62mg, 0.155mmol)。

[0483] ^1H NMR (399MHz, DMSO- d_6) δ 12.34 (s, 1H), 7.67 (s, 1H), 7.62-7.53 (m, 3H), 7.22 (d, 1H), 7.09 (t, 1H), 6.63 (dd, 1H), 6.51 (t, 1H), 5.75 (d, 2H), 5.31 (s, 2H), 2.66 (s, 3H)。

[0484] LC/MS (方法B): RT=0.99min; m/z=400 [M+H] $^+$

[0485] 实施例198:4-[4-(环丙基乙炔基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0486] 步骤1:5-溴-4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯

[0487] 从4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶(10.53g,59.67mmol)开始,按照制备例17所述的方法得到白色固体状产物(14.43g,41.63mmol,93%)。

[0488] ^1H NMR (399MHz, DMSO- d_6) δ 8.11 (s, 1H), 2.69 (s, 3H), 1.62 (s, 9H)。

[0489] 步骤2:5-(2-{[(叔丁氧基)羰基]氨基}吡啶-4-基)-4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯

[0490] 从步骤1所得到的化合物(1g,2.89mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始,按照制备例3所述的方法得到浅黄色固体状所需产物(1.059g,2.3mmol,80%)。

[0491] ^1H NMR (399MHz, DMSO- d_6) δ 9.89 (s, 1H), 8.31 (dd, 1H), 8.02 (s, 1H), 7.97 (t, 1H), 7.20 (dd, 1H), 2.71 (s, 3H), 1.64 (s, 9H), 1.48 (s, 9H)。

[0492] LC/MS (方法B): RT=1.49min; m/z=460 [M+H] $^+$

[0493] 步骤3:5-(2-{[(叔丁氧基)羰基]氨基}吡啶-4-基)-4-(环丙基乙炔基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁酯(制备例27)

[0494] 向步骤2所得到的化合物(100mg,0.22mmol)在Et₃N(4ml)和THF(1mL)中的溶液中加入乙炔基环丙烷(3eq)和CuI(0.3eq)。将溶液用氮气净化5分钟,然后加入Pd(PPh₃)₂Cl₂(0.3eq)并将反应混合物在CEM微波反应器上于80℃搅拌5小时。将反应混合物冷却至室温并真空浓缩。将残余物通过快速色谱纯化,用MeOH和DCM洗脱得到白色固体状产物(70mg,0.143mmol,66%)。

[0495] LC/MS (方法B): RT=1.51min; m/z=490 [M+H] $^+$

[0496] 步骤4:4-[4-(环丙基乙炔基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺

[0497] 从步骤3所得到的化合物(70mg,0.143mmol)开始,按照制备例7所述的方法得到白色固体状所需产物(32mg,0.11mmol,77%)。

[0498] ^1H NMR (399MHz, DMSO- d_6) δ 12.27 (s, 1H), 7.91 (d, 1H), 7.67 (d, 1H), 6.67 (dd, 1H), 6.59 (t, 1H), 5.91 (s, 2H), 2.60 (s, 3H), 1.50 (tt, 1H), 0.85 (m, 2H), 0.66 (m, 2H)。

[0499] LC/MS (方法B): RT=0.76min; m/z=290 [M+H] $^+$

[0500] 下表4中的实施例159-204通过通用方法XI-XVIII所描述的方法用适宜的可购买的硼酸酯、醇、胺和乙炔基制备。也包括了实施例162、164、168、169、174、178、193、198的化合物。

[0501] 表4:HRMS (TOF, ESI) 数据

[0502]

实施例	结构式	分子式	计算的精确质量	实测值 m/z	加合物
159	4-{2-甲基-4-[(E)-2-苯基乙烯基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₀ H ₁₇ N ₅	327.1484	328.1564	[M - H] ⁺
160	4-[2-甲基-4-(2-苯基乙基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₀ H ₁₉ N ₅	329.1640	328.1574	[M - H] ⁺

[0503]

161	4-[4-(1 <i>H</i> -吡啶-2-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₀ H ₁₆ N ₆	340.1436	341.1519	[M - H] ⁺
162	4-[4-(3-氟-5-甲氧基苯基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₁₉ H ₁₆ FN ₅ O	349.1339	348.1269	[M - H] ⁻
163	4-(2-甲基-4-苯基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基)吡啶-2-胺	C ₁₈ H ₁₅ N ₅	301.1327	302.1396	[M - H] ⁺
164	4-[4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₁₉ H ₁₃ F ₂ N ₅ O ₂	381.1037	380.0972	[M - H] ⁻
165	4-{2-甲基-4-[4-(吡咯烷-1-基甲基)苯基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₂₃ H ₂₄ N ₆	384.2062	385.2135	[M - H] ⁺
166	4-{4-[(2,6-二氟苯氧基)甲基]-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₁₉ H ₁₅ F ₂ N ₅ O	367.1245	366.1172	[M - H] ⁻
167	4-[4-(3-甲氧基苯基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₁₉ H ₁₇ N ₅ O	331.1433	330.1369	[M - H] ⁻
168	4-{2-甲基-4-[3-(三氟甲基)苯基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₁₉ H ₁₄ F ₃ N ₅	369.1201	368.1140	[M - H] ⁻
169	4-(2-甲基-4-{4-[(4-甲基哌嗪-1-基)甲基]苯基}-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基)吡啶-2-胺	C ₂₄ H ₂₇ N ₇	413.2328	412.2268	[M - H] ⁻
170	4-[4-(5-氟吡啶-3-基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₁₇ H ₁₃ FN ₆	320.1186	319.1112	[M - H] ⁻
171	4-{2-甲基-4-[3-(吡咯烷-1-基)苯基]-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基}吡啶-2-胺	C ₂₂ H ₂₂ N ₆	370.1906	369.1839	[M - H] ⁻
172	4-[4-(4-乙氧基苯基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]吡啶-2-胺	C ₂₀ H ₁₉ N ₅ O	345.1590	346.1656	[M + H] ⁺

[0504]

173	4-[4-(2,3-二氢-1,4-苯并二𫞟英-6-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{20}H_{17}N_5O_2$	359.1382	360.1440	$[M + H]^+$
174	4-(2-甲基-4-{3-[3-(吗啉-4-基)丙氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	$C_{25}H_{28}N_6O_2$	444.2274	445.2250	$[M + H]^+$
175	4-[5-(2-氨基吡啶-4-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-基]-2-氟苄腈	$C_{19}H_{13}FN_6$	344.1186	343.1119	$[M + H]^+$
176	4-{4-[(3,3-二氟吡咯烷-1-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	$C_{17}H_{18}F_2N_6$	344.1561	343.1486	$[M + H]^+$
177	4-{4-[(3,3-二氟哌啶-1-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	$C_{18}H_{20}F_2N_6$	358.1718	357.1622	$[M + H]^+$
178	4-[4-(2,3-二氢-1H-吡嗪-1-基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{21}H_{20}N_6$	356.1749	355.1683	$[M + H]^+$
179	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{19}H_{15}N_5O_2$	345.1226	344.1127	$[M + H]^+$
180	4-[4-(3,5-二氟苯基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{18}H_{13}F_2N_5$	337.1139	336.1057	$[M + H]^+$
181	4-{2-甲基-4-[3-(三氟甲氧基)苯基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	$C_{19}H_{14}F_3N_5O$	385.1150	384.1086	$[M + H]^+$
182	4-[4-(1-苯并噻吩-2-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{20}H_{15}N_5S$	357.1048	356.0969	$[M + H]^+$
183	4-[4-(1-苯并呋喃-2-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	$C_{20}H_{15}N_5O$	341.1277	340.1217	$[M + H]^+$

[0505]

184	4-[2-甲基-4-(5-甲基-1-苯并噻吩-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₁ H ₁₇ N ₅ S	371.1205	372.1210	[M + H] ⁺
185	4-[4-(7-氯-1-苯并噻吩-2-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₀ H ₁₄ ClN ₅ S	391.0658	392.0712	[M + H] ⁺
186	4-[2-甲基-4-(1-甲基-1H-吡唑-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₁ H ₁₈ N ₆	354.1593	353.1534	[M + H] ⁺
187	4-[4-(3,4-二氢萘-2-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₂ H ₁₉ N ₅	353.1640	352.1583	[M + H] ⁺
188	4-[2-甲基-4-(1,2,3,4-四氢萘-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₂ H ₂₁ N ₅	355.1797	354.1732	[M + H] ⁺
189	4-{2-甲基-4-[(2S)-1,2,3,4-四氢萘-2-基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₂ H ₂₁ N ₅	355.1797	354.1716	[M + H] ⁺
190	4-{2-甲基-4-[(2R)-1,2,3,4-四氢萘-2-基]-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₂ H ₂₁ N ₅	355.1797	354.1728	[M + H] ⁺
191	4-[4-(7-氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₉ H ₁₄ FN ₅ O ₂	363.1132	362.1022	[M + H] ⁺
192	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	C ₁₉ H ₁₆ N ₆ O ₂	360.1335	361.1420	[M + H] ⁺
193	4-(2-甲基-4-{[2-(三氟甲基)苯氧基]甲基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₀ H ₁₆ F ₃ N ₅ O	399.1307	398.1246	[M + H] ⁺
194	4-{4-[(2-氟苯基)乙炔基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₀ H ₁₄ FN ₅	343.1233	342.1116	[M + H] ⁺

[0506]

