(19) ORGANISATION AFRICAINE DE LA PROPRIETE INTELLECTUELLE

(51) Inter. Cl.[8] C07D 471/04; A61P 35/00; A61K 31/4162

(11) N° 16493

FASCICULE DEBREVET D'INVENTION

(21) Numéro de dépôt:1201300307
(PCT/EP12/051283)

(22) Date de dépôt :27/01/2012

(30) Priorité(s) :
FR n° 1150651 du 27/01/2011

(24) Délivré le :30/06/2014

(45) Publié le : 21.10.2015

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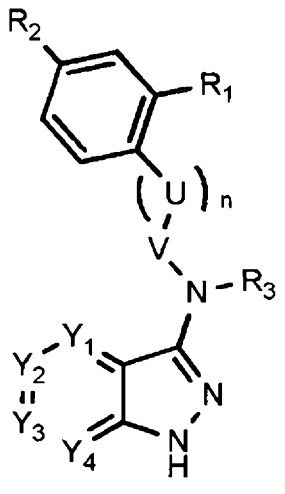
(54) **Titre :Derivatives of azaindazole or diazaindazole type as medicament.**

(57) **Abrégé :**

The present invention relates to a compound of following formula (I) :



(I)

or a pharmaceutically acceptable salt or solvate of same, a tautomer of same, or a stereoisomer or mixture of stereoisomers of same in any proportions, such as a mixture of enantiomers, notably a racemic mixture; as well as to the use of same as a drug, notably intended for the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease; to the use of same as a kinase inhibitor; to the pharmaceutical compositions comprising same; and to methods for the preparation of same.

DERIVATIVES OF AZAINDAZOLE OR DIAZAINDAZOLE TYPE AS MEDICAMENT

The present invention relates to azaindazole and diazaindazole fused bicyclic derivatives, as well as to the therapeutic use of same, notably in the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease, as well as to methods for synthesizing same.

Protein kinases are enzymes that play a key role in cell signal transduction. They are involved in physiological processes such as cell proliferation, mitosis, differentiation, cell invasion and mobility, and apoptosis, for example.

Deregulation of the physiological mechanisms controlled by protein kinases is central to the appearance and development of many pathologies, notably including cancers. It is of particular note that many oncogenes and proto-oncogenes correspond to protein kinases.

Consequently, these enzymes are seen to play an important role during the various stages of tumor development and thus they constitute important pharmaceutical targets for cancer treatments.

Tyrosine kinase receptors (TKRs) form a particular class of protein kinases among which, among others, mention may be made of ALK, EGFR, Her2, PDGFR, Kit, VEGFR, IGFR, FGFR, Trk, Axl, Mer, Met, Ron and Ret. In this subfamily, ALK is regarded as a particularly relevant target because it is genetically modified in certain tumor pathologies and thus acquires an oncogenic nature. More precisely, chromosomal translocations leading to the production of fused protein kinases (ALK-X) which are then constitutively activated cause the development of certain cancers. ALK in oncogenic form is expressed by various tumor pathologies of different histological types. These pathologies are thus ALK-dependent. ALK in oncogenic form exists only in tumor cells and is not expressed by normal cells. For this reason, this protein kinase provides the opportunity to specifically target ALK-dependent tumor tissues while saving healthy tissues from significant toxic effects (Ott G.R. *et al.*, Anticancer Agents Med. Chem., **2010**, *10(3)*, 236-49).

Several cases of chromosomal translocations involving ALK, related to cancer pathologies, have already been documented. For example, the fusion protein NPM-ALK

is associated with anaplastic large-cell lymphoma (ALCL) for which an optimal treatment remains to be developed. Similarly, the fusion protein EML4-ALK is associated with tumor development in a subpopulation of patients suffering from non-small cell lung cancer. Mutated forms of ALK have also been observed in neuroblastoma.

c-Src is also a protein kinase whose activation state proved to be negatively correlated with the survival of patients suffering from various forms of cancer, including non-small cell lung cancer (Byers L.A. *et al.*, Clin. Cancer Res. **2009**, *15(22)*, 6852-6861).

For this reason, and because of its involvement in many key mechanisms such as cell cycle progression, adhesion, proliferation, migration and control of apoptosis, this protein is also regarded as a target of interest in oncology.

It has been shown in particular that the inhibition of this target, by both biochemical and pharmacological means, induced effects such as a reduction in cell proliferation, a stopping of the mitotic cycle and a slowing of tumor growth *in vivo*. In the particular case of non-small cell lung cancer, the inhibition of c-Src by an inhibitor (dasatinib) led to the observation, *in vitro*, of inhibition of the migration and the invasion of the cells concerned.

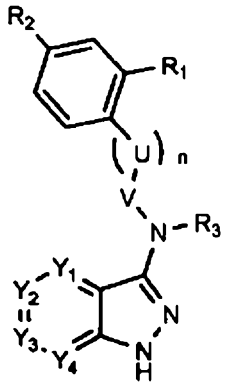
Nevertheless, in terms of the control of tumor cell proliferation, it has been proposed that c-Src inhibition alone only induces a partial and/or transitory pharmacological response.

Consequently, there continues to be a need for inhibitors with a composite mode of action that are capable of intervening at several targets, in particular at several targets of the same signaling pathway, proposed as being more effective, with an improved therapeutic index and less likely to give rise to phenomena of compensation, resistance or therapeutic escape.

The compounds of the present invention thus have the property of inhibiting or modulating the enzymatic activity of protein kinases in general and ALK and c-Src in particular. Consequently, said compounds can be used as drug in the treatment of proliferative diseases such as cancer.

Additional indications in inflammation or in affections of the central nervous system may also be pursued.

More particularly, the present invention thus has as an object a compound of following general formula (I):



(I)

or a pharmaceutically acceptable salt or solvate of same, a tautomer of same, a stereoisomer or a mixture of stereoisomers of same in any proportions, such as a mixture of enantiomers, notably a racemic mixture,

wherein:

- Y_1 and Y_4 each represent, independently of each other, a CH group or a nitrogen atom,
- Y_2 represents a nitrogen atom or a CH or C-X-Ar group,
- Y_3 represents a nitrogen atom or a C-X-Ar or C-W group,

on the condition that:

- at least one and at most two Y_1, Y_2, Y_3, and Y_4 groups represent a nitrogen atom,
- Y_2 and Y_4 cannot represent a nitrogen atom at the same time,
- when Y_2=C-X-Ar, then Y_3 represents a nitrogen atom or a C-W group, and
- when Y_3=C-X-Ar, then Y_2 represents a nitrogen atom or a CH group,

- **Ar** represents an aryl or heteroaryl group optionally substituted by one or more groups selected from a halogen atom, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$halothioalkoxy, CN, NO_2, OR_{11}, SR_{12}, $NR_{13}R_{14}$, CO_2R_{15}, $CONR_{16}R_{17}$, SO_2R_{18}, $SO_2NR_{19}R_{20}$, COR_{21}, $NR_{22}COR_{23}$, $NR_{24}SO_2R_{25}$, and $R_{26}NR_{27}R_{28}$ and/or optionally fused to a heterocycle,

- **X** represents a divalent group selected from O, S, S(O), $S(O)_2$, NR_4, $S(NR_4)$, $S(O)(NR_4)$, $S(O)_2(NR_4)$, NR_4S, $NR_4S(O)$, $NR_4S(O)_2$, CH_2, CH_2S, $CH_2S(O)$, $CH_2S(O)_2$, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, CH_2CH_2, CH=CH, C≡C, CH_2O, OCH_2, NR_4CH_2, and CH_2NR_4,
- **W** represents an R_5, SR_5, OR_5 or NR_5R_6 group,
- **U** represents a CH_2 or NH group, one or more hydrogen atoms which may be replaced by a $(C_1$-$C_6)$alkyl group,
- **V** represents C(O), C(S) or CH_2,
- **n** represents 0 or 1,
- $\mathbf{R_1}$ represents a hydrogen atom, or an OR_7 or NR_7R_8 group,
- $\mathbf{R_2}$ represents a hydrogen atom, an optionally substituted heterocycle, NO_2, OR_9 or NR_9R_{10},
- $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_{11}}$ to $\mathbf{R_{25}}$ and $\mathbf{R_{27}}$ to $\mathbf{R_{28}}$ each represent, independently of each other, a hydrogen atom or a $(C_1$-$C_6)$alkyl group,
- $\mathbf{R_5}$ and $\mathbf{R_6}$ each represent, independently of each other, a hydrogen atom or a $(C_1$-$C_6)$alkyl, optionally substituted aryl or optionally substituted benzyl group,
- $\mathbf{R_7}$, $\mathbf{R_8}$, $\mathbf{R_9}$ and $\mathbf{R_{10}}$ each represent, independently of each other, a hydrogen atom or an optionally substituted $(C_1$-$C_6)$alkyl or $(C_3$-$C_{12})$cycloalkyl group or an optionally substituted heterocycle, and
- $\mathbf{R_{26}}$ represents $(C_1$-$C_6)$alkyl.

In the preceding definitions, all the combinations of substituents or variables are possible insofar as they lead to stable compounds.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "$(C_1$-$C_6)$ alkyl" refers to saturated linear or branched hydrocarbon chains comprising 1 to 6 carbon atoms. It may be a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl or hexyl group.

The term "$(C_1$-$C_6)$alkoxy" refers to a $(C_1$-$C_6)$ alkyl chain linked to the rest of the molecule via an oxygen atom. As an example, mention may be made of methoxy, ethoxy, propoxy, isopropoxy, butoxy or *tert*-butoxy groups.

The term "(C_1-C_6)thioalkoxy" refers to a (C_1-C_6) alkyl chain linked to the rest of the molecule via a sulfur atom. As an example, mention may be made of thiomethoxy, thioethoxy, thiopropoxy, thioisopropoxy, thiobutoxy or thio-*tert*-butoxy groups.

The term "(C_1-C_6)haloalkyl" refers to a (C_1-C_6) alkyl chain such as defined above wherein one or more hydrogen atoms are replaced by a halogen atom such as defined above. It may be in particular a trifluoromethyl group.

The term "(C_1-C_6)haloalkoxy" refers to a (C_1-C_6)alkoxy chain such as defined above wherein one or more hydrogen atoms are replaced by a halogen atom such as defined above. It may be in particular a trifluoromethoxy group.

The term "(C_1-C_6)halothioalkoxy" refers to a (C_1-C_6)thioalkoxy chain such as defined above wherein one or more hydrogen atoms are replaced by a halogen atom such as defined above. It may be in particular a trifluorothiomethoxy group.

The term "(C_3-C_{12})cycloalkyl" refers to cyclic hydrocarbon systems comprising from 3 to 12 carbon atoms and comprising one or more rings, in particular fused rings. As an example, mention may be made of an adamantyl or cyclohexyl group.

The term "aryl" refers to an aromatic hydrocarbon group preferably comprising from 6 to 14 carbon atoms and comprising one or more fused rings, such as, for example, a phenyl or naphthyl group. Advantageously, it is a phenyl group.

The term "heteroaryl" refers to a cyclic aromatic group comprising 5 to 7 atoms included in the ring or a bicyclic aromatic group comprising 8 to 11 atoms included in the rings, wherein 1 to 4 of the atoms included in the rings are a heteroatom selected independently from sulfur, nitrogen and oxygen atoms, and wherein the other atoms included in the rings are carbon atoms. Examples of heteroaryl groups include furyl, thienyl, pyridinyl, and benzothienyl groups.

The term "heterocycle" refers either to a stable monocycle containing from 4 to 7 cyclic atoms, or to a stable bicycle containing from 8 to 11 cyclic atoms, which may be either saturated or unsaturated, wherein 1 to 4 of the cyclic atoms are a heteroatom selected independently from sulfur, nitrogen and oxygen atoms, and wherein the other cyclic atoms are carbon atoms. As an example, mention may be made of furan, pyrrole, thiophene, thiazole, isothiazole, oxadiazole, imidazole, oxazole, isoxazole, pyridine, piperidine, pyrazine, piperazine, tetrahydropyran, pyrimidine, quinazoline, quinoline, quinoxaline, benzofuran, benzothiophene, indoline, indolizine, benzothiazole,

benzothienyl, benzopyran, benzoxazole, benzo[1,3]dioxole, benzisoxazole, benzimidazole, chromane, chromene, dihydrobenzofuran, dihydrobenzothienyl, dihydroisoxazole, isoquinoline, dihydrobenzo[1,4]dioxane, imidazo[1,2-a]pyridine, furo[2,3-c]pyridine, 2.3-dihydro-1*H*-indene, [1,3]dioxolo[4,5-c]pyridine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrimidine, tetrahydronaphthalene, benzo[b][1,4]oxazin.

In the context of the present invention, "optionally substituted" means that the group in question is optionally substituted by one or more substituents which may be selected in particular from a halogen atom, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$halothioalkoxy, CN, NO_2, OR_{11}, SR_{12}, $NR_{13}R_{14}$, CO_2R_{15}, $CONR_{16}R_{17}$, SO_2R_{18}, $SO_2NR_{19}R_{20}$, COR_{21}, $NR_{22}COR_{23}$, $NR_{24}SO_2R_{25}$, and $R_{26}NR_{27}R_{28}$, wherein $\mathbf{R_{11}}$ to $\mathbf{R_{28}}$ are such as defined above.

In the present invention, "pharmaceutically acceptable" refers to that which is useful in the preparation of a pharmaceutical composition that is generally safe, nontoxic and neither biologically nor otherwise undesirable and that is acceptable for veterinary and human pharmaceutical use.

"Pharmaceutically acceptable salt or solvate" of a compound refers to salts and solvates which are pharmaceutically acceptable, as defined herein, and which has the desired pharmacological activity of the parent compound.

Acceptable salts for the therapeutic use of the compounds of the present invention include the conventional nontoxic salts of the compounds of the invention such as those formed from pharmaceutically acceptable organic or inorganic acids or from pharmaceutically acceptable organic or inorganic bases. As an example, mention may be made of salts derived from inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid and sulfuric acid, and those derived from organic acids such as acetic acid, trifluoroacetic acid, propionic acid, succinic acid, fumaric acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, glutamic acid, benzoic acid, salicylic acid, toluenesulfonic acid, methanesulfonic acid, stearic acid and lactic acid. As an example, mention may be made of salts derived from inorganic bases such as soda, potash or calcium hydroxide and salts derived from organic bases such as lysine or arginine.

These salts may be synthesized from the compounds of the invention containing a basic or acidic part and the corresponding acids or bases according to conventional chemical methods well known to the person skilled in the art.

Acceptable solvates for the therapeutic use of the compounds of the present invention include conventional solvates such as those formed during the last step of the preparation of the compounds of the invention due to the presence of solvents. As an example, mention may be made of solvates due to the presence of water or ethanol.

In the context of the present invention, "stereoisomer" refers to a geometric isomer or an optical isomer.

Geometric isomers result from the different position of substituents on a double bond which can then have a Z or E configuration.

Optical isomers result notably from the different position in space of substituents on a carbon atom comprising four different substituents. This carbon atom thus constitutes a chiral or asymmetrical center. Optical isomers include diastereoisomers and enantiomers. Optical isomers that are mirror images of each other but are non-superimposable are enantiomers. Optical isomers that are not mirror images of each other are diastereoisomers.

In the context of the present invention, "tautomer" refers to a constitutional isomer of the compound obtained by prototropy, *i.e.*, by migration of a hydrogen atom and a change in location of a double bond. The different tautomers of a compound are generally interconvertible and are in equilibrium in solution in proportions which may vary according to the solvent used, the temperature or the pH.

According to a first embodiment, Y_4=N.

Y_2=C-X-Ar and Y_3 preferably represents a C-W group.

In particular:

- Y_1=CH or N, and advantageously CH,
- Y_2=C-X-Ar,
- Y_3=C-W, and
- Y_4=N.

According to a second embodiment, Y_1 and/or Y_4 represent a nitrogen atom.

In this case, Y_2 and Y_3 preferably do not represent a nitrogen atom.

In particular:

- Y_1 and/or Y_4 = N,
- Y_2=CH or C-X-Ar, and
- Y_3=C-W or C-X-Ar.

Advantageously, **X** represents a divalent group selected from O, S, S(O), $S(O)_2$, NR_4, CH_2, CH_2S, $CH_2S(O)$, $CH_2S(O)_2$, $NHS(O)_2$, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, CH=CH, C≡C, CH_2O, OCH_2, NR_4CH_2, and CH_2NR_4.

In aprticular, **X** represents a divalent group selected from S, S(O), $S(O)_2$, NR_4, CH_2, CH_2S, $CH_2S(O)$, $CH_2S(O)_2$, $NHS(O)_2$, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, C≡C, CH_2O, OCH_2, NR_4CH_2, and CH_2NR_4.

More particularly, **X** may be selected from S, S(O), $S(O)_2$, CH_2, CH_2S, $CH_2S(O)$, $CH_2S(O)_2$, $NHS(O)_2$, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, CH=CH, and C≡C.

In particular, **X** may be selected from S, $S(O)_2$, CH_2, SCH_2, $S(O)_2CH_2$, $S(O)_2NH$, CH_2S, $CH_2S(O)_2$, $NHS(O)_2$, CH_2CH_2, and C≡C.

X may notably be selected from S, S(O), $S(O)_2$, NR_4, CH_2, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, C≡C, OCH_2, and NR_4CH_2; notably from S, $S(O)_2$, CH_2, SCH_2, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, and C≡C, wherein the first atom of these groups is bound to atom C of the C-X-Ar chain.

X may be in particular S, $S(O)_2$, SCH_2, $S(O)_2CH_2$, $S(O)_2NH$, CH_2S, $CH_2S(O)_2$, or $NHS(O)_2$; and notably S, $S(O)_2$, SCH_2, $S(O)_2CH_2$, or $S(O)_2NH$, wherein the first atom of these groups is bound to atom C of the C-X-Ar chain.

Advantageously, **Ar** represents a heteroaryl group, such as pyridine, or an aryl group, such as phenyl, optionally substituted by one or more groups selected from a halogen atom, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$halothioalkoxy, CN, NO_2, OR_{11}, SR_{12}, $NR_{13}R_{14}$, CO_2R_{15}, $CONR_{16}R_{17}$, SO_2R_{18}, $SO_2NR_{19}R_{20}$, COR_{21}, $NR_{22}COR_{23}$, and $NR_{24}SO_2R_{25}$; and/or optionally fused to a heterocycle.

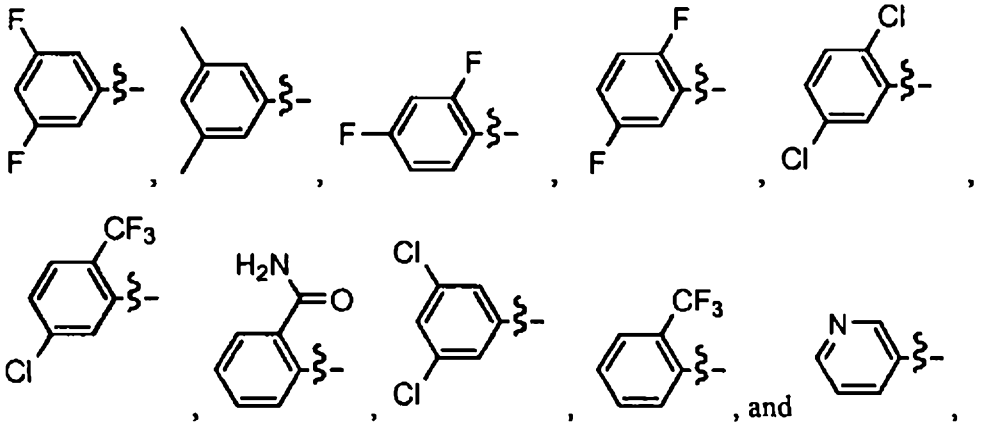
More particularly, **Ar** may represent an aryl group, such as phenyl, optionally substituted by one or more groups selected from a halogen atom, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$halothioalkoxy, CN, NO_2, OR_{11}, SR_{12},

$NR_{13}R_{14}$, CO_2R_{15}, $CONR_{16}R_{17}$, SO_2R_{18}, $SO_2NR_{19}R_{20}$, COR_{21}, $NR_{22}COR_{23}$, and $NR_{24}SO_2R_{25}$.

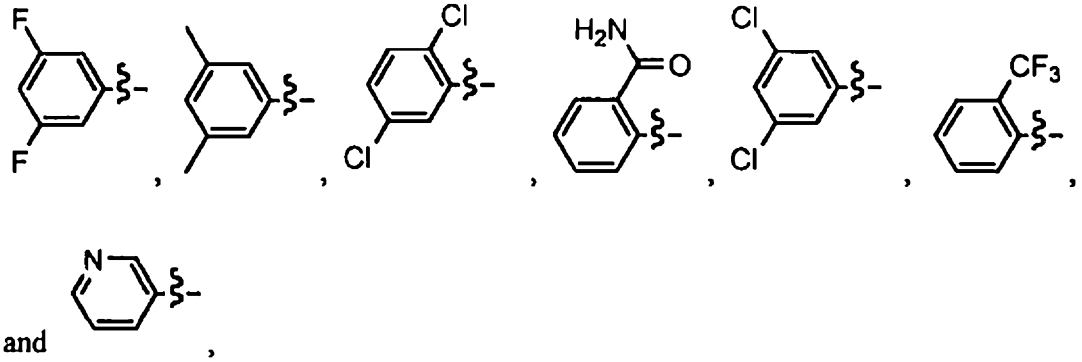
Ar may notably represent an aryl group, such as phenyl, optionally substituted by one or more groups selected from a halogen atom, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, and $CONR_{16}R_{17}$, and in particular from a halogen atom such as fluorine, $(C_1\text{-}C_6)$alkyl such as methyl, and $CONR_{16}R_{17}$ such as $CONH_2$.

Ar can also represent a pyridine group.

