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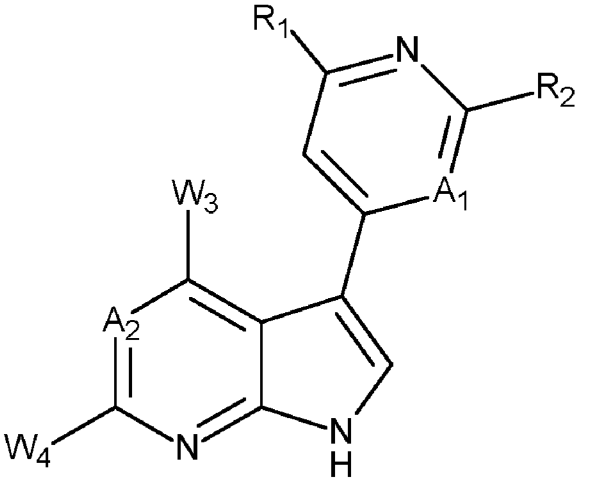
(54) Title: NEW PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES AS DUAL DYRK1/CLK1 INHIBITORS



(I)

(57) Abstract: (Formula I) Compounds of formula (I) usefull 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

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.
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. 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 GLI1, 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]. 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. 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].

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.

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 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 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].

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. 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.

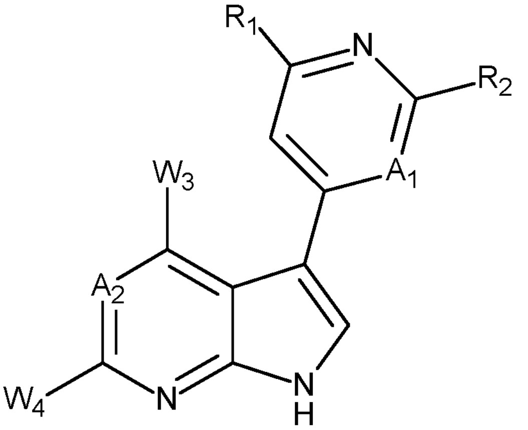
Alternative splicing regulated by CLK1 has also been described to play a role in neurodegenerative diseases, including Alzheimer's and Parkinson's, *via* phosphorylation of the SR proteins of the spliceosome [Jain *et al*, Curr Drug Targets. 2014;15(5):539-50]. In the case of Alzheimer's, CLK1 is known 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):



(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 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, SO_2 and nitrogen, which may include fused, bridged or spiro ring systems,
- "-(C_0-C_6)alkylene-" refers either to a covalent bond (-C_0alkylene-) 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 (C_1-C_6)alkyl, linear or branched (C_2-C_6)alkenyl group, linear or branched (C_2-C_6)alkynyl group, linear or branched

$(C_1\text{-}C_6)$alkoxy optionally substituted by $-NR_cR_d$ or by from 1 to 3 halogen atoms, linear or branched $(C_1\text{-}C_6)$alkyl-S-, hydroxy, oxo (or *N*-oxide where appropriate), nitro, cyano, $-C(O)\text{-}OR_c$, $-C(O)\text{-}R_c$, $-O\text{-}C(O)\text{-}R_d$, $-C(O)\text{-}NR_cR_d$, $-NR_c\text{-}C(O)\text{-}R_d$, $-NR_cR_d$, linear or branched $(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$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, R_1 represents a hydrogen and R_2 a $-NH_2$ group.

In one embodiment of the invention, A_1 represents a CH group.

In another embodiment of the invention, A_1 represents a nitrogen atom.

In a preferred embodiment of the invention, A_2 represents a nitrogen atom.

Alternatively, A_2 represents a CH group. When A_2 represents a CH group, A_1 represents preferably a CH group.

In another embodiment of the invention, W_3 represents a linear or branched $(C_1\text{-}C_6)$alkoxy, $-O\text{-}(C_0\text{-}C_6)$alkylene-$Cy_1$, $-O\text{-}(C_0\text{-}C_6)$alkylene-$Cy_1\text{-}Cy_2$, $-NR_a\text{-}(C_1\text{-}C_6)$alkylene-$Cy_1\text{-}Cy_2$,

-NR_a-(C_0-C_6)alkylene-Cy_1-O-(C_1-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.

Alternatively, W_3 represents a Cy_1 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.

In an other embodiment, W_3 represents: (i) a –NR_a-Cy_1 group, wherein Cy_1 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-(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 mentioned previously.

In a specific embodiment, W_3 represents a -phenylene-(C_0-C_6)alkylene-Cy_2.

More preferably, 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.

Preferred W_4 groups are as follows: methyl ; propan-2-yl ; prop-1-en-2-yl ; ethenyl ; cyano ; ethynyl ; cyclopropyl ; cyclopropylethynyl. Methyl group is even more preferred.

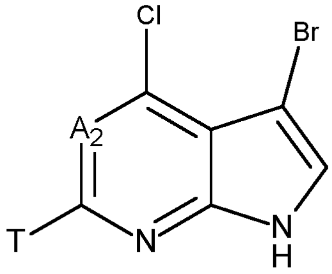
Preferred compounds according to the invention are included in the following group:

- 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-(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,

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

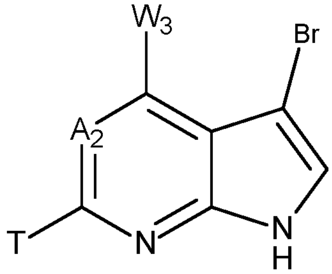
The invention relates also to a process for the preparation of compounds of formula (I), which process is characterised in that there is used as starting material the compound of formula (II):



(II)

wherein T represents a halogen atom, a methane-sulfanyl group, a cycloalkyl group or a linear or branched (C_1-C_6)alkyl group, and A_2 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) :



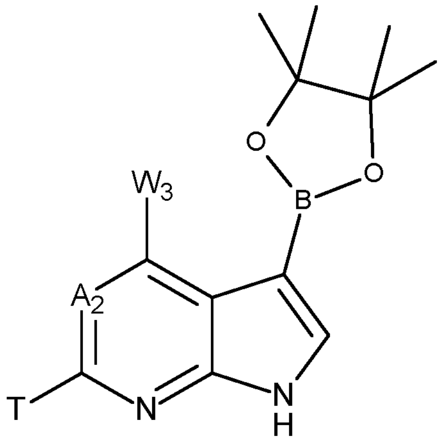
(III)

wherein T is as defined previously, A_2 and W_3 are as defined in formula (I),
which compound of formula (III) is either :

(i) 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,

(ii) or directly subjected to coupling with an appropriate boronic acid derivative,

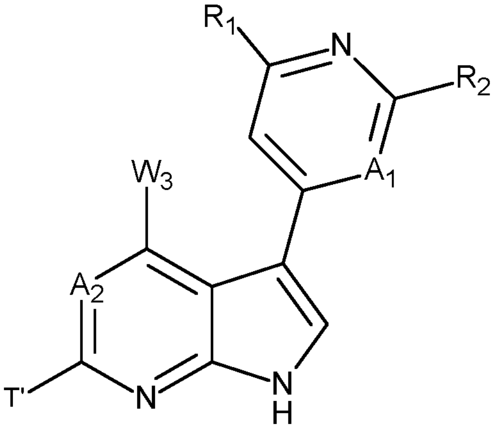
(iii) or subjected to coupling with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane to yield :



(III')

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

to yield compound of formula (IV) :


(IV)

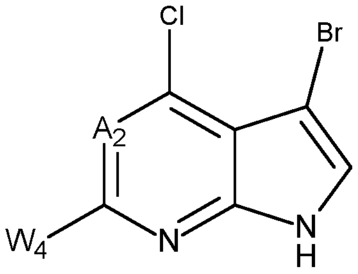
wherein T' represents represents a halogen atom, a cyano group, a cycloalkyl group or a linear or branched (C_1-C_6)alkyl group, and A_1, A_2, R_1, R_2 and W_3 are as defined in formula (I),

which compound of formula (IV):
- 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),

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 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):

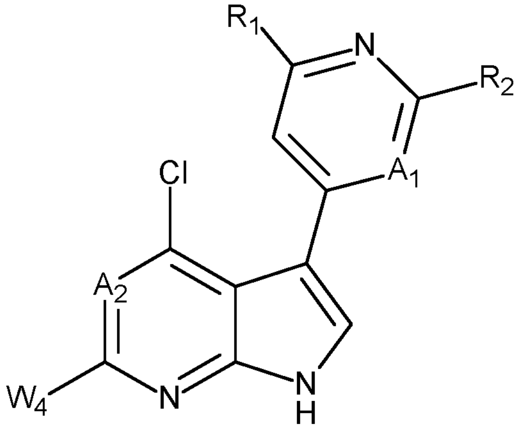


(II)

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,

to yield compound of formula (V):



(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,

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 $\equiv\!-\!R_3$ 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 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 obsesity.

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
Bn	benzyl
Boc	*tert*-butyloxycarbonyl protecting group
dppf	1,1'-bis(diphenylphosphino)ferrocene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-diméthylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dtbpf	1,1'-bis(di-*tert*-butylphosphino)ferrocene
eq.	equivalent
Et	ethyl
IPA	isopropanol
HPLC-MS	liquid chromatography–mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
mCBPA	*meta*-chloroperoxybenzoic acid
Me	methyl
NBS	*N*-bromosuccinimide
^{n}Bu	*n*-butyl
^{n}BuPAd$_2$	*n*-butyldiademantylphosphine
Pd/C	palladium on carbon
Ph	phenyl
PPh$_3$	triphenylphosphine
pTSA	*para*-toluenesulfonic acid
RT	retention time
sat.	saturated

SEM	[2-(trimethylsilyl)ethoxy]methyl
^{t}Bu	*tert*-butyl
TFA	trifuoroacetic acid
THF	tetrahydrofurane

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 by automated flash chromatography using a Combiflash R_f apparatus (Teledyne Isco Inc.) using RediSep R_f prepacked 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 F_{254} silica gel.

The compounds of the present invention were characterized by high performance liquid 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 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.

Temperature: 55 °C.

Mobile Phase: A - H_20 + 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

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 × 20 mm i.d. column from Phenomenex, running at a flow rate of 20 cm^3min^{-1} with UV diode array detection (210–400 nm) and mass-directed collection.

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.

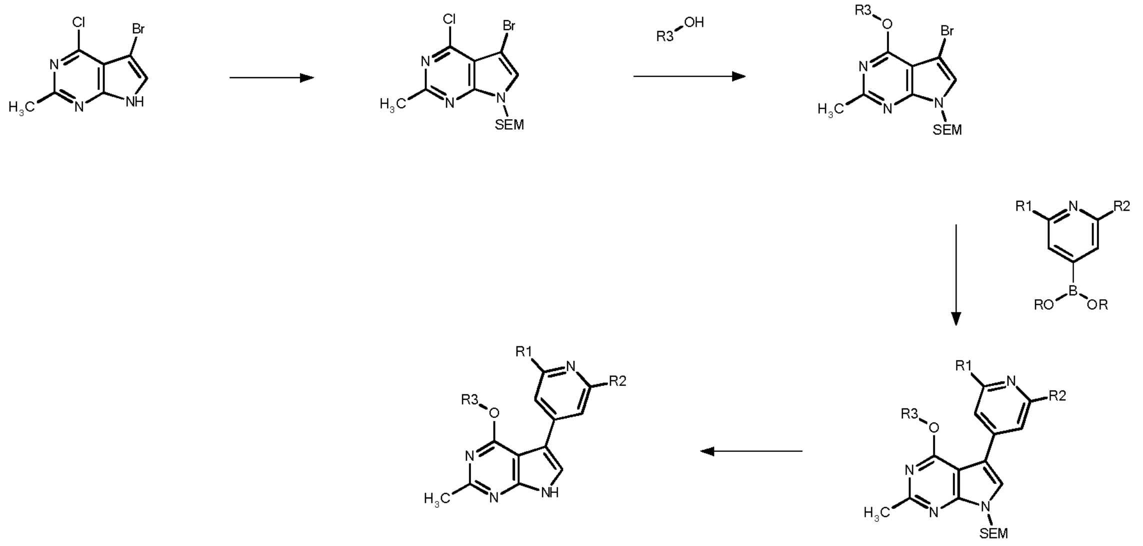
At pH 9: solvent A = 10 mM ammonium acetate in HPLC grade water + 0.08% v/v ammonia solution. Solvent B = 95% v/v HPLC grade acetonitrile + 5% v/v solvent A + 0.08% v/v ammonia solution.

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.