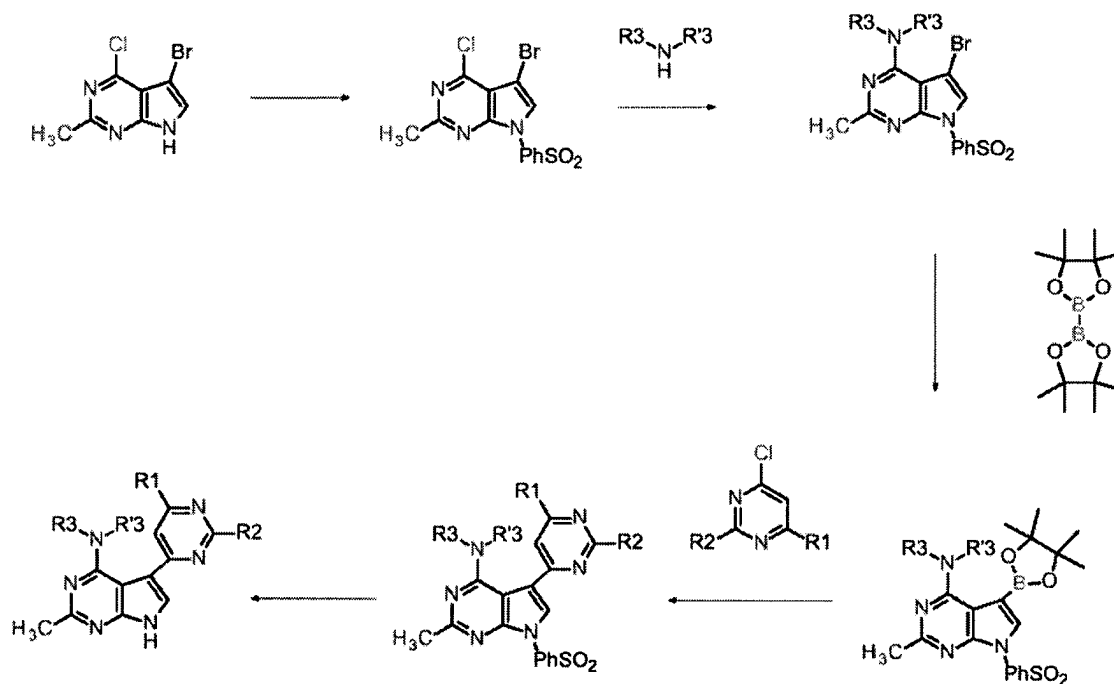
195	4-[2-甲基-4-(5,6,7,8-四氢萘-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₂₂ H ₂₁ N ₅	355.1797	356.1805	[M + H] ⁺
196	4-[4-(环丙基乙炔基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2,6-二胺	C ₁₇ H ₁₆ N ₆	304.1436	305.1458	[M + H] ⁺
197	4-{4-[(2-甲氧基苯基)乙炔基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₁ H ₁₇ N ₅ O	355.1433	356.1442	[M + H] ⁺
198	4-[4-(环丙基乙炔基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]吡啶-2-胺	C ₁₇ H ₁₅ N ₅	289.1327	288.1228	[M + H] ⁻
199	4-(2-甲基-4-{3-[3-(哌啶-1-基)丙氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₆ H ₃₀ N ₆ O	442.2481	443.2474	[M + H] ⁺
200	4-(2-甲基-4-{3-[3-(4-甲基哌啶-1-基)丙氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₆ H ₃₁ N ₇ O	457.2590	456.2477	[M + H] ⁻
201	4-{4-[3-(2-氯乙氧基)苯基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基}吡啶-2-胺	C ₂₀ H ₁₈ ClN ₅ O	379.1200	378.1140	[M + H] ⁻
202	4-(2-甲基-4-{3-[2-(吡咯烷-1-基)乙氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₄ H ₂₆ N ₆ O	414.2168	415.2165	[M + H] ⁺
203	4-(4-{3-[2-(二甲基氨基)乙氧基]苯基}-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₂ H ₂₄ N ₆ O	388.2012	389.1996	[M + H] ⁺
204	4-(2-甲基-4-{3-[2-(吗啉-4-基)乙氧基]苯基}-7H-吡咯并[2,3-d]嘧啶-5-基)吡啶-2-胺	C ₂₄ H ₂₆ N ₆ O ₂	430.2117	431.2096	[M + H] ⁺

[0507] 实施例160利用制备例5中所述的方法从实施例159制备。实施例188利用制备例5中所述的方法从实施例187制备。实施例189和190通过手性固定相制备型HPLC从实施例188制备。实施例191按照制备例14描述的方法从2-(7-氟-1,3-苯并二氧杂环戊烯-5-基)-4,4,5,5-四甲基-1,3,2-二氧硼戊环(从6-溴-4-氟-1,3-苯并二氧杂环戊烯制备)制备。¹H NMR

(399MHz, 氯仿-d) δ 7.18 (d, 1H), 7.08 (s, 1H), 6.05 (s, 2H), 1.35 (s, 12H)。

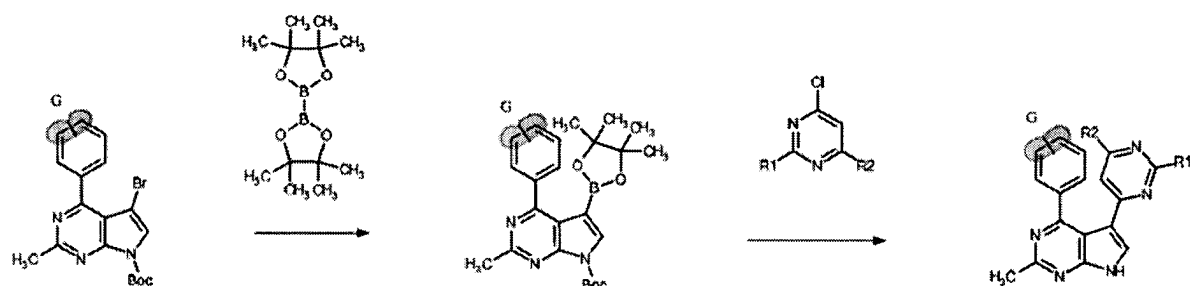
[0508] 通用方法XIX

[0509]



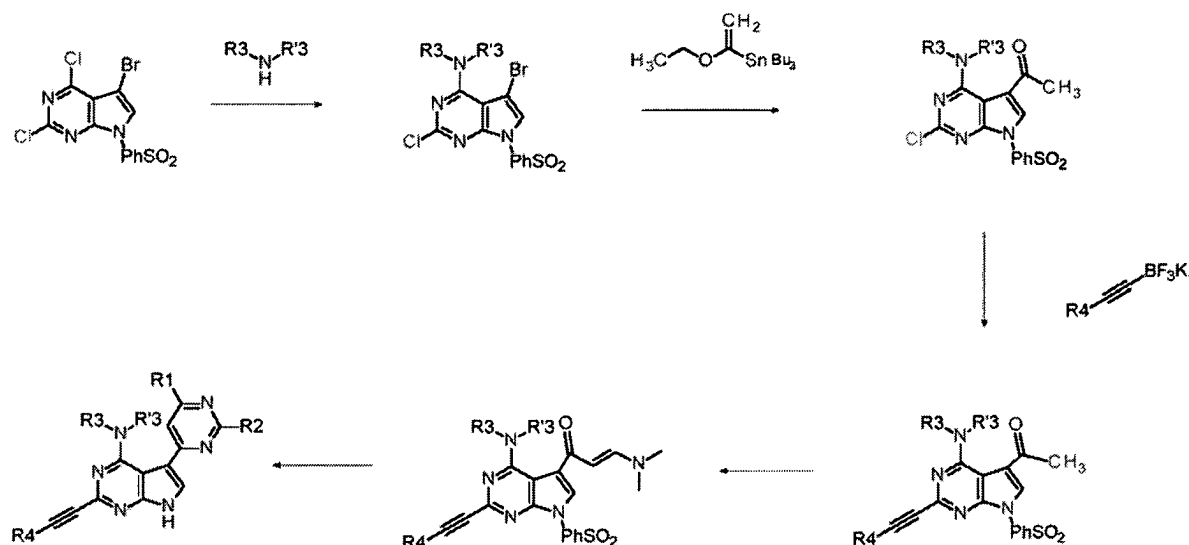
[0510] 通用方法XX

[0511]



[0512] 通用方法XXI

[0513]



[0514] 在通用方法XIX、XX和XXI中:

[0515] -R₁和R₂如式(I)中所定义,

[0516] -R₃代表氢原子、直链或支链的(C₁-C₆)烷基、-(C₀-C₆)亚烷基-Cy₁、-(C₀-C₆)亚烷基-Cy₁-Cy₂、-(C₀-C₆)亚烷基-Cy₁-O-(C₁-C₆)亚烷基-Cy₂,应当理解的是,Cy₁和Cy₂彼此独立地代表环烷基、杂环烷基、芳基或杂芳基,

[0517] 并且R'₃代表氢原子或直链或支链的(C₁-C₆)烷基,[0518] 或者R₃和R'₃与携带它们的氮原子形成杂环烷基或杂芳基,[0519] -R₄代表氢原子、直链或支链的(C₁-C₆)烷基或环烷基,

[0520] -G代表选自式(I)中所定义的取代基列表的基团,应当理解的是,苯基可以被1至4个独立的G基团取代。

[0521] **实施例206:** 5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0522] 步骤1: 7-(苯磺酰基)-5-溴-4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶

[0523] 从4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶(1g, 4.06mmol)开始,按照制备例19所述的方法得到白色固体状所需产物(1.264g, 3.27mmol, 81%)。

[0524] ¹H NMR (399MHz, DMSO-d₆) δ 8.31 (s, 1H), 8.24-8.16 (m, 2H), 7.85-7.78 (m, 1H), 7.73-7.65 (m, 2H), 2.69 (s, 3H)。

[0525] LC/MS (方法B): RT=1.46min; m/z=387 [M+H]⁺

[0526] 步骤2: 7-(苯磺酰基)-5-溴-N-[(2,6-二氟苄基)甲基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0527] 从步骤1所得到的化合物(1.2g, 3.10mmol)和(2,6-二氟苄基)甲胺(2eq)开始,采用制备例8所述的方法得到白色固体状所需产物(1.410g, 2.86mmol, 92%)。

[0528] LC/MS (方法B): RT=1.52min; m/z=493 [M+H]⁺

[0529] 步骤3: 7-(苯磺酰基)-N-[(2,6-二氟苄基)甲基]-2-甲基-5-(四甲基-1,3,2-二氧硼戊环-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(制备例28)

[0530] 向步骤2所得到的化合物(1g, 2.03mmol)的THF(5mL)溶液中加入双(频哪醇合)二

硼(1.2eq)、KOAc(3eq)和PdCl₂(PPh₃)₂(10%wt)。将形成的混合物在氮气氛下脱气5分钟,然后在CEM微波反应器上于140℃加热1小时。将反应混合物用硅藻土塞过滤,用EtOAc洗涤。将有机层用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到白色固体状所需产物(0.675g,1.25mmol,62%)。

[0531] LC/MS(方法B):RT=1.63min;m/z=541[M+H]⁺

[0532] 步骤4:5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7-(苯磺酰基)-7H-吡咯并[2,3-d]嘧啶-4-胺

[0533] 从步骤3所得到的化合物(0.915g,1.69mmol)和4-氯嘧啶-2-胺(1.5eq)开始,按照制备例3所述的方法得到浅棕色固体状产物(0.551g,1.08mmol,64%)。

[0534] ¹H NMR(399MHz,DMSO-d₆) δ10.79(t,1H),8.44(s,1H),8.29(d,1H),8.20-8.13(m,2H),7.80(m,1H),7.65(t,2H),7.40-7.24(m,2H),7.01(t,2H),6.70(s,2H),4.90(d,2H),2.38(s,3H)。

[0535] LC/MS(方法B):RT=1.41min;m/z=508[M+H]⁺

[0536] 步骤5:5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0537] 从步骤4得到的化合物(0.551g,1.08mmol)开始,按照制备例20所述的方法得到浅橙色固体状所需产物(0.159g,0.432mmol,40%)。

[0538] ¹H NMR(399MHz,DMSO-d₆) δ11.97(s,1H),10.63(s,1H),8.14(d,1H),8.04(s,1H),7.33(m,1H),7.12(d,1H),7.06(q,2H),6.35(s,2H),4.91(d,2H),2.36(s,3H)。

[0539] LC/MS(方法B):RT=0.96min;m/z=368[M+H]⁺

[0540] 实施例208:5-(2-氨基嘧啶-4-基)-N-(1,3-苯并二氧杂环戊烯-4-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0541] 步骤1:7-(苯磺酰基)-5-溴-4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶