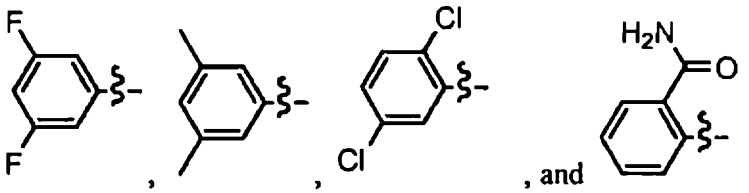
Ar may notably be selected from the following groups:



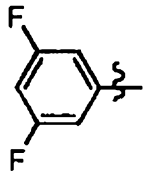
notably from the following groups:



in particular, from the following groups:



Ar may advantageously represent the group:



W may advantageously represent an R_5, SR_5, OR_5 or NR_5R_6 group, and preferably R_5, OR_5 or NR_5R_6, with $\mathbf{R_5}$ and $\mathbf{R_6}$ representing, independently of each other, a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group.

W may represent in particular H, OMe, Me, OH or NH_2, and notably H.

Advantageously, $\mathbf{R_3}$ represents a hydrogen atom.

U may represent more particularly a CH_2 or NH group.

Advantageously, **n** may represent 0.

V may represent more particularly a C(O) or C(S) group, and advantageously a C(O) group.

According to a particular embodiment of the invention:

- $\mathbf{R_3}$=H,
- **U**=CH_2 or NH,
- **V**=C(O) or C(S), and notably C(O), and
- **n**=0 or 1, and notably 0.

According to another particular embodiment of the invention:

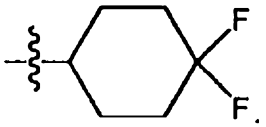
- **V**=C(O) or C(S), and notably C(O), and
- **n**=0.

According to still another particular embodiment of the invention:

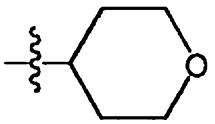
- $\mathbf{R_3}$=H,
- **V**=C(O) or C(S), and notably C(O), and
- **n**=0.

$\mathbf{R_1}$ may represent more particularly a hydrogen atom or an NR_7R_8 group, with $\mathbf{R_7}$ notably representing a hydrogen atom and $\mathbf{R_8}$ notably representing an optionally substituted $(C_3\text{-}C_{12})$cycloalkyl group or an optionally substituted heterocycle.

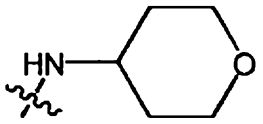
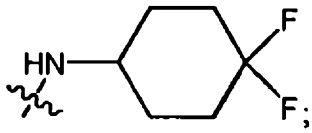
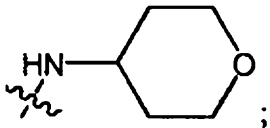
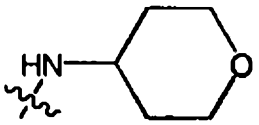
The $(C_3\text{-}C_{12})$cycloalkyl group may be in particular a cyclohexyl. It may be substituted by one or more halogen atoms. It may be in particular the group:



The heterocyclic group may be in particular a tetrahydropyran, notably unsubstituted. It may thus be the following group:



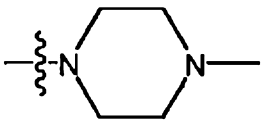
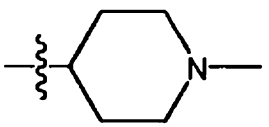
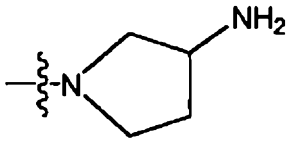
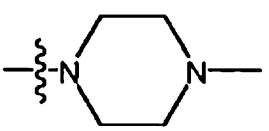
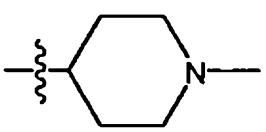
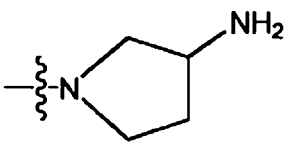
R_1 may thus represent more particularly one of the following groups:

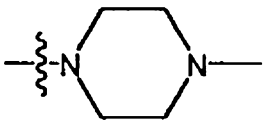
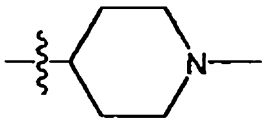
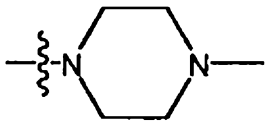
H,  and  ; and notably H and  ; and advantageously  .

R_2 may represent more particularly an optionally substituted heterocycle (notably substituted by $(C_1\text{-}C_6)$alkyl or NH_2), NO_2 or NR_9R_{10}, with notably $R_9=R_{10}=H$ or else R_9 and R_{10} each represent H or an optionally substituted $(C_1\text{-}C_6)$alkyl.

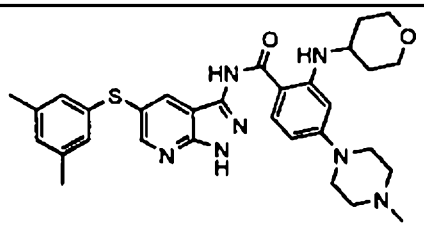
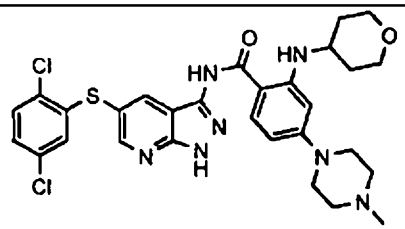
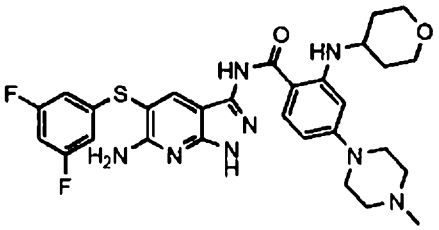
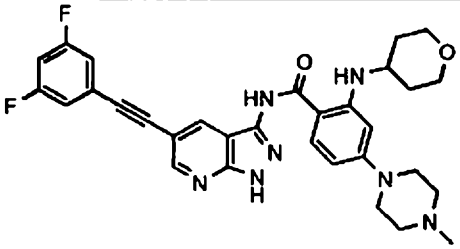
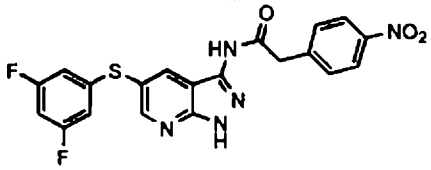
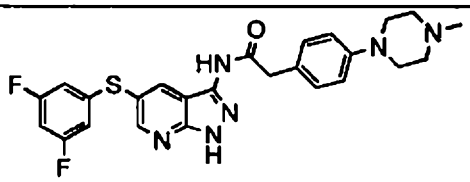
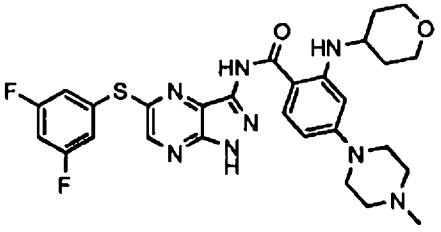
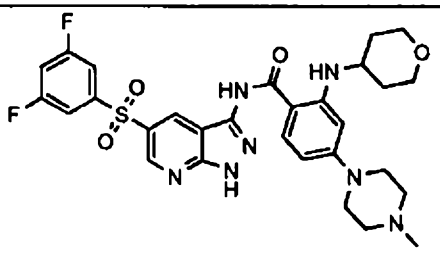
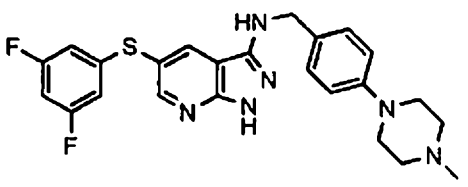
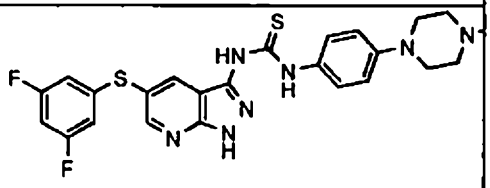
R_2 may represent in particular an optionally substituted heterocycle, notably substituted by $(C_1\text{-}C_6)$alkyl or NH_2. The heterocycle may be in particular a heterocycle with 5 or 6 members comprising at least one nitrogen atom, and in particular one or two. The heterocycle may thus be selected from piperazine, piperidine and pyrrolidine.

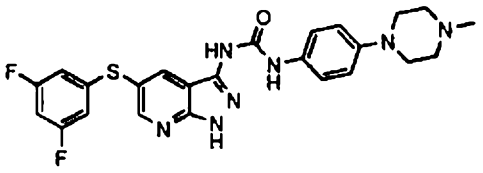
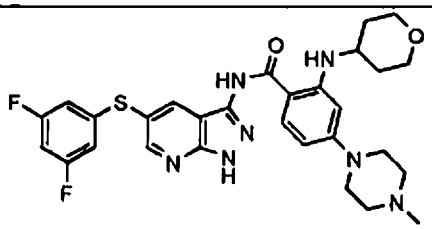
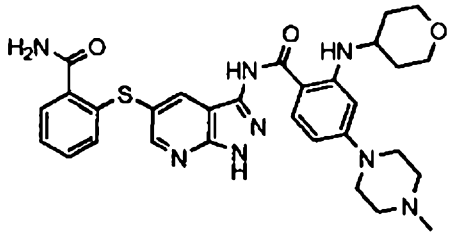
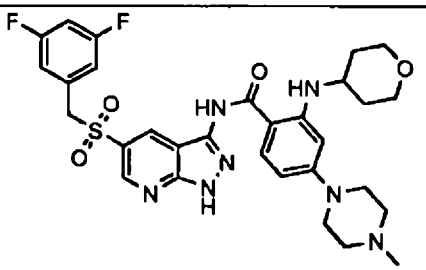
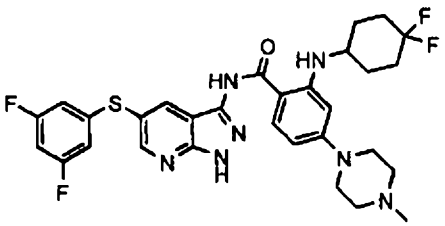
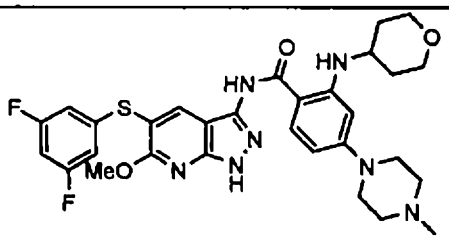
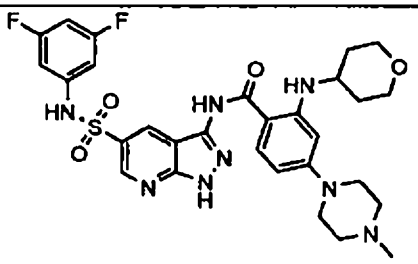
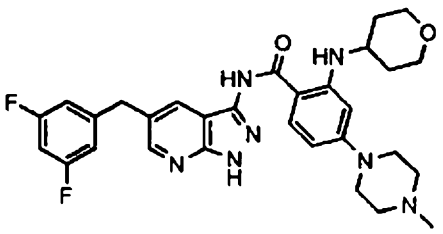
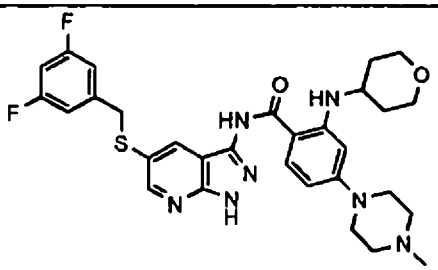
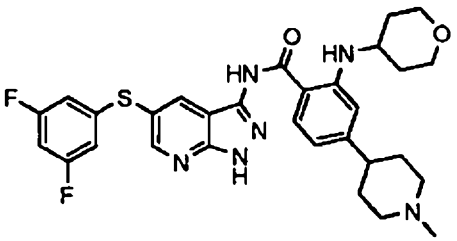
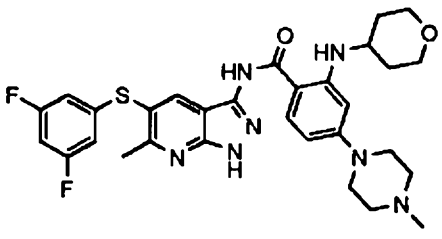
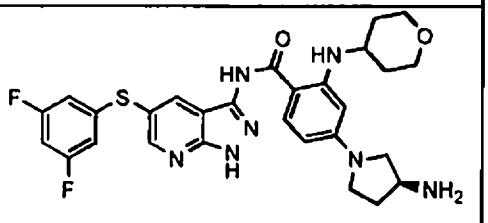
R_2 may notably represent one of the following groups:

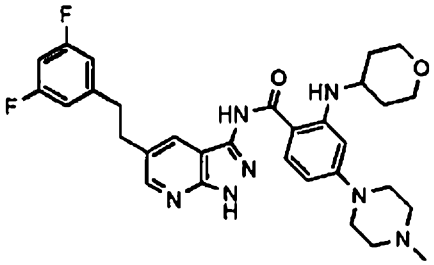
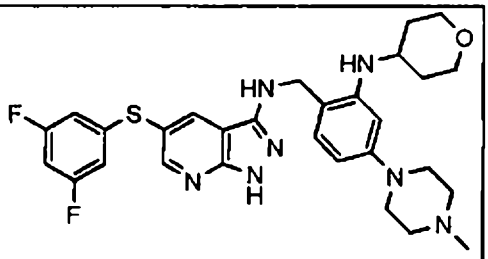
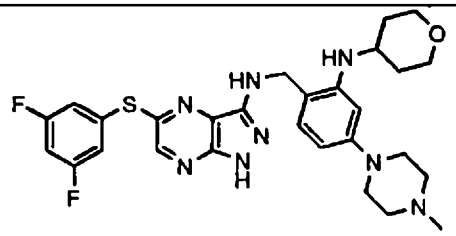
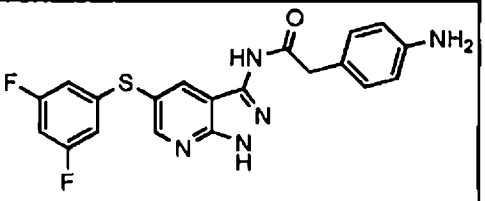
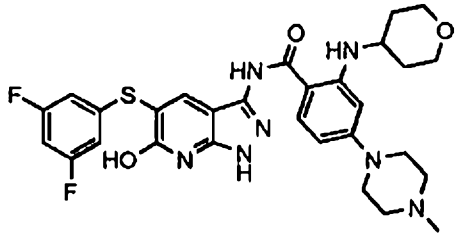
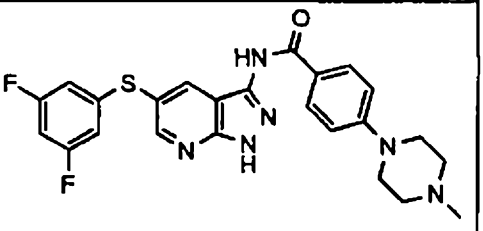
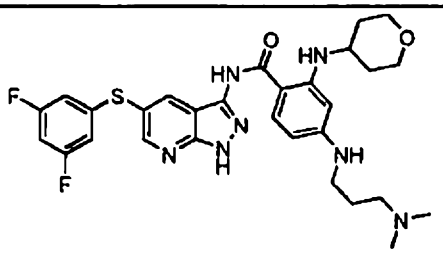
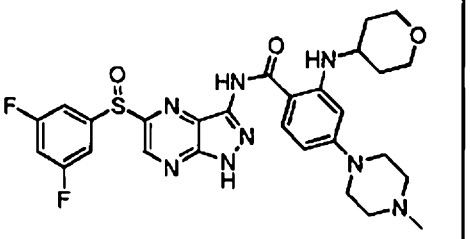
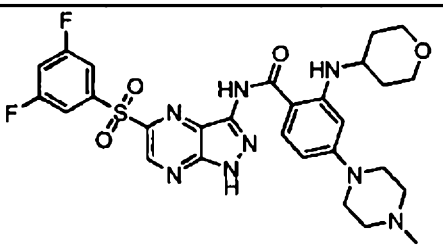
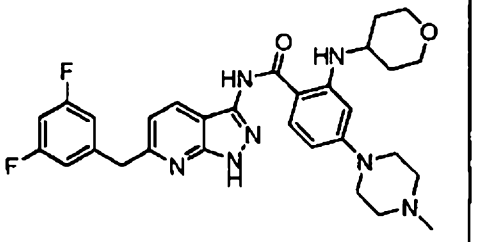
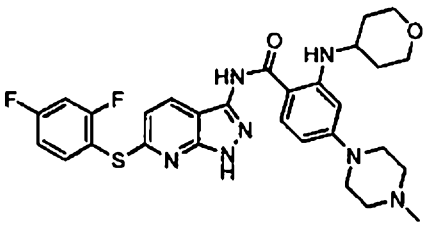
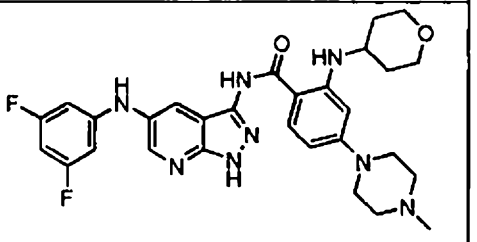
NH_2, $NH(CH_2)_3NMe_2$, $NMe(CH_2)_3NMe_2$, NO_2,  ,  , and  ; and notably NH_2, NO_2,  ,  , and  ; and in

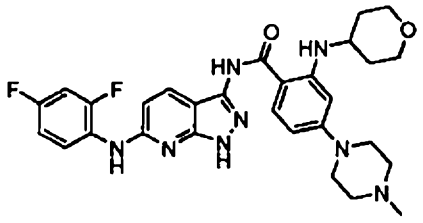
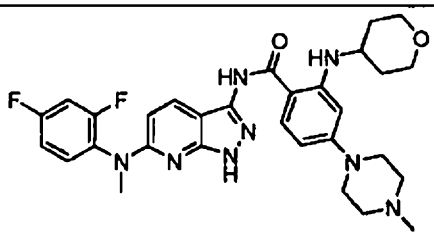
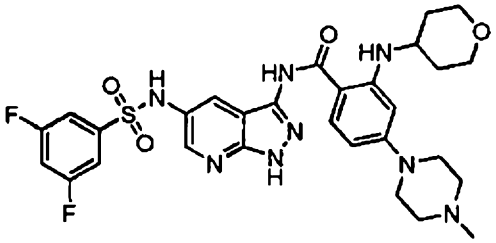
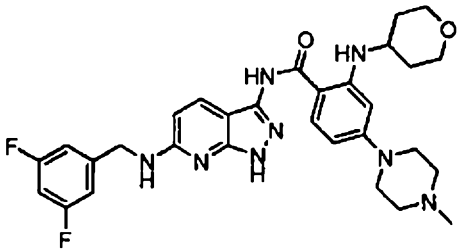
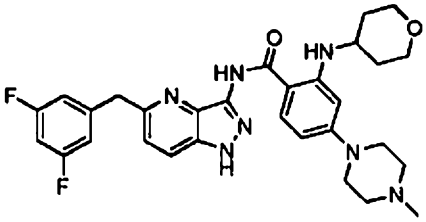
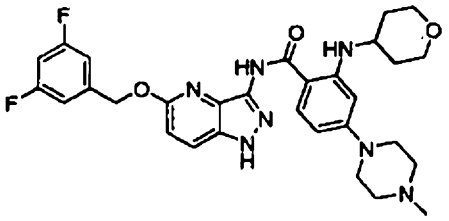
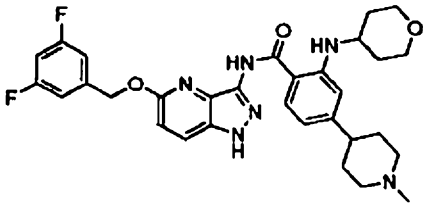
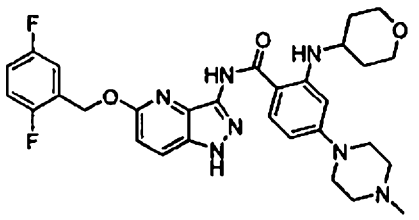
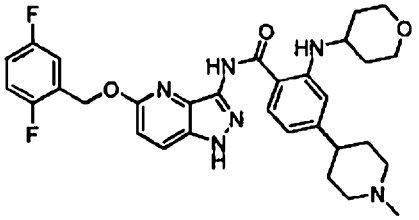
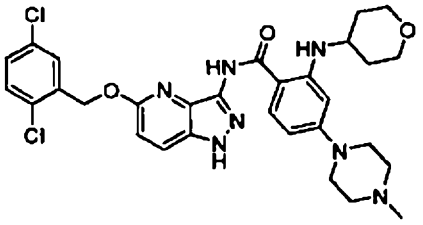
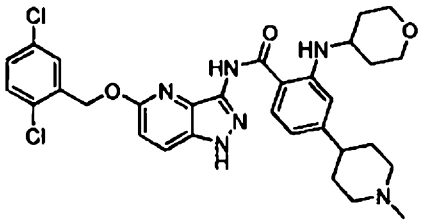
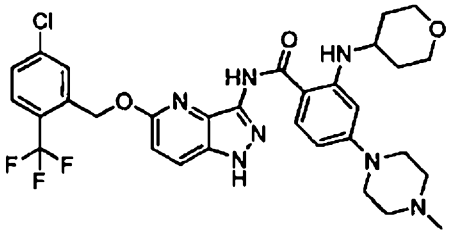
particular  , and  ; and more particularly  .