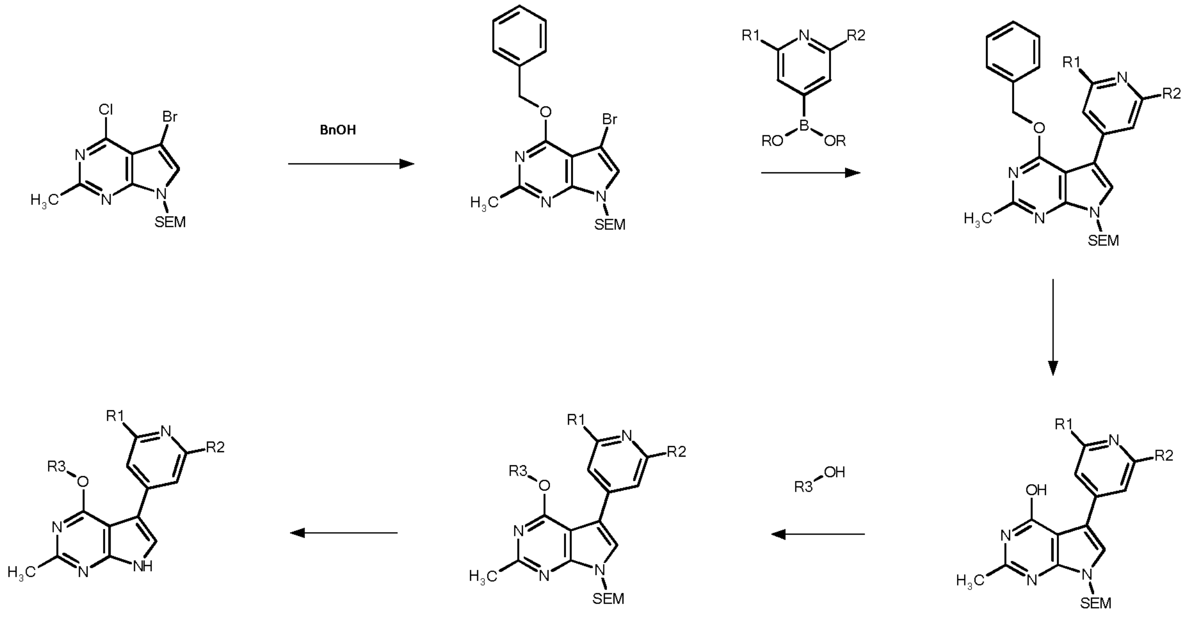
Some compounds of the present invention were characterised using an Agilent 1290 Infinity II series instrument connected to an Agilent TOF 6230 single quadrupole with an ESI source. High resolution mass spectra were recorded in positive-negative switching mode ionization unless otherwise stated. UV detection 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 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.

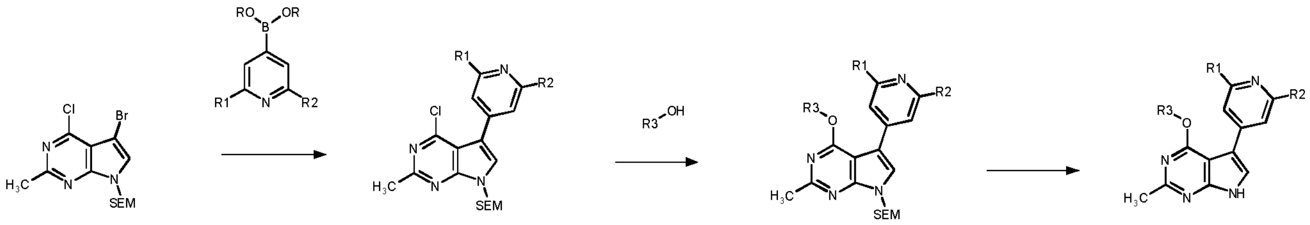
General Procedure I



General Procedure II



General Procedure III



In **General Procedures I, II and III** :

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

- R_3 represents 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, 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.

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

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

To a solution of 5-bromo-4-chloro-2-methyl-7*H*-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 N_2. 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 N_2. The reaction mixture was diluted with diethyl ether (100 mL), washed with brine (4 x 50 mL), dried over $MgSO_4$ 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.

^{1}H 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 N_2. 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. NH_4Cl solution (20 mL) and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ 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 N_2. Potassium carbonate (3 eq) and Pd(dtbpf)Cl_2 (10% wt) were added and the resulting mixture was degassed under N_2 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 $MgSO_4$ 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 $MgSO_4$ 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.

^{1}H 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 $[M+H]^+$

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

Step 1: 4-(benzyloxy)-5-bromo-2-methyl-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-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, 91%) was obtained as a light yellow oil.

^{1}H 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 $[M+H]^+$

Step 2: 4-(benzyloxy)-2-methyl-5-(2-methylpyridin-4-yl)-7-{[2-(trimethylsilyl)ethoxy] methyl}-7H-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 to give the product (1.311 g, 2.8 mmol, 64%) as a brown oil.

^{1}H 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 H_2 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

^{1}H 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 (3*R*)-3-(hydroxymethyl)piperidine-1-carboxylate (1.5 eq) in THF(5 mL) was added PPh_3 (1.5 eq) at room temperature under N_2. 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.

^{1}H 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 N_2 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 NH_3 solution in MeOH. The fractions were concentrated *in vacuo* and the residue was purified via flash chromatography using 2N NH_3 solution in MeOH and DCM as eluent to give the desired product (18 mg, 0.024 mmol, 17%) as a white solid.

^{1}H 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 $[M+H]^+$

<u>Example 20:</u> 4-[2-methyl-4-(1-phenylethoxy)-7*H*-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}-7*H*-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.

^{1}H 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.

^{1}H 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

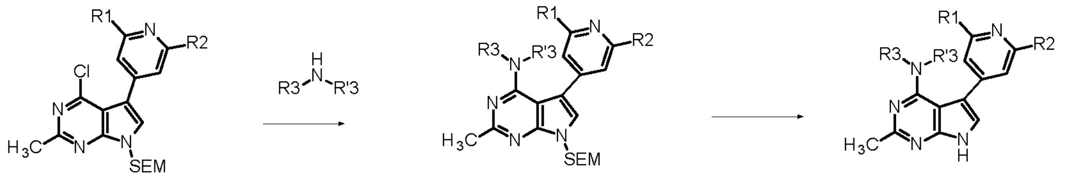
Example	Structure	Mol Formula	Calcd Exact Mass	Found m/z	Adduct
1	4-methoxy-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C13 H12 N4 O	240.1011	241.1082	[M + H]$^+$
2	4-(4-methoxy-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine	C13 H13 N5 O	255.1120	256.1196	[M + H]$^+$
3	5-(2-fluoropyridin-4-yl)-4-methoxy-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine	C13 H11 F N4 O	258.0917	259.0996	[M + H]$^+$
4	4-methoxy-2-methyl-5-(2-methylpyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C14 H14 N4 O	254.1168	255.1238	[M + H]$^+$

5	2-methyl-5-(2-methylpyridin-4-yl)-4-(thiophen-3-ylmethoxy)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C18 H16 N4 O S	336.1045	337.1129	$[M + H]^+$
6	2-methyl-5-(2-methylpyridin-4-yl)-4-[(3*R*)-piperidin-3-ylmethoxy]-7*H*-pyrrolo[2,3-*d*]pyrimidine	C19 H23 N5 O	337.1903	338.1982	$[M + H]^+$
7	4-(cyclopropylmethoxy)-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C16 H16 N4 O	280.1324	281.1400	$[M + H]^+$
8	4-(2-cyclopropylethoxy)-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C17 H18 N4 O	294.1481	293.1409	$[M - H]^-$
9	4-[2-(1*H*-indol-3-yl)ethoxy]-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C22 H19 N5 O	369.1590	370.1657	$[M + H]^+$
10	2-methyl-4-(2-phenylethoxy)-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C20 H18 N4 O	330.1481	331.1547	$[M + H]^+$
11	4-(benzyloxy)-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C19 H16 N4 O	316.1324	317.1391	$[M + H]^+$
12	2-methyl-5-(pyridin-4-yl)-4-[2-(pyrrolidin-1-yl)ethoxy]-7*H*-pyrrolo[2,3-*d*]pyrimidine	C18 H21 N5 O	323.1746	324.1818	$[M + H]^+$
13	2-methyl-4-[2-(piperidin-1-yl)ethoxy]-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C19 H23 N5 O	337.1903	338.1975	$[M + H]^+$

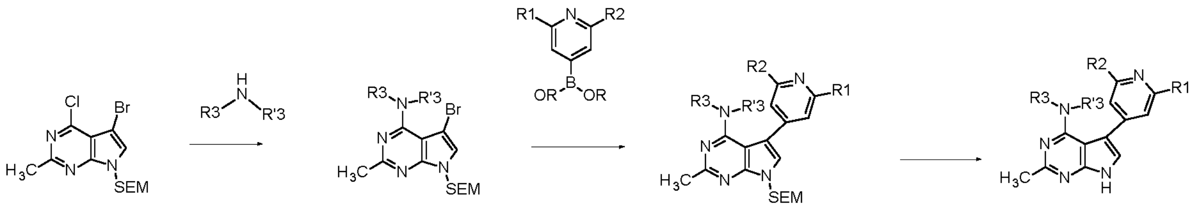
14	2-methyl-5-(pyridin-4-yl)-4-(tetrahydrofuran-2-ylmethoxy)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C17 H18 N4 O2	310.1430	311.1508	$[M + H]^+$
15	4-(cyclopentylmethoxy)-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C18 H20 N4 O	308.1637	309.1711	$[M + H]^+$
16	2-methyl-4-[(5-methyl-1,2-oxazol-3-yl) methoxy]-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine	C17 H15 N5 O2	321.1226	322.1299	$[M + H]^+$
17	4-[2-methyl-4-(thiophen-3-ylmethoxy)-7*H*-pyrrolo[2,3-*d*]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)-7*H*-pyrrolo[2,3-*d*]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)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C17 H15 N5 O S	337.0997	338.1072	$[M + H]^+$
20	4-[2-methyl-4-(1-phenylethoxy)-7*H*-pyrrolo[2,3-*d*]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]-7*H*-pyrrolo[2,3-*d*]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)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C18 H16 N6 O	332.1386	333.1453	$[M + H]^+$

23	4-[2-methyl-4-(pyridin-4-ylmethoxy)-7*H*-pyrrolo[2,3-*d*]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-7*H*-pyrrolo[2,3-*d*]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-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}methyl)benzonitrile	C20 H16 N6 O	356.1386	357.1464	$[M + H]^+$
26	4-{4-[(4-methoxybenzyl)oxy]-2-methyl-7*H*-pyrrolo[2,3-*d*]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}-7*H*-pyrrolo[2,3-*d*]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)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C16 H14 N6 O S	338.0950	339.1019	$[M + H]^+$

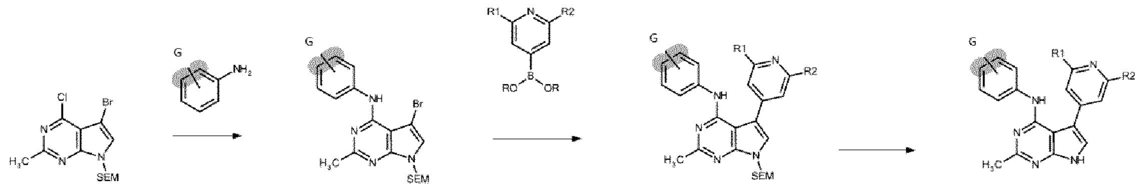
General Procedure IV



General Procedure V



General Procedure VI



In **General Procedures IV, V** and **VI**:

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

- R_3 represents a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, $-(C_0\text{-}C_6)$alkylene-Cy_1, $-(C_0\text{-}C_6)$alkylene-Cy_1-Cy_2, $-(C_0\text{-}C_6)$alkylene-Cy_1-O-$(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$alkyl group,

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.

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

*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} -7*H*-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 °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 $MgSO_4$ 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.

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.

^{1}H 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)

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

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}-7*H*-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.

^{1}H 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.

^{1}H 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.

^{1}H 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 $[M+H]^+$

<u>Example 52</u>*:* 5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-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-(trimethylsilyl)ethoxy]methyl}-7*H*-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-(trimethylsilyl) ethoxy]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-7*H*-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}-7*H*-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 N_2. 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 $MgSO_4$ 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.