[0542] 从4-氯-2-甲基-7H-吡咯并[2,3-d]嘧啶(1g,4.06mmol)开始,按照制备例19所述的方法得到白色固体状所需产物(1.264g,3.27mmol,81%)。

[0543] ¹H NMR(399MHz,DMSO-d₆) δ8.31(s,1H),8.24-8.16(m,2H),7.85-7.78(m,1H),7.73-7.65(m,2H),2.69(s,3H)。

[0544] LC/MS(方法B):RT=1.46min;m/z=387[M+H]⁺

[0545] 步骤2:7-(苯磺酰基)-N-(1,3-苯并二氧杂环戊烯-4-基甲基)-5-溴-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0546] 从步骤1所得到的化合物(0.5g,1.29mmol)和1,3-苯并二氧杂环戊烯-4-基甲胺(2eq)开始,采用制备例8所述的方法得到白色固体状所需产物(0.562g,1.12mmol,87%)。

[0547] ¹H NMR(399MHz,DMSO-d₆) δ8.19-8.11(m,2H),7.82-7.72(m,2H),7.66(dd,2H),7.10(t,1H),6.86-6.71(m,3H),6.03(s,2H),4.69(d,2H),2.41(s,3H)。

[0548] LC/MS(方法B):RT=1.52min;m/z=501[M+H]⁺

[0549] 步骤3:7-(苯磺酰基)-N-(1,3-苯并二氧杂环戊烯-4-基甲基)-2-甲基-5-(四甲基-1,3,2-二氧硼戊环-2-基)-7H-吡咯并[2,3-d]嘧啶-4-胺(制备例28)

[0550] 向步骤2所得到的化合物(0.25g,0.5mmol)的THF(5mL)溶液中加入双(频哪醇合)二硼(1.2eq)、KOAc(3eq)和PdCl₂(PPh₃)₂(10%wt)。将形成的混合物在氮气氛下脱气5分钟,

然后在CEM微波反应器上于140℃加热1小时。将反应混合物用硅藻土塞过滤,用EtOAc洗涤。将有机层用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用EtOAc和异己烷洗脱得到白色固体状产物(0.227g,0.414mmol,83%)。

[0551] LC/MS(方法B):RT=1.61min;m/z=549[M+H]⁺

[0552] 步骤4:4-[7-(苯磺酰基)-4-[(1,3-苯并二氧杂环戊烯-4-基甲基)氨基]-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺

[0553] 从步骤3所得到的化合物(227mg,0.414mmol)和4-氯嘧啶-2-胺(1.5eq)开始,按照制备例3所述的方法得到浅棕色固体状所需产物(85mg,0.165mmol,40%)。

[0554] ¹H NMR(399MHz,DMSO-d₆) δ9.54(s,2H),8.26-8.17(m,2H),7.82-7.72(m,1H),7.72-7.64(m,3H),7.54(s,2H),6.80-6.63(m,3H),6.51(t,1H),5.93(s,2H),4.60(d,2H),2.44(s,3H)。

[0555] LC/MS(方法B):RT=1.44min;m/z=549[M+H]⁺

[0556] 步骤5:5-(2-氨基嘧啶-4-基)-N-(1,3-苯并二氧杂环戊烯-4-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺

[0557] 从步骤4得到的化合物(85mg,0.165mmol)开始,按照制备例20所述的方法得到浅橙色固体状所需产物(25mg,0.066mmol,40%)。

[0558] ¹H NMR(399MHz,DMSO-d₆) δ12.00(s,1H),10.55(t,1H),8.14(d,1H),8.06(d,1H),7.13(d,1H),6.91-6.72(m,3H),6.22(s,2H),6.03(s,2H),4.81(d,2H),2.37(s,3H)。

[0559] LC/MS(方法B):RT=0.935min;m/z=376[M+H]⁺

[0560] 实施例210:4-[4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺

[0561] 步骤1:4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-5-(4,4,5,5-四甲基-1,3,2-二氧硼戊环-2-基)-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁基酯

[0562] 从5-溴-4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-7-甲酸叔丁基酯(参见实施例164,步骤2)(240mg,0.51mmol)开始,按照制备例28所述的方法得到白色固体状所需产物(75mg,0.145mmol,28%)。

[0563] LC/MS(方法B):RT=1.62min;m/z=516[M+H]⁺

[0564] 步骤2:4-[4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺

[0565] 从步骤1所得到的化合物(75mg,0.145mmol)和4-氯嘧啶-2-胺(1.5eq)开始,按照制备例18所述的方法得到白色固体状所需产物(7mg,0.018mmol,13%)。

[0566] ¹H NMR(399MHz,DMSO-d₆) δ12.52(s,1H),8.01-7.92(m,2H),7.40(d,1H),7.32(m,1H),7.22(dd,1H),6.21(d,1H),6.10(s,2H),2.72(s,3H)。LC/MS(方法B):RT=1.02min;m/z=383[M+H]⁺

[0567] 实施例211:4-[4-(3,4-二氢异喹啉-2(1H)-基)-2-乙炔基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺

[0568] 步骤1:2-[7-(苯磺酰基)-5-溴-2-氯-7H-吡咯并[2,3-d]嘧啶-4-基]-1,2,3,4-四氢异喹啉

[0569] 从7-(苯磺酰基)-5-溴-2,4-二氯-7H-吡咯并[2,3-d]嘧啶(按照W02007/042299所

述的方法制备) (0.875g, 2.15mmol) 和1,2,3,4-四氢异喹啉 (2.5eq) 开始, 采用制备例8所述的方法得到浅黄色固体状所需产物 (1.044g) (LC-MS显示纯度约为80%)。该化合物不经进一步纯化直接使用。

[0570] LC/MS (方法B) : RT=1.69min; m/z=505 [M+H]⁺

[0571] 步骤2: 1-[7-(苯磺酰基)-2-氯-4-(1,2,3,4-四氢异喹啉-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]乙-1-酮 (制备例29)

[0572] 将步骤1中得到的化合物 (0.52g, 1.03mmol)、LiCl (2.5eq)、四(三苯基膦) 钯 (0.1eq) 和三丁基(1-乙氧基乙烯基) 锡 (1.2eq) 在氮气氛及室温下溶于1,4-二恶烷 (10mL)。将反应混合物在氮气氛下于100℃搅拌过夜。将反应混合物冷却至室温, 加入2N HCl溶液 (5mL) 并将反应混合物搅拌1小时。将反应混合物用饱和碳酸氢钠水溶液 (20mL) 和EtOAc (20mL) 稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到产物 (0.448g)。LC-MS显示纯度约为70%。该化合物不经进一步纯化直接使用。

[0573] LC/MS (方法B) : RT=1.55min; m/z=467 [M+H]⁺

[0574] 步骤3: 叔丁基二甲基[2-(三氟硼烷基) 乙炔基] 硅烷钾 (制备例30)

[0575] 向叔丁基二甲基[2-(四甲基-1,3,2-二氧硼戊环-2-基) 乙炔基] 硅烷 (0.973g, 3.65mmol) 的丙酮 (15mL) 溶液中加入氟氢化钾 (4eq) 的水 (5mL) 溶液并将悬浮液升温至室温过夜。将反应混合物真空浓缩并将残余物用温热的丙酮研磨得到白色固体状产物 (0.705g, 2.86mmol), 其不经进一步纯化直接使用。

[0576] ¹H NMR (399MHz, DMSO-d₆) δ 0.89 (s, 9H), 0.00 (s, 6H)。

[0577] 步骤4: 1-[7-(苯磺酰基)-2-[2-(叔丁基二甲基硅烷基) 乙炔基]-4-(1,2,3,4-四氢异喹啉-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]乙-1-酮

[0578] 从步骤2所得到的化合物 (0.400g, 0.86mmol) 和叔丁基二甲基[2-(三氟硼烷基) 乙炔基] 硅烷钾 (1.78eq) 开始, 按照制备例10所述的方法得到黄色油状所需产物 (0.220g, 0.35mmol, 45%)。

[0579] LC/MS (方法B) : RT=1.75min; m/z=571 [M+H]⁺

[0580] 步骤5: 1-[7-(苯磺酰基)-2-[2-(叔丁基二甲基硅烷基) 乙炔基]-4-(1,2,3,4-四氢异喹啉-2-基)-7H-吡咯并[2,3-d]嘧啶-5-基]-3-(二甲基氨基) 丙-2-烯-1-酮 (制备例31)

[0581] 向步骤4得到的化合物 (0.220g, 0.35mmol) 的DMF (5mL) 溶液中加入N,N-二甲基甲酰胺二甲缩醛 (6eq)。将反应混合物于90℃搅拌3小时。将混合物冷却至室温, 用水 (20mL) 和EtOAc (20mL) 稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用EtOAc和异己烷洗脱得到黄色油状产物 (84mg, 0.134mmol, 35%)。

[0582] LC/MS (方法B) : RT=1.69min; m/z=626 [M+H]⁺

[0583] 步骤6: 4-[4-(3,4-二氢异喹啉-2(1H)-基)-2-乙炔基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺 (制备例32)

[0584] 向步骤5得到的化合物 (84mg, 0.134mmol) 的THF (3mL) 溶液中加入TBAF (1M的THF溶液, 1.1eq)。将反应混合物在1小时内升温至室温。将混合物用DCM (10mL)

稀释,用饱和碳酸氢钠水溶液洗涤,用硫酸镁干燥并真空浓缩。将残余物溶于丁-1-醇(3mL),加入碳酸胍(1.5eq)和甲醇钠(4eq)并将反应混合物在CEM微波反应器上于130℃搅拌30分钟。将混合物倒入水(10mL)和DCM(10mL)中。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将粗产物通过快速硅胶色谱纯化,用10%MeOH的DCM溶液洗脱,然后通过HPLC在pH=4下纯化得到黄色固体状产物(1.4mg,0.004mmol,3%)。

[0585] ^1H NMR (399MHz, DMSO- d_6) δ 12.39 (s, 1H), 8.13 (d, 1H), 7.77 (s, 1H), 7.18-7.06 (m, 3H), 7.02-6.94 (m, 1H), 6.75 (d, 1H), 6.54 (s, 2H), 4.56 (s, 2H), 4.05 (s, 1H), 3.64 (t, 2H), 2.76 (t, 2H)。

[0586] LC/MS (方法B): RT=1.13min; m/z=368 [M+H] $^+$

[0587] 下表5中的实施例205-212通过通用方法XIX、XXI所描述的方法用适宜的可购买到的硼酸酯、胺和乙炔基制备。也包括了实施例208、210、211的化合物。

[0588] 表5: HRMS (TOF, ESI) 数据

[0589]