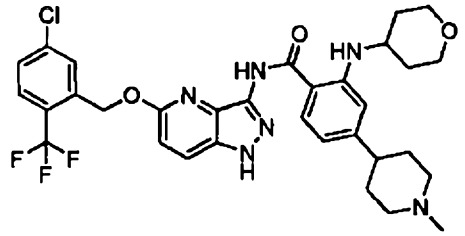
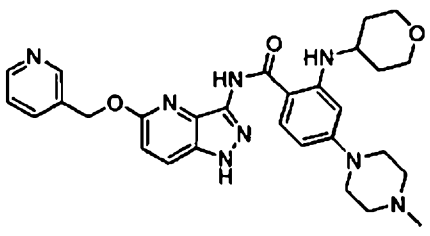
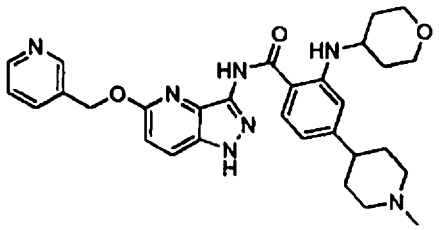
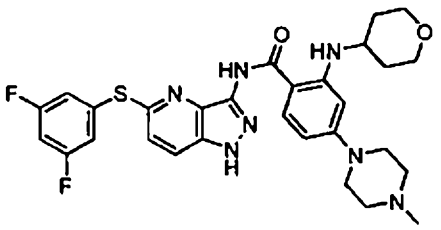
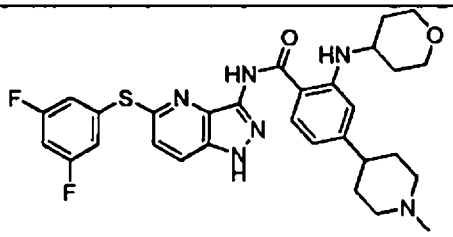
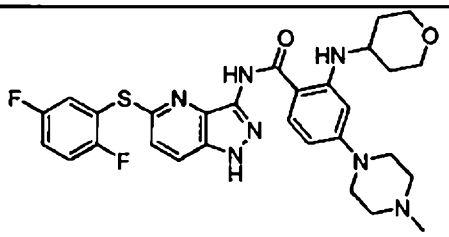
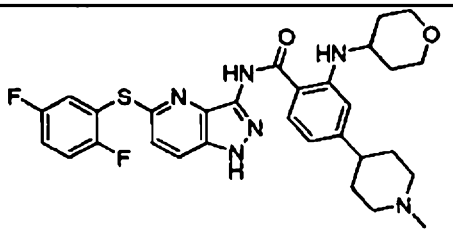
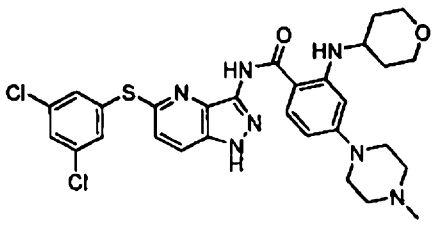
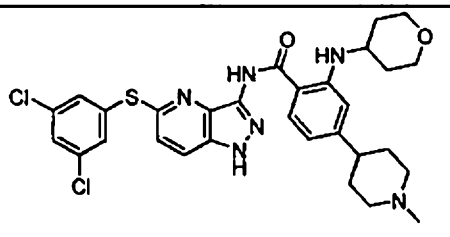
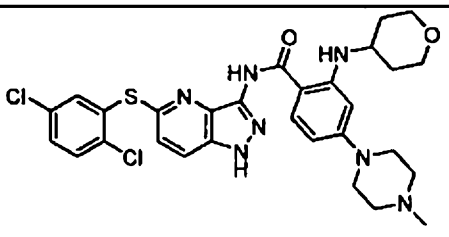
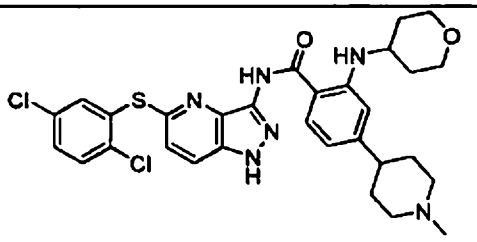
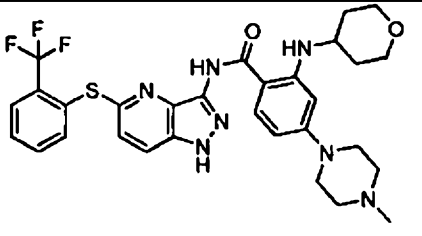
The compounds of the present invention may be selected from the compounds cited in the following table:

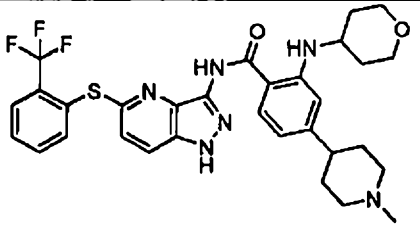
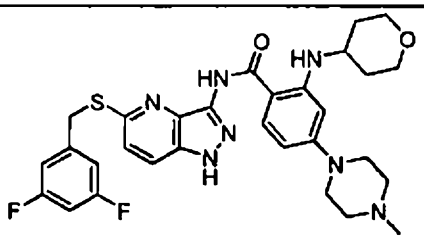
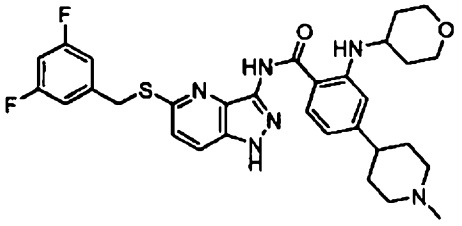
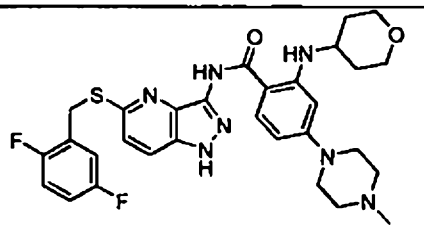
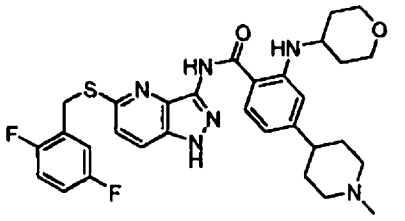
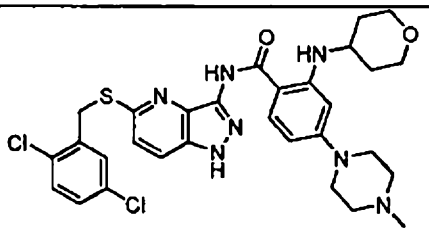
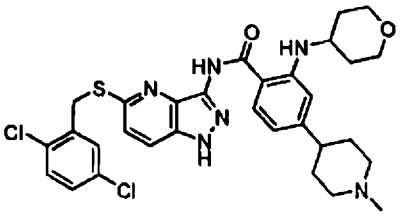
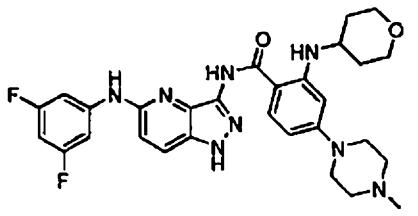
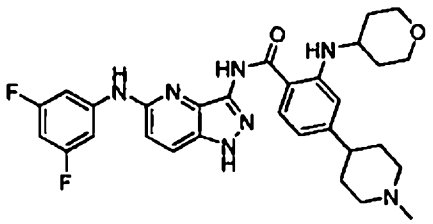
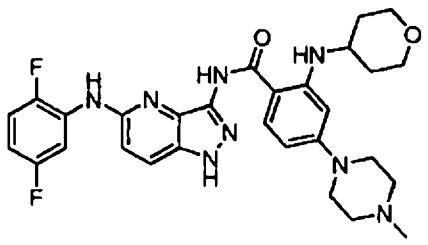
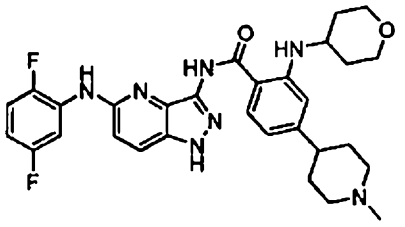
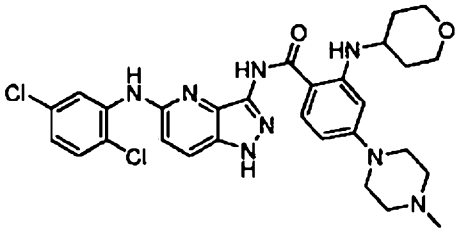
14-2		14-10	
14-11		15	
26-4		26-8	
27		27-1	
28		29	

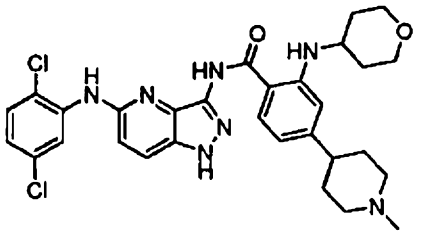
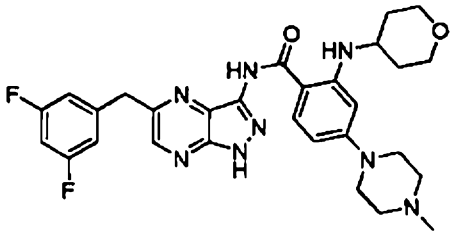
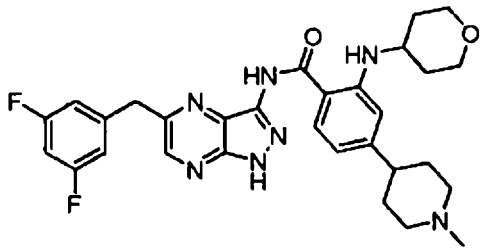
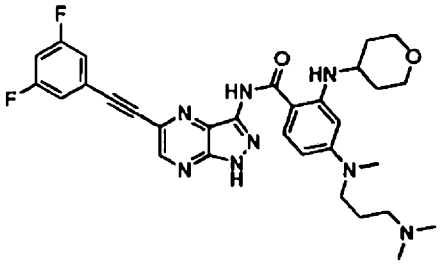
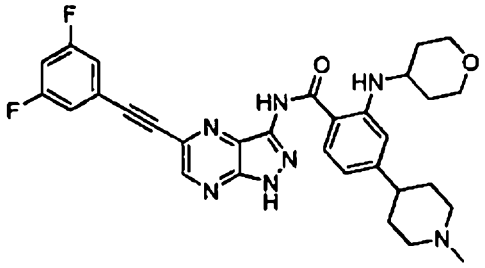
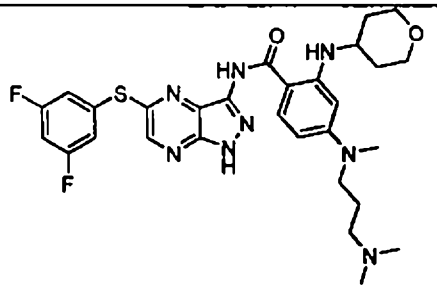
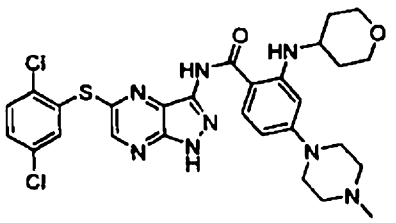
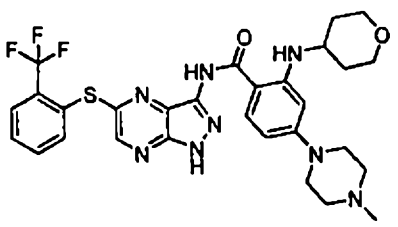
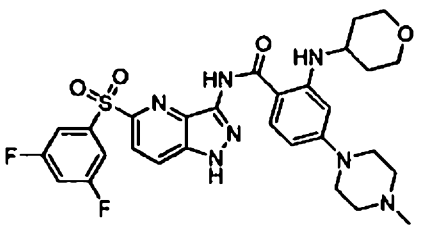
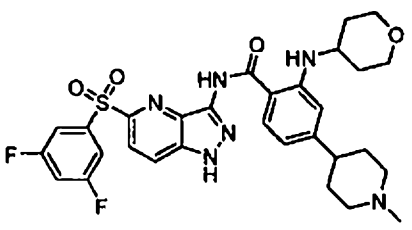
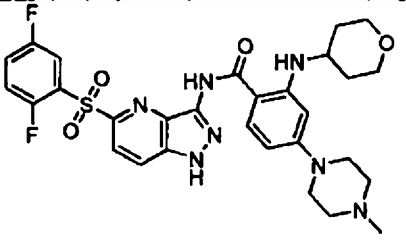
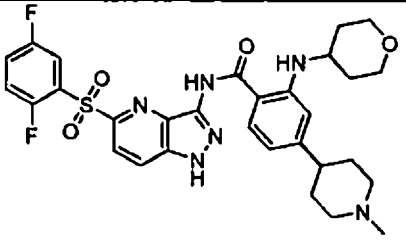
29-a		30	
30-1		30-3	
30-4		30-5	
30-8		30-9	
30-10		30-11	
30-12		30-a	

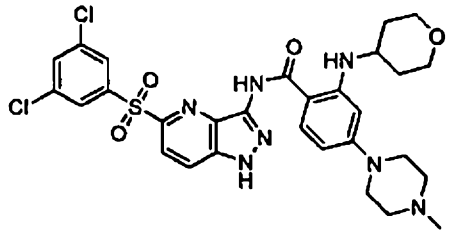
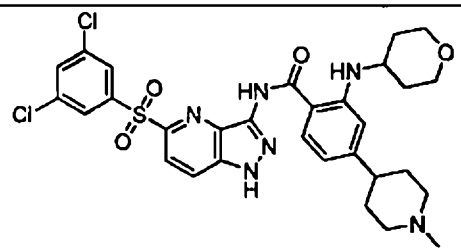
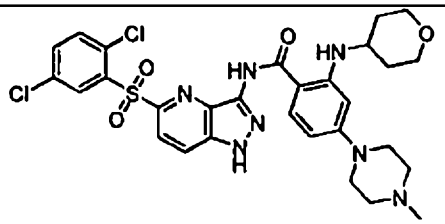
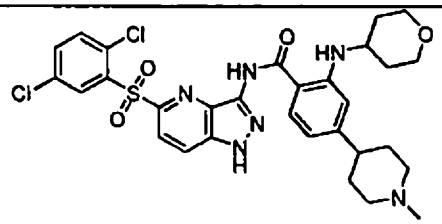
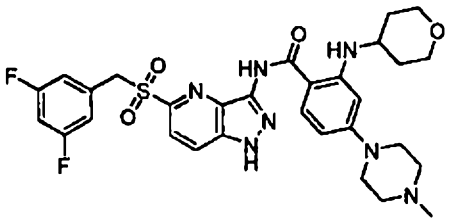
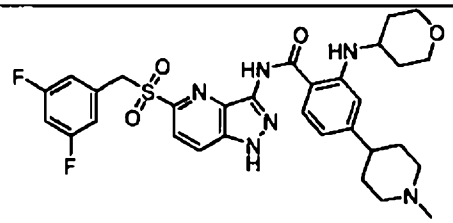
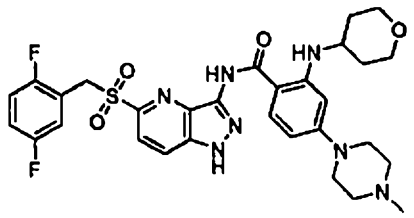
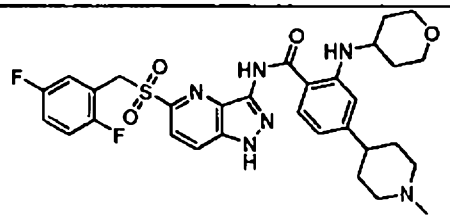
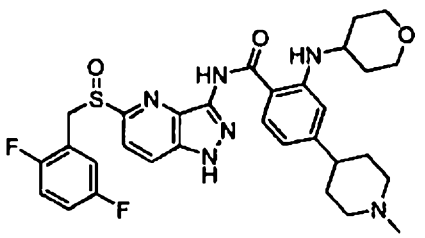
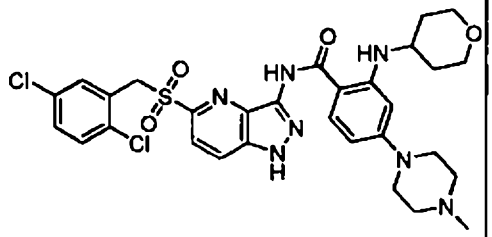
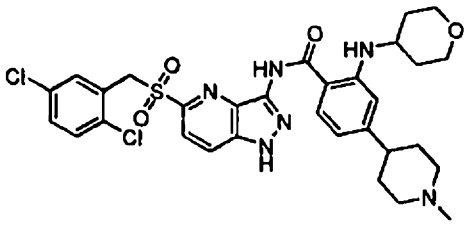
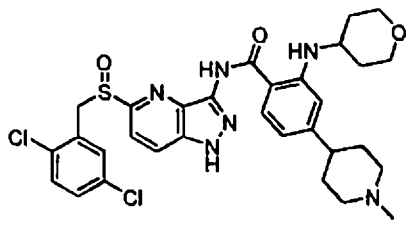
31		32	
32-1		33	
35		26-12	
30-69		27-2	
27-3		27-4	
30-73		14bis	

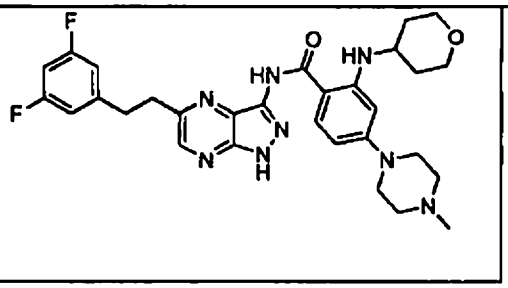
30-70		30-71	
30-72		27-5	
30-13		30-14	
30-15		30-16	
30-17		30-18	
30-19		30-20	

30-21		30-22	
30-23		30-24	
30-25		30-26	
30-27		30-28	
30-29		30-30	
30-31		30-32	

30-33		30-34	
30-35		30-36	
30-37		30-38	
30-39		30-40	
30-41		30-42	
30-43		30-44	

30-45		30-46	
30-47		30-48	
30-49		30-50	
30-51		30-52	
30-53		30-54	
30-55		30-56	

30-57		30-58	
30-59		30-60	
30-61		30-62	
30-63		30-64	
30-65		30-66	
30-67		30-68	

31-1	

The present invention also has as an object a compound according to the invention of formula (I) such as defined above, to be used as a drug, notably intended for the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease, in particular cancer.

The present invention also relates to the use of a compound of formula (I) such as defined above, for the manufacture of a drug, notably intended for the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease, in particular cancer.

The present invention also relates to a method for the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease, in particular cancer, comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) such as defined above.

The cancer may be more particularly in this case colon cancer, breast cancer, kidney cancer, liver cancer, pancreatic cancer, prostate cancer, glioblastoma, non-small cell lung cancer, neuroblastoma, inflammatory myofibroblastic tumor, diffuse B-cell lymphoma or anaplastic large-cell lymphoma.

The present invention also relates to a compound according to the invention of formula (I) such as defined above, to be used as a drug intended for the treatment of a disease associated with a kinase, and in particular a tyrosine kinase such as the kinases ALK, Abl and/or c-Src, and in particular ALK. The disease may be in particular associated with ALK and at least one other kinase, for example Abl or c-Src, in particular ALK and c-Src.

The present invention also has as an object a compound according to the invention of formula (I) such as defined above, to be used as a kinase inhibitor, and in particular an inhibitor of tyrosine kinases such as ALK, Abl and/or c-Src, and in

particular ALK. The compounds according to the invention may notably be used as an inhibitor of ALK and at least one other kinase, for example Abl or c-Src. Preferentially, the compounds according to the invention are inhibitors of ALK and c-Src.

In the context of the present invention, "disease associated with a kinase" or "kinase-associated disease" refers to any diseases, and in particular diseases related to deregulation of cell proliferation, in particular cancers, due to deregulation of the expression or activity of said kinase compared to its normal state of expression or activity. Deregulation of the expression of said kinase may be modification of the sequence expressed or modification of the quantity of protein expressed. These deregulations may lead to changes in cells which may, in particular, result in proliferative disorders including cancers. Preferentially, according to the invention, kinase-associated diseases may be cancers related to deregulation of ALK and/or c-Src activity such as, for example, colon cancer, breast cancer, kidney cancer, liver cancer, pancreatic cancer, prostate cancer, glioblastoma, non-small cell lung cancer, neuroblastoma, inflammatory myofibroblastic tumors, diffuse B-cell lymphoma and anaplastic large-cell lymphoma.

According to the invention, the expression "inhibitor of kinases" or "kinase inhibitor" refers to molecules that are able to interact with the kinase and to reduce its activity. Preferentially, the use of a kinase inhibitor according to the invention makes it possible to suppress the activity of said kinase.

The present invention also relates to a pharmaceutical composition comprising at least one compound of formula (I) such as defined above, and at least one pharmaceutically acceptable excipient.

The pharmaceutical compositions according to the invention may be formulated notably for oral administration or for injection, wherein said compositions are intended for mammals, including humans.

The active ingredient may be administered in unit dosage forms of administration, in mixture with standard pharmaceutical carriers, to animals or to humans. The compounds of the invention as active ingredients may be used in doses ranging between 0.01 mg and 1000 mg per day, given in a single dose once per day or administered in several doses throughout the day, for example twice a day in equal

doses. The dose administered per day advantageously is between 5 mg and 500 mg, even more advantageously between 10 mg and 200 mg. It may be necessary to use doses outside these ranges as determined by the person skilled in the art.

The pharmaceutical compositions according to the invention may further comprise at least one other active ingredient, such as an anticancer agent.

The present invention also has as an object a pharmaceutical composition comprising:

(i) at least one compound of formula (I) such as defined above, and

(ii) at least one other active ingredient, such as an anticancer agent,

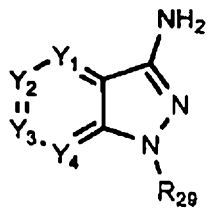
as a combination product for simultaneous, separate or sequential use.

The present invention also relates to a pharmaceutical composition such as defined above to be used as a drug, notably intended for the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease, in particular cancer.

The present invention also has as an object method for the preparation of the compounds of formula (I) according to the invention.