^{1}H 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)-*N*,*N*,2-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C14 H16 N6	268.1436	269.1519	$[M + H]^+$
30	4-[2-methyl-4-(pyrrolidin-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C16 H18 N6	294.1593	295.1672	$[M + H]^+$
31	4-{4-[3-(dimethylamino)pyrrolidin-1-yl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C18 H23 N7	337.2015	338.2085	$[M + H]^+$
32	5-(2-aminopyridin-4-yl)-N-benzyl-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H18 N6	330.1593	331.1661	$[M + H]^+$

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

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

43	*N*-benzyl-2-methyl-5-(2-methylpyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H19 N5	329.1640	330.1709	$[M + H]^+$
44	2-methyl-5-(pyridin-4-yl)-*N*-(thiophen-3-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C17 H15 N5 S	321.1048	322.1121	$[M + H]^+$
45	2-methyl-5-(2-methylpyridin-4-yl)-*N*-(thiophen-3-ylmethyl)-7*H*-pyrrolo[2,3-*d*] pyrimidin-4-amine	C18 H17 N5 S	335.1205	336.1283	$[M + H]^+$
46	2-methyl-*N*-[(5-methyl-1,2-oxazol-3-yl)methyl]-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C17 H16 N6 O	320.1386	321.1450	$[M + H]^+$
47	2-methyl-*N*-[(5-methyl-1,2-oxazol-3-yl) methyl]-5-(2-methylpyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H18 N6 O	334.1542	335.1613	$[M + H]^+$

48	5-(2-aminopyridin-4-yl)-*N*-(cyclohexylmethyl)-2-methyl-7*H*-pyrrolo [2,3-*d*]pyrimidin-4-amine	C19 H24 N6	336.2062	337.2134	$[M + H]^+$
49	5-(2-aminopyridin-4-yl)-2-methyl-*N*-(1-phenylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H20 N6	344.1749	345.1814	$[M + H]^+$
50	5-(2-aminopyridin-4-yl)-*N*-(3-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H17 F N6	348.1499	349.1567	$[M + H]^+$
51	5-(2-aminopyridin-4-yl)-*N*-(2-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H17 F N6	348.1499	347.1430	$[M - H]^-$
52	5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 F2 N6	366.1405	365.1341	$[M - H]^-$

53	5-(2-aminopyridin-4-yl)-2-methyl-*N*-(pyridin-2-ylmethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H17 N7	331.1545	330.1471	$[M - H]^-$
54	5-(2-aminopyridin-4-yl)-*N*-(4-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H17 F N6	348.1499	347.1416	$[M - H]^-$
55	5-(2-aminopyridin-4-yl)-*N*-(2-methoxybenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H20 N6 O	360.1699	359.1611	$[M - H]^-$
56	5-(2-aminopyridin-4-yl)-2-methyl-*N*-(2-methylbenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H20 N6	344.1749	343.1675	$[M - H]^-$
57	5-(2-aminopyridin-4-yl)-*N*-(2-chlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H17 Cl N6	364.1203	363.1139	$[M - H]^-$

58	5-(2-aminopyridin-4-yl)-*N*-(2-chloro-6-methylbenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H19 Cl N6	378.1360	377.1292	$[M - H]^-$
59	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(5-methyl-1,2-oxazol-3-yl)methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C17 H17 N7 O	335.1495	334.1417	$[M - H]^-$
60	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(3-methylpyridin-2-yl)methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H19 N7	345.1702	344.1630	$[M - H]^-$
61	5-(2-aminopyridin-4-yl)-*N*-(2,6-dichlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 Cl2 N6	398.0813	397.0746	$[M - H]^-$
62	5-(2-aminopyridin-4-yl)-*N*-(2-chloro-6-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 Cl F N6	382.1109	381.1045	$[M - H]^-$

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

68	5-(2-aminopyridin-4-yl)-2-methyl-N-[(1*R*)-1-phenylethyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H20 N6	344.1749	343.1680	$[M - H]^-$
69	5-(2-aminopyridin-4-yl)-*N*-(2-fluoro-6-methoxybenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H19 F N6 O	378.1604	377.1534	$[M - H]^-$
70	5-(2-aminopyridin-4-yl)-*N*-(2-fluoro-6-methylbenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H19 F N6	362.1655	361.1593	$[M - H]^-$
71	5-(2-aminopyridin-4-yl)-*N*-[(3-fluoropyridin-2-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H16 F N7	349.1451	348.1370	$[M - H]^-$
72	5-(2-aminopyridin-4-yl)-*N*-(1*H*-indol-6-ylmethyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H19 N7	369.1702	368.1629	$[M - H]^-$

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

78	5-(2-aminopyridin-4-yl)-2-methyl-*N*-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 F3 N7	399.1419	398.1370	$[M - H]^-$
79	5-(2-aminopyridin-4-yl)-*N*-(2-ethoxybenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H22 N6 O	374.1855	373.1783	$[M - H]^-$
80	5-(2-aminopyridin-4-yl)-*N*-[2-methoxy-6-(trifluoromethyl)benzyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H19 F3 N6 O	428.1572	427.1491	$[M - H]^-$
81	5-(2-aminopyridin-4-yl)-*N*-(2,3-dichlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 Cl2 N6	398.0813	397.0744	$[M - H]^-$
82	5-(2-aminopyridin-4-yl)-*N*-[1-(2,6-difluorophenyl)ethyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H18 F2 N6	380.1561	379.1500	$[M - H]^-$

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

88	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(3-phenyl-1,2-oxazol-5-yl)methyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C22 H19 N7 O	397.1651	396.1584	$[M - H]^-$
89	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[2-(trifluoromethoxy)benzyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H17 F3 N6 O	414.1416	413.1342	$[M - H]^-$
90	5-(2-aminopyridin-4-yl)-*N*-[(1*R*,2*R*)-2-(benzyloxy)cyclohexyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H19 N7 O	428.2325	427.2252	$[M - H]^-$
91	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[(1*R*)-1,2,3,4-tetrahydronaphthalen-1-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C22 H22 N6	370.1906	369.1829	$[M - H]^-$
92	5-(2-aminopyridin-4-yl)-*N*-(2,5-dichlorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 Cl2 N6	398.0813	397.0746	$[M - H]^-$

93	5-(2-aminopyridin-4-yl)-*N*-cyclohexyl-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H22 N6	322.1906	321.1830	$[M - H]^-$
94	5-(2-aminopyridin-4-yl)-*N*-(3-chloro-2-methylbenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H19 Cl N6	378.1360	377.1288	$[M - H]^-$
95	5-(2-aminopyridin-4-yl)-*N*-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H19 N7 O	349.1651	348.1587	$[M - H]^-$
96	4-[4-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C18 H22 N6	322.1906	323.1978	$[M - H]^+$

98	5-(2-aminopyridin-4-yl)-*N*-[(3-methoxypyridin-2-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H19 N7 O	361.1651	362.1728	$[M - H]^+$
99	5-(2-aminopyridin-4-yl)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H20 N6	356.1749	357.1823	$[M + H]^+$
100	5-(2-aminopyridin-4-yl)-2-methyl-*N*-(3,3,3-trifluoropropyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C15 H15 F3 N6	336.1310	335.1250	$[M - H]^-$
101	4-[4-(3-azaspiro[5.5]undec-3-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C22 H28 N6	376.2375	375.2309	$[M - H]^-$
102	4-[2-methyl-4-(8-methyl-2-azaspiro[4.5]dec-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C22 H28 N6	376.2375	377.2441	$[M - H]^+$

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

108	4-[4-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C20 H24 N6	348.2062	347.1993	[M - H]$^{-}$
110	4-{2-methyl-4-[(4a*R*,8a*R*)-octahydroisoquinolin-2(1*H*)-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C21 H26 N6	362.2219	361.2154	[M - H]$^{-}$
111	4-{2-methyl-4-[(4a*R*,8a*S*)-octahydro isoquinolin-2(1*H*)-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C21 H26 N6	362.2219	361.2145	[M - H]$^{-}$
112	5-(2-aminopyridin-4-yl)-*N*-(2,3-dihydro-1-benzofuran-3-ylmethyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H20 N6 O	372.1699	373.1761	[M - H]$^{+}$

113	5-(2-aminopyridin-4-yl)-*N*-[1-(3-methoxypyridin-2-yl)ethyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H21 N7 O	375.1808	376.1876	[M - H]$^+$
114	4-[4-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridine-2,6-diamine	C20 H20 F N7 O	393.1713	394.1774	[M - H]$^+$
117	4-(4-{[(1*S*)-1-(2-methoxyphenyl)ethyl]amino}-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridine-2,6-diamine	C21 H23 N7 O	389.1964	390.2023	[M - H]$^+$

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

123	5-(2-aminopyridin-4-yl)-*N*-(2,2-difluoro-2-phenylethyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H18 F2 N6	380.1561	381.1635	[M - H]$^+$
124	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[2-(pyridin-2-yl)ethyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H19 N7	345.1702	346.1767	[M - H]$^+$
125	4-{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine + 4-{4-[(2*S*,6*R*)-2,6-dimethylmorpholin-4-yl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C18 H22 N6 O	338.1855	339.1931	[M - H]$^+$
126	4-{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridine-2,6-diamine + 4-{4-[(2*S*,6*R*)-2,6-dimethylmorpholin-4-yl]-2-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridine-2,6-diamine	C18 H23 N7 O	353.1964	354.2044	[M - H]$^+$
127	5-(2-aminopyridin-4-yl)-*N*-(1,3-benzodioxol-4-ylmethyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H18 N6 O2	374.1491	375.1494	[M - H]$^+$

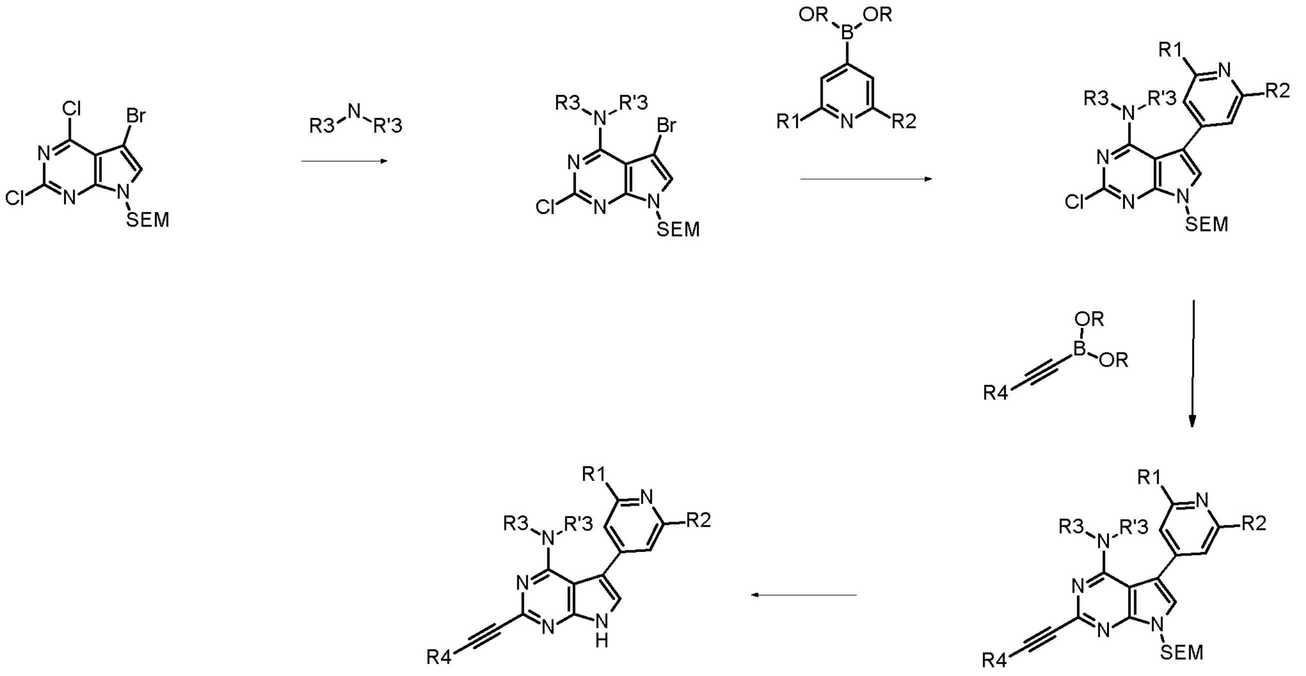
128	4-{4-[(1,3-benzodioxol-4-ylmethyl)amino]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridine-2,6-diamine	C20 H19 N7 O2	389.1600	390.1593	$[M - H]^+$
129	5-(2-aminopyridin-4-yl)-2-methyl-*N*-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H16 N6	316.1436	317.1458	$[M - H]^+$
130	5-(2-aminopyridin-4-yl)-2-methyl-*N*-[2-(trifluoromethyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H15 F3 N6	384.1310	385.1326	$[M - H]^+$
131	4-(2-methyl-4-{[2-(trifluoromethyl)phenyl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridine-2,6-diamine	C19 H16 F3 N7	399.1419	400.1434	$[M - H]^+$
132	5-(2-aminopyridin-4-yl)-*N*-(1,3-benzodioxol-5-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H16 N6 O2	360.1335	361.1332	$[M - H]^+$