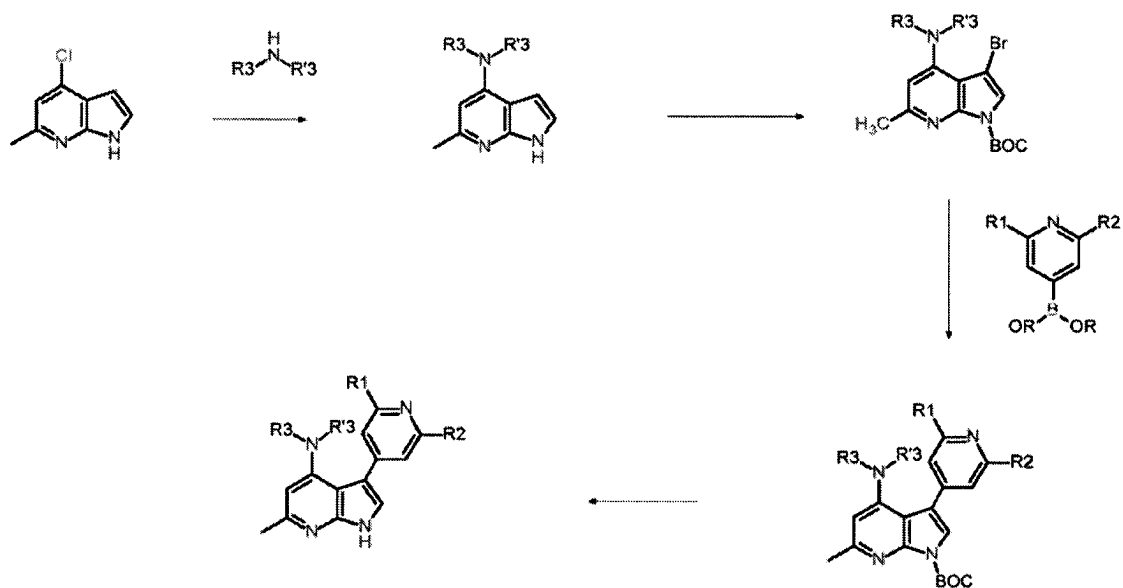
实施例	结构式	分子式	计算的精确质量	实测值 m/z	加合物
205	5-(2-氨基-6-甲基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$\text{C}_{19}\text{H}_{17}\text{F}_2\text{N}_7$	381.1513	382.1569	[M + H] $^+$
206	5-(2-氨基嘧啶-4-基)-N-(2,6-二氟苄基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$\text{C}_{18}\text{H}_{15}\text{F}_2\text{N}_7$	367.1357	368.1413	[M + H] $^+$
207	4-[4-(1-苯并噻吩-2-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺	$\text{C}_{19}\text{H}_{14}\text{N}_6\text{S}$	358.1001	359.1020	[M + H] $^+$
208	5-(2-氨基嘧啶-4-基)-N-(1,3-苯并二氧杂环戊烯-4-基甲基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-4-胺	$\text{C}_{19}\text{H}_{17}\text{N}_7\text{O}_2$	375.1444	374.1375	[M + H] $^-$
209	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺	$\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_2$	346.1178	347.1190	[M + H] $^+$
210	4-[4-(2,2-二氟-1,3-苯并二氧杂环戊烯-5-基)-2-甲基-7H-吡咯并[2,3-d]嘧啶-5-基]嘧啶-2-胺	$\text{C}_{18}\text{H}_{12}\text{F}_2\text{N}_6\text{O}_2$	382.0990	381.0912	[M + H] $^-$

[0590]

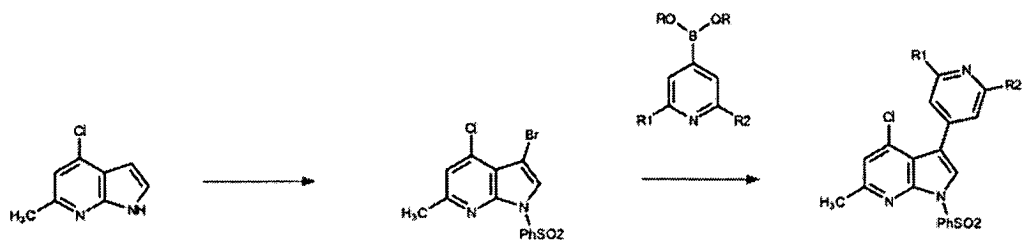
211	4-[4-(3,4-二氢异喹啉-2(1 <i>H</i>)-基)-2-乙炔基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-5-基]嘧啶-2-胺	$C_{21}H_{17}N_7$	367.1545	366.1442	$[M + H]^+$
212	5-(6-氨基嘧啶-4-基)- <i>N</i> -(2,6-二氟苄基)-2-甲基-7 <i>H</i> -吡咯并[2,3- <i>d</i>]嘧啶-4-胺	$C_{18}H_{15}F_2N_7$	367.1357	368.1376	$[M + H]^+$

[0591] 通用方法XXII

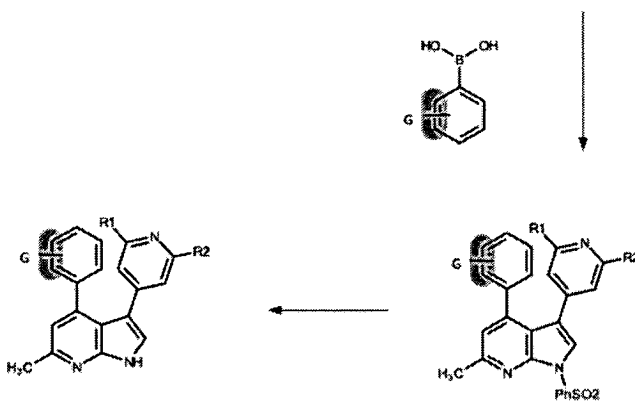
[0592]



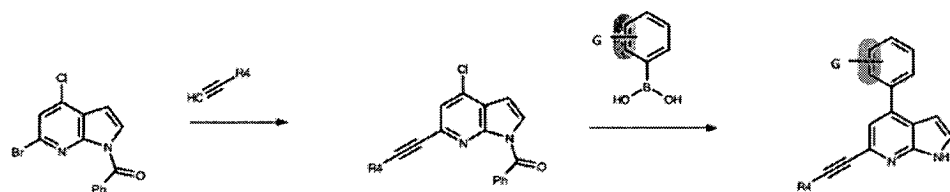
[0593] 通用方法XXIII



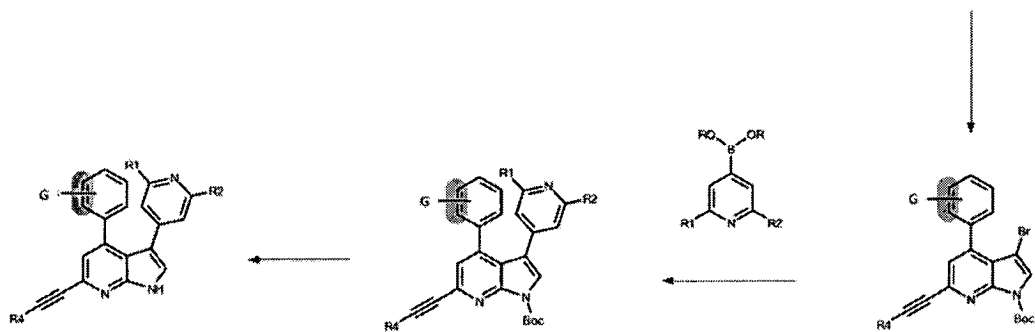
[0594]



[0595] 通用方法XXIV

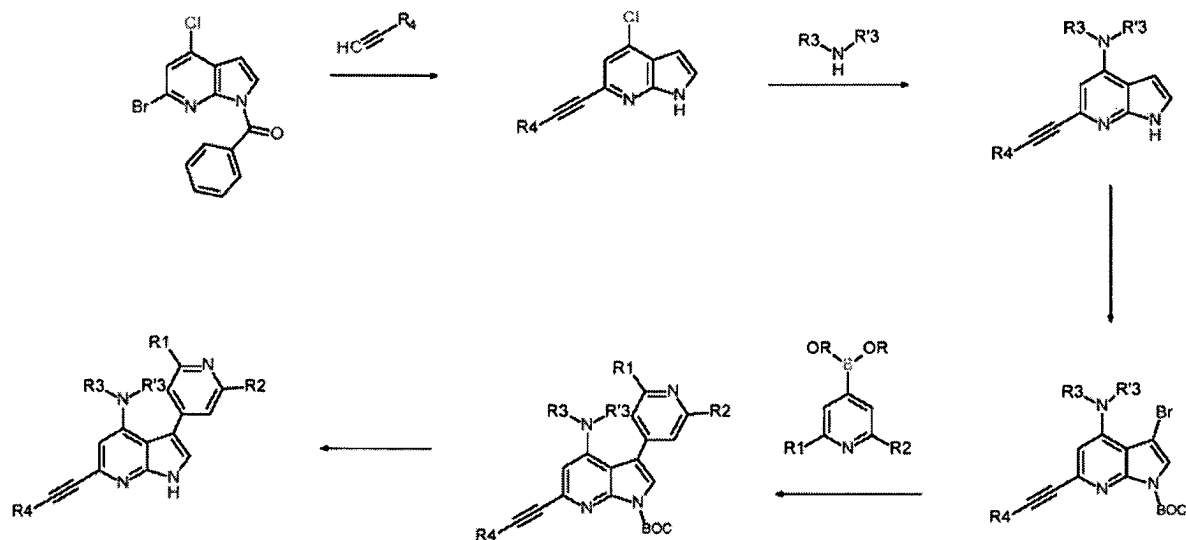


[0596]



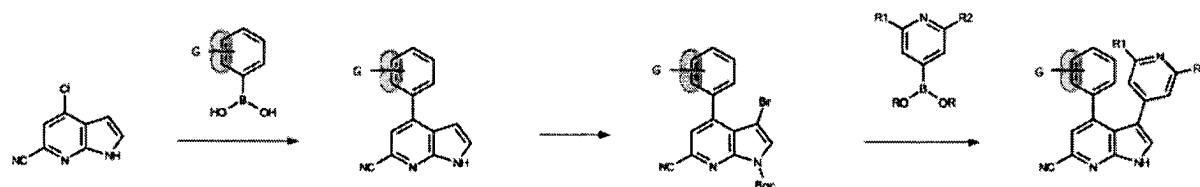
[0597] 通用方法XXV

[0598]



[0599] 通用方法XXVI

[0600]



[0601] 在通用方法XXII至XXIV中:

[0602] -R₁和R₂如式(I)中所定义,

[0603] -R₃代表氢原子、直链或支链的(C₁-C₆)烷基、-(C₀-C₆)亚烷基-Cy₁、-(C₀-C₆)亚烷基-Cy₁-Cy₂、-(C₀-C₆)亚烷基-Cy₁-O-(C₁-C₆)亚烷基-Cy₂,应当理解的是,Cy₁和Cy₂彼此独立地代表环烷基、杂环烷基、芳基或杂芳基,

[0604] 并且R'₃代表氢原子或直链或支链的(C₁-C₆)烷基,[0605] 或者R₃和R'₃与携带它们的氮原子形成杂环烷基或杂芳基,[0606] -R₄代表氢原子、直链或支链的(C₁-C₆)烷基或环烷基,