According to a first embodiment, the present invention relates to a method for the preparation of a compound of formula (I) according to the invention wherein V=C(O) or C(S), preferably C(O), and notably U=CH_2, comprising the following successive steps:

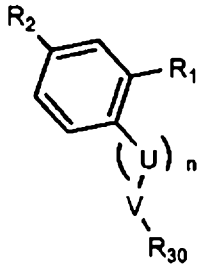
(a1) coupling between a compound of following formula (A):



(A)

wherein Y_1, Y_2, Y_3 and Y_4 are such as defined above, and R_{29} represents a hydrogen atom or an N-protecting group,

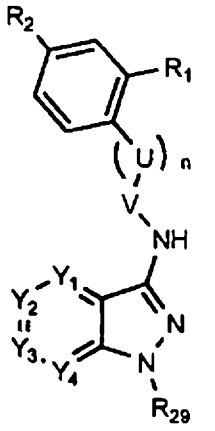
with a compound of following formula (B):



(B)

wherein R_1, R_2, U and n are such as defined above, V=C(O) or C(S), and R_{30}=OH or a leaving group such as Cl,

to yield a compound of following formula (C):



(C)

wherein Y_1, Y_2, Y_3, Y_4, R_1, R_2, R_{29}, U and n are such as defined above and V=C(O) or C(S),

(b1) optionally substitution of the nitrogen atom bound to V of the compound of formula (C) obtained in the preceding step with an R_3 group other than H and/or deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group to yield a compound of formula (I) with V=C(O) or C(S), and

(c1) optionally forming of a salt of the compound of formula (I) obtained in the preceding step to yield a pharmaceutically acceptable salt of same.

In the context of the present invention, "N-protecting group" refers to any substituent that protects the NH or NH_2 group against undesirable reactions such as the N-protecting groups described in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York (1981)) and Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1 to 8 (J. Wiley & Sons, 1971 to 1996). N-protecting groups include carbamates, amides, N-alkylated derivatives, amino acetal derivatives, N-

benzylated derivatives, imine derivatives, enamine derivatives and N-heteroatom derivatives. In particular, the N-protecting group consists of formyl, acetyl, benzoyl, pivaloyl, phenylsulfonyl, trityl (triphenylmethyl), *tert*-butyl, benzyl (Bn), t-butyloxycarbonyl (BOC), benzyloxycarbonyl (Cbz), p-methoxybenzyloxycarbonyl, p-nitrobenzyl-oxycarbonyl, trichloroethoxycarbonyl (TROC), allyloxycarbonyl (Alloc), 9-fluorenylmethyloxycarbonyl (Fmoc), trifluoro-acetyl, benzyl carbamates (substituted or not) and the like. It may be in particular a trityl, *tert*-butyl or BOC group.

In the context of the present invention, "leaving group" refers to a chemical group which may be easily displaced by a nucleophile during a nucleophilic substitution reaction, wherein the nucleophile is more particularly an amine, and notably a primary or secondary amine. Such a leaving group may be more particularly a halogen atom such as a chlorine atom, a mesylate (CH_3-$S(O_2)O$-), a triflate (CF_3-$S(O)_2O$-) or a tosylate (*p*-Me-C_6H_4-$S(O)_2O$-).

Step (a1):

Coupling between (A) and (B) may be carried out by techniques well known to the person skilled in the art.

When $\mathbf{R_{30}}$=OH, the coupling may be carried out under peptide coupling conditions. It may thus be carried out in the presence of a coupling agent such as diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), carbonyldiimidazole (CDI), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or O-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU); optionally combined with a secondary coupling agent such as N-hydroxysuccinimide (NHS), N-hydroxybenzotriazole (HOBt), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazole (HOOBt), 1-hydroxy-7-azabenzotriazole (HAt) or N-hydroxysulfosuccinimide (sulfo NHS). Peptide coupling may moreover be carried out in an aprotic solvent such as tetrahydrofuran, dioxane and dichloromethane.

When $\mathbf{R_{30}}$ is a leaving group such as Cl, coupling may be carried out in the presence of a base such as pyridine, triethylamine or diisopropylethylamine (DIPEA). The reaction may be carried out in an aprotic solvent such as tetrahydrofuran, toluene or dichloromethane, or in a base solvent such as pyridine.

The compounds of formula (A) and (B) can be prepared by the methods described in further detail below.

Step (b1):

In the context of the present invention, "deprotection" refers to the process by which a protecting group is eliminated once the selective reaction is completed. Certain protecting groups may be preferred over others due to their convenience or their relative ease of elimination.

The deprotection step may be carried out under conditions well known to the person skilled in the art.

The substitution step may also be carried out by techniques well known to the person skilled in the art. If necessary, functionalities that may be sensitive to the reaction conditions of the substitution step may be protected beforehand and then deprotected once substitution is carried out.

Thus, if a step of deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group and a step of substitution of the nitrogen atom bound to V with an R_3 group must be carried out, the order in which these two steps are carried out will depend on the reaction conditions of each of these steps.

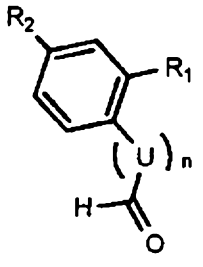
Moreover, it may also be necessary to carry out additional steps of functionalization of the molecule by techniques known to the person skilled in the art.

Step (c1):

This step may be carried out in the presence of a pharmaceutically acceptable organic or inorganic acid or a pharmaceutically acceptable organic or inorganic base such as defined above.

According to a second embodiment, the present invention relates to a method for the preparation of a compound of formula (I) according to the invention wherein $V=CH_2$, and notably $U=CH_2$, comprising the following successive steps:

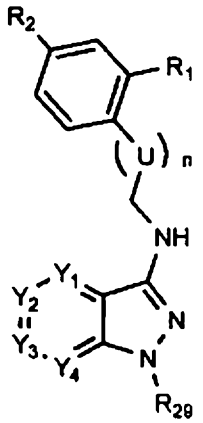
(a2) reducing amination reaction between a compound of formula (A) such as defined above and an aldehyde of following formula (D):



(D)

wherein R_1, R_2, U and n are such as defined above,

to yield a compound of following formula (E):



(E)

wherein Y_1, Y_2, Y_3, Y_4, R_1, R_2, R_{29}, U and n are such as defined above,

(b2) optionally deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group and/or substitution of the nitrogen atom bound to V with an R_3 group other than H of the compound of formula (E) obtained in the preceding step to yield a compound of formula (I) with $V=CH_2$, and

(c2) optionally forming of a salt of the compound of formula (I) obtained in the preceding step to yield a pharmaceutically acceptable salt of same.

Step (a2):

This step is carried out in the presence of a reducing agent such as a borohydride and in particular $NaBH_4$, $NaBH(OAc)_3$ or $NaBH_3CN$.

This reaction is more particularly carried out at room temperature, *i.e.*, at a temperature ranging between 15°C and 40°C, in particular between 20°C and 30°C.

The reaction may be typically carried out in a solvent such as dichloroethane (DCE), tetrahydrofuran (THF) or acetonitrile, optionally in the presence of water, acetic acid or trifluoroacetic acid.

The compounds of formula (A) and (D) can be prepared by the methods described in further detail below.

Step (b2): see step (b1)

Step (c2): see step (c1)

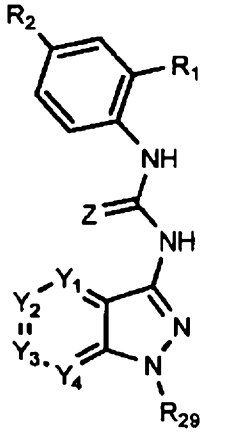
According to a third embodiment, the present invention relates to a method for the preparation of a compound of formula (I) according to the invention wherein V=C(O) or C(S), n=1 and U=NH, comprising the following successive steps:

(a3) coupling between a compound of formula (A) such as defined above and a compound of following formula (F):

(F)

wherein R_1 and R_2 are such as defined above and Z=O or S,

to yield a compound of following formula (G):



(G)

wherein Y_1, Y_2, Y_3, Y_4, R_1, R_2, R_{29}, and Z are such as defined above,

(b3) optionally deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group and/or substitution of the nitrogen atom bound to V with an R_3 group other than H of the compound of formula (G) obtained in the preceding step to yield a compound of formula (I) with V=C(O) or C(S), n=1 and U=NH, and

(c3) optionally forming of a salt of the compound of formula (I) obtained in the preceding step to yield a pharmaceutically acceptable salt of same.

Step (a3):

This step may be carried out under conditions well known to the person skilled in the art.

A polar or non-polar protic solvent may be more particularly used such as dichloromethane, acetone, acetonitrile, tetrahydrofuran or dioxane.

The compounds of formula (A) and (F) can be prepared by the methods described in further detail below.

Step (b3): see step (b1)

Step (c3): see step (c1)

Once the compound of formula (I) is obtained by any one of the preceding methods, it may be separated from the reaction medium by techniques well known to the person skilled in the art, and notably by evaporation of the solvent, crystallization and filtration, etc.

The compound obtained may be purified if necessary by techniques well known to the person skilled in the art, and notably by high-performance liquid chromatography (HPLC), silica gel chromatography, recrystallization when the compound is crystalline, etc.

Thus, the compounds of formula (I) according to the present invention can be prepared by the various methods summarized in diagrams 1a and 1b below.

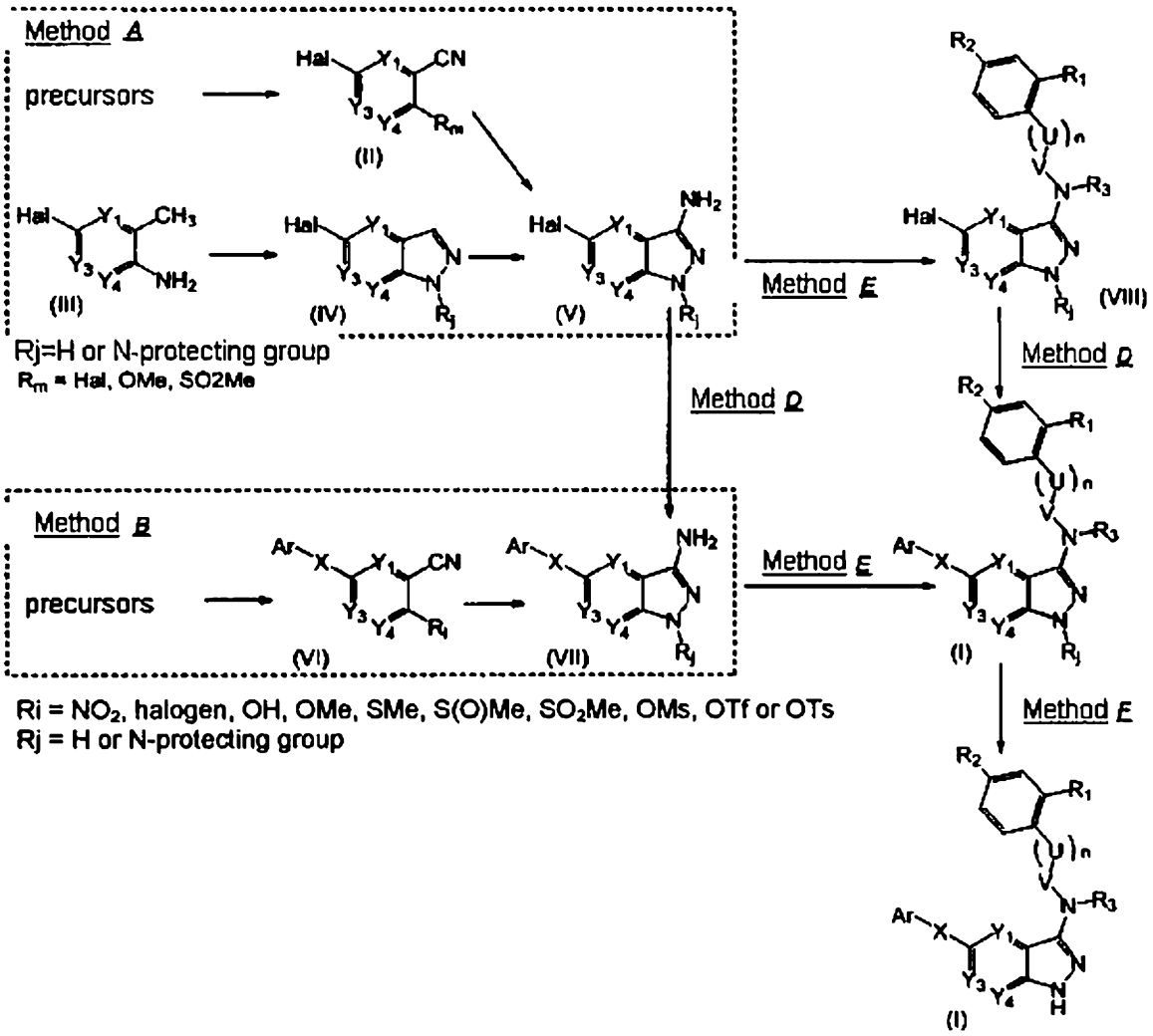
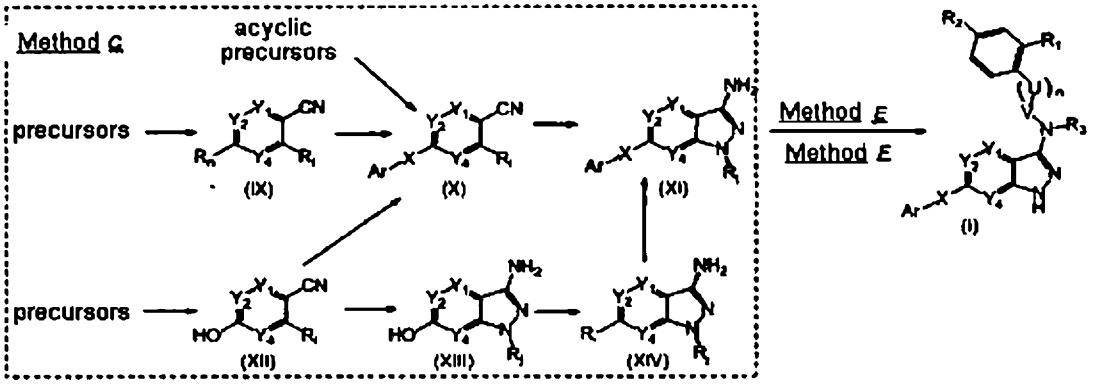


Diagram 1a



Rl = NO_2, halogen, OH, OMe, SMe, S(O)Me, SO_2Me, OMs, OTf or OTs
Rj = H or N-protecting group
Rn = Hal, OMs, OTs or OTf

(Tf represents an $-SO_2CF_3$ group and Ts represents a tosyl group)

Diagram 1b

Method A:

According to method A, compounds of formula (I) are obtained by the preliminary synthesis of compounds of general formula (V) characterized by a halogenated heterobicyclic ring having an exocyclic primary amine. These compounds are obtained via the synthesis of intermediates of general formula (II) or (III).

Method A1:

Method A1, presented in diagram 2 (iodized compounds) or 3 (brominated compounds) below, describes the general process giving access to compounds of general formula (V) with W defined as in the description of general formula (I), and notably H, (C_1-C_6)alkyl or aryl, and R_j=H or N-protecting group.

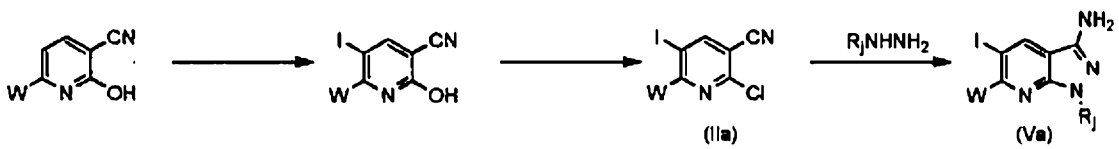


Diagram 2

In the context of diagram 2, the optionally substituted 2-chloro-5-iodonicotinonitrile (IIa) is obtained from the corresponding hydroxynicotinonitrile by the successive use of an iodination agent such as N-iodosuccinimide (NIS), or molecular iodine with an inorganic base such as, for example, K_2CO_3 or Na_2CO_3, notably in a polar solvent such as hot DMF, followed by treatment with phosphorus oxychloride, pure or diluted in a high boiling-point non-polar solvent, or any other equivalent chlorination agent well known to the person skilled in the art. Reaction temperatures are between -20°C and 200°C. The compound (IIa) thus obtained is then transformed into optionally substituted 5-iodo-pyrazolo[3,4-b]pyridine-3-amine (Va) by its reaction, preferably under heat, in the presence of a hydrazine optionally carrying an N-protecting group such as trityl, *tert*-butyl or BOC.

The brominated analogues of general formula (V) as described in diagram 1a may be obtained by the use of the method described in the following references: Witherington *et al.*, Bioorg. Med. Chem. Lett., **2003**, *13*, 1577-1580 and Lijuan Chen *et al.*, Bioorg. Med. Chem. Lett., **2010**, *20*, 4273-4278. For reasons of convenience, these

molecules were obtained by the use of the reaction sequence presented in following diagram 3.

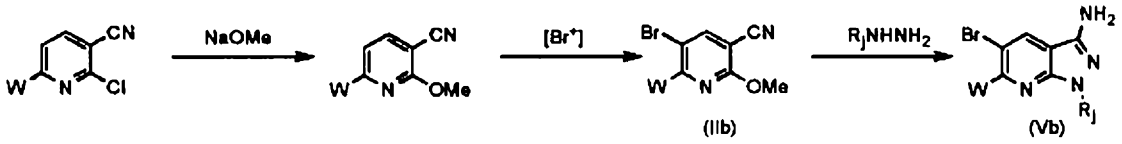


Diagram 3

The optionally functionalized 2-methoxy-nicotinotrile is obtained, for example, by reaction of sodium methanolate in methanol at a temperature between -20°C and the boiling point of the mixture. Alternatively, this compound may be obtained by methylation of 2-hydroxynicotinonitrile or other methods described above. Bromination of 2-methoxy-nicotinonitrile is typically carried out with dibromine in acetic acid at a temperature varying between 20°C and 110°C. Formation of the pyrazole is typically carried out by reaction of an excess of hydrazine, functionalized or not, at a temperature varying between 20°C and 100°C in the presence of a polar solvent such as water, ethanol, tetrahydrofuran (THF) or any other solvent with comparable properties. Alternatively, the use of hydrazine in a saline or hydrated form, without solvent, is also possible.

Method A2:

Method A2 relates to the synthesis of the functionalized pyrazolopyrazines presented in diagram 4 below with R_j=H or N-protecting group, Hal=halogen and in particular W=H, (C_1-C_6)alkyl or aryl.

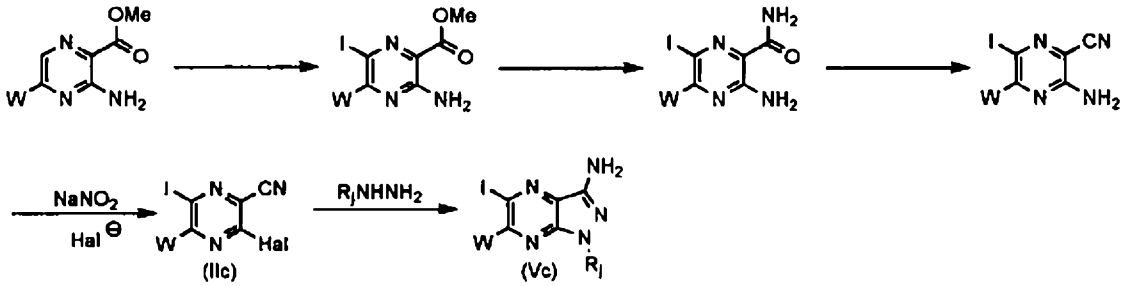


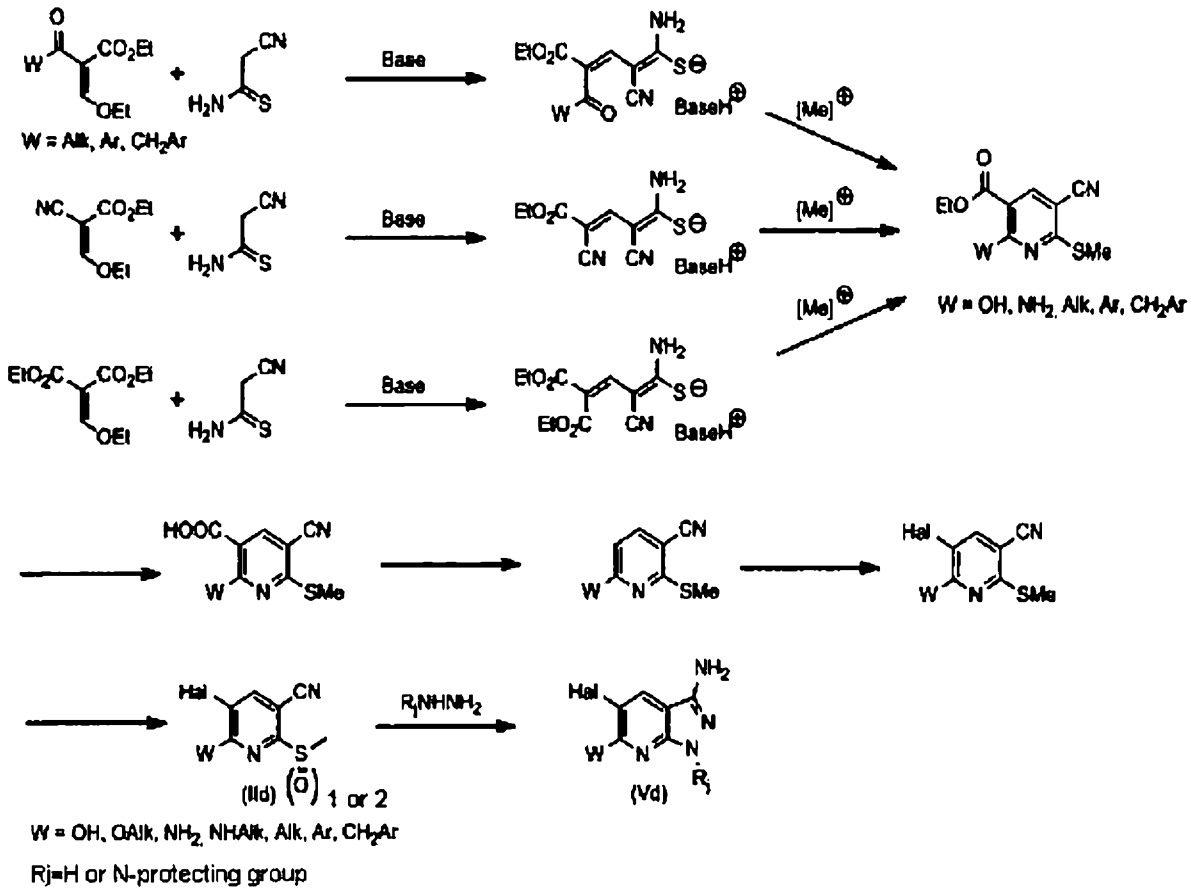
Diagram 4

The optionally functionalized 3-amino-6-iodopyrazine-2-carboxamides are typically obtained in two steps from the corresponding methyl 3-aminopyrazine-2-

carboxylates by iodination in the presence of N-iodosuccinimide or molecular iodine optionally in the presence of a cofactor such as KIO_3, $AgCO_2CF_3$, Ag_2SO_4, $AlCl_3$, $CuCl_2$ or HgO, followed by a conversion reaction of the methyl ester function into carboxamide, notably by the use of ammonia in a polar solvent such as water, methanol or THF at temperatures varying between 0°C and 100°C. The carboxamide function of the optionally functionalized 3-amino-6-iodopyrazine-2-carboxamide is then converted into nitrile by the use of dehydration agents such as, in particular, CCl_4/PPh_3, $SOCl_2$, $PhSO_2Cl$, P_2O_5, TsCl, $COCl_2$, DCC/py (N,N'-dicyclohexylcarbodiimide/pyridine) or $(COCl)_2$ used as the case may be in the presence of an organic base such as pyridine. The preferred method involves the use of phosphorus oxychloride in dimethylformamide (DMF). Deprotection of the dimethylformimidamide function is carried out by treatment with acid such as aqueous hydrochloric acid or any other reagent with equivalent properties. Formation of the pyrazole ring is carried out by a Sandmeyer reaction, well known to the person skilled in the art, followed by a reaction in the presence of a hydrazine, functionalized or not, under conditions as described in the methods above. Alternatively, the diazonium salt, an intermediate of the Sandmeyer reaction, may be reduced by the use, for example, of tin chloride in an acid medium or any other equivalent agent, in order to form a hydrazine function that can undergo intramolecular cyclization under the effect of heat.