133	4-[4-(4-methoxypiperidin-1-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C18 H22 N6 O	338.1855	339.1871	$[M - H]^+$
134	4-[2-methyl-4-(morpholin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C16 H18 N6 O	310.1542	311.1565	$[M - H]^+$
135	4-[4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C18 H18 N8	346.1654	347.1663	$[M - H]^+$
136	4-[4-(7,8-dihydropyrido[3,4-b]pyrazin-6(5*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C19 H18 N8	358.1654	359.1659	$[M - H]^+$
137	4-[2-methyl-4-(2-methylmorpholin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C17 H20 N6 O	324.1699	323.1544	$[M - H]^-$

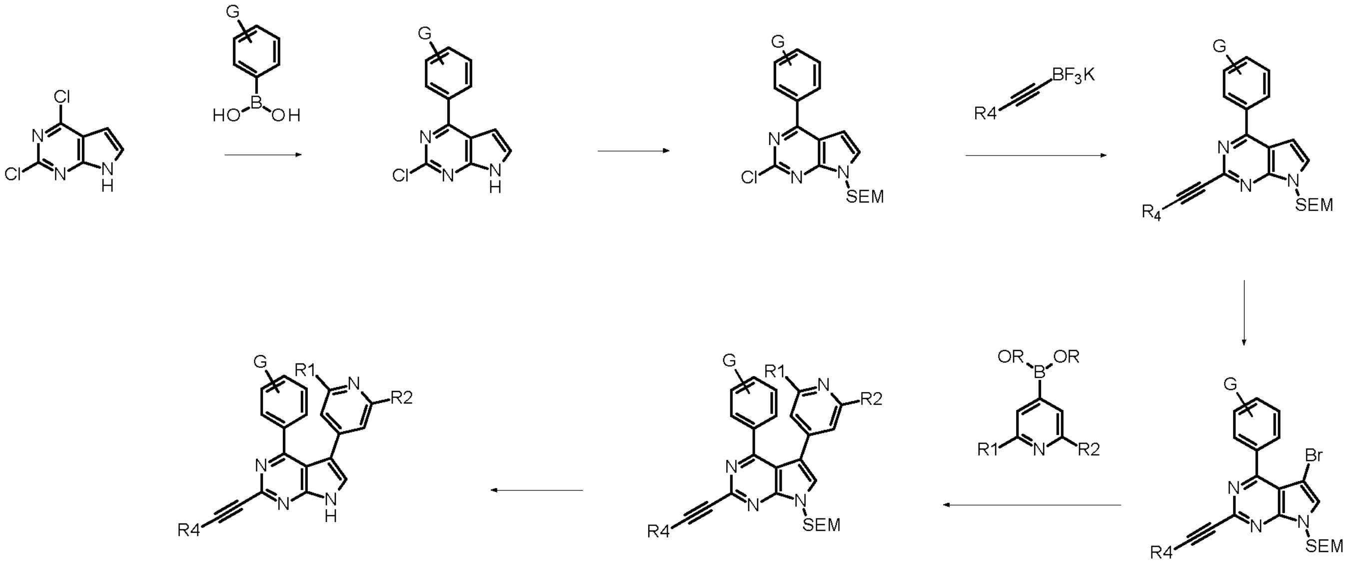
138	4-[4-(3-methoxypiperidin-1-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C18 H22 N6 O	338.1855	339.1855	$[M - H]^+$
139	4-[4-(4-methoxypiperidin-1-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridine-2,6-diamine	C18 H23 N7 O	353.1964	354.1972	$[M - H]^+$
140	4-[2-methyl-4-(morpholin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridine-2,6-diamine	C16 H19 N7 O	325.1651	326.1724	$[M - H]^+$
141	4-[4-(5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridine-2,6-diamine	C18 H19 N9	361.1763	362.1764	$[M - H]^+$
142	4-[4-(7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridine-2,6-diamine	C19 H19 N9	373.1763	374.1760	$[M - H]^+$

143	4-[2-methyl-4-(2-methylmorpholin-4-yl)-7*H*-pyrrolo[2,3-*d*]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-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridine-2,6-diamine	C18 H23 N7 O	353.1964	354.1978	$[M - H]^+$
145	*N*-[2-methoxy-6-(trifluoromethyl)benzyl]-2-methyl-5-(pyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H18 F3 N5 O	413.1463	414.1468	$[M - H]^+$
146	*N*-[2-methoxy-6-(trifluoromethyl)benzyl]-2-methyl-5-(2-methylpyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C22 H20 F3 N5 O	427.1620	428.1633	$[M - H]^+$

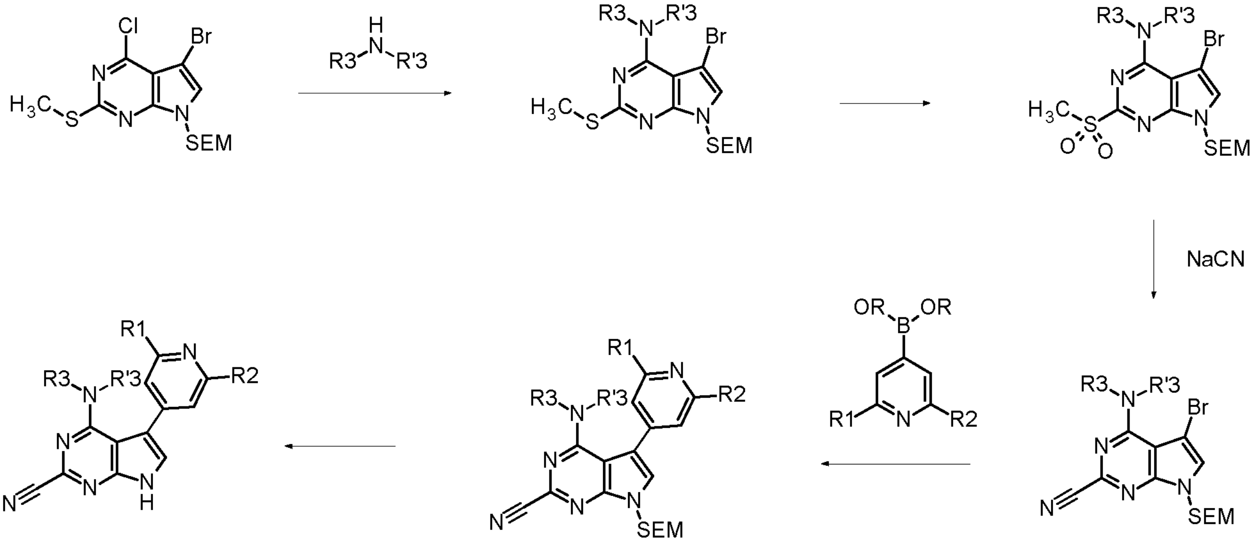
General Procedure VII



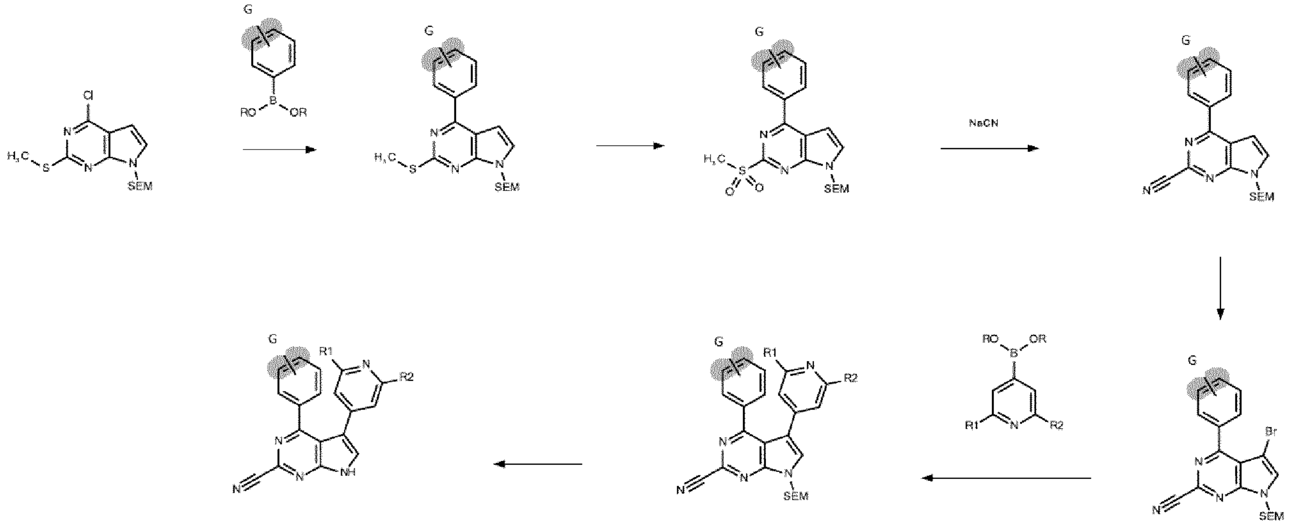
General Procedure VIII



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),

- 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 148: 5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-ethynyl-7*H*-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}-7*H*-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.

^{1}H 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 $[M+H]^+$

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 N_2. 2M Na_2CO_3 aq. solution (1 mL) and tetrakis(triphenylphosphine)palladium (0.08 mmol) were added and the resulting mixture was degassed under N_2 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 $MgSO_4$ 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 $[M+H]^+$

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.

^{1}H 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)-7*H*-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.

^{1}H 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.

^{1}H 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 N_2 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 $MgSO_4$ 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.

^{1}H 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.

^{1}H 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]-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile

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

Starting from 5-bromo-4-chloro-2-(methylsulfanyl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-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.

^{1}H 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)***

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 N_2. 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. $NaHCO_3$ (20 mL) solution and DCM (20 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ and 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)***

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 N_2 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 $MgSO_4$ 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.

^{1}H 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).

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 procedure described in **Preparation 3**, the desired product (0.135 g, 1.51 mmol, 49%) was obtained as a white solid.

^{1}H 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).

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 white solid.

^{1}H 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]$^+$

<u>Example 158:</u> 4-(1,3-benzodioxol-5-yl)-5-(2,6-diaminopyridin-4-yl)-7*H*-pyrrolo[2,3-*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.

^{1}H 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.

^{1}H 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.

^{1}H 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 N_2 at room temperature. The reaction mixture was stirred at 80 °C overnight under N_2. 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.
^{1}H NMR (399 MHz, $CDCl_3$) 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.
^{1}H 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

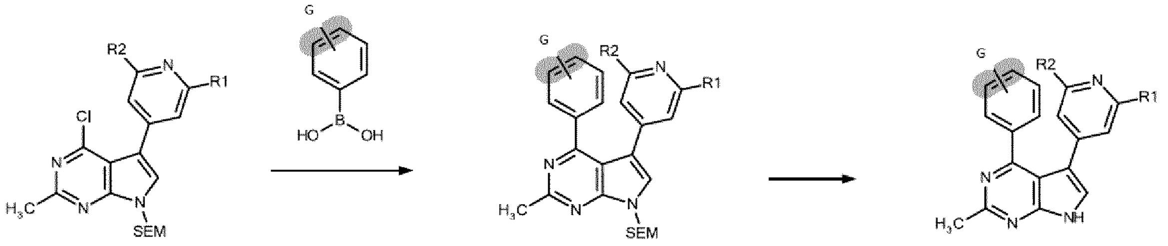
Example	Structure	Mol Formula	Calcd Exact Mass	Found m/z	Adduct
147	5-(2-aminopyridin-4-yl)-2-cyclopropyl-*N*-(2,6-difluorobenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H18 F2 N6	392.1561	391.1494	$[M - H]^-$
148	5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-ethynyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H14 F2 N6	376.1248	375.1193	$[M - H]^-$
149	5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-(prop-1-en-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H18 F2 N6	392.1561	391.1479	$[M - H]^-$
150	5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-(propan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C21 H20 F2 N6	394.1718	393.1650	$[M - H]^-$
151	5-(2-aminopyridin-4-yl)-*N*-(2,6-difluorobenzyl)-2-ethenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C20 H16 F2 N6	378.1405	377.1342	$[M - H]^-$

152	5-(2-aminopyridin-4-yl)-2-(cyclopropylethynyl)-N-(2,6-difluorobenzyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C23 H18 F2 N6	416.1561	417.1618	$[M - H]^+$
153	4-[4-(1,3-benzodioxol-5-yl)-2-(cyclopropylethynyl)-7*H*-pyrrolo[2,3-*d*]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)-7*H*-pyrrolo[2,3-*d*]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-7*H*-pyrrolo[2,3-*d*]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-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C20 H13 N5 O2	355.1069	356.1108	$[M - H]^+$