[0607] -G代表选自式(I)中所定义的取代基列表的基团,应当理解的是,苯基可以被1至4个独立的G基团取代。

[0608] 实施例213: 3-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-6-甲基-1H-吡咯并[2,3-b]吡啶-4-胺

[0609] 步骤1: N-[(2,6-二氟苄基)甲基]-6-甲基-1H-吡咯并[2,3-b]吡啶-4-胺(制备例33)

[0610] 向4-氯-6-甲基-1H-吡咯并[2,3-b]吡啶(0.5g, 3mmol)的MeCN(15mL)溶液中在氮气及室温下加入2,6-二氟苄基胺(2eq)和pTSA·H₂O(2eq)。将反应混合物在CEM微波反应器中于150℃加热4小时。将混合物用饱和NaHCO₃水溶液(20mL)和EtOAc(20mL)稀释。将有机层分离,用盐水洗涤,用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化,用MeOH和DCM洗脱得到黄色固体状产物(0.521g, 1.90mmol, 63%)。

[0611] ¹H NMR (399MHz, DMSO-d₆) δ 10.96 (s, 1H), 7.43 (tt, 1H), 7.20-7.08 (m, 2H), 6.95

(d, 1H), 6.77 (t, 1H), 6.53 (d, 1H), 6.15 (s, 1H), 4.44 (d, 2H), 2.35 (s, 3H)。

[0612] LC/MS (方法A): RT=1.82min; m/z=274 [M+H]⁺

[0613] 步骤2: 3-溴-4-[(2,6-二氟苯基)甲基]氨基}-6-甲基-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0614] 从步骤1所得到的化合物(0.415g, 1.51mmol)开始, 按照制备例17所述的方法得到固体状所需产物(0.280g, 0.61mmol, 40%)。

[0615] ¹H NMR (399MHz, 氯仿-d) δ 7.36 (s, 1H), 7.33-7.23 (m, 1H), 6.95 (t, 2H), 6.46 (s, 1H), 6.20 (d, 1H), 4.57 (d, 2H), 2.59 (s, 3H), 1.65 (s, 10H)。

[0616] LC/MS (方法A): RT=2.53min; m/z=452 [M+H]⁺

[0617] 步骤3: 3-(2-氨基吡啶-4-基)-4-[(2,6-二氟苯基)甲基]氨基}-6-甲基-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0618] 从步骤2所得到的化合物(0.280g, 0.61mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.4eq)开始, 按照制备例3所述的方法得到米色固体状所需产物(0.154g, 0.33mmol, 53%)。

[0619] LC/MS (方法B): RT=0.99min; m/z=466 [M+H]⁺

[0620] 步骤4: 3-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-6-甲基-1H-吡咯并[2,3-b]吡啶-4-胺

[0621] 从步骤3所得到的化合物(0.154g, 0.33mmol)开始, 按照制备例7所述的方法得到白色固体状产物(0.110g, 0.30mmol, 91%)。

[0622] ¹H NMR (399MHz, DMSO-d₆) δ 11.43 (s, 1H), 7.85 (d, 1H), 7.42 (tt, 1H), 7.20-7.07 (m, 3H), 6.51-6.43 (m, 2H), 6.29 (s, 1H), 5.89 (s, 2H), 5.23 (t, 1H), 4.49 (d, 2H), 2.39 (s, 3H)。

[0623] LC/MS (方法A): RT=1.58min; m/z 366 [M+H]⁺

[0624] 实施例214: 4-[4-(5-氟吡啶-3-基)-6-甲基-1H-吡咯并[2,3-b]吡啶-3-基]吡啶-2-胺

[0625] 步骤1: 1-(苯磺酰基)-3-溴-4-氯-6-甲基-1H-吡咯并[2,3-b]吡啶

[0626] 从4-氯-6-甲基-1H-吡咯并[2,3-b]吡啶(0.713g, 4.27mmol)开始, 按照制备例19所述的方法得到白色固体状所需产物(0.493g, 1.28mmol, 30%)。

[0627] ¹H NMR (399MHz, DMSO-d₆) δ 8.21-8.13 (m, 3H), 7.81-7.72 (m, 1H), 7.70-7.62 (m, 2H), 7.41 (s, 1H), 2.56 (s, 3H)。

[0628] LC/MS (方法B): RT=1.52min; m/z=386 [M+H]⁺

[0629] 步骤2: 4-[1-(苯磺酰基)-4-氯-6-甲基-1H-吡咯并[2,3-b]吡啶-3-基]吡啶-2-胺

[0630] 从步骤1所得到的化合物(0.493g, 1.28mmol)和4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-胺(1.4eq)开始, 按照制备例3所述的方法得到浅黄色固体状所需产物(0.200g, 0.501mmol, 39%)。

[0631] ¹H NMR (399MHz, DMSO-d₆) δ 8.27-8.17 (m, 2H), 8.00-7.91 (m, 2H), 7.81-7.63 (m, 3H), 7.38 (s, 1H), 6.64 (dd, 1H), 6.57 (d, 1H), 5.99 (s, 2H), 2.57 (s, 3H)。

[0632] LC/MS (方法B): RT=1.13min; m/z=399 [M+H]⁺

[0633] 步骤3: 4-[1-(苯磺酰基)-4-(5-氟吡啶-3-基)-6-甲基-1H-吡咯并[2,3-b]吡啶-

3-基]吡啶-2-胺

[0634] 从步骤2所得到的化合物(0.133g, 0.33mmol)和(5-氟吡啶-3-基)硼酸(1.1eq)开始,按照制备例3所述的方法得到浅棕色固体状产物(97mg, 0.211mmol, 63%)。

[0635] ^1H NMR (399MHz, DMSO- d_6) δ 8.48 (d, 1H), 8.31-8.23 (m, 2H), 8.19 (t, 1H), 7.97 (s, 1H), 7.82-7.73 (m, 1H), 7.73-7.63 (m, 2H), 7.62-7.44 (m, 4H), 7.33 (s, 1H), 6.16 (m, 1H), 5.89 (dd, 1H), 5.77 (s, 2H), 2.65 (s, 3H)。

[0636] LC/MS (方法B): RT=1.1min; m/z=460 [M+H] $^+$

[0637] 步骤4: 4-[4-(5-氟吡啶-3-基)-6-甲基-1H-吡咯并[2,3-b]吡啶-3-基]吡啶-2-胺

[0638] 从步骤3所得到的化合物(97mg, 0.211mmol)开始,按照制备例20所述的方法得到白色固体状所需产物(20mg, 0.06mmol, 30%)。

[0639] ^1H NMR (399MHz, DMSO- d_6) δ 12.06 (s, 1H), 8.49 (d, 1H), 8.26 (d, 1H), 7.63 (s, 1H), 7.56-7.46 (m, 2H), 7.10 (s, 1H), 6.08 (d, 1H), 5.87 (dd, 1H), 5.62 (s, 2H), 2.61 (s, 3H)。

[0640] LC/MS (方法A): RT=1.67min; m/z=320 [M+H] $^+$

[0641] 实施例215: 4-[6-(环丙基乙炔基)-4-(2,3-二氢-1,4-苯并二噁英-6-基)-1H-吡咯并[2,3-b]吡啶-3-基]吡啶-2-胺

[0642] 步骤1: 1-苯甲酰基-4-氯-6-(环丙基乙炔基)-1H-吡咯并[2,3-b]吡啶

[0643] 从1-苯甲酰基-6-溴-4-氯-1H-吡咯并[2,3-b]吡啶(按照W02009/087225所述的方法制备)(1.12g, 3.72mmol)和乙炔基环丙烷(3eq)开始,按照制备例27所述的方法得到浅棕色固体状所需产物(1.053g, 3.28mmol, 88%)。LC/MS (方法B): RT=1.52min; m/z=321 [M+H] $^+$

[0644] 步骤2: 6-(环丙基乙炔基)-4-(2,3-二氢-1,4-苯并二噁英-6-基)-1H-吡咯并[2,3-b]吡啶

[0645] 从步骤1所得到的化合物(0.5g, 1.56mmol)和(2,3-二氢-1,4-苯并二噁英-6-基)硼酸(1.2eq)开始,按照制备例3所述的方法得到棕色固体状所需产物(0.234g, 0.74mmol, 47%)。

[0646] LC/MS (方法B): RT=1.35min; m/z=316 [M+H] $^+$

[0647] 步骤3: 3-溴-6-(环丙基乙炔基)-4-(2,3-二氢-1,4-苯并二噁英-6-基)-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0648] 从步骤2所得到的化合物(0.234g, 0.74mmol)开始,按照制备例17所述的方法得到浅黄色固体状所需产物(0.326g, 0.658mmol, 89%)。

[0649] LC/MS (方法B): RT=1.7min; m/z=497 [M+H] $^+$

[0650] 步骤4: 3-(2-[(叔丁氧基)羰基]氨基)吡啶-4-基)-6-(环丙基乙炔基)-4-(2,3-二氢-1,4-苯并二噁英-6-基)-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0651] 从步骤3所得到的化合物(0.326g, 0.658mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始,按照制备例3所述的方法得到浅黄色固体状所需产物(0.211g, 0.347mmol, 53%)。

[0652] LC/MS (方法A): RT=3.05min; m/z=609 [M+H] $^+$

[0653] 步骤5: 4-[6-(环丙基乙炔基)-4-(2,3-二氢-1,4-苯并二噁英-6-基)-1H-吡咯并

[2,3-b]吡啶-3-基]吡啶-2-胺

[0654] 从步骤4得到的化合物(0.211g, 0.347mmol)开始,按照制备例7所述的方法得到白色固体状所需产物(54mg, 0.132mmol, 38%)。

[0655] ^1H NMR (399MHz, DMSO- d_6) δ 12.08 (s, 1H), 7.72 (s, 1H), 7.50 (d, 1H), 7.07 (s, 1H), 6.73-6.60 (m, 3H), 6.05 (m, 1H), 5.89 (dd, 1H), 5.52 (s, 2H), 4.20 (ddd, 4H), 1.60 (tt, 1H), 0.98-0.87 (m, 2H), 0.87-0.76 (m, 2H)。

[0656] LC/MS (方法A): RT=2.16; m/z=409 [M+H] $^+$

[0657] 实施例216: 3-(2-氨基吡啶-4-基)-6-(环丙基乙炔基)-N-(2,6-二氟苄基)-1H-吡咯并[2,3-b]吡啶-4-胺

[0658] 步骤1: 4-氯-6-(环丙基乙炔基)-1H-吡咯并[2,3-b]吡啶 (制备例34)

[0659] 向1-苯甲酰基-6-溴-4-氯-1H-吡咯并[2,3-b]吡啶 (按照W02009/087225所述的方法制备) (1.52g, 4.54mmol) 在Et₃N (15mL) 和THF (3mL) 中的溶液中加入乙炔基环丙烷 (3eq) 和CuI (0.3eq)。将溶液用氮气净化5分钟, 然后加入Pd(PPh₃)₂Cl₂ (0.3eq) 并将反应混合物于室温下搅拌过夜。向反应混合物中加入水 (1mL) 并在CEM微波反应器上于80℃加热1小时。将混合物用水 (20mL) 和DCM (20mL) 稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用MeOH和DCM洗脱, 然后用异己烷研磨得到米色固体状产物 (0.652g, 3mmol, 66%)。