Method A3:

Method A3 aims at obtaining derivatives of general formula (V) featuring a variable function in position 6 of the pyrazolopyridine bicycle. It is detailed in diagram 5 below.



(Alk=(C_1-C_6)alkyl, Ar=aryl, CH_2Ar=benzyl, H=halogen)

Diagram 5

Reaction of the cyanothioacetamide with ethyl 3-ethoxyacrilates variously substituted according to methods described notably by Litrivnor *et al.* in Russ. Chem. Bull., **1999**, *48(1)*, 195-196 and Tsann-Long Su *et al.* in J. Med. Chem., **1988**, *31*, 1209-1215 make it possible to yield access, in two steps, to ethyl 5-cyano-6-(methylthio)nicotinates carrying a variable functionality in position 2. These syntheses are typically carried out, for the first step, in an anhydrous polar solvent such as, for example, ethanol at a temperature ranging between 0°C and 70°C in the presence of an organic base such as methylmorpholine, triethylamine, DIPEA (N,N-diisopropylethylamine) or DBU (1,8-diazabicyclo[5,4,0]undec-7-ene). The second step of intramolecular cyclization and of alkylation is typically carried out by the heating to a temperature ranging between 20°C and 100°C of a solution of the intermediate thioamidate in a polar solvent, for example ethanol in the presence of a suitable alkylating agent such as alkyl halide or dialkyl sulfate.

The 5-cyano-6-(methylthio)nicotinic acids substituted in position 2 are typically obtained by saponification of the corresponding ethyl esters according to methods well known to the person skilled in the art, notably by the use of hot lithium hydroxide. Decarboxylation of these compounds is carried out by heat treatment in a high boiling-point solvent such as diphenylether at a temperature ranging between 150°C and 250°C.

Halogenation reactions principally aim at obtaining iodinated, brominated or chlorinated derivatives, more particularly iodinated derivatives. The latter are typically obtained by a molecular iodine treatment in the presence of a silver salt such as, for example, Ag_2SO_4 in a polar solvent such as ethanol at a temperature ranging between 0°C and 70°C. Alternative methods, notably those based on other salts such as KIO_3, $AgCO_2CF_3$, $AlCl_3$, $CuCl_2$ or HgO, or other iodination agents such as N-iodosuccinimide, are also considered. The conceivable bromination methods typically rely on agents such as N-bromosuccinimide or dibromine according to methods well known to the person skilled in the art.

In the case in which W=OH (typically resulting from the use of diethyl 2-(ethoxymethylene)malonate), the corresponding compounds are protected by an alkylation reaction. This reaction is notably carried out by the use of methyl iodide or bromomethane, and silver carbonate in dioxane, THF, acetonitrile or acetone, or any other equivalent agent such as dimethylsulfate. The 5-halo-2-(methylthio)

nicotinonitriles obtained are subjected to oxidation of their thiomethoxy function, typically by the use of m-CPBA (m-chloroperbenzoic acid), oxone or any other equivalent agent, to lead to the formation of the corresponding sulfoxide. These compounds, which may contain variable quantities of the corresponding sulfone, are engaged in a reaction in the presence of an optionally substituted hydrazine to form the corresponding 5-halogeno-pyrazolo[3,4-b]pyridin-3-amine carrying a variable functionality in position 6.

Method A4:

Method A4 aims at obtaining derivatives of general formula (V) from the compounds of general formula (III) via intermediate formation of compounds of formula (IV). These compounds are typically obtained by the pathway presented in diagram 6. The following references illustrate the method used: Gueiffier *et al.* Heterocycles, **1999**, *51(7)*, 1661-1667; Gui-Dong Zhu *et al.* Bioorg. Med. Chem., **2007**, *15*, 2441-2452.

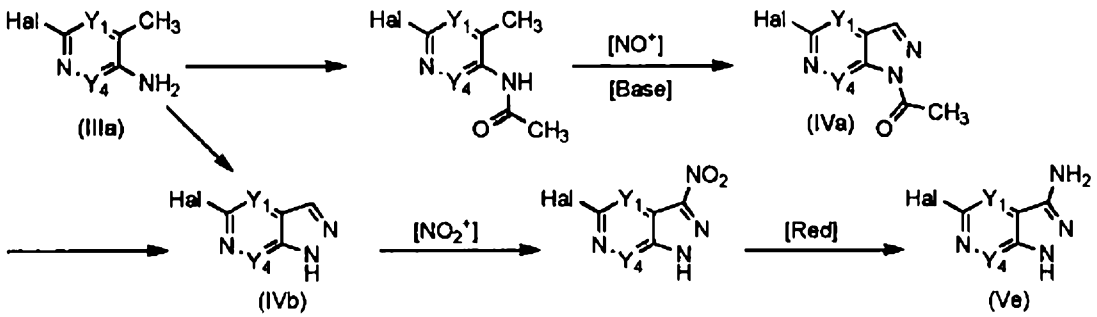


Diagram 6

The compounds of general formula (IIIa), acetylated beforehand by one or another of the methods well known to the person skilled in the art, are subjected to the action of isoamyl nitrite, sodium nitrite or any other equivalent organic or inorganic nitrite, in water or acetic acid, for periods typically varying from 1 to 3 days at temperatures varying between 0°C and 40°C. The compounds of general formula (IVa) thus obtained are deprotected in acidic conditions, for example by the use of hydrochloric acid, before being subjected to the action of nitration agents such as concentrated nitric acid or potassium nitrate in sulfuric acid at temperatures varying between 0°C and 25°C.

It should be noted that the direct conversion of compounds of general formula (IIIa) into deprotected compounds (IVb) is possible in general.

The nitropyrazoles thus obtained are typically reduced into aminopyrazoles of general formula (Ve) by the use of $SnCl_2$ in hydrochloric acid. Alternative methods include the use of iron, zinc or tin in acidic conditions and methods of catalytic hydrogenation in the presence of complexes of platinum, nickel or Pd/C under an atmosphere of hydrogen or in the presence of equivalent agents such as cyclohexadiene, cyclohexene, sodium borohydride or hydrazine.

Method B:

According to method B, the compounds of formula (I) are obtained by the preliminary synthesis of compounds of general formula (VI) characterized by a functionalized heterobicyclic ring possessing an exocyclic amine. These compounds are obtained via the synthesis of intermediates of general formula (VI).

Method B1:

Method B1 is represented in diagram 7 below, with W notably representing H, (C_1-C_6)alkyl, aryl or benzyl.

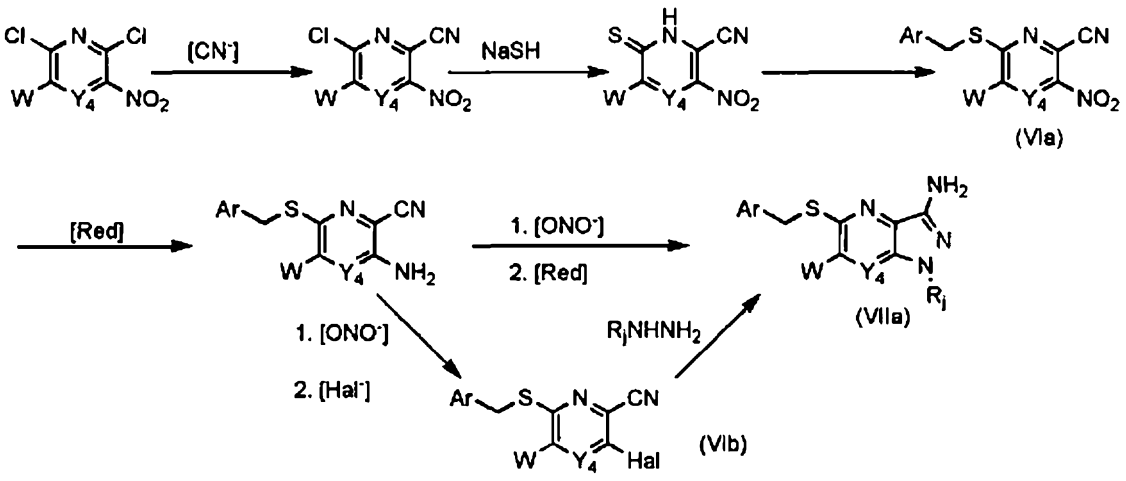


Diagram 7

The 3-nitro-6-thioxo-1,6-dihydropyridin-2-carbonitrile and 3-nitro-6-thioxo-1,6-dihydropyrazine-2-carbonitrile derivatives, optionally functionalized in position 5, are typically obtained from the corresponding 2,6-dichloro-3-nitropyridines or 2,6-dichloro-

3-nitropyrazines by the successive reactions of a cyanide salt, such as copper cyanide, in a high boiling-point polar solvent such as N-methylpyrrolidone at temperatures ranging between 100°C and 200°C; followed by the reaction of aqueous sodium hydrosulfite in a polar solvent. These compounds are then alkylated, for example by the use of a substituted benzyl bromide, in basic medium, according to methods well known to the person skilled in the art. The preferred protocol includes the use of an aprotic and anhydrous polar solvent such as acetone carrid at its boiling point and an organic base such as pyridine, triethylamine or DIPEA, or an inorganic base such as sodium, potassium or calcium carbonate. Reactions for reducing the nitro function in amine are preferentially carried out by the use of $SnCl_2$ in hydrochloric acid. Alternative methods include the use of iron, zinc or tin in acidic conditions and methods of catalytic hydrogenation in the presence of complexes of platinum, nickel or Pd/C under an atmosphere of hydrogen or in the presence of equivalent agents such as cyclohexadiene, cyclohexene, sodium borohydride or hydrazine.

In certain cases, the product of the reduction reaction, in addition to having a primary amine, has a carboxamide function resulting from hydrolysis of the nitrile function. In this case, isolation of the corresponding 3-aminopicolinonitriles or 3-aminopyrazine-2-carbonitriles may be carried out by dehydration of the carboxamide into nitrile via the use of phosphorus oxychloride in the presence of DMF or any other method well known to the person skilled in the art. Lastly, formation of the aminopyrazole ring is carried out preferentially by the formation of a diazonium, obtained by the successive reaction at low temperature of isoamyl nitrite, sodium nitrite or any other equivalent organic or inorganic nitrite, in water, hydrochloric acid, acetic acid or sulfuric acid, at temperatures varying between 0°C and 20°C, followed by its reduction into hydrazine and intramolecular cyclization activated by heating of the reaction medium. The reduction reaction is preferentially carried out with tin chloride in acidic conditions but may also be carried out by catalytic hydrogenation or any other method well known to the person skilled in the art. In an alternative to this last step, it is conceivable that the intermediate diazonium undergoes a Sandmeyer reaction during which this functional group is substituted by a halogen atom, such as iodine, by the reaction of an adequate salt, such as NaI. If this option is preferred, formation of the

aminopyrazole ring is carried out by the use of a hydrazine, functionalized or not, in a polar solvent such as ethanol at temperatures varying between 25°C and 150°C.

Method B2:

Alternatively, it is possible to take advantage of an aromatic nucleophilic substitution reaction to functionalize the pyridine or pyrazine ring in position 6. In this case the nucleophiles used are phenols, thiophenols, benzyl alcohols or thiobenzyl alcohols as well as anilines or benzylamines, functionalized or not. The general reaction diagram 8a is presented below, notably with W=H, (C_1-C_6)alkyl, aryl or benzyl.

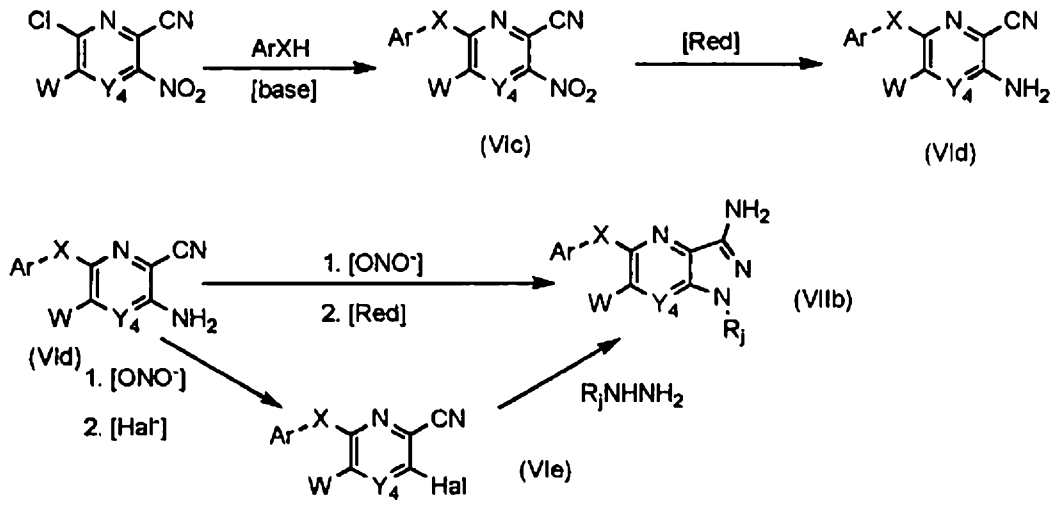


Diagram 8a

In the case in which X=O or S, the 6-chloro-3-nitropicolinonitriles and 6-chloro-3-nitropyrazine-2-carbonitriles, optionally substituted in position 5, are reacted in the presence of the suitable nucleophile, alcohol or thiol, in a polar solvent such as acetonitrile in the presence of an inorganic base such as potassium or sodium carbonate. Solvents such as DMSO (dimethylsulfoxide), DMF (dimethylformamide), acetone, THF (tetrahydrofuran) or pyridine may also be considered. If necessary, these reactions may be catalyzed by the action of copper and may also be carried out without solvent. Typically, the preferred protocol involves temperatures ranging between 20°C and 150°C.

Alternatively, the use of bases such as pyridine, DIPEA, diisopropylamine, triethylamine, DBU, potassium *tert*-butylate, NEt_3 or NaH is also possible.

In the case in which X=N, toluene is a preferred solvent and triethylamine (NEt3) the base of choice.

The following steps, up to the compounds of general formula (VIIb), are identical to those documented in method B1 above.

Method B3:

Method B3, presented in diagram 8b below, is a variant of method B2 characterized by a first step resulting from a catalytic coupling reaction between a benzyl boronate, in acid or ester form, and a 6-chloro-3-nitropicolinonitrile or 6-chloro-3-nitropyrazine-2-carbonitrile derivative. It is also well known to the person skilled in the art that catalytic coupling reactions using alternative catalysts and benzyl derivatives are also possible. Among these, the Stille reaction, based on tin complexes, or those based on organozinc compounds may be considered.

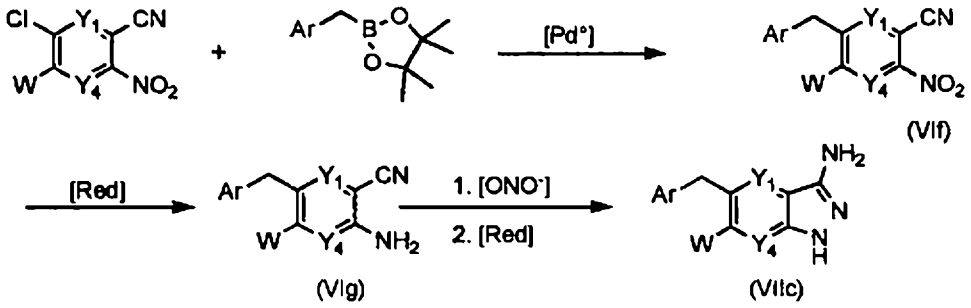


Diagram 8b

An optionally substituted 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane is obtained beforehand, for example from the corresponding benzyl chloride and octamethyl-bi-dioxaborolane in dioxane in the presence of potassium acetate and $Pt(dppf)Cl_2$ (dppf=1,1'-bis(diphenylphosphino)ferrocene). This compound is brought together with a 6-chloro-3-nitropicolinonitrile, a 6-chloro-3-nitropyrazine-2-carbonitrile optionally substituted in position 5 or a 5-chloro-2-nitronicotinonitrile optionally substituted in position 6 and a palladium catalyst such as $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$, an organic base such as triethylamine or an alcoholate, or an inorganic base such as sodium, potassium or cesium carbonate in a solvent such as toluene, benzene, THF or dioxane. The preferred reaction temperatures are between 20°C and 100°C. The products of these reactions correspond to substituted 6-benzyl-3-nitropicolinonitrile, 6-

benzyl-3-nitropyrazine-2-carbonitrile or 5-benzyl-2-nitronicotinonitrile derivatives for which the following transformation steps are reproduced from method B1 above.

Method B4:

Method B4, presented in diagram 9 below, gives access to pyrazolopyridine and pyrazolopyrazines bicycles featuring optionally functionalized aryl sulfonamide functions, with R_1=(C_1-C_6)alkyl and notably W=H, (C_1-C_6)alkyl, aryl or benzyl.

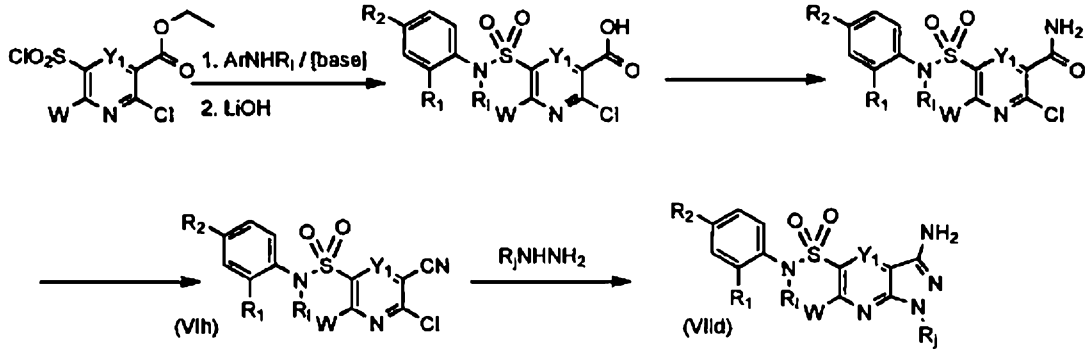


Diagram 9

The ethyl 2-chloro-5-(chlorosulfonyl)nicotinate derivatives required for this reaction sequence may be obtained according to the methods described by Levett P.C. *et al.*, Org. Proc. Res. Dev., **2002**, *6(6)*, 767-772; WO 01/98284 and WO 2008/010964.

The formation of sulfonamides is typically carried out by mixing the 2-chloro-5-(chlorosulfonyl)nicotinate of interest with a primary or secondary aniline, optionally functionalized, in an aprotic solvent such as dichloromethane, THF, acetone or acetonitrile in the presence of an organic base such as triethylamine (NEt_3), pyridine or DIPEA. The use of an inorganic base such as sodium or potassium carbonate may also be considered. The optimal reaction temperatures are between 0°C and 70°C.

The saponification reaction of the product thus obtained, notably by the use of lithium hydroxide in a THF/water mixture, gives access to the corresponding 2-chloro-5-(N-phenylsulfamoyl)nicotinic acids.

The corresponding acid chlorides are prepared by treatment with thionyl chloride in toluene under reflux or by any other dehydrochlorination method well known to the person skilled in the art. The reaction of these intermediates with aqueous ammonia makes it possible to form optionally functionalized 2-chloro-5-(N-

phenylsulfamoyl)nicotinamides which are then engaged in a dehydration reaction, notably by the use of $POCl_3$, at a temperature ranging between 75°C and 150°C. The alternative use of agents such as P_2O_5 or trifluoroacetic anhydride and pyridine may also be considered.

Lastly, these derivatives of general formula (VIh) are reacted in the presence of a hydrazine, functionalized or not, in a polar solvent such as ethanol at temperatures varying between 25°C and 150°C to form the corresponding derivatives of general formula (VIId).

Method B5:

Method B5, presented in diagram 10 below, gives access to pyrazolopyridine bicycles featuring optionally functionalized benzyl ether functions, notably with W=H, $(C_1\text{-}C_6)$alkyl, aryl or benzyl.