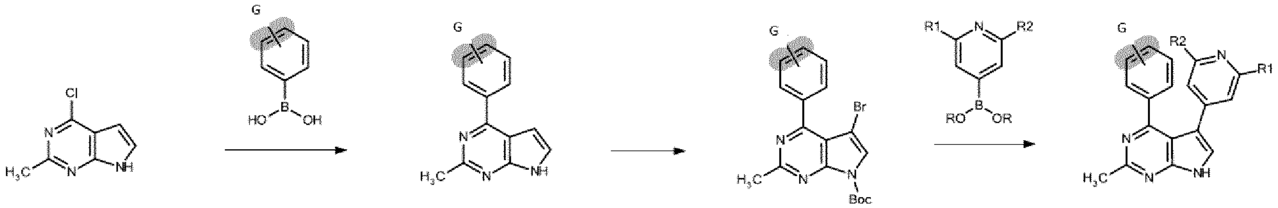
157	5-(2-aminopyridin-4-yl)-4-[(2,6-difluorobenzyl)amino]-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile	C19 H13 F2 N7	377.1200	378.1242	$[M - H]^+$
158	4-(1,3-benzodioxol-5-yl)-5-(2,6-diaminopyridin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-2-carbonitrile	C19 H13 N7 O2	371.1131	370.1036	$[M - H]^-$

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

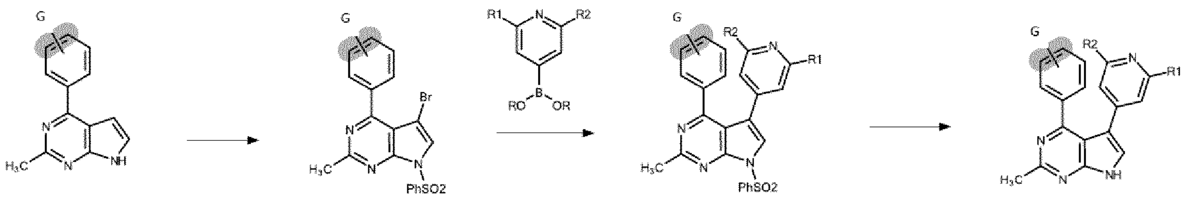
General Procedure XI



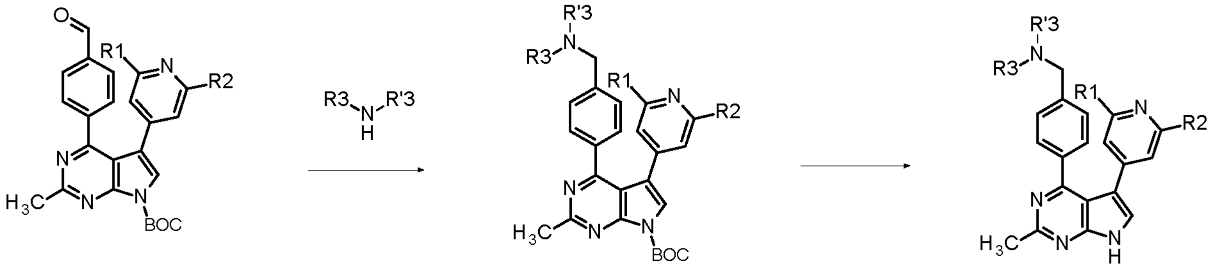
General Procedure XII



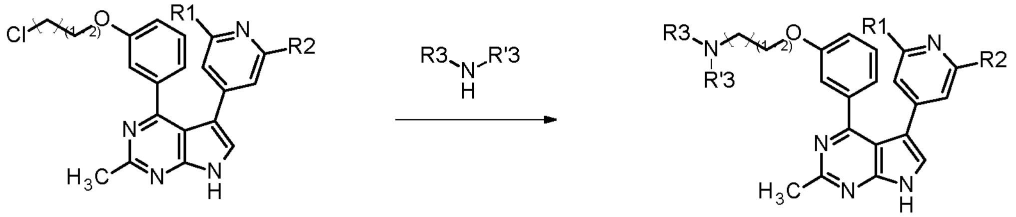
General Procedure XIII



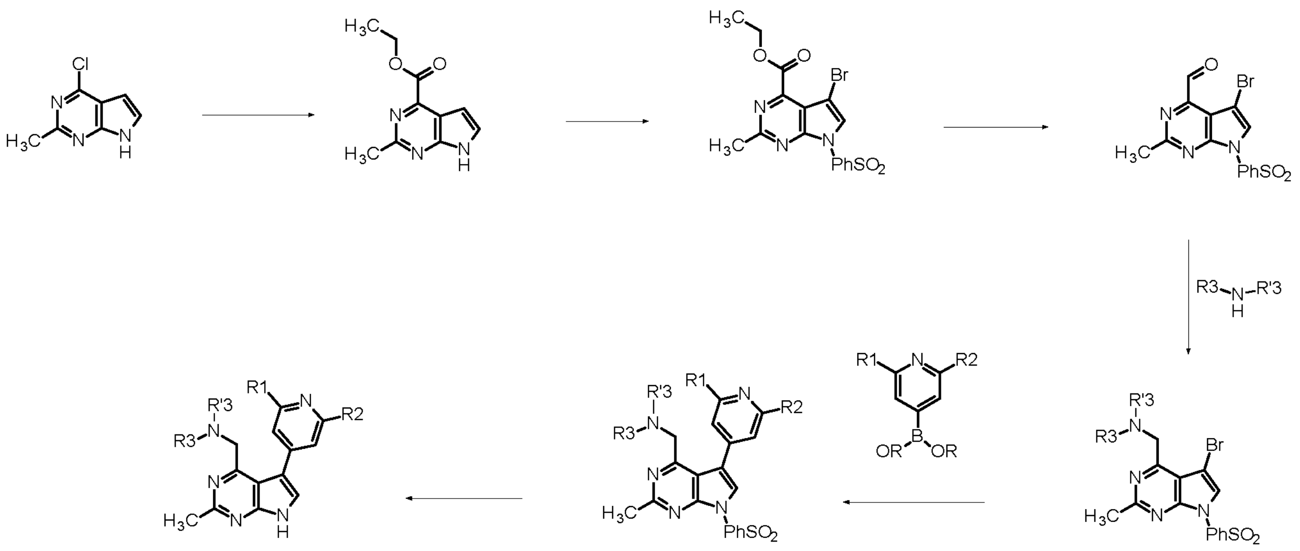
General Procedure XIV



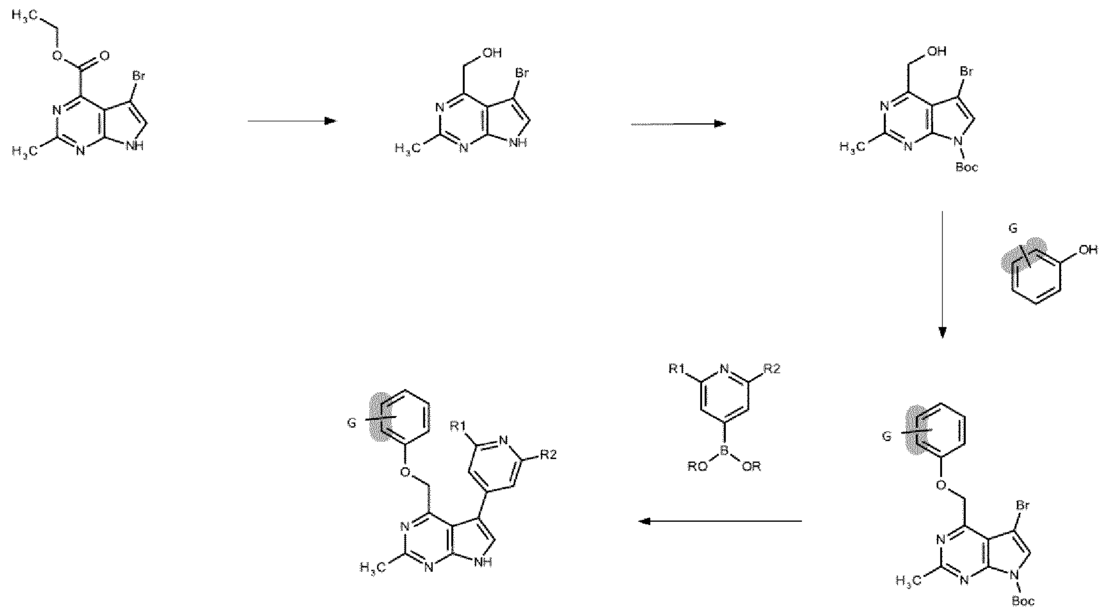
General Procedure XV



General Procedure XVI



General Procedure XVII



In **General Procedures XI to XVII:**

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

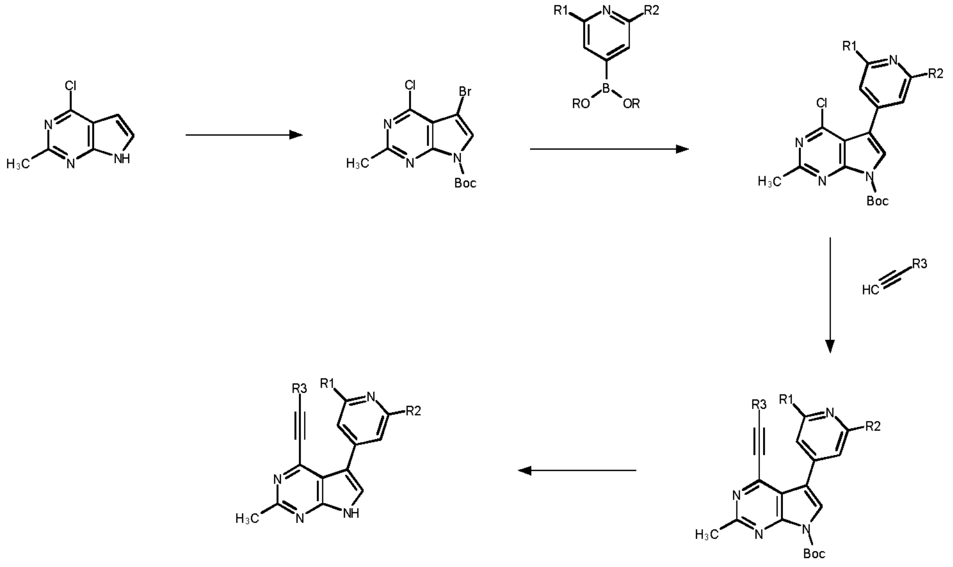
- R_3 represents a hydrogen atom, a linear or branched $(C_1\text{-}C_6)$alkyl group, $-(C_0\text{-}C_6)$alkylene-Cy_1, $-(C_0\text{-}C_6)$alkylene-Cy_1-Cy_2, $-(C_0\text{-}C_6)$alkylene-Cy_1-O-$(C_1\text{-}C_6)$alkylene-Cy_2, it being understood that Cy_1 and Cy_2, independently of one another, represent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

and R'_3 represents a hydrogen atom or a linear or branched $(C_1\text{-}C_6)$alkyl group,

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 R_3 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-7*H*-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}-7*H*-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.

^{1}H 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 N_2 and the reaction mixture was allowed to warm to room temperature over 4 hours. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (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 $[M+H]^+$

<u>Example 164:</u> 4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7*H*-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-7*H*-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 N_2. Cesium carbonate (2 eq) and Pd(dppf)Cl_2 (10% wt) were added and the resulting mixture was degassed under N_2 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 N_2 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 N_2 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 $MgSO_4$ 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.

^{1}H 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 N_2. Potassium carbonate (3 eq) and Pd(dtbpf)Cl_2 (10% wt) were added and the resulting mixture was degassed under N_2 for 5 minutes. The reaction mixture was heated at 65 °C overnight under N_2, cooled to room temperature and diluted with water (10 mL) and DCM (50 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ 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. $NaHCO_3$, dried over $MgSO_4$ 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.

^{1}H 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]-7*H*-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]-7*H*-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 N_2 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 N_2. 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 $MgSO_4$ 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 K_2CO_3 (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.

^{1}H 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}-7*H*-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-7*H*-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 N_2. The reaction mixture was stirred overnight. Then, it was diluted with sat aq. $NaHCO_3$ solution (10 mL) and DCM (10 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ 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.

^{1}H 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.

^{1}H 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}-7*H*-pyrrolo [2,3-*d*]pyrimidin-5-yl)pyridin-2-amine ***(Preparation 23)***

To a solution of 4-{4-[3-(3-chloropropoxy)phenyl]-2-methyl-7*H*-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), K_2CO_3 (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.

^{1}H 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-1*H*-indol-1-ylmethyl)-2-methyl-7*H*-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-7*H*-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 N_2. 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.

^{1}H 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.

^{1}H 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 N_2. 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. $MgSO_4$ 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 $[M+H]^+$

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%) was obtained as a white solid.

^{1}H NMR (399 MHz, DMSO-d6) 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 $[M+H]^+$

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.

^{1}H NMR (399 MHz, DMSO-d6) 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 $[M+H]^+$

Example 193: 4-(2-methyl-4-{[2-(trifluoromethyl)phenoxy]methyl}-7*H*-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 $LiBH_4$ (2 eq) portion wise at 0 °C under N_2. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (10 mL) solution and EtOAc (10 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ 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.