[0660] ^1H NMR (399MHz, DMSO- d_6) δ 12.04 (s, 1H), 7.65 (d, 1H), 7.24 (s, 1H), 6.50 (d, 1H), 1.59 (tt, 1H), 1.01-0.85 (m, 2H), 0.89-0.72 (m, 2H)。

[0661] LC/MS (方法B): RT=1.31min; m/z=217 [M+H] $^+$

[0662] 步骤2: 6-(环丙基乙炔基)-N-[(2,6-二氟苄基)甲基]-1H-吡咯并[2,3-b]吡啶-4-胺 (制备例35)

[0663] 将步骤1中得到的化合物 (0.3g, 1.38mmol)、2,6-二氟苄基胺 (1.2eq)、BrettPhos (0.01eq) 和BrettPhos预催化剂 (0.01eq) 加入到微波小瓶中。将小瓶用特氟龙螺纹盖密封, 然后排空气体并用氮气回填。在室温及氮气氛下加入LiHMDS (1M的THF溶液, 2eq)。将反应混合物在CEM微波反应器中于65℃加热4小时。将反应混合物用1N HCl (2mL) 溶液终止反应并用DCM (50mL) 稀释。将有机层分离, 用盐水洗涤, 用硫酸镁干燥并真空浓缩。将残余物通过快速色谱纯化, 用MeOH和DCM洗脱得到浅棕色固体状产物 (0.429g, 1.32mmol, 96%)。

[0664] ^1H NMR (399MHz, DMSO- d_6) δ 11.13 (t, 1H), 7.43 (tt, 1H), 7.20-7.06 (m, 3H), 6.94 (t, 1H), 6.59 (dd, 1H), 6.33 (s, 1H), 4.44 (d, 2H), 1.53 (tt, 1H), 0.96-0.81 (m, 2H), 0.80-0.66 (m, 2H)。

[0665] LC/MS (方法B): RT=1.12min; m/z=324 [M+H] $^+$

[0666] 步骤3: 3-溴-6-(环丙基乙炔基)-4-[(2,6-二氟苄基)甲基]氨基]-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0667] 从步骤2所得到的化合物 (0.429g, 1.32mmol) 开始, 按照制备例17所述的方法得到米色固体状所需产物 (0.463g, 0.921mmol, 69%)。

[0668] ^1H NMR (399MHz, 氯仿- d) δ 7.42 (s, 1H), 7.29 (m, 1H), 7.01-6.92 (m, 2H), 6.69 (s, 1H), 6.19 (t, 1H), 4.56 (d, 2H), 1.64 (s, 9H), 1.50 (m, 1H), 1.00-0.86 (m, 4H)。

[0669] LC/MS (方法B): RT=1.61min; m/z=502 [M+H] $^+$

[0670] 步骤4: 3-(2-{[(叔丁氧基)羰基]氨基}吡啶-4-基)-6-(环丙基乙炔基)-4-{[(2,6-二氟苯基)甲基]氨基}-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0671] 从步骤3所得到的化合物(0.463g, 0.921mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始,按照制备例3所述的方法得到浅黄色固体状所需产物(0.233g, 0.378mmol, 41%)。

[0672] ^1H NMR (399MHz, 氯仿-d) δ 8.25-8.19 (m, 1H), 8.06 (d, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.27-7.21 (m, 1H), 7.02 (dd, 1H), 6.95-6.85 (m, 2H), 6.72 (s, 1H), 4.86 (t, 1H), 4.45 (d, 2H), 1.67 (s, 9H), 1.55 (s, 9H), 1.53-1.48 (m, 1H), 0.97-0.82 (m, 4H)。

[0673] LC/MS (方法B): RT=1.64min; m/z=616 [M+H]⁺

[0674] 步骤5: 3-(2-氨基吡啶-4-基)-6-(环丙基乙炔基)-N-(2,6-二氟苯基)-1H-吡咯并[2,3-b]吡啶-4-胺

[0675] 从步骤4得到的化合物(0.233g, 0.378mmol)开始,按照制备例7所述的方法得到白色固体状所需产物(88mg, 0.211mmol, 56%)。

[0676] ^1H NMR (399MHz, DMSO-d₆) δ 11.61 (s, 1H), 7.85 (d, 1H), 7.48-7.36 (m, 1H), 7.32 (s, 1H), 7.14 (t, 2H), 6.50-6.42 (m, 3H), 5.91 (s, 2H), 5.31 (t, 1H), 4.48 (d, 2H), 1.56 (tt, 1H), 0.91 (m, 2H), 0.80-0.71 (m, 2H)。

[0677] LC/MS (方法B): RT=1.09min; m/z=416 [M+H]⁺

[0678] 实施例223: 3-(2-氨基吡啶-4-基)-4-(1,3-苯并二氧杂环戊烯-5-基)-1H-吡咯并[2,3-b]吡啶-6-甲腈

[0679] 步骤1: 4-(1,3-苯并二氧杂环戊烯-5-基)-1H-吡咯并[2,3-b]吡啶-6-甲腈

[0680] 从4-氯-1H-吡咯并[2,3-b]吡啶-6-甲腈(按照Synthesis, 2008, (2), 201-204制备)(100mg, 0.56mmol)和(1,3-苯并二氧杂环戊烯-5-基)硼酸(1.1eq)开始,按照制备例3所述的方法得到黄色固体状所需产物(84mg, 0.32mmol, 57%)。

[0681] ^1H NMR (399MHz, DMSO-d₆) δ 12.38 (s, 1H), 7.93-7.82 (m, 1H), 7.75 (s, 1H), 7.43-7.31 (m, 2H), 7.12 (d, 1H), 6.78 (dd, 1H), 6.14 (s, 2H)。

[0682] LC/MS (方法B): RT=1.23min; m/z=264 [M+H]⁺

[0683] 步骤2: 4-(1,3-苯并二氧杂环戊烯-5-基)-3-溴-6-氰基-1H-吡咯并[2,3-b]吡啶-1-甲酸叔丁酯

[0684] 从步骤1所得到的化合物(0.289g, 1.1mmol)开始,按照制备例17所述的方法得到黄色固体状所需产物(0.373g, 0.84mmol, 77%)。

[0685] ^1H NMR (399MHz, DMSO-d₆) δ 8.33 (s, 1H), 7.87 (s, 1H), 7.14-7.04 (m, 2H), 6.98 (dd, 1H), 6.14 (s, 2H), 1.64 (s, 9H)。

[0686] 步骤3: 3-(2-氨基吡啶-4-基)-4-(1,3-苯并二氧杂环戊烯-5-基)-1H-吡咯并[2,3-b]吡啶-6-甲腈

[0687] 从步骤2所得到的化合物(0.180g, 0.41mmol)和N-[4-(四甲基-1,3,2-二氧硼戊环-2-基)吡啶-2-基]氨基甲酸叔丁酯(1.1eq)开始,按照制备例3所述的方法进行制备。将粗品反应混合物真空浓缩并按照制备例7所述的方法将残余物溶于DCM (2mL) 和TFA (1.5mL)。将粗品反应混合物真空浓缩并将残余物用MeOH研磨得到TFA盐形式的产物(49mg, 0.137mmol, 34%)。

[0688] ^1H NMR (399MHz, DMSO- d_6) δ 13.10 (d, 2H), 8.38 (d, 1H), 7.79 (s, 1H), 7.67 (t, 3H), 6.98 (d, 1H), 6.85 (d, 1H), 6.71 (dd, 1H), 6.49-6.30 (m, 2H), 6.05 (s, 2H)。

[0689] LC/MS (方法B): RT=0.97min; m/z=356 [M+H] $^+$

[0690] 下表6中的实施例213-225通过通用方法XXII-XXVI所描述的方法用适宜的可购买到的硼酸酯、胺和乙炔基制备。也包括了实施例213、214、215、216、223的化合物。

[0691] 表6: HRMS (TOF, ESI) 数据

[0692]

实施例	结构式	分子式	计算的精确质量	实测值 m/z	加合物
213	3-(2-氨基吡啶-4-基)-N-(2,6-二氟苄基)-6-甲基-1H-吡咯并[2,3-b]吡啶-4-胺	$\text{C}_{20}\text{H}_{17}\text{F}_2\text{N}_5$	365.1452	366.1514	[M + H] $^+$
214	4-[4-(5-氟吡啶-3-基)-6-甲基-1H-吡咯并[2,3-b]吡啶-3-基]吡啶-2-胺	$\text{C}_{18}\text{H}_{14}\text{FN}_5$	319.1233	320.1299	[M + H] $^+$
215	4-[6-(环丙基乙炔基)-4-(2,3-二氢-1,4-苯并二噁英-6-基)-1H-吡咯并[2,3-b]吡啶-3-基]吡啶-2-胺	$\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2$	408.1586	409.1618	[M + H] $^+$
216	3-(2-氨基吡啶-4-基)-6-(环丙基乙炔基)-N-(2,6-二氟苄基)-1H-吡咯并[2,3-b]吡啶-4-胺	$\text{C}_{24}\text{H}_{19}\text{F}_2\text{N}_5$	415.1609	416.1638	[M + H] $^+$

[0693]

217	4-[4-(2,3-二氢-1,4-苯并二𫞧英-6-基)-6-甲基-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2-胺	C ₂₁ H ₁₈ N ₄ O ₂	358.1430	359.1428	[M + H] ⁺
218	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-6-(环丙基乙炔基)-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2,6-二胺	C ₂₄ H ₁₉ N ₅ O ₂	409.1539	410.1570	[M + H] ⁺
219	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-6-(环丙基乙炔基)-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2-胺	C ₂₄ H ₁₈ N ₄ O ₂	394.1430	395.1430	[[M + H] ⁺
220	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-6-乙炔基-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2-胺	C ₂₁ H ₁₄ N ₄ O ₂	354.1117	355.1120	[M + H] ⁺
221	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-6-乙炔基-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2,6-二胺	C ₂₁ H ₁₅ N ₅ O ₂	369.1226	368.1146	[M + H] ⁺
222	4-[4-(1,3-苯并二氧杂环戊烯-5-基)-6-甲基-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2-胺	C ₂₀ H ₁₆ N ₄ O ₂	344.1273	343.1191	[M + H] ⁺
223	3-(2-氨基吡啶-4-基)-4-(1,3-苯并二氧杂环戊烯-5-基)-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-6-甲腈	C ₂₀ H ₁₃ N ₅ O ₂	355.1069	354.1014	[M + H] ⁺
224	4-(1,3-苯并二氧杂环戊烯-5-基)-3-(2,6-二氨基吡啶-4-基)-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-6-甲腈	C ₂₀ H ₁₄ N ₆ O ₂	370.1178	371.1170	[M + H] ⁺
225	4-[6-甲基-4-(4-甲基-3,4-二氢-2 <i>H</i> -1,4-苯并𫞧嗪-6-基)-1 <i>H</i> -吡咯并[2,3- <i>b</i>]吡啶-3-基]吡啶-2-胺	C ₂₂ H ₂₁ N ₅ O	371.1746	372.1738	[M + H] ⁺