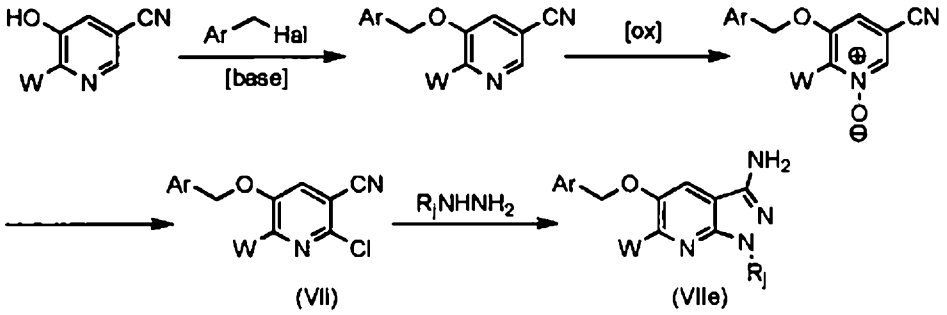


Diagram 10

The method described below is inspired by the work of J. Baldwin *et al.*, J. Heterocyclic. Chem., **1980**, *17(3)*, 445-448. The 5-hydroxynicotinonitrile derivatives, optionally functionalized in position 6, are alkylated, typically by the use of an optionally functionalized benzyl halide in the presence of a base. The preferred method requires the use of an aprotic polar solvent such as DMF and a base such as NaH. The optimal reaction temperatures are between 20°C and 100°C. Alternatively, the solvents which may be used include, for example, THF, DMSO, dioxane, acetonitrile, dichloromethane or acetone and bases such as ^{t}BuOK, DIPEA, pyridine, triethylamine, DBU or sodium, potassium or cesium carbonate.

Oxidation of the pyridine ring into pyridine-N-oxide is typically carried out by use of m-CPBA in dichloromethane at room temperature. Nevertheless, many

alternative methods are conceivable, notably those based on the use of sodium percarbonate in the presence of a rhenium catalyst, sodium perborate in the presence of acetic acid or the urea-hydrogen peroxide complex.

Treatment of these pyridine-N-oxide derivatives with phosphorus oxychloride leads to the formation of the corresponding 2-chloronicotinonitriles (VI).

Their reaction under heat with a hydrazine, functionalized or not, in a polar solvent such as isopropanol or ethanol leads to the formation of the pyrazolopyridine bicycles (VIIe) sought.

Method B6:

Method B6, presented in diagram 10a below, gives access to optionally functionalized pyrazolopyridine and pyrazolopyrazine bicycles featuring with reversed sulfonamide functions, notably with W=H, (C_1-C_6)alkyl, aryl or benzyl.

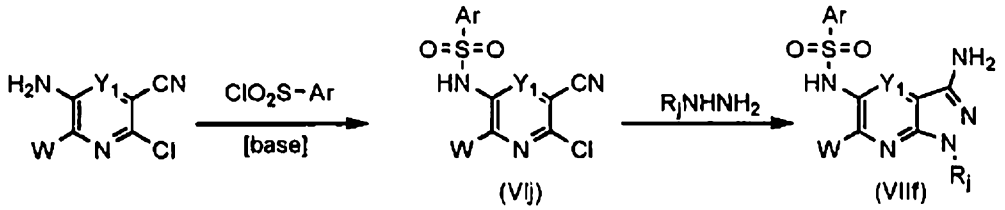


Diagram 10a

Le method described below consists in forming a sulfonamide function from an aromatic amine and an arylsulfonyl halide, or any other equivalent reagent, in the presence of a base, which can optionally be introduced as solvent or co-solvent. Alternatively, the arylsulfonyl halide or its equivalent can be generated *in situ*.

Their reaction under heat with a hydrazine, functionalized or not, in a polar solvent such as isopropanol or ethanol leads to the formation the desired pyrazolopyridine and pyrazolopyrazine bicycles (VIIf).

Method C:

Method C aims at the preparation of compounds of general formula (XI) as described in diagram 1.

Method C1:

Method C1, presented in diagram 11 below, is intended for the preparation of pyrazolopyridines and pyrazolopyrazines functionalized at position 6 with R_n=halogen,

mesylate, tosylate or triflate, X=O, S, NH, N-(C_1-C.)alkyl, and optionally CH_2 for (Xc) and (Xd), and R_j=H or N-protecting group.

This method can also be used to carry out the synthesis of molecules comprising a diatomic X group corresponding notably to an ArX group representing: -$ArCH_2NH$-, -$ArCH_2N(R_4)$-, -$ArCH_2O$-, -$ArCH_2S$-, -$ArCH_2CH_2$-, -ArCHCH-, or -ArCC-.

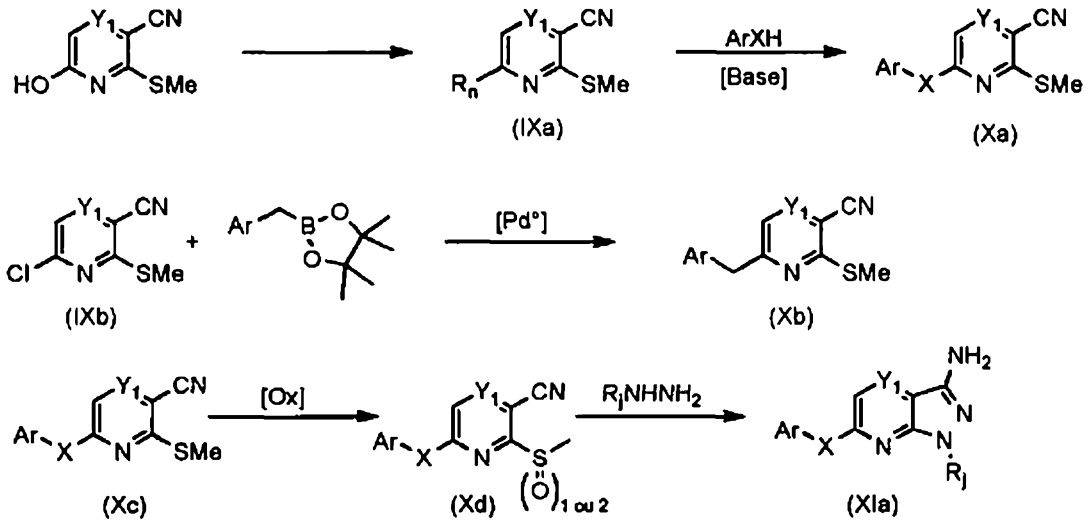


Diagram 11

The 6-hydroxy-2-(methylthio)nicotinonitriles or 5-hydroxy-3-(methylthio) pyrazine-2-carbonitriles are subjected to a dehydrochlorination reaction, typically in the presence of phosphorus oxychloride, with or without solvent, at temperatures varying between 70°C and 180°C. If a solvent is used, a high boiling-point non-polar solvent such as toluene or xylene will be preferred. Alternatively, it is possible to activate the 6-hydroxy-2-(methylthio)nicotinonitriles and 5-hydroxy-3-(methylthio)pyrazine-2-carbonitriles by their derivation into sulfonic esters via the formation of the corresponding tosylates, mesylates or triflates. If this option is preferred, the use of tosyl, mesyl or triflyl chlorides in a solvent such as toluene, dichloromethane, THF, acetonitrile, acetone or dioxane in the presence of an organic or inorganic base gives access to these derivatives.

The 6-chloro-2(methylthio)nicotinonitriles and 5-chloro-3-(methylthio)pyrazine-2-carbonitriles respectively obtained, or their sulfonic ester analogues if this option is preferred, are then reacted with a nucleophile such as a phenol, an aniline or a

thiophenol in the context of aromatic nucleophilic substitution. In this case, the reaction is carried out in a polar solvent such as DMSO, DMF, acetone, THF or acetonitrile, in the presence of a base such as potassium *tert*-butylate or NaH. If necessary, these reactions may be catalyzed by the action of copper and may also be carried out without solvent. Typically, the preferred protocol involves temperatures ranging between 20°C and 150°C.

Alternatively, the use of organic bases such as pyridine, diisopropylamine, triethylamine or DBU, or inorganic bases such as sodium or potassium carbonate is also possible.

Alternatively, the compounds of formula (IXb) may give rise to a catalytic coupling reaction such as a Suzuki reaction. In this case, these compounds are brought together with an optionally substituted 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane already described in preceding method B3, a palladium catalyst such as $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$, an organic base such as triethylamine or an alcoholate, or an inorganic base such as sodium, potassium or cesium carbonate in a solvent such as toluene, benzene, THF or dioxane. The preferred reaction temperatures are between 20°C and 100°C.

The derivatives obtained by one or another of these methods are then oxidized, typically by the use of m-CPBA or oxone to form the corresponding methyl sulfoxides or methyl sulfones. These compounds, sometimes obtained as mixtures, are used as-is in the aminopyrazole ring formation reaction by use of an optionally substituted hydrazine in a polar solvent such as ethanol at temperatures varying between 25°C and 150°C.

Alternatively, it is possible to modify the reaction sequence, notably by reversing the synthesis steps.

Method C2:

Method C2, presented in diagram 12 below, is intended for the preparation of pyrazolopyridines and pyrazolopyridazines functionalized at position 6 with X=O, S, NH, N-(C_1-C.)alkyl, or CH_2 and R_j=H or N-protecting group.

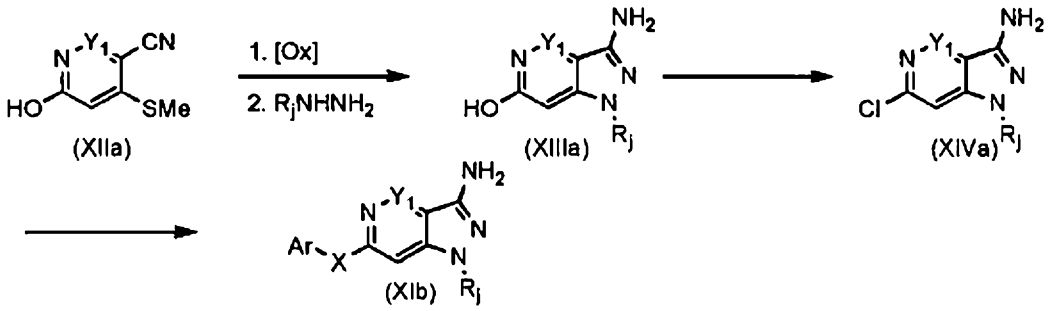


Diagram 12

The 6-hydroxy-4-(methylthio)nicotinonitrile or 6-hydroxy-4-(methylthio) pyridazin-3-carbonitrile derivatives are oxidized, typically by the use of m-CPBA or oxone to form the corresponding methyl sulfoxides or methyl sulfones. These compounds, sometimes obtained as mixtures, are used as-is in the aminopyrazole ring formation reaction by use of an optionally substituted hydrazine in a polar solvent such as ethanol at temperatures varying between 25°C and 150°C.

The pyrazolopyridines and pyrazolopyridazines thus obtained are subjected to a dehydrochlorination reaction, typically in the presence of phosphorus oxychloride, with or without solvent, at temperatures varying between 70°C and 180°C. If a solvent is used, a high boiling-point non-polar solvent such as toluene or xylene will be preferred. The optionally substituted 6-chloro-pyrazolo[4,3-c]pyridin-3-amine and 6-chloro-pyrazolo[4,3-c]pyridazin-3-amine respectively obtained are then reacted with a nucleophile such as a phenol, an aniline or a thiophenol in the context of aromatic nucleophilic substitution. In this case, the reaction is carried out in a polar solvent such as DMSO, DMF, acetone, THF or acetonitrile, in the presence of a base such as potassium *tert*-butylate or NaH. If necessary, these reactions may be catalyzed by the action of copper and may also be carried out without solvent. Typically, the preferred protocol involves temperatures ranging between 20°C and 150°C.

Alternatively, the use of organic bases such as pyridine, diisopropylamine, triethylamine or DBU, or inorganic bases such as sodium or potassium carbonate is also possible.

Alternatively, the compounds of formula (XIVa) may give rise to a catalytic coupling reaction such as a Suzuki reaction. In this case, these compounds are brought together with an optionally substituted 2-benzyl-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane described above in preceding method B3, a palladium catalyst such as $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$, an organic base such as triethylamine or an alcoholate, or an inorganic base such as sodium, potassium or cesium carbonate in a solvent such as toluene, benzene, THF or dioxane. The preferred reaction temperatures are between 20°C and 100°C.

Method C3:

Method C3, presented in diagram 12a below, is a variant of method C1 based on the regioselective functionalization of 2,6-dichloronicotinonitrile either by an anionic nucleophile such as a phenate or a thiophenate, or by an organometallic such as a benzylzinc chloride. In the latter case, the reaction is catalyzed for example with a palladium(II) complex. The transformation of the chloronicotinonitrile thus obtained in the corresponding pyrazolopyridine, in the case where Y_1 = CH, is carried out as previously described in method A1.

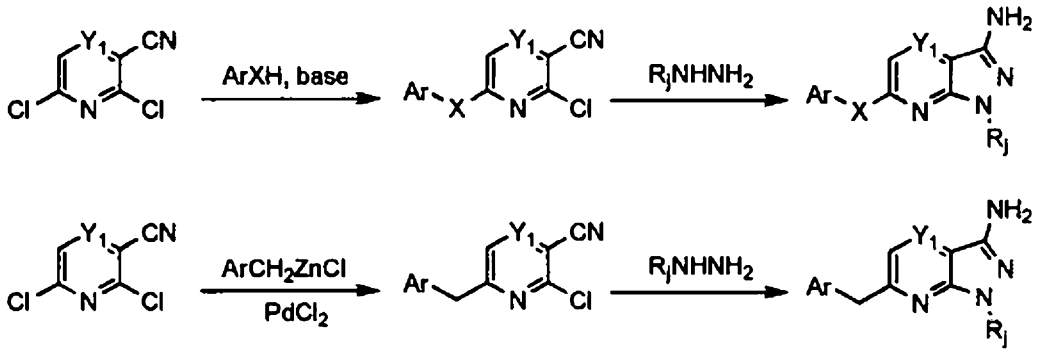


Diagram 12a

Method D:

These methods have as an object the synthesis of compounds of general formula (I) or (VII) by the use of various catalytic coupling methods.

Method D1:

Method D1, presented in diagram 13 below, makes use of the coupling reaction as described in J.A.C.S., **1984**, *106*, 158 between an organozinc compound prepared *in situ* and an aryl bromide catalyzed by palladium complexes.

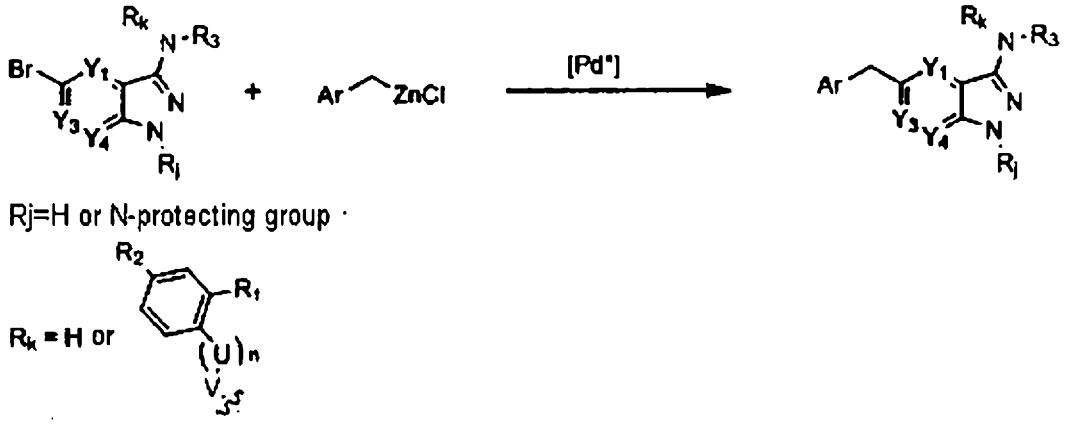


Diagram 13

The optionally substituted 3-amino-diazaindazoles or 3-amino-azaindazoles are brought together with a zinc benzyl chloride, optionally substituted, in an aprotic polar solvent such as THF or dioxane, in the presence of a catalytic quantity of a palladium complex such as $(dppf)_2PdCl_2 \cdot CH_2Cl_2$. The coupling reaction is carried out at temperatures ranging between 25°C and 100°C.

Method D2:

Method D2, presented in diagram 14 below, makes use of the coupling reaction as described by Gueiffier A. *et al.*, Tetrahedron, **2006**, *62*, 6042-6049, between a thiol, in particular a thiophenol or a benzylthiol, and an aryl iodide catalyzed by copper complexes.

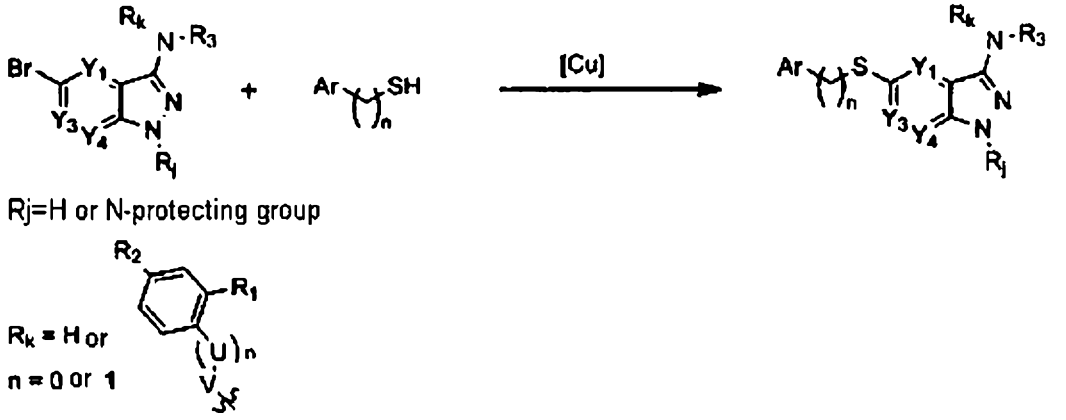


Diagram 14

This reaction is typically carried out in a high boiling-point polar solvent such as 2-propanol in the presence of a catalytic quantity of polyethylene glycol, a metal salt such as copper iodide (CuI) and an excess of an inorganic base such as potassium carbonate, calcium carbonate or sodium carbonate. The reaction temperatures typically vary between 50°C and 100°C.

Method D3:

Method D3, presented in diagram 15 below, makes use of the coupling reaction as described by Sonogashira, K. *et al.* in Tetrahedron Lett., 1975, *16*, 4467-4470 between an acetylene derivative and an aryl halide catalyzed by copper and palladium complexes.

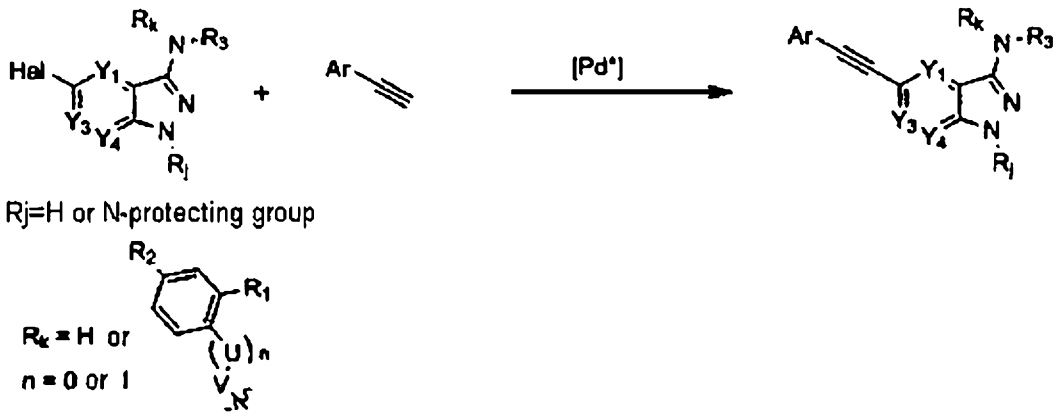


Diagram 15

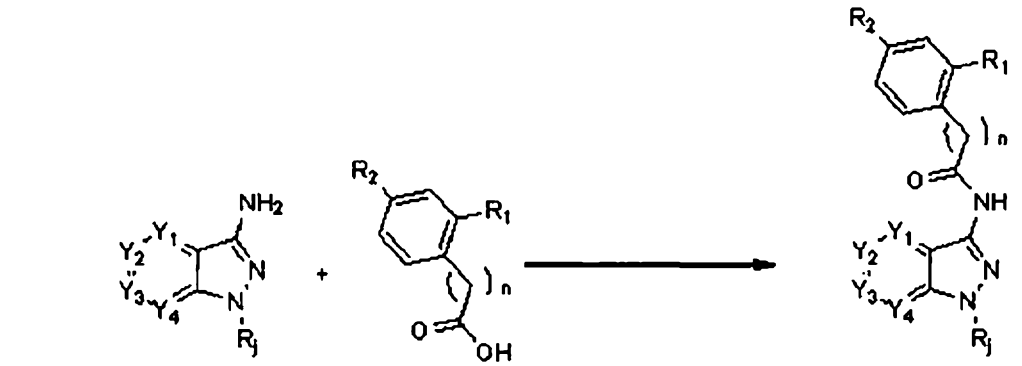
Such a reaction is typically carried out by the reaction under an inert atmosphere of a heteroaryl halide with a stoichiometric quantity of an optionally substituted ethynylbenzene in the presence of a catalytic quantity of a palladium complex, for example $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, a catalytic quantity of a copper salt, for example CuI, and an organic base such as triethylamine or DIPEA, or an inorganic base such as potassium or cesium carbonate. The protocol generally involves reaction temperatures ranging between 20°C and 45°C in solvents including DMF, THF, dioxane or diethyl ether.

Method E:

The protocols of method E aim at functionalizing the exocyclic amine of aminopyrazole rings by their reaction with an intermediate featuring an electrophile function, optionally generated *in situ*, such as acid chloride, an isocyanate, a isothiocyanate or an aldehyde.