^{1}H 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.

^{1}H 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).

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

Example 198: 4-[4-(cyclopropylethynyl)-2-methyl-7*H*-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-7*H*-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.

^{1}H 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

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.

^{1}H 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-(cyclopropyl ethynyl)-2-methyl-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (**Preparation 27**)*

To a solution of the compound obtained in Step 2 (100 mg, 0.22 mmol) in Et_3N (4 ml) and THF (1 mL) was added ethynylcyclopropane (3 eq) and CuI (0.3 eq) at room temperature. The solution was purged with N_2 for 5 minutes before adding $Pd(PPh_3)_2Cl_2$ (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.
^{1}H NMR (399 MHz, DMSO-d6) 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]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C20 H17 N5	327.1484	328.1564	$[M - H]^+$

160	4-[2-methyl-4-(2-phenylethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C20 H19 N5	329.1640	328.1574	$[M - H]^-$
161	4-[4-(1*H*-indol-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C19 H16 F N5 O	349.1339	348.1269	$[M - H]^-$
163	4-(2-methyl-4-phenyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C23 H24 N6	384.2062	385.2135	[M - H]$^+$
166	4-{4-[(2,6-difluorophenoxy)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C19 H15 F2 N5 O	367.1245	366.1172	[M - H]$^-$
167	4-[4-(3-methoxyphenyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C19 H17 N5 O	331.1433	330.1369	[M - H]$^-$
168	4-{2-methyl-4-[3-(trifluoromethyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C19 H14 F3 N5	369.1201	368.1140	[M - H]$^-$
169	4-(2-methyl-4-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine	C24 H27 N7	413.2328	412.2268	[M - H]$^-$

170	4-[4-(5-fluoropyridin-3-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C22 H22 N6	370.1906	369.1839	$[M - H]^-$
172	4-[4-(4-ethoxyphenyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-2-fluorobenzonitrile	C19 H13 F N6	344.1186	343.1119	$[M + H]^-$
176	4-{4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C17 H18 F2 N6	344.1561	343.1486	$[M + H]^-$
177	4-{4-[(3,3-difluoropiperidin-1-yl)methyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C18 H20 F2 N6	358.1718	357.1622	$[M + H]^-$
178	4-[4-(2,3-dihydro-1*H*-indol-1-ylmethyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C21 H20 N6	356.1749	355.1683	$[M + H]^-$
179	4-[4-(1,3-benzodioxol-5-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C19 H15 N5 O2	345.1226	344.1127	$[M + H]^-$

180	4-[4-(3,5-difluorophenyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C18 H13 F2 N5	337.1139	336.1057	$[M + H]^-$
181	4-{2-methyl-4-[3-(trifluoromethoxy)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C19 H14 F3 N5 O	385.1150	384.1086	$[M + H]^-$
182	4-[4-(1-benzothiophen-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C20 H15 N5 S	357.1048	356.0969	$[M + H]^-$
183	4-[4-(1-benzofuran-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C20 H15 N5 O	341.1277	340.1217	$[M + H]^-$
184	4-[2-methyl-4-(5-methyl-1-benzothiophen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C21 H17 N5 S	371.1205	372.1210	$[M + H]^+$

185	4-[4-(7-chloro-1-benzothiophen-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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*H*-indol-2-yl)-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C22 H21 N5	355.1797	354.1732	$[M + H]^-$
189	4-{2-methyl-4-[(2*S*)-1,2,3,4-tetrahydronaphthalen-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C22 H21 N5	355.1797	354.1716	$[M + H]^-$

190	4-{2-methyl-4-[(2*R*)-1,2,3,4-tetrahydronaphthalen-2-yl]-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C20 H14 F N5	343.1233	342.1116	$[M + H]^-$

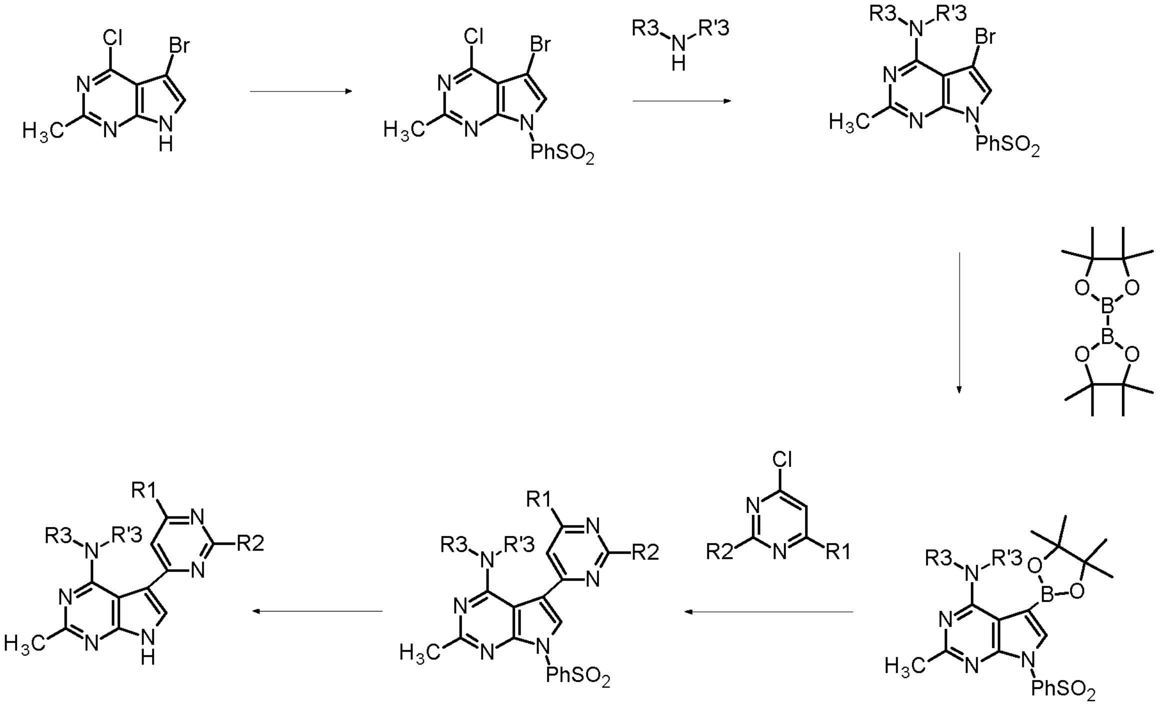
195	4-[2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridin-2-amine	C22 H21 N5	355.1797	356.1805	[M + H]$^+$
196	4-[4-(cyclopropylethynyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyridine-2,6-diamine	C17 H16 N6	304.1436	305.1458	[M + H]$^+$
197	4-{4-[(2-methoxyphenyl)ethynyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C21 H17 N5 O	355.1433	356.1442	[M + H]$^+$
198	4-[4-(cyclopropylethynyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]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}-7*H*-pyrrolo[2,3-*d*]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*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine	C26 H31 N7 O	457.2590	456.2477	[M + H]$^-$
201	4-{4-[3-(2-chloroethoxy)phenyl]-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-2-amine	C20 H18 Cl N5 O	379.1200	378.1140	[M + H]$^-$
202	4-(2-methyl-4-{3-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine	C24 H26 N6 O	414.2168	415.2165	[M + H]$^+$
203	4-(4-{3-[2-(dimethylamino)ethoxy]phenyl}-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine	C22 H24 N6 O	388.2012	389.1996	[M + H]$^+$
204	4-(2-methyl-4-{3-[2-(morpholin-4-yl)ethoxy]phenyl}-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)pyridin-2-amine	C24 H26 N6 O2	430.2117	431.2096	[M + H]$^+$

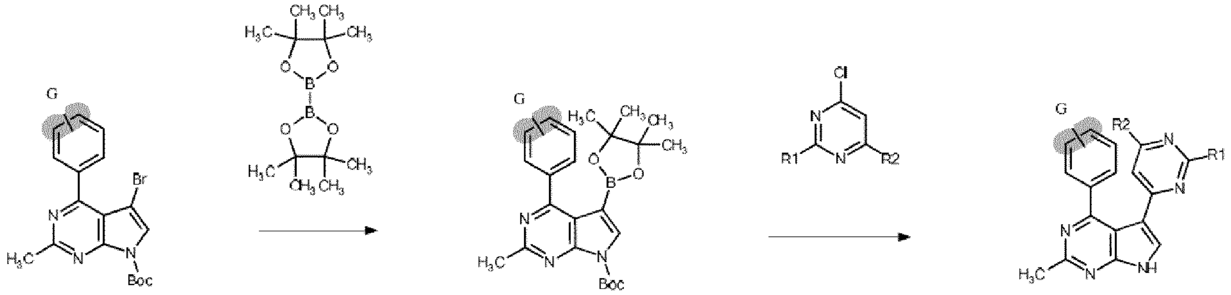
Example 160 was prepared from **Example 159** using method described in **Preparation 5.** **Example 188** was prepared from **Example 187** using method described in **Preparation 5.** **Example 189 and 190** were prepared from **Example 188** by preparative HPLC with a chiral stationary phase. **Example 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**. ^{1}H NMR (399 MHz, Chloroform-d) δ 7.18 (d, 1H), 7.08 (s, 1H), 6.05 (s, 2H), 1.35 (s, 12H).

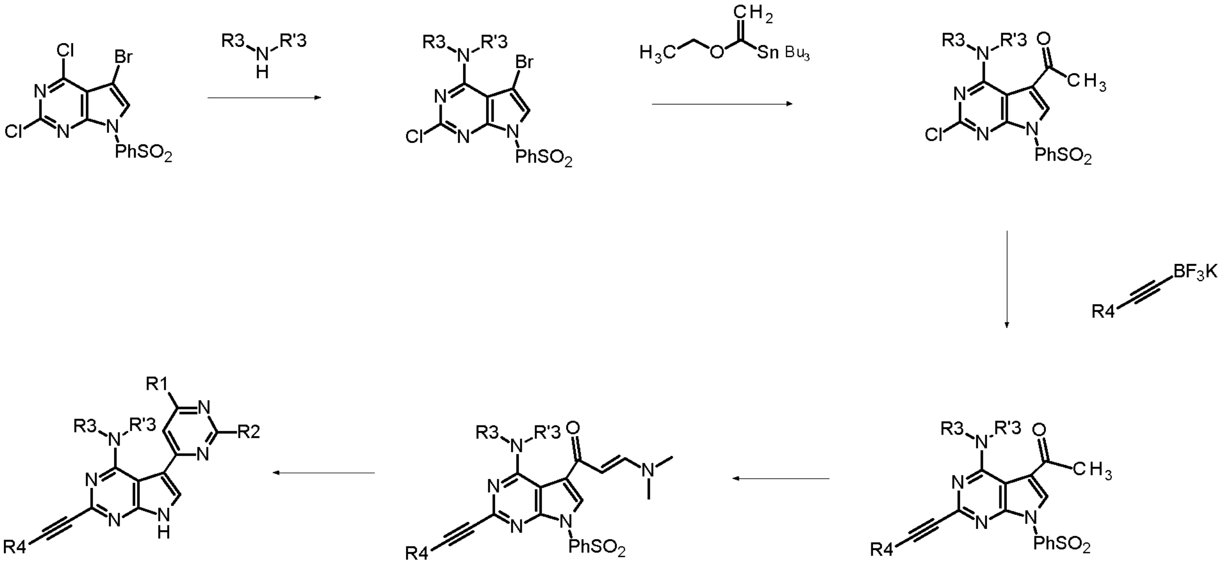
General Procedure XIX



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 $(C_1\text{-}C_6)$alkyl group, $-(C_0\text{-}C_6)$alkylene-Cy_1, $-(C_0\text{-}C_6)$alkylene-Cy_1-Cy_2, $-(C_0\text{-}C_6)$alkylene-Cy_1-O-$(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$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 206: 5-(2-aminopyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-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-7*H*-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.

^{1}H 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 $PdCl_2(PPh_3)_2$ (10% wt). The resulting mixture was degassed under N_2 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 $MgSO_4$ 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 $[M+H]^+$

<u>Example 208:</u> 5-(2-aminopyrimidin-4-yl)-*N*-(1,3-benzodioxol-4-ylmethyl)-2-methyl-7*H*-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-7*H*-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.

^{1}H 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.

^{1}H 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 $PdCl_2(PPh_3)_2$ (10% wt). The resulting mixture was degassed under N_2 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 $MgSO_4$ 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.

^{1}H 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.

^{1}H 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-7*H*-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-7*H*-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.

^{1}H 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 $[M+H]^+$

<u>Example 211</u>: 4-[4-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-ethynyl-7*H*-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 N_2 at room temperature. The reaction mixture was stirred at 100 °C overnight under N_2. 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. $NaHCO_3$ (20 mL) solution and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ 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 biflouride (4 eq) in water (5mL) 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.