[0694] 药理学研究

[0695] 实施例A: 激酶TR-FRET试验

[0696] 采用时间分辨荧光共振能量转移 (TR-FRET) 试验评估对人类激酶活性的抑制, 试验在384孔反应板中进行。在该试验中, 将来自Carna Biosciences的全长人类激酶DYRK1A (NM_001396, ref. 04-130; 2.0ng/μl)、DYRK1B (NM_004714, ref. 04-131; 1.2ng/μl)、

CLK1 (NM_001162407, ref. 04-126; 0.7ng/ μ l)、CDK9 (NM_001261, ref. 04-110; 0.9ng/ μ l) 或 GSK3 β (NM_001146156, ref. 04-141; 2.0ng/ μ l) 在室温下与ATP (Sigma A2383, 10 μ M) 和 ULIGHT™-标记的人髓磷脂碱性蛋白 (MBP) 肽底物 (Perkin Elmer TRF0109, 100nM) 一起在由 50mM HEPES pH7.4, 1mM EGTA, 10mM MgCl₂, 2mM DTT和0.01% Tween20组成的反应缓冲液中孵育40分钟 (DYRK1A和DYRK1B) 或100分钟 (CLK1、CDK9和GSK3 β)。本发明的测试化合物以 0.1nM至30 μ M的浓度范围加入到反应缓冲液中。加入EDTA (Sigma E7889, 10mM) 终止反应后, 加入识别MBP中的磷酸化-Thr232的钼标记的鼠单克隆抗体 (Perkin Elmer TRF0201, 1nM)。1小时后, 将反应板用荧光阅读器 (**EnVision®**, Perkin Elmer) 在620nm和665nm读取 (在 340nm激发): 当钼供体荧光团被波长为340nm的光激发时, 发生向受体的能量转移 (620nm), 其将发出波长为665nm的光。于是由发射光的相对强度测得DYRK1A激酶的活性以及活性的抑制。从浓度-活性曲线计算出激酶活性抑制50%所需的测试化合物的浓度IC₅₀。结果见表 1。

[0697] 实施例B: 激酶ADP试验

[0698] His-TEV-DYRK1A激酶结构域 (aa127-485) 的活性通过在使用ATP (Sigma Aldrich A7699) 磷酸化肽底物Woodtide (Zinnsser Analytic) 的过程中所产生的ADP的累积量来测定。酶反应在含有15mM Hepes; 20mM NaCl; 1mM EGTA; 10mM MgCl₂; 0.02% Tween20和0.1mg/ml牛丙种球蛋白的测定缓冲液 (pH 7.4) 中进行。本发明的测试化合物以一定的浓度范围在 30℃下、在20nM DYRK1A酶、40 μ M肽底物和20 μ M ATP的存在下加入反应缓冲液中10分钟。加入检测试剂 (DiscoverX 90-0083), 先加ADP Hunter Plus试剂A, 然后是ADP Hunter Plus试剂B。在30℃下孵育20分钟后, 加入ADP Hunter Plus终止溶液。在590nm下测定荧光强度。从浓度-活性曲线计算出激酶活性抑制50%所需的测试化合物的浓度IC₅₀。结果见表1。

[0699] 实施例C: 细胞DYRK1A自身磷酸化试验

[0700] 在第0天, 将人U2-OS骨肉瘤细胞接种于12孔培养板 (每孔100,000个细胞) 并在37℃下、在5% CO₂的存在下在1ml含有GlutaMAX™ (Gibco 36600) 并且补充有50单位/ml青霉素、50 μ g/ml链霉素、10mM Hepes缓冲液 (pH=7.4) 和10%胎牛血清 (FCS, Sigma F7524) 的McCoy's 5A (改性) 培养基中孵育。在第1天, 将培养基用500 μ l含有GlutaMAX™ (Gibco 51985)、150ng含有全长野生型人DYRK1A (NM_001396) 编码序列的具有HA标记的pcDNA3.1质粒 (Invitrogen)、0.3%阳离子脂质体Lipofectamine (Invitrogen 18324-020) 和0.6% Plus试剂 (Invitrogen Cat N°11514-015) 的优化培养基替换。5小时后, 将培养基用900 μ l含有GlutaMAX™ (Gibco 36600) 的McCoy's 5A (改性) 培养基替换。第2天, 将细胞暴露于一定浓度范围的本发明测试化合物5小时。然后将细胞用磷酸盐缓冲的盐水溶液洗涤并将细胞在由150mM NaCl、20mM Tris-HCl pH 7.4、1% Triton X-100、1mM EGTA、1mM EDTA以及蛋白酶 (1% v/v; 539134; Calbiochem) 和磷酸酶 (1% v/v; 524625; Calbiochem) 抑制剂合剂组成的裂解缓冲液 (每孔50 μ l裂解缓冲液) 中裂解。采用蛋白质印迹或中尺度ELISA平台测定磷酸-Ser520-DYRK1A的相对水平。对于蛋白质印迹分析, 将裂解物在含有5% v/v β -巯基乙醇的Laemmli样品缓冲液 (Bio-Rad) 中稀释, 于95℃加热5分钟, 然后在Tris-甘氨酸凝胶或 NuPage Bis-Tris凝胶 (Novex; Invitrogen) 上解析。在所有的凝胶中均包含生物素化分子量标准物 (Cell Signaling Technology)。将蛋白质转移到硝酸纤维素膜 (Hybond, ECL; Amersham) 上, 所述的膜在含有5% 奶的Tris-缓冲的盐水/0.1% 吐温20 (TBST) 中封闭并用

抗-磷酸-Ser520-DYRK1A抗体 (Eurogentec SE6974-75; 0.23 μ g/ml 5%BSA) 或抗DYRK1A抗体 (Abnova H00001859; 0.5 μ g/ml 5%奶) 中在4℃下探查过夜。将过氧化物酶标记的二级抗体在5%奶中稀释并在20℃下涂抹到膜上1小时。化学发光检测采用ECL-plus蛋白质印迹检测试剂盒 (Amersham) 进行并在ECL plus Hyperfilm (Amersham) 上记录。使用Bio-Rad GS-800校准型光密度计对印迹进行扫描并用TotalLab软件 (Amersham) 进行蛋白质印迹的定量分析。从描绘每个浓度下的磷酸-Ser520-DYRK1A与总DYRK1A信号之比的剂量-响应曲线计算抑制磷酸-Ser520-DYRK1A的IC₅₀值。对于中尺度ELISA分析, 将裂解物转移到用BSA封闭的含有预先结合的抗-HA捕获抗体 (Novus biological NB600-364; 15 μ g/ml) 的ELISA板上并在室温下振摇1小时。然后加入抗-磷酸-Ser520-DYRK1A抗体 (Eurogentec SE6974-75; 2.3-3.0mg/ml) 和抗DYRK1A抗体 (Abnova H00001859; 3 μ g/ml), 在室温下孵育1小时后加入磺胺类标记的抗兔检测抗体 (ref MSD R32AB; 1 μ g/ml) 和磺胺类标记的抗鼠检测抗体 (ref MSD R32-AC-1; 1 μ g/ml)。再经过1小时后, 加入读取缓冲液并将平板在Sector Imager 2400 (MesoScale) 上读取。从剂量-响应曲线计算抑制磷酸-Ser520-DYRK1A的IC₅₀值。结果表明, 本发明的化合物是细胞DYRK1A Ser520自身磷酸化的强抑制剂。结果见表1。

[0701] 实施例D: 在肿瘤异种移植中抑制DYRK1A自身磷酸化的药效学试验

[0702] 为了进行抑制DYRK1A自身磷酸化的药效学研究, 对雌性SCID小鼠皮下注射RS4; 11人急性淋巴细胞白血病细胞。当肿瘤达到200-300mm³大小时, 将小鼠随机分为均匀的3组并以最高100mg/kg的剂量单次口服本发明的化合物。在治疗后的不同时间, 通常为2小时和6小时, 将治疗组和对照组的小鼠处死, 切除肿瘤并将蛋白在由150mM NaCl、20mM Tris-HCl pH 7.4、1% Triton X-100、1mM EGTA、1mM EDTA以及蛋白酶 (1% v/v; 539134; Calbiochem) 和磷酸酶 (1% v/v; 524625; Calbiochem) 抑制剂合剂组成的组织裂解缓冲液中提取。用蛋白质印迹检测磷酸-Ser520-DYRK1A的相对水平。为此, 将裂解物在含有5% v/v β -巯基乙醇的Laemmli样品缓冲液 (Bio-Rad) 中稀释, 于95℃加热5分钟, 然后在Tris-甘氨酸凝胶或NuPage Bis-Tris凝胶 (Novex; Invitrogen) 上解析。在所有的凝胶中均包含生物素化分子量标准物 (Cell Signaling Technology)。将蛋白质转移到硝酸纤维素膜 (Hybond, ECL; Amersham) 上, 所述的膜在含有5%奶的Tris-缓冲的盐水/0.1%吐温20 (TBST) 中封闭并用抗-磷酸-Ser520-DYRK1A抗体 (Eurogentec SE6974-75; 0.23 μ g/ml 5%BSA) 或抗DYRK1A抗体 (Abnova H00001859; 0.5 μ g/ml 5%奶) 中在4℃下探查过夜。将过氧化物酶标记的二级抗体在5%奶中稀释并在20℃下涂抹到膜上1小时。化学发光检测采用ECL-plus蛋白质印迹检测试剂盒 (Amersham) 进行并在ECL plus Hyperfilm (Amersham) 上记录。使用Bio-Rad GS-800校准型光密度计对印迹进行扫描并用TotalLab软件 (Amersham) 进行蛋白质印迹的定量分析。用每个剂量下的磷酸-Ser520-DYRK1A与总DYRK1A信号之比来计算与对照肿瘤相比磷酸-Ser520-DYRK1A的抑制百分比。结果表明, 本发明的化合物是肿瘤DYRK1A Ser520自身磷酸化的强抑制剂。

[0703] 实施例E: 在肿瘤异种移植中的效力研究

[0704] 为了进行抗肿瘤效力研究, 对雌性裸NCR nu/nu小鼠皮下注射U87-MG人成胶质细胞瘤细胞。当肿瘤达到约150mm³大小时, 将小鼠随机分为均匀的8组并以最高200mg/kg的剂量每日一次口服给药本发明的化合物, 持续3周。通过每周至少用游标卡尺测量两次肿瘤大小来监测抗肿瘤效力, 并记录体重以记录潜在的一般毒性。指定某天的肿瘤生长抑制 (TGI)