Method E1:

Method E1, presented in diagram 16 below, aims at the transformation of the primary exocyclic amine function of aminopyrazole compounds into an amide function.



Rj=H or N-protecting group

Diagram 16

These compounds are synthesized via the corresponding 3-aminopyrazole by the addition of adequate acid chloride prepared beforehand by the use of oxalyl chloride and a catalytic quantity of DMF in a solvent such as tetrahydrofuran. These acid chlorides may be obtained by the use of alternative methods, such as those based on the use of thionyl chloride or phosphorus oxychloride, well known to the person skilled in the art. The condensation of acid chlorides on aminopyrazoles is typically carried out in an aprotic solvent such as tetrahydrofuran, toluene or dichloromethane in the presence of a base such as DIPEA, pyridine or triethylamine.

Alternatively, the use of a base as a solvent, in particular pyridine, is a possibility.

Alternatively, this type of reaction may be conducted in a biphasic system according to the well-known Schotten-Baumann method.

Alternatively, formation of the amide bond may be carried out from the corresponding 3-aminopyrazole and the acid of interest by the use of peptide coupling conditions using reagents such as HOBt (hydroxybenzotriazole), TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate), HATU (2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) or carbonyldiimidazole at a temperature ranging between -20°C and 100°C in an aprotic solvent such as tetrahydrofuran, dioxane, dichloromethane or any solvent with similar properties.

Method E2:

Derivatives characterized by the presence of a secondary amine in position 3 of the aminopyrazole ring are synthesized by a reducing amination reaction according to diagram 17 below.

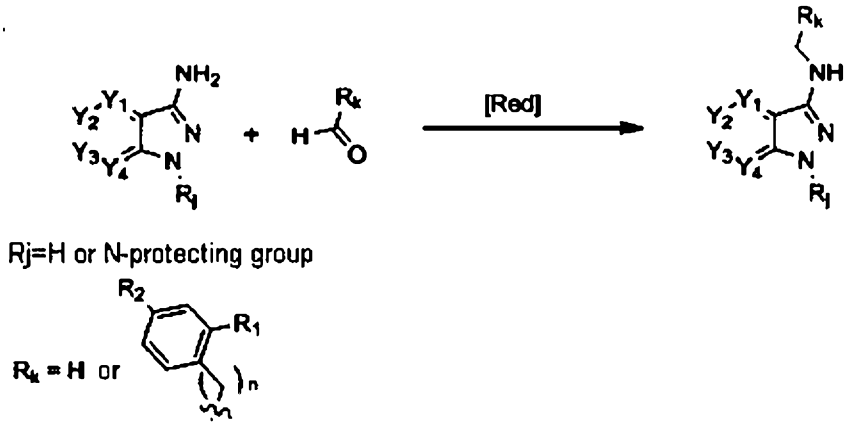


Diagram 17

Reducing amination reactions are typically carried out by mixing adequate stoichiometric quantities of aminopyrazole and aldehyde in a solvent such as DCE (dichloroethane), THF or acetonitrile, optionally in the presence of a quantity of water, TFA (trifluoroacetic acid) or acetic acid, by adding successive fractions of a reducing agent such as $NaBH_4$, $NaBH(OAc)_3$ or $NaBH_3CN$. These reactions are typically carried out at room temperature.

Method E3:

Derivatives carrying a 3-ureido or 3-thioureido function are obtained by the reaction, presented in diagram 18 below, of an aminopyrazole with an isocyanate or

isothiocyanate obtained according to methods well known to the person skilled in the art.

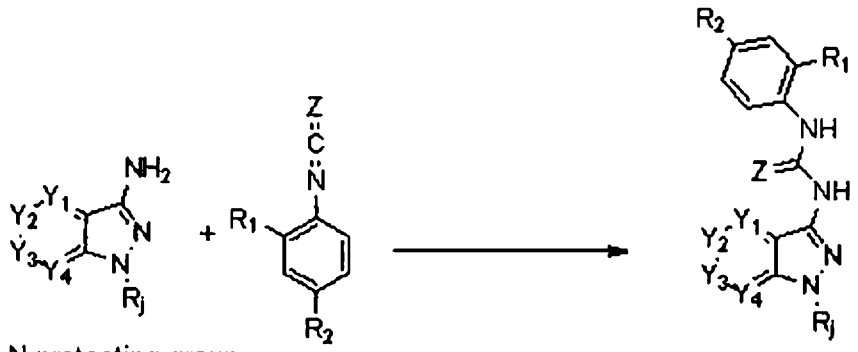


Diagram 18

In a typical reaction, the reaction mixture is prepared in a polar or non-polar aprotic solvent such as dichloromethane, acetone, DMF, DMA, acetonitrile, THF or dioxane carried at temperatures varying between 20°C and the boiling point of the chosen solvent. If necessary, recourse to a weakly nucleophilic organic or inorganic base may prove to be necessary. In this case, sodium hydride is a possible option.

Method F: post-synthetic deprotections and modifications

Method F1: deprotections

The trifluoroacetate protecting groups are removed by the action of an organic base such as triethylamine or pyridine in a polar solvent such as methanol, ethanol or THF at the reflux temperatures of the solvents used.

The *tert*-butyl or trityl protecting groups carried by the pyrazole rings are displaced by the action of a strong acid, typically TFA, in a non-polar solvent such as dichloromethane or DCE.

Method F2: alkyne reductions

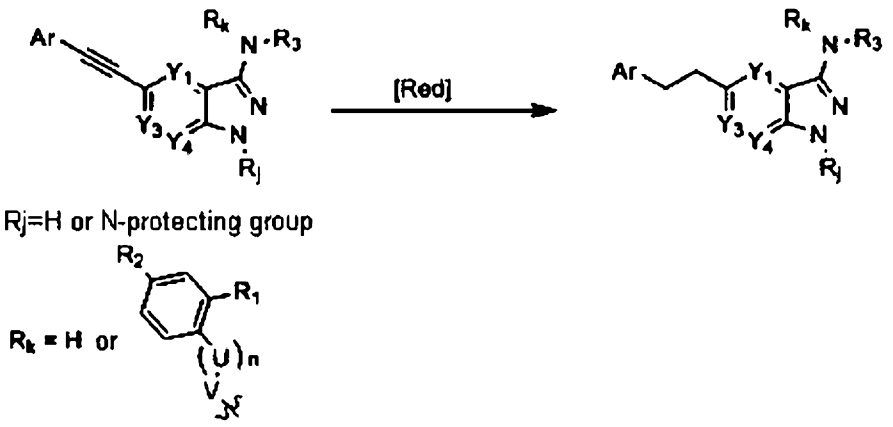


Diagram 19

Reactions for reducing diaryl alkynes into diaryl alkanes are typically carried out by catalytic hydrogenation, under hydrogen pressure, in the presence of catalysts such as PtO_2, Pt, Pd/C, Ni or Rh. Alternatively, the use of DIBAL-H (diisobutylaluminum hydride) in the presence or the absence of a catalyst such as Cp_2TiCl_2 is conceivable.

Method F3: oxidation of sulfides into sulfones and sulfoxides

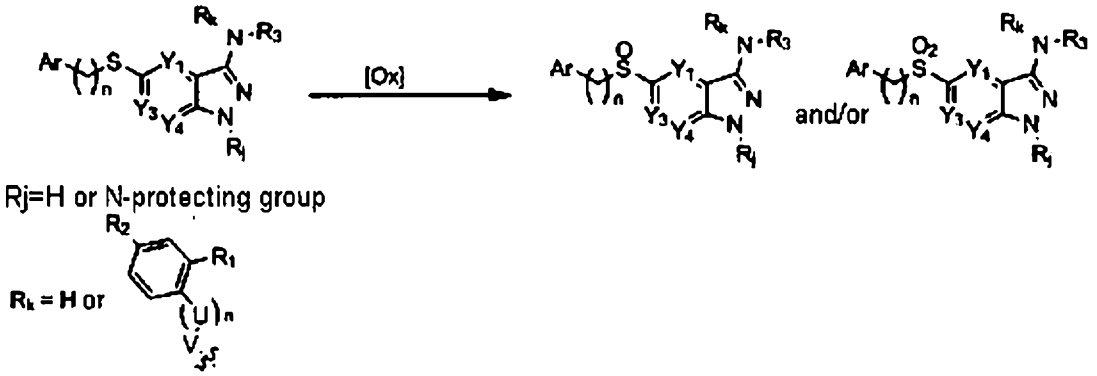


Diagram 20

Oxidation reactions of sulfides into sulfoxides are typically carried out via the use of oxone in a mixture of polar solvents such as THF/MeOH or DMF/water. The optimal reaction temperatures are typically between 25°C and 50°C.

Many alternative methods are available, and some give the possibility of producing semi-oxidized derivatives, namely sulfoxides. Such alternative methods include the use of m-CPBA, $KMnO_4/MnO_2$ in dichloromethane, H_2O_2 (30%) in a biphasic medium and the presence of a phase transfer catalyst or a catalyst in the form of a urea complex (UHP).

The combined use of H_2O_2 and metal complexes such as $Sc(OTf)_3$ promotes partial oxidation derivatives.

Other known methods include, for example, the use of $CAN/NaBrO_3$ (CAN=ceric ammonium nitrate).

The examples which follow illustrate the invention without limiting its scope in any way.

EXAMPLES

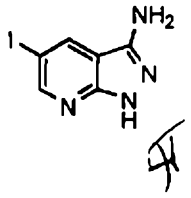
The following abbreviations are used:

DMSO	Dimethylsulfoxide
EI	Electron impact
ES	Electrospray
LCMS	Liquid chromatography – mass spectrometry
mg	milligram
mL	milliliter
NMR	Nuclear magnetic resonance

I. Synthesis of the compounds according to the invention

Examples of method A1

Example 1: 5-iodo-1H-pyrazolo[3,4-b]pyridine-3-amine



Example 1a: 2-hydroxy-5-iodonicotinonitrile

9 g (0.5 eq) of N-iodosuccinimide at room temperature is added to a solution of 10 g (83 mmol) of 2-hydroxynicotinonitrile in 150 ml of anhydrous dimethylformamide. The reaction mixture is stirred at 60°C. After 30 minutes of stirring, 9 g (0.5 eq) of N-iodosuccinimide is added and then the reaction mixture is stirred at 60°C for 5 hours. The solvent is evaporated and the precipitate formed is filtered, rinsed with water and with diethyl ether and then dried under vacuum to yield 18.5 g (90%) of 2-hydroxy-5-iodonicotinonitrile in the form of a beige powder.

LCMS (EI, m/z): (M+1) 246.93

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.79 (1H, s, OH), 8.36 (1H, d, CH_{arom}), 8.04 (1H, d, CH_{arom}).

Example 1b: 2-chloro-5-iodonicotinonitrile

30.7 ml (329 mmol) of phosphorus oxychloride at 0°C and 6 drops of sulfuric acid are added to 9 g (6.6 mmol) of 2-hydroxy-5-iodonicotinonitrile. The reaction mixture is heated at 110°C for 5 hours and then at room temperature overnight. The reaction mixture is poured in a beaker containing ice and a little water, and a precipitate is formed. The mixture is allowed to gradually return to room temperature and then is filtered and rinsed with water. The solid is dried to yield 6.8 g (70%) of 2-chloro-5-iodonicotinonitrile.

LCMS (EI, m/z): (M+1) 265.45

^{1}H NMR: δH ppm (400 MHz, DMSO): 9.61 (1H, d, CH_{arom}), 9.14 (1H, d, CH_{arom}).

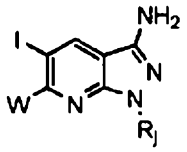
Example 1: 5-iodo-1H-pyrazolo[3,4-b]pyridine-3-amine

Hydrazine (3.86 ml, 79 mmol) is added at room temperature to 7 g (26.5 mmol) of a solution of 2-chloro-5-iodonicotinonitrile in 25 ml of propan-2-ol. The reaction mixture is heated at 85°C for 7 hours and then at room temperature overnight. The suspended solid is filtered, rinsed with isopropanol and then with ether and dried in an oven at 50°C to give 6 g (87%) of 5-iodo-1H-pyrazolo[3,4-b]pyridine-3-amine.

LCMS (EI, m/z): (M+1) 260.95

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.12 (1H, bs, NH), 8.51(1H, d, CH_{arom}), 8.45 (1H, d, CH_{arom}), 5.64 (2H, bs, NH_2).

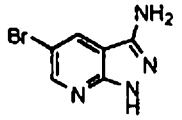
The following compounds were obtained according to the same method.



Ex.**	W	R_1	Compound name	Yield	Mass MH^+
1-2	H	t-butyl	1-*tert*-butyl-5-iodo-1H-pyrazolo[3,4-b]pyridin-3-amine	68 %	317.05
1-3	Me	H	5-iodo-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-amine	93 %	275.02

** ^{1}H NMR, DMSO-d_6, Ex. 1-2: 8.55 (1H, bs, CH_{arom}), 8.42 (1H, bs, CH_{arom}), 6.33 (1H, bs, CH_{arom}), 1.57 (9H, s, CH).; 1-3: 11.92 (1H, s, NH), 8.55 (1H, s, CH_{arom}), 5.59 (2H, bs, NH_2), 2.66 (3H, s, CH_3).

Example 2: 5-bromo-1H-pyrazolo[3,4-b]pyridine-3-amine



Example 2a: 2-methoxy-nicotinonitrile

4.98 g (217 mmol) of sodium is added to 80 ml of anhydrous methanol. The reaction medium is stirred at room temperature for 10 minutes and then 10 g (72.2 mmol) of 2-chloronicotinonitrile is added at 0°C. The reaction medium is stirred at 25°C for 16 hours. The reaction is hydrolyzed by slowly adding water at 0°C. After returning to room temperature, the precipitate obtained is filtered, rinsed with water and then dried at 50°C to yield 7.85 g (81%) of 2-methoxy-nicotinonitrile in the form of a yellow solid.

LCMS (EI, m/z): (M+1) 135.04

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.46-8.48 (1H, dd, CH_{arom}), 8.25-8.27 (1H, dd, CH_{arom}), 7.17-7.20 (1H, dd, CH_{arom}), 3.99 (3H, s, CH_3).

Example 2b: 5-bromo-2-methoxy-nicotinonitrile

12.23 g (149 mmol) of sodium acetate and then 7.66 ml (149 mmol) of bromine at 0°C are added to 10 g (74.6 mmol) of a solution of 2-methoxy-nicotinonitrile in 29 ml of acetic acid. The reaction mixture is heated at 70°C overnight. After returning to room temperature, the reaction medium is added to an ice bath and the precipitate obtained is filtered, rinsed with water and then dried at 50°C to yield 11.6 g (73%) of 5-bromo-2-methoxy-nicotinonitrile in the form of a white solid.

LCMS (EI, m/z): (M+1) 214.95

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.61 (1H, d, CH_{arom}), 8.60 (1H, d, CH_{arom}), 3.98 (3H, s, CH_3)

Example 2: 5-bromo-1H-pyrazolo[3,4-b]pyridine-3-amine

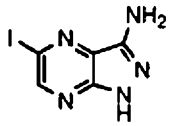
35 ml (23.47 mmol) of hydrazine is added at room temperature to 5 g (23.47 mmol) of 5-bromo-2-methoxynicotinonitrile. The reaction medium is carried at 100°C for 3 hours. After returning to room temperature, the precipitate obtained is filtered, rinsed with water and then dried at 50°C to yield 3.6 g (72%) of 5-bromo-1H-pyrazolo[3,4-b]pyridine-3-amine in the form of a yellow solid.

LCMS (EI, m/z): (M+1) 214.05

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.18 (1H, s, NH), 8.38 (1H, d, CH_{arom}), 8.37 (1H, d, CH_{arom}), 5.66 (2H, s, NH).

Examples of method A2

Example 3: 5-iodo-1H-pyrazolo[3,4-b]pyrazine-3-amine



Example 3a: methyl 3-amino-6-iodopyrazine-2-carboxylate

1.5 equivalents of N-iodosuccinimide are added at room temperature to 5 g (32.7 mmol) of a methyl 3-aminopyrazine-2-carboxylate solution in 25 ml of dimethylformamide. The reaction medium is heated at 65°C for 1 hour, added together with 0.5 equivalents of N-iodosuccinimide and maintained at 65°C for 24 hours. After returning to room temperature, the solvent is evaporated and then the product is extracted several times with dichloromethane. The organic phases are combined, washed with 10% sodium bisulfite solution, dried on magnesium sulfate and concentrated to yield 8 g (88%) of methyl 3-amino-6-iodopyrazine-2-carboxylate in the form of a yellow solid.

LCMS (EI, m/z): (M+1) 280

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.50 (1H, s, CH_{arom}), 7.50 (2H, bs, NH_2), 3.20 (3H, s, CH_3).

Example 3b: 3-amino-6-iodopyrazine-2-carboxamide

30 ml of ammonia in water is added under magnetic stirring to 15 g (53.8 mmol) of a solution of methyl 3-amino-6-iodopyrazine-2-carboxylate in 150 ml of methanol. The reaction medium is stirred at 25°C for 48 hours. After evaporation of the solvents, the precipitate obtained is filtered, rinsed with water and then dried at 50°C to yield 12.50 g of 3-amino-6-iodopyrazine-2-carboxamide (88%) in the form of a beige solid.

LCMS (EI, m/z): (M+1) 265.02

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.35 (1H, s, CH_{arom}), 7.85 (1H, bs, NH), 7.60 (3H, bs, NH), 3.25 (3H, s, CH_3)

Example 3c: N'-(3-cyano-5-iodopyrazine-2-yl)-N,N-dimethylformimidamide

13.59 ml (146 mmol) of phosphorus oxychloride is added drop by drop at 0°C to 11 g (41.7 mmol) of a solution of 3-amino-6-iodopyrazine-2-carboxamide in 80 ml of dimethylformamide. The reaction mixture is stirred at room temperature overnight and then poured in a beaker containing ice and a little water. The pH is adjusted to 8 with 1 N soda solution; a precipitate is formed. The mixture is allowed to gradually return to room temperature and then the solid formed is filtered, rinsed with water and dried at 50°C to yield 10.50 g of N'-(3-cyano-5-iodopyrazine-2-yl)-N,N-dimethyl formimidamide (84%) in the form of a beige solid.

LCMS (EI, m/z): (M+1) 302.07

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.69 (1H, s, CH_{arom}), 8.67 (1H, s, CH_{ethyl}), 3.20 (3H, s, CH_3), 3.11 (3H, s, CH_3).

Example 3d: 3-amino-6-iodopyrazine-2-carbonitrile

77 ml (77 mmol) of 1 M hydrochloric acid solution is added to 7.7 g (25.6 mmol) of N'-(3-cyano-5-iodopyrazin-2-yl)-N,N-dimethylformimidamide. The reaction medium is heated at 50°C for 4 hours and then stirred at room temperature overnight. The precipitate formed is filtered, rinsed with water and dried at 50°C to yield 6 g (95%) of 3-amino-6-iodopyrazine-2-carbonitrile in the form of a beige solid.

LCMS (EI, m/z): (M+1) 247.0

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.49 (1H, s, CH_{arom}), 7.53 (2H, bs, NH_2).

Example 3e: 3-chloro-6-iodopyrazine-2-carbonitrile

64.3 ml of hydrochloric acid is added at -5°C to 7.7 g (31.3 mmol) of 3-amino-6-iodopyrazine-2-carbonitrile. At this temperature, a sodium nitrite solution (4.32 g,

62.6 mmol) dissolved in 9 ml of water is added to the reaction mixture and is stirred for 4 hours at -50°C and then at room temperature overnight. Another equivalent of sodium nitrite is added to the reaction mixture and the precipitate formed is filtered, rinsed with water and dried at 50°C to yield 3.65 g (44%) of 3-chloro-6-iodopyrazine-2-carbonitrile in the form of a beige solid.

LCMS (EI, m/z): (M+1) 266.49

^{1}H NMR: δH ppm (400 MHz, DMSO): 9.13 (1H, s, CH_{arom})

Example 3: 5-iodo-1H-pyrazolo[3,4-b]pyrazine-3-amine

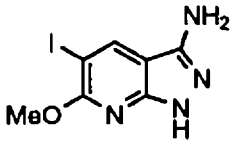
0.74 ml (9.8 mmol) of hydrazine is added to 2.6 g (9.80 mmol) of a solution of 3-chloro-6-iodopyrazine-2-carbonitrile in 15 ml of butanol. The reaction mixture is heated at 110°C for 5 hours and then left at room temperature overnight. The suspended solid is filtered, rinsed with butanol and then dried in an oven at 50°C to yield 2.2 g (86%) of 5-iodo-1H-pyrazolo[3,4-b]pyrazine-3-amine in the form of a brown solid.

LCMS (EI, m/z): (M+1) 262.02

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.59 (1H, bs, NH), 8.60 (1H, d, CH_{arom}), 5.83 (2H, bs, NH_2).

Examples of method A3

Example 4: 5-iodo-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-amine



Example 4a: ethyl 5-cyano-2-hydroxy-6-(methylthio)nicotinate

Ethyl 5-cyano-2-hydroxy-6-(methylthio)nicotinate is obtained by following the procedure of Ya. Yu. Yakunin *et al.*, Russian Chemical Bulletin, **1999**, *48(1)*, 195-6 with a total yield of 34%.

LCMS (EI, m/z): (M-1) 237.22

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.72 (1H, bs, OH), 8.40 (1H, s, CH_{arom}), 4.29 (2H, q, CH_2), 2.64 (3H, s, CH_3), 1.30 (3H, t, CH_3).

Example 4b: 5-cyano-2-hydroxy-6-(methylthio)nicotinic acid

4.16 g (2 eq) of lithium hydroxide monohydrate is added at room temperature to a solution of 11.8 g (49.5 mmol) of ethyl 5-cyano-2-hydroxy-6-(methylthio)nicotinate in 100 ml of ethanol and 100 ml of water. The reaction mixture is stirred at 60°C for 2 hours. The ethanol is evaporated and 1 N aqueous soda is added. The aqueous phase is washed with ethyl acetate and then re-acidified by adding 1 N aqueous hydrogen chloride (pH=1). The precipitate formed is filtered, rinsed with water and with diethyl ether and then dried under vacuum to yield 9.9 g (95%) of 5-cyano-2-hydroxy-6-(methylthio)nicotinic acid in the form of a brown powder.