^{1}H 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 N_2. 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 $MgSO_4$ 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 N_2. 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. $NaHCO_3$ solution, dried over $MgSO_4$ 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 $MgSO_4$ 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.

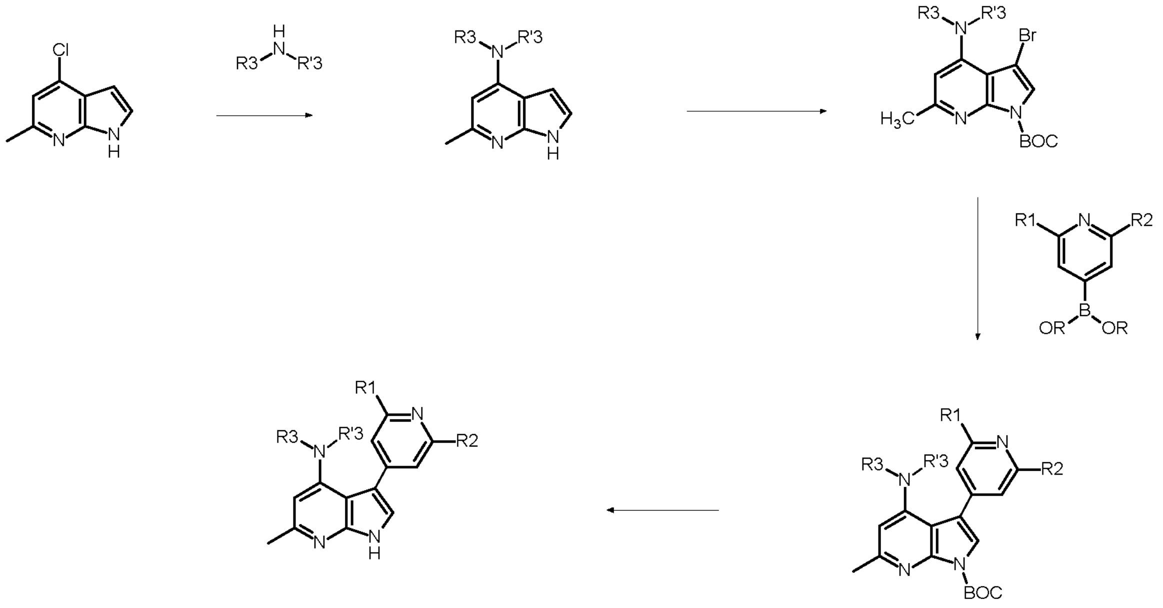
Table 5: HRMS (TOF, ESI) data

Example	Structure	Mol Formula	Calcd Exact Mass	Found m/z	Adduct
205	5-(2-amino-6-methylpyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C19 H17 F2 N7	381.1513	382.1569	$[M + H]^+$
206	5-(2-aminopyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H15 F2 N7	367.1357	368.1413	$[M + H]^+$

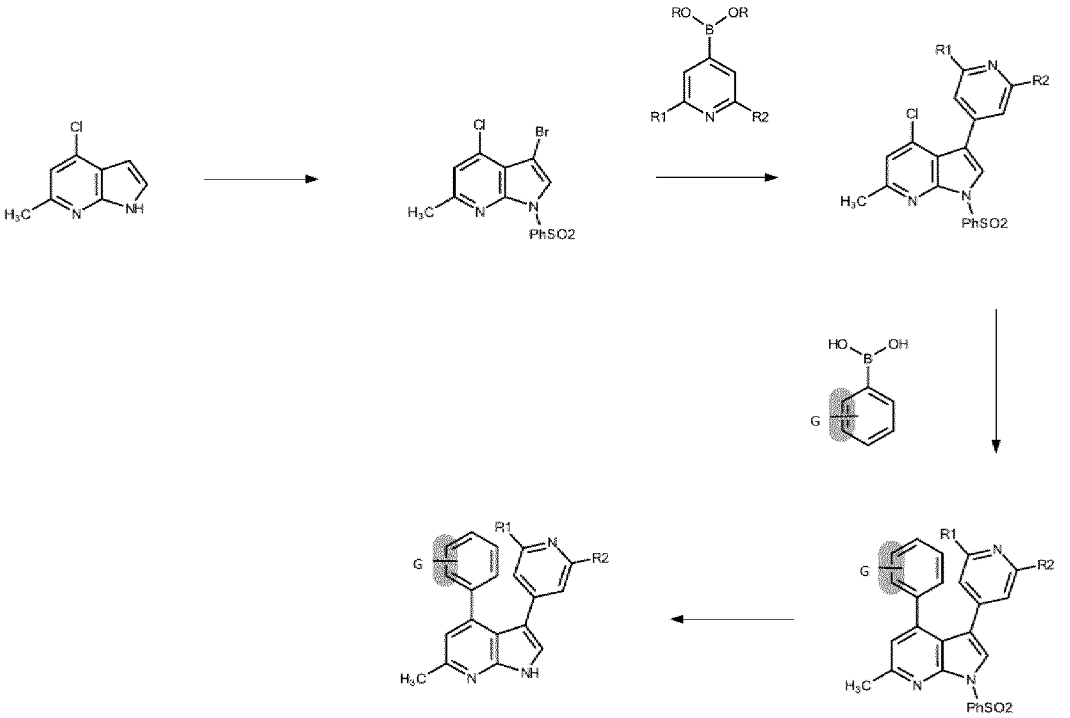
207	4-[4-(1-benzothiophen-2-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyrimidin-2-amine	$C_{19}H_{14}N_6S$	358.1001	359.1020	$[M + H]^+$
208	5-(2-aminopyrimidin-4-yl)-*N*-(1,3-benzodioxol-4-ylmethyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	$C_{19}H_{17}N_7O_2$	375.1444	374.1375	$[M + H]^-$
209	4-[4-(1,3-benzodioxol-5-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyrimidin-2-amine	$C_{18}H_{14}N_6O_2$	346.1178	347.1190	$[M + H]^+$
210	4-[4-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyrimidin-2-amine	$C_{18}H_{12}F_2N_6O_2$	382.0990	381.0912	$[M + H]^-$
211	4-[4-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-ethynyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]pyrimidin-2-amine	$C_{21}H_{17}N_7$	367.1545	366.1442	$[M + H]^-$

212	5-(6-aminopyrimidin-4-yl)-*N*-(2,6-difluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine	C18 H15 F2 N7	367.1357	368.1376	$[M + H]^+$

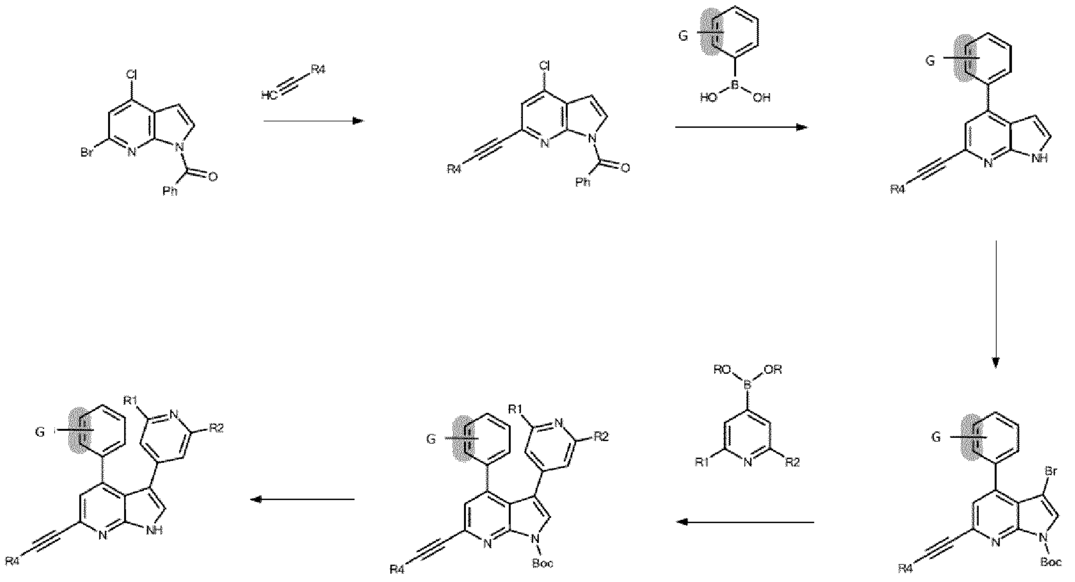
General Procedure XXII



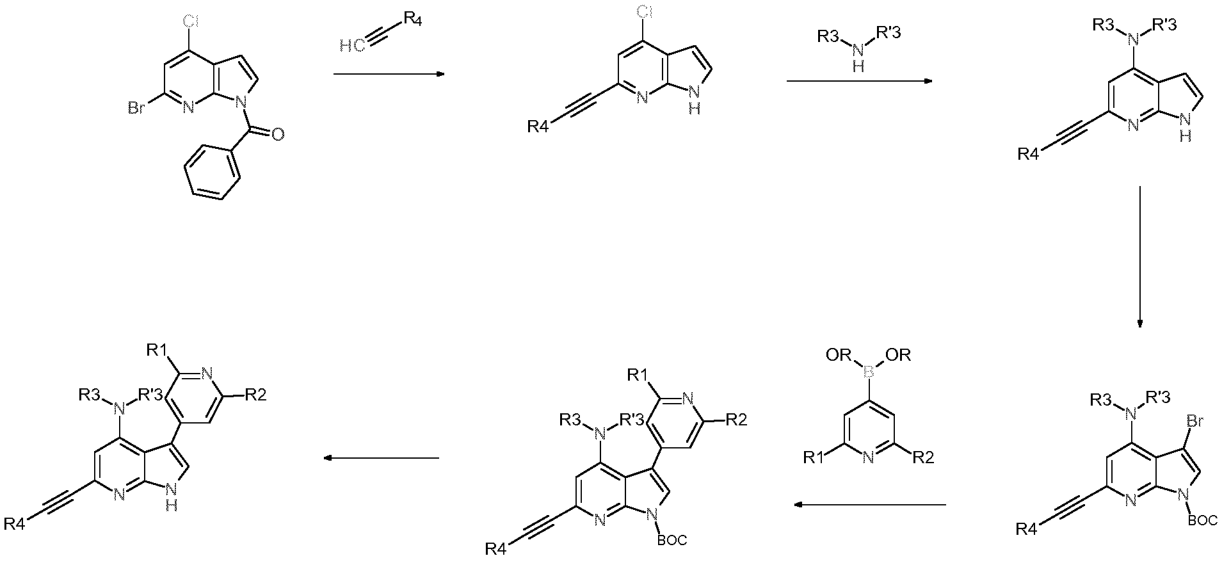
General Procedure XXIII



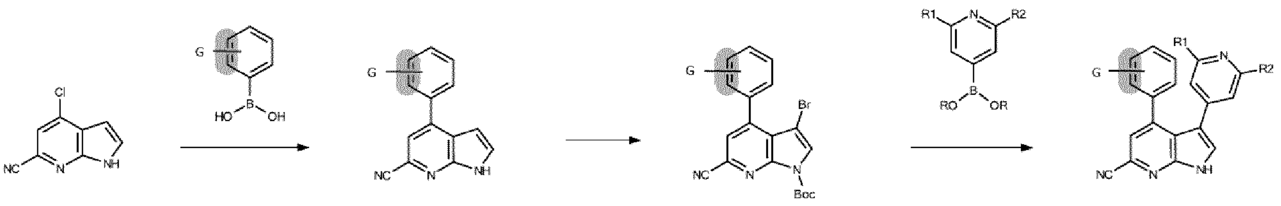
General Procedure XXIV



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 $(C_1\text{-}C_6)$alkyl group, $-(C_0\text{-}C_6)$alkylene-Cy_1, $-(C_0\text{-}C_6)$alkylene-Cy_1-Cy_2, $-(C_0\text{-}C_6)$alkylene-Cy_1-O-$(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$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 $(C_1\text{-}C_6)$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-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine

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-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 g, 3 mmol) in MeCN (15 mL) was added 2,6-difluorobenzylamine (2 eq) and pTSA.H_2O (2 eq) under N_2 at room temperature. The reaction mixture was heated at 150 °C in a CEM microwave reactor for 4 hours. The mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) solution and EtOAc (20 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$ 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.

^{1}H NMR (399 MHz, 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).

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 described in **Preparation 17**, the desired product (0.280 g, 0.61 mmol, 40%) was obtained as a solid.

^{1}H 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 $[M+H]^+$

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 $[M+H]^+$

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.

^{1}H NMR (399 MHz, 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).

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

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

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

Starting from 4-chloro-6-methyl-1*H*-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.

^{1}H NMR (399 MHz, 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).

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

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.