百分比用如下公式计算： $(1 - [\text{RTV (治疗的)} / \text{RTV (未治疗的)}]) \times 100$ ，其中RTV=与开始治疗时相比在指定某天的相对肿瘤体积。结果表明，本发明的化合物是肿瘤生长的强抑制剂。

[0705] 表1:Dyrk1/Clk1抑制剂的IC₅₀

[0706]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Clk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 1		0.047				
实施例 2	0.018	0.023	0.0222		4.41	0.48
实施例 3		0.241				
实施例 4	0.0253	0.044	0.044		10	
实施例 5	0.0094	0.015	0.0005		10	
实施例 6		0.07				
实施例 7		0.039				
实施例 8		0.038				
实施例 9		0.06				
实施例 10		0.085				
实施例 11	0.0173	0.012	0.0132		10	
实施例 12		2.041				
实施例 13		1.373				
实施例 14		0.043				
实施例 15	0.0355	0.032	0.0143		10	
实施例 16	0.0149	0.011	0.0178	0.0328	10	0.1402
实施例 17	0.009	0.006	0.0013	0.0166	1.8543	0.0093
实施例 18	0.0151	0.012	0.0003	0.024	10	0.0663
实施例 19		0.025				
实施例 20	0.0197	0.013				

[0707]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Clk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 21	0.0102	0.023	0.0091		3.7762	
实施例 22		0.018				
实施例 23		0.015				
实施例 24		0.066				
实施例 25	0.0031	0.012	0.0079	0.0177	10	0.036
实施例 26		0.029				
实施例 27	0.0444	0.04	0.0522		10	
实施例 28		0.011				
实施例 29		0.062				
实施例 30		0.827				
实施例 31		1.068				
实施例 32	0.0056	0.015	0.0012		10	0.323
实施例 33		0.165				
实施例 34		0.278				
实施例 35	0.0248	0.043	0.0094		10	0.8865
实施例 36	0.0091	0.027	0.0062		5.5232	0.4857
实施例 37	0.007	0.025	0.0005		10	0.358
实施例 38		0.149				
实施例 39		0.084				
实施例 40		0.051				
实施例 41		0.158				
实施例 42		0.233				
实施例 43		0.278				
实施例 44		0.249				
实施例 45	0.2005	0.496			30	0.6864

[0708]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Ctk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 46		0.369				
实施例 47		0.372				
实施例 48	0.043	0.044			10	0.208
实施例 49		0.127				
实施例 50		0.045				
实施例 51	0.0029	0.013			10	0.126
实施例 52	0.0043	0.007	0.0027	0.0167	10	0.0232
实施例 53	0.0233	0.021			10	0.2375
实施例 54	0.0129	0.032			10	0.5105
实施例 55	0.0102	0.009	0.0043	0.0157	1.3025	0.0058
实施例 56	0.0114	0.012			2.5354	0.0117
实施例 57	0.0026	0.015	0.0098	0.0233	8.0604	0.0497
实施例 58	0.0215	0.01	0.0175	0.0245	10	0.0337
实施例 59	0.0102	0.042	0.0191		10	0.2587
实施例 60	0.003	0.011			10	0.0206
实施例 61	0.0062	0.01	0.0029	0.0129	10	0.0115
实施例 62	0.0186	0.008	0.0002	0.0162	10	0.021
实施例 63	0.0107	0.014			10	0.0408
实施例 64	0.0059	0.015	0.0093		10	0.2335
实施例 65	0.0709	0.069			30	0.8984
实施例 66	0.0107	0.045			10	0.3
实施例 67		0.094				
实施例 68		0.059				
实施例 69	0.0016	0.006	0.0011		0.6478	0.0036
实施例 70	0.0025	0.009	0.0015	0.0152	1.5031	0.027

[0709]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Clk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A - 细胞试验
实施例 71	0.0051	0.008	0.0074	0.0237	10	0.031
实施例 72	0.021	0.013			10	0.3
实施例 73	0.0059	0.038			10	0.3
实施例 74	0.0012	0.014		0.0184	10	0.1115
实施例 75	0.0143	0.037			10	0.3
实施例 76	0.0063	0.01	0.0005		10	0.0672
实施例 77		0.057				
实施例 78	0.0013	0.01	0.0145	0.0293	10	0.0721
实施例 79	0.0021	0.008	0.008		10	0.105
实施例 80	0.0059	0.004	0.0106		10	0.0156
实施例 81	0.0085	0.014	0.0141		10	0.1659
实施例 82	0.001	0.045	0.0199		10	
实施例 83	0.0006	0.081	0.0404		10	
实施例 84		0.006				0.0097
实施例 86		0.121				
实施例 87		1.939				
实施例 88		2.091				
实施例 89	0.0492	0.077			30	
实施例 90		10				
实施例 91		0.038				
实施例 92		0.087				
实施例 93		0.176				
实施例 94	0.0077	0.019	0.0112	0.0378	3	0.1549
实施例 95	0.0979	0.066			30	0.5344
实施例 96	0.0023	0.009	0.0315	0.0151	3	0.0119

[0710]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Clk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 97		0.063				
实施例 98		0.022		0.0241		0.1923
实施例 99	0.0086	0.029	0.0293	0.0549	3	0.1921
实施例 100		0.161				
实施例 101		0.034				0.3
实施例 102		0.293				
实施例 103		0.694				
实施例 104	0.0081	0.015	0.0167	0.0225	3	0.1055
实施例 105		0.121				
实施例 106		0.018		0.0171		0.1769
实施例 107		0.666				
实施例 108	0.0027	0.009	0.0092	0.0283	3	0.0491
实施例 109		0.524				
实施例 110		0.048				
实施例 111		0.013				
实施例 112		0.234				
实施例 113		0.114				
实施例 114		0.009		0.0162		0.006
实施例 115	0.0031	0.005	0.0094	0.0172	3	0.0185
实施例 116		0.005		0.0136		0.0009
实施例 117	0.0059	0.01	0.0093	0.0195		0.0377
实施例 118		0.011				
实施例 119	0.0066	0.02	0.0192	0.0828	3	0.2317
实施例 120		0.115				
实施例 121		0.066				

[0711]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Ctk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 122		0.05				
实施例 123		0.071		0.0615		0.3
实施例 124		0.296				
实施例 125	0.053	0.073			3.72	
实施例 126		0.418				
实施例 127		0.011				0.0169
实施例 128		0.009				0.0093
实施例 129		0.072				
实施例 130		0.26				
实施例 131		0.6				
实施例 132	0.0338	0.122			30	
实施例 133		0.269				
实施例 134		0.848				
实施例 135		0.091				
实施例 136		0.169				
实施例 137		0.336				
实施例 138		0.407				
实施例 139		0.883				
实施例 140		1.223				
实施例 141		0.417				
实施例 142		0.512				
实施例 143		1.057				
实施例 144		0.545				
实施例 145		0.042				0.4706
实施例 146		0.172				

[0712]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Clk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A -细胞试验
实施例 147		0.17				
实施例 148	0.0042	0.007	0.0144	0.0303	10	0.0335
实施例 149		0.734				
实施例 150	0.0034	0.74			1.1651	
实施例 151		0.028				
实施例 152		0.012				0.0101
实施例 153		0.011				0.0146
实施例 154		0.013				0.053
实施例 155		0.024				0.3
实施例 156		0.029				
实施例 157		0.26				
实施例 158	0.0655	0.15			30	
实施例 159		0.012				0.0187
实施例 160		0.184				
实施例 161	0.0091	0.028	0.0252	0.1222	3	0.1501
实施例 162		0.014				
实施例 163		0.026		0.1041		0.1974
实施例 164		0.015				0.0883
实施例 165		0.301				
实施例 166		0.025		0.2476		0.1179
实施例 167		0.015		0.042		0.0444
实施例 168		0.01				
实施例 169		0.216				
实施例 170		1.824				0.3
实施例 171		0.033				

[0713]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Ctk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 172		0.037				
实施例 173	0.0045	0.013	0.0051	0.0334	3	0.0497
实施例 174		0.07				
实施例 175		0.146				
实施例 176		0.196				
实施例 177		0.532				
实施例 178	0.0052	0.013	0.0141	0.1795	3	0.0782
实施例 179	0.0031	0.014	0.0115	0.0425	10	0.0365
实施例 180		0.079				
实施例 181		0.019				0.15
实施例 182		0.013				0.0142
实施例 183		0.006				0.029
实施例 184		0.012				0.0319
实施例 185	0.0048	0.011	0.0158	0.0631	10	0.012
实施例 186	0.0053	0.017	0.0211	0.0927	10	0.0855
实施例 187	0.003	0.013	0.0081	0.0649	11.639	0.0342
实施例 188		0.07				
实施例 189		0.062				0.3
实施例 190		0.419				
实施例 191		0.006				0.0443
实施例 192		0.008				0.048
实施例 193		0.116				
实施例 194		0.007				0.017
实施例 195		0.008				0.0071
实施例 196		0.023				0.1715

[0714]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Clk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A-细胞试验
实施例 197		0.009				
实施例 198		0.017				0.1193
实施例 199		0.148				
实施例 200		0.027				
实施例 201		0.012				
实施例 202		0.144				
实施例 203		0.155				
实施例 204		0.089				
实施例 205		0.055				
实施例 206	0.0071	0.008	0.0133	0.0238	10	0.0015
实施例 207	0.0049	0.01	0.0181	0.0545	7.8293	0.0694
实施例 208		0.01				0.0041
实施例 209		0.032				0.1571
实施例 210		0.05				0.3
实施例 211		0.027				
实施例 212		0.009				
实施例 213	0.0026	0.008	0.0092	0.0172	3	0.057
实施例 214		0.242				
实施例 215		0.019				0.1032
实施例 216	0.0145	0.021	0.0219	0.1212	10	0.0807
实施例 217	0.0027	0.01	0.0077	0.0261	10	0.0385
实施例 218		0.015				0.0289
实施例 219		0.019				0.0325
实施例 220		0.034				0.1933
实施例 221		0.016				0.1323

[0715]

	IC ₅₀ (μM) Dyrk1A TR-FRET 试验	IC ₅₀ (μM) Dyrk1A ADP 试验	IC ₅₀ (μM) Dyrk1B TR-FRET 试验	IC ₅₀ (μM) Cdk1 TR-FRET 试验	IC ₅₀ (μM) CDK9 TR-FRET 试验	IC ₅₀ (μM) P-Ser520- Dyrk1A -细胞试验
实施例 222		0.008				0.0442
实施例 223		0.043				0.3
实施例 224		0.03				0.2249
实施例 225		0.037				

[0716] 实施例F:药物组合物:片剂

[0717] 1000片包含5mg剂量的选自实施例1至225的化合物的片剂

[0718] 选自实施例1至225的化合物.....5g

[0719] 小麦淀粉.....20g

[0720] 玉米淀粉.....20g

[0721] 乳糖.....30g

[0722] 硬脂酸镁.....2g

[0723] 二氧化硅.....1g

[0724] 羟丙基纤维素.....2g。

Abstract

(Formula I) Compounds of formula (I) usefull for the treatment of cancer, neurodegenerative disorders and metabolic disorders.