^{1}H 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.
^{1}H 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.
^{1}H 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]$^+$

<u>Example 215:</u> 4-[6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-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-1*H*-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-(cyclopropyl ethynyl)-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.

^{1}H NMR (399 MHz, DMSO-d6) 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 $[M+H]^+$

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

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

To a solution of 1-benzoyl-6-bromo-4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (prepared following procedure described in *WO2009/087225*) (1.52 g, 4.54 mmol) in Et_3N (15 ml) and THF (3 mL) was added ethynylcyclopropane (3 eq) and CuI (0.3 eq) at room temperature. The solution was purged with N_2 for 5 minutes before adding $Pd(PPh_3)_2Cl_2$ (0.3 eq) and the reaction mixture was stirred at room temperature overnight. Water (1 mL) 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 $MgSO_4$ 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 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****)*

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 N_2. LiHMDS (1M solution in THF, 2 eq) was added at room temperature under N_2. The 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 $MgSO_4$ 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.

^{1}H 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]$^+$

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.

^{1}H 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-(cyclopropyl ethynyl)-4-{[(2,6-difluorophenyl)methyl]amino}-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

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.

^{1}H 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

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.

^{1}H NMR (399 MHz, 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).
LC/MS (method B): RT = 1.09 min; *m/z* = 416 $[M+H]^+$

Example 223: 3-(2-aminopyridin-4-yl)-4-(1,3-benzodioxol-5-yl)-1*H*-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-1*H*-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) following procedure described in **Preparation 3**, the desired product (84 mg, 0.32 mmol, 57%) was obtained as a yellow solid.
^{1}H NMR (399 MHz, 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).
LC/MS (method B): RT = 1.23 min; *m/z* = 264 $[M+H]^+$

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.
^{1}H NMR (399 MHz, 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).

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 *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.

^{1}H 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).

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 m/z	Adduct
213	3-(2-aminopyridin-4-yl)-*N*-(2,6-difluoro benzyl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine	C20 H17 F2 N5	365.1452	366.1514	[M + H]$^+$
214	4-[4-(5-fluoropyridin-3-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C18 H14 F N5	319.1233	320.1299	[M + H]$^+$
215	4-[6-(cyclopropylethynyl)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C25 H20 N4 O2	408.1586	409.1618	[M + H]$^+$

216	3-(2-aminopyridin-4-yl)-6-(cyclopropylethynyl)-*N*-(2,6-difluorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine	C24 H19 F2 N5	415.1609	416.1638	[M + H]$^+$
217	4-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C21 H18 N4 O2	358.1430	359.1428	[M + H]$^+$
218	4-[4-(1,3-benzodioxol-5-yl)-6-(cyclopropylethynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridine-2,6-diamine	C24 H19 N5 O2	409.1539	410.1570	[M + H]$^+$
219	4-[4-(1,3-benzodioxol-5-yl)-6-(cyclopropylethynyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C24 H18 N4 O2	394.1430	395.1430	[[M + H]$^+$
220	4-[4-(1,3-benzodioxol-5-yl)-6-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C21 H14 N4 O2	354.1117	355.1120	[M + H]$^+$

221	4-[4-(1,3-benzodioxol-5-yl)-6-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridine-2,6-diamine	C21 H15 N5 O2	369.1226	368.1146	[M + H]$^-$
222	4-[4-(1,3-benzodioxol-5-yl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C20 H16 N4 O2	344.1273	343.1191	[M + H]$^-$
223	3-(2-aminopyridin-4-yl)-4-(1,3-benzodioxol-5-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-6-carbonitrile	C20 H13 N5 O2	355.1069	354.1014	[M + H]$^-$
224	4-(1,3-benzodioxol-5-yl)-3-(2,6-diamino pyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-6-carbonitrile	C20 H14 N6 O2	370.1178	371.1170	[M + H]$^+$
225	4-[6-methyl-4-(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]pyridin-2-amine	C22 H21 N5 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 Carna 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 *U*Light^{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 $MgCl_2$, 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 IC_{50} 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 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-y-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 IC_{50} 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% CO_2 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 µg/ml in 5% BSA) or anti DYRK1A antibody (Abnova H00001859; 0.5 µg/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). IC_{50} 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 µg/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 µg/ml) was then added for 1 hour at RT, followed by addition of Sulfa-TAG anti-rabbit detection antibody (ref MSD R32AB; 1 µg/ml) and Sulfa-TAG anti-mouse detection antibody (ref MSD R32-AC-1; 1 µg/ml). After a further 1 hour, Read Buffer was added and plates were read on the Sector Imager 2400 (Mesoscale). IC_{50} 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 mm^3, 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 µg/ml in 5% BSA) or anti DYRK1A antibody (Abnova H00001859; 0.5 µg/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 mm^3, mice were randomized into homogeneous groups of 8 and treated orally with the compounds of the invention at doses of 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-[RTV(treated)/RTV(untreated)])x100, 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: IC$_{50}$ 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) Clk1 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) Clk1 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) Clk1 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				

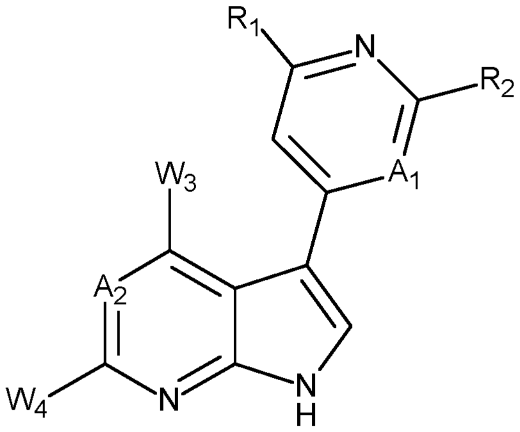
	IC_{50} (µM) Dyrk1A TR-FRET assays	IC_{50} (µM) Dyrk1A ADP assays	IC_{50} (µM) Dyrk1B TR-FRET assays	IC_{50} (µM) Clk1 TR-FRET assays	IC_{50} (µM) CDK9 TR-FRET assays	IC_{50} (µM) P-Ser520-Dyrk1A -Cell assay
Example 215		0,019				0,1032
Example 216	0,0145	0,021	0,0219	0,1212	10	0,0807
Example 217	0,0027	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
Lactose	30 g
Magnesium stearate	2 g
Silica..	1 g
Hydroxypropylcellulose	2 g

CLAIMS

1. Compound of formula (I):



(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 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, SO_2 and nitrogen, which may include fused, bridged or spiro ring systems,
- "-(C_0-C_6)alkylene-" refers either to a covalent bond (-C_0alkylene-) 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 (C_1-C_6)alkyl, linear or branched (C_2-C_6)alkenyl group, linear or branched (C_2-C_6)alkynyl group, linear or branched (C_1-C_6)alkoxy optionally substituted by $-NR_cR_d$ or by from 1 to 3 halogen atoms, linear or branched (C_1-C_6)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 (C_1-C_6)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 (C_1-C_6)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 R_1 represents a hydrogen and R_2 a $-NH_2$ group.

3. Compound of formula (I) according to claim 1 or 2, wherein A_1 represents a CH group.

4. Compound of formula (I) according to claim 1 or 2, wherein A_1 represents a nitrogen atom.

5. Compound of formula (I) according to one of claims 1 to 3, wherein A_2 represents a nitrogen atom.

6. Compound of formula (I) according to one of claims 1 to 3, wherein A_2 represents a CH group.

7. Compound of formula (I) according to claim 6, wherein A_2 represents a CH group and A_1 represents a CH group.

8. Compound of formula (I) according to one of claims 1 to 7, wherein W_3 represents a linear or branched $(C_1\text{-}C_6)$alkoxy, $\text{-O-}(C_0\text{-}C_6)$alkylene-$Cy_1$, $\text{-O-}(C_0\text{-}C_6)$alkylene-$Cy_1$-$Cy_2$, $\text{-NR}_a\text{-}(C_1\text{-}C_6)$alkylene-$Cy_1$-$Cy_2$, $\text{-NR}_a\text{-}(C_0\text{-}C_6)$alkylene-$Cy_1$-O-$(C_1\text{-}C_6)$alkylene-$Cy_2$, -$Cy_1$-O-$(C_0\text{-}C_6)$alkylene-$Cy_2$, -$(C_1\text{-}C_6)$alkylene-$Cy_1$, -$(C_2\text{-}C_6)$alkenylene-$Cy_1$, -$(C_2\text{-}C_6)$alkynylene-$Cy_1$, -$(C_1\text{-}C_6)$alkylene-O-$Cy_1$, 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 W_3 represents a Cy_1 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 W_3 represents: (i) a –NR_a-Cy_1 group, wherein Cy_1 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-(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,

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.

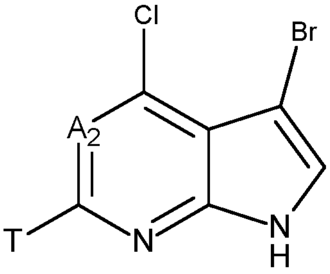
18. Compound of formula (I) according to claim 1 which is 5-(2-aminopyridin-4-yl)-*N*-(2-chloro-6-fluorobenzyl)-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

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. 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):

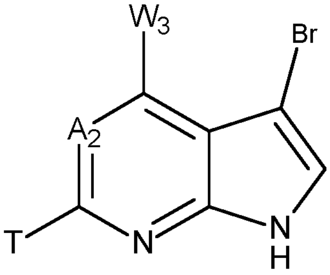


(II)

wherein T represents a halogen atom, a methane-sulfanyl group, a cycloalkyl group or a linear or branched (C_1-C_6)alkyl group, and A_2 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) :



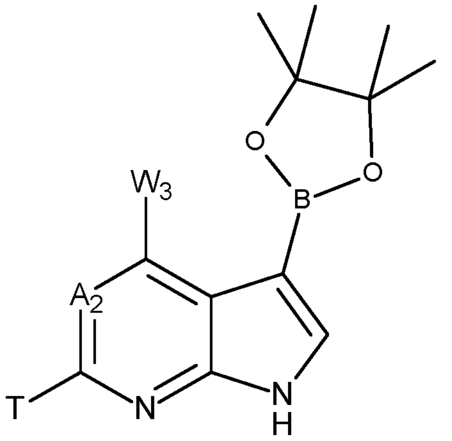
(III)

wherein T is as defined previously, A_2 and W_3 are as defined in formula (I), which compound of formula (III) is either :

(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,

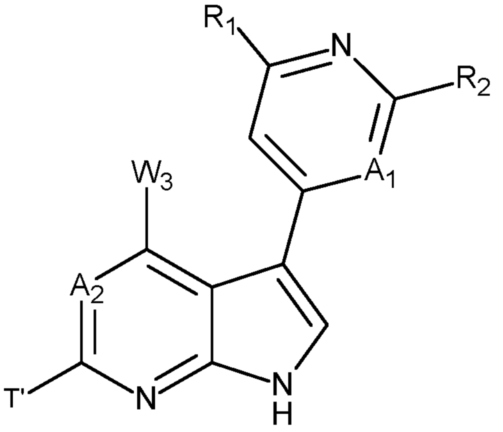
(v) or subjected to coupling with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane to yield :



(III')

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

to yield compound of formula (IV) :



(IV)

wherein T' represents represents a halogen atom, a cyano group, a cycloalkyl group or a linear or branched (C_1-C_6)alkyl group, and A_1, A_2, R_1, R_2 and W_3 are as defined in formula (I),

which compound of formula (IV):

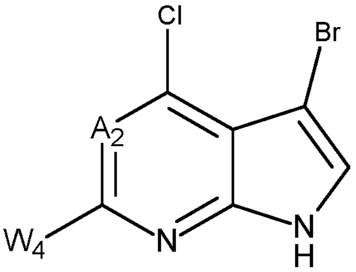
- may be subjected to coupling with an appropriate alkynyl (or alkenyl) boronic acid derivative or alkynyl (or alkenyl) (trifluoro)borate derivative salt, when T' represents a halogen atom,

to yield the compounds of formula (I),

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.

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):

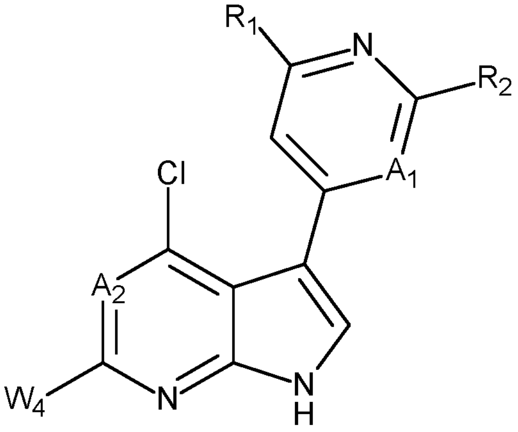


(II)

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,

to yield compound of formula (V):



(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,
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

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