LCMS (EI, m/z): (M-1) 209.09

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.32 (1H, s, CH_{arom}), 2.61 (3H, s, CH_3).

Example 4c: 6-hydroxy-2-(methylthio)nicotinonitrile

A solution of 6 g (28.5 mmol) of 5-cyano-2-hydroxy-6-(methylthio)nicotinic acid in 35 ml of diphenyl ether is stirred at 250°C for 4 hours. After returning to room temperature, 100 ml of cyclohexane is added and the reaction medium is triturated for 30 minutes. The solid formed is filtered, rinsed thoroughly with cyclohexane and then dried under vacuum to yield 2.87 g (60%) of 6-hydroxy-2-(methylthio)nicotinonitrile in the form of a brown powder.

LCMS (EI, m/z): (M+1) 167.12

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.16 (1H, bs, OH), 7.92 (1H, d, CH_{arom}), 6.46 (1H, d, CH_{arom}), 2.59 (3H, s, CH_3).

Example 4d: 6-hydroxy-5-iodo-2-(methylthio)nicotinonitrile

6 g (1.6 eq) of silver sulfate and 4.58 g (1.5 eq) of iodine are added successively to a solution of 2 g (12 mmol) of 6-hydroxy-2-(methylthio)nicotinonitrile in 200 ml of ethanol. The reaction medium is stirred at room temperature for 2 hours. The solid is filtered and the residue rinsed thoroughly with methanol. The filtrate is evaporated and then taken up in ethyl acetate. The organic phase is washed with water three times, dried on magnesium sulfate and evaporated to yield 3.18 g (90%) of 6-hydroxy-5-iodo-2-(methylthio)nicotinonitrile in the form of a yellow powder.

LCMS (EI, m/z): (M+1) 292.93

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.96 (1H, bs, OH), 8.38 (1H, s, CH_{arom}), 2.62 (3H, s, CH_3).

Example 4e: 5-iodo-6-methoxy-2-(methylthio)nicotinonitrile

905 µl (2 eq) of methyl iodide and 2.1 g (1.05 eq) of silver carbonate are added successively to a solution of 2.12 g (7.26 mmol) of 6-hydroxy-5-iodo-2-(methylthio)nicotinonitrile in 20 ml of 1,4-dioxane. The reaction medium is stirred at 60°C for 5 hours. The solid is filtered and the residue rinsed thoroughly with methanol. The filtrate is evaporated and the residue purified by silica column chromatography (4:6 dichloromethane/cyclohexane as eluent) to yield 1.52 g (68%) of 5-iodo-6-methoxy-2-(methylthio)nicotinonitrile in the form of a white powder.

LCMS (EI, m/z): (M+1) 306.95

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.50 (1H, s, CH_{arom}), 4.04 (3H, s, CH_3), 2.63 (3H, s, CH_3).

Example 4f: 5-iodo-6-methoxy-2-(methylsulfinyl)nicotinonitrile

1.42 g (1.1 eq) of 70% 3-chloroperbenzoic acid is added to a solution of 1.6 g (5.23 mmol) of 5-iodo-6-methoxy-2-(methylthio)nicotinonitrile in 20 ml of dichloromethane. The reaction medium is stirred at room temperature for 1 hour. Ethyl acetate is added and the organic phase is washed with saturated sodium bicarbonate solution, dried on magnesium sulfate, filtered and evaporated to yield 1.63 g (97%) of 5-iodo-6-methoxy-2-(methylsulfinyl)nicotinonitrile in the form of a white powder which may also contain 5-iodo-6-methoxy-2-(methylsulfonyl)nicotinonitrile in small proportions (<20%). If necessary, the mixture is used as-is in the following steps.

LCMS (EI, m/z): (M+1) 322.95

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.86 (1H, s, CH_{arom}), 4.05 (3H, s, CH_3), 2.95 (3H, s, CH_3).

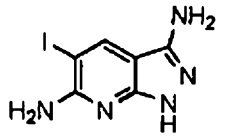
Example 4: 5-iodo-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-amine

294 µl (1.2 eq) of hydrazine monohydrate is added to a solution of 1.63 g (5.05 mmol) of 5-iodo-6-methoxy-2-(methylsulfinyl)nicotinonitrile in 30 ml of 2-propanol. The reaction medium is stirred at 80°C for 9 hours. After returning to room temperature, the solid formed is filtered and rinsed with 2-propanol to yield 1.14 g (78%) of 5-iodo-6-methoxy-1*H*-pyrazolo[3,4-b]pyridin-3-amine in the form of a white powder.

LCMS (EI, m/z): (M+1) 291.00

^{1}H NMR: δH ppm (400 MHz, DMSO): 11.87 (1H, s, NH), 8.49 (1H, s, CH_{arom}), 5.49 (2H, bs, NH_2), 3.90 (3H, s, CH_3).

Example 5: 5-iodo-1H-pyrazolo[3,4-b]pyridine-3,6-diamine



Example 5a: 4-methylmorpholinium (2,4)-ethyl-5-amino-2,4-dicyano-5-mercaptopenta-2,4-dienoate

4-methylmorpholinium (2,4)-ethyl-5-amino-2,4-dicyano-5-mercaptopenta-2,4-dienoate is prepared according to the procedure described by V.D. Dyachenko *et al.*, Chemistry of Heterocyclic Compounds, **2005**, *41(4)*, 503-10 with a yield of 50%.

^{1}H NMR: δH ppm (400 MHz, DMSO): 9.60 (1H, bs, NH), 8.66 (1H, s, CH), 8.33 (1H, bs, NH), 7.43 (1H, bs, NH), 4.08 (2H, q, CH_2), 3.82-4.02 (2H, m, CH_2), 3.55-3.78 (2H, m, CH_2), 3.24-3.42 (2H, m, CH_2), 3.98-3.17 (2H, m, CH_2), 2.81 (3H, s, CH_3), 1.19 (3H, t, CH_3).

Example 5b: ethyl 2-amino-5-cyano-6-(methylthio)nicotinate

2.73 ml (1 eq) of methyl iodide is added to a solution of 14.2 g (43.8 mmol) of 4-methylmorpholinium (2,4)-ethyl-5-amino-2,4-dicyano-5-mercaptopenta-2,4-dienoate in 78 ml of *N,N*-dimethylformamide. The reaction mixture is stirred at room temperature for 1 hour and then at 75°C for 20 hours. After returning to room temperature, water is added and the solid formed is filtered and dried under vacuum to yield 10.31 g (100%) of ethyl 2-amino-5-cyano-6-(methylthio)nicotinate in the form of a beige powder.

LCMS (EI, m/z): (M+1) 238.20

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.25 (1H, s, CH_{arom}), 8.19 (1H, bs, NH), 7.99 (1H, bs, NH), 4.27 (2H, q, CH_2), 2.58 (3H, s, CH_3), 1.31 (3H, t, CH_3).

Example 5c: 2-amino-5-cyano-6-(methylthio)nicotinic acid

3.08 g (2 eq) of lithium hydroxide monohydrate is added at room temperature to a solution of 8.7 g (36.7 mmol) of ethyl 2-amino-5-cyano-6-(methylthio)nicotinate in 87 ml of ethanol and 87 ml of water. The reaction mixture is stirred at 60°C for 2 hours. The ethanol is evaporated and 1 N aqueous soda is added. The aqueous phase is washed with ethyl acetate and then re-acidified by adding 1 N aqueous hydrogen chloride (pH=1). The precipitate formed is filtered, rinsed with water and with diethyl ether and then dried under vacuum to yield 7.67 g (quantitative) of 2-amino-5-cyano-6-(methylthio)nicotinic acid in the form of a brown powder.

LCMS (EI, m/z): (M+1) 210.16

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.28 (1H, bs, CO_2H), 8.21 (1H, s, CH_{arom}), 8.13 (2H, bs, NH_2), 2.57 (3H, s, CH_3).

Example 5d: 6-amino-2-(methylthio)nicotinonitrile

A solution of 3 g (14.3 mmol) of 2-amino-5-cyano-6-(methylthio)nicotinic acid in 30 ml of diphenyl ether is stirred at 255°C for 60 hours. After returning to room temperature, 60 ml of cyclohexane is added and the reaction medium is triturated for 30 minutes. The solid formed is filtered and then rinsed thoroughly with cyclohexane. The solid is redissolved in ethyl acetate and then the organic phase is washed with water, dried on magnesium sulfate, filtered and then evaporated to yield 1.32 g (55%) of 6-amino-2-(methylthio)nicotinonitrile in the form of a brown powder.

LCMS (EI, m/z): (M+1) 166.13

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.58 (1H, d, CH_{arom}), 7.12 (2H, bs, NH_2), 6.20 (1H, d, CH_{arom}), 2.51 (3H, s, CH_3).

Example 5e: 6-amino-5-iodo-2-(methylthio)nicotinonitrile

3.75 g (1.5 eq) of silver sulfate and 2.85 g (1.4 eq) of iodine are added successively to a solution of 1.32 g (8.02 mmol) of 6-amino-2-(methylthio)nicotinonitrile in 65 ml of ethanol. The reaction medium is stirred at room temperature for 3 hours. The solid is filtered and the residue rinsed thoroughly with methanol. The filtrate is evaporated and redissolved in ethyl acetate. The organic phase is washed with water three times, dried on magnesium sulfate and evaporated to yield 1.89 g (81%) of 6-amino-5-iodo-2-(methylthio)nicotinonitrile in the form of a brown powder.

LCMS (EI, m/z): (M+1) 291.99

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.13 (1H, s, CH_{arom}), 7.19 (1H, broad flat singlet, NH_2), 2.51 (3H, s, CH_3).

Example 5f: 6-amino-5-iodo-2-(methylsulfinyl)nicotinonitrile

1.77 g (1.1 eq) of 70% 3-chloroperbenzoic acid is added to a solution of 1.89 g (6.51 mmol) of 6-amino-5-iodo-2-(methylthio)nicotinonitrile in 60 ml of dichloromethane. The reaction medium is stirred at room temperature for 1 hour. Ethyl acetate is added and the organic phase is washed with saturated sodium bicarbonate solution, dried on magnesium sulfate, filtered and evaporated to yield 1.5 g (75%) of 6-amino-5-iodo-2-(methylsulfinyl)nicotinonitrile in the form of a white powder which

may also contain 6-amino-5-iodo-2-(methylsulfonyl)nicotinonitrile in small proportions (<20%). If necessary, the mixture is used as-is in the following steps.

LCMS (EI, m/z): (M+1) 307.98

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.45 (1H, s, CH_{arom}), 7.70 (2H, broad flat singlet, NH_2), 2.84 (3H, s, CH_3).

Example 5: 5-iodo-1H-pyrazolo[3,4-b]pyridine-3,6-diamine

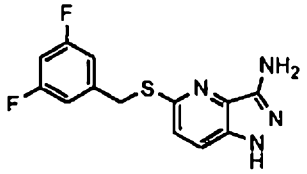
275 µl (2 eq) of hydrazine monohydrate is added to a solution of 872 mg (2.84 mmol) of 6-amino-5-iodo-2-(methylsulfinyl)nicotinonitrile in 11 ml of 2-propanol. The reaction medium is stirred at 80°C for 3 hours. Water is added and the product is extracted with ethyl acetate. The organic phase is dried on magnesium sulfate, filtered and evaporated. The residue is triturated in a minimum of diisopropyl ether. The solid is filtered to yield 523 mg (67%) of 5-iodo-1H-pyrazolo[3,4-b]pyridin-3,6-diamine in the form of a brown powder.

LCMS (EI, m/z): (M+1) 276.00

^{1}H NMR: δH ppm (400 MHz, DMSO): 11.23 (1H, s, NH), 8.26 (1H, s, CH_{arom}), 6.11 (2H, bs, NH_2), 5.25 (2H, bs, NH_2).

Examples of method B1

Example 6: 5-(3,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine



Example 6a: 6-chloro-3-nitropicolinonitrile

2,6-Dichloro-3-nitropyridine (5.18 mmol, 1 g) is mixed with 5 ml of N-methyl-2-pyrrolidinone in a microwave reactor. The reaction mixture is heated at 180°C for 15 minutes (6 bars). The crude reaction product is dissolved in ethyl acetate, filtered and washed several times using an aqueous phase. The organic phase is collected, dried on magnesium sulfate and dry concentrated. The crude product thus obtained is purified by silica gel chromatography (heptane/AcOEt) to yield, after concentration, 0.62g (65%) of a brown oil.

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.81 (1H, d, CH_{arom}), 8.18 (1H, d, CH_{arom}).

Example 6b: 3-nitro-6-thioxo-1,6-dihydropyridine-2-carbonitrile

One equivalent of NaSH:H_2O is added to a solution of 6-chloro-3-nitropicolinonitrile (5.45 mmol, 1 g) in 20 ml of EtOH. The color turns orange. The reaction medium is stirred at room temperature for 30 minutes. The crude reaction product is then concentrated, redissolved in ethyl acetate and extracted several times using an acidic aqueous phase (1 N HCl) and then a neutral phase. The organic phase is concentrated and the crude reaction product recrystallized in acetone to yield 0.64 g (79%) of yellow crystals.

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.71 (1H, d, CH_{arom}), 8.27 (1H, d, CH_{arom}).

Example 6c: 6-(3,5-difluorobenzylthio)-3-nitropicolinonitrile

A mixture of 3-nitro-6-thioxo-1,6-dihydropyridin-2-carbonitrile (4.42 mmol, 1.34g), 3,5-diflurobenzylbenzylbromide (8.83 mmol, 1.828 g), and K_2CO_3 (11.04 mmol, 1.525 g) in 5 ml of acetone is heated at 70°C for 10 hours and then evaporated under reduced pressure. The residue is purified by silica gel chromatography (AcOEt/heptane) to yield 1.33 g (98%) of the expected product.

LCMS (ES-): m/z 306 (M-H+).

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.53 (1H, d, CH_{arom}), 7.91 (1H, d, CH_{arom}), 7.21 (2H, m), 7.17 (1H, m), 4.55 (2H, CH_2).

Example 6d: 3-amino-6-(3,5-difluorobenzylthio)picolinamide

A mixture of 6-(3,5-difluorobenzylthio)-3-nitropicolinonitrile (0.05 g, 0.163 mmol) and PtO_2 (0.739 mg, 3.25 µmol) in 10 ml of MeOH is placed under stirring at atmospheric pressure of hydrogen for 2 hours. The catalyst is filtered, the solution is concentrated and the residue thus obtained is purified by silica gel chromatography (AcOEt/heptane) to yield, after concentration, 0.04 g (83%) of white crystals.

LCMS (ES+) m/z: 296 (MH+).

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.84 (1H, broad s, NH), 7.40 (1H, broad s, NH), 7.14 (1H, d, CH_{arom}), 7.08 (4H, m, CH_{arom}), 6.80 (2H, broad s, NH_2), 4.43 (2H, s, CH_2).

Example 6e: 3-amino-6-(3,5-difluorobenzylthio)picolinonitrile

A mixture of 3-amino-6-(3,5-difluorobenzylthio)picolinoamide (2.37 mmol, 0.7 g) and P_2Cl_5 (9.48 mmol, 1.346 g), 20 ml of toluene and 1 ml of ionic solvent (1-butyl-3-methylimidazolium tetrafluoroborate) are placed in a microwave reactor and then heated

at 140°C for 30 minutes. The crude reaction product is then concentrated under reduced pressure and the orange crystals thus obtained are redissolved in ethyl acetate and washed using saturated aqueous $NaHCO_3$ solution. The organic phase is dried on magnesium sulfate and then concentrated to yield 0.7 g of a brown oil. This crude reaction product is purified by silica gel chromatography (AcOEt/heptane + 0.1% of NEt_3) to yield, after concentration, 0.15 g (23%) of orange crystals.

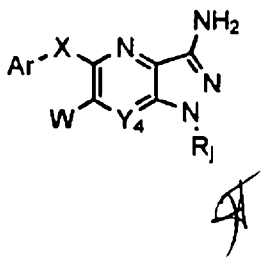
^1H NMR: δH ppm (400 MHz, DMSO): 7.73 (1H, d, CH_{arom}), 7.25 (2H, m, CH_{arom}), 7.18 (1H, m), 6.85 (1H, d), 5.43 (2H, CH_2).

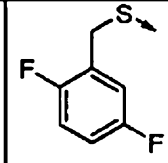
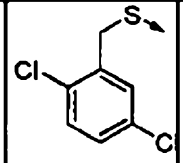
Example 6: 5-(3,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine

A solution cooled to 0°C of $NaNO_2$ in 3 ml of water is added drop by drop to a solution at 0°C of 3-amino-6-(3,5-difluorobenzylthio)picolinonitrile (1.587 mmol, 0.44g) in 15 ml of 6 N HCl solution. After 15 minutes, a solution cooled to 0°C of $SnCl_2 \cdot 2H_2O$ diluted in 4 ml of 12 N HCl is added drop by drop. The reaction medium is then stirred at 25°C for 1 hour. The solution is extracted with ethyl acetate and then washed using saturated $NaHCO_3$ solution and then saturated NaCl solution. The organic phase is collected, dried on magnesium sulfate and then concentrated under reduced pressure. The residue is purified by silica gel chromatography (AcOEt/heptane) to yield, after concentration of the organic phases, 0.07 g (15%) of black crystals.

^1H NMR: δH ppm (400 MHz, DMSO): 11.64 (1H, s, NH), 7.63 (1H, d, CH_{arom}), 7.21 (2H, m, CH_{arom}), 7.13 (1H, d, CH_{arom}), 7.04 (1H, m, CH_{arom}), 5.38 (2H, s, NH_2), 4.51 (2H, s, CH_2).

The following compounds are obtained by a similar method:

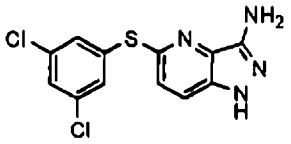


Ex.**	ArX	W	Y_4	R_j	Compound names	Yield	Mass MH+
6-2		H	CH	H	5-(2,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine	5% 4 steps	293.0
6-3		H	CH	H	5-(2,5-dichlorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine	3% 4 steps	324.9

** ^{1}H NMR: δH ppm (400 MHz, DMSO): **6-2**: 11.65 (1H, s, NH), 7.64 (1H, dd, CHarom, J=8.8Hz), 7.42-7.51 (1H, m, CHarom), 7.20-7.25 (1H, m, CHarom), 7.14 (1H, dd, CHarom, J=8.8Hz), 7.01-7.11 (1H, m, CHarom), 5.37-5.41 (2H, m, NH2), 4.49 (2H, s). **6-3**: 11.65 (1H, s, NH), 7.83 (1H, m, CHarom), 7.61 (1H, dd, CHarom, J=8.8Hz), 7.50 (1H, m, CHarom), 7.28-7.32 (1H, m, CHarom), 7.10 (1H, dd, CHarom, J=8.8Hz), 7.01-7.11 (1H, m, CHarom), 5.42 (2H, s, NH2), 4.47 (2H, s).

Examples of method B2

Example 7: 5-(3,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine



Example 7a: 6-(3,5-dichlorophenylthio)-3-nitropicolinonitrile

A mixture of 6-chloro-3-nitropicolinonitrile (3.70g, 0.02 mol), 3,5-dichlorobenzenethiol (3.60 g, 0.02 mol) and K_2CO_3 (5.6 g, 0.04 mol) in 100 ml of acetonitrile is carried at 70°C for 16 hours. The crude reaction product is diluted in an ethyl acetate fraction and washed using an aqueous phase. The organic phase is dried with sodium sulfate and the residue is purified by silica gel chromatography (AcOEt/petroleum ether) to yield 5.4 g (80%) of a yellow solid.

Example 7b: 3-amino-6-(3,5-dichlorophenylthio)picolinonitrile

10 ml of concentrated HCl is added to a solution of 6-(3,5-dichlorophenylthio)-3-nitropicolinonitrile (3.4 g, 0.01 mol) in 50 ml of methanol under stirring. The reaction medium is refluxed, added together with 1.68 g (0.03 mol) of iron and stirred for 10

minutes. After returning to room temperature, the reaction mixture is added together with 100 ml of ethyl acetate and 50 ml of water. The pH is adjusted to 10 using 30% soda solution and the organic phase is extracted and then dried on anhydrous sodium sulfate before being concentrated. The residue is purified by silica gel chromatography (ethyl acetate/petroleum ether) to yield, after concentration of the fractions, 2.82 g (91%) of a yellow solid.

LCMS (m/e): 296(M+H+). %.

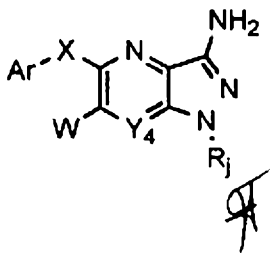
Example 7: 5-(3,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine

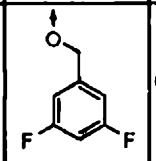
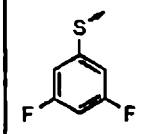
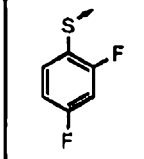
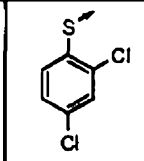
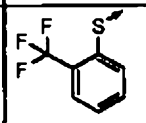
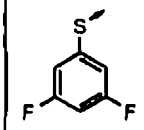
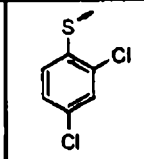
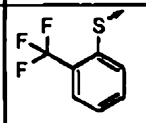
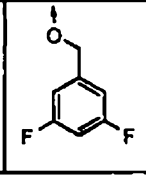
A solution of 350 mg of $NaNO_2$ (5.07 mmol) in water (2 ml) is added to a stirring solution of 1.5 g of 3-amino-6-(3,5-dichlorophenylthio)picolinonitrile (5.07 mmol) in 100 ml of 50% sulfuric acid at 0°C. The mixture is stirred for 20 minutes at 0-5°C. A solution of 2.9 g of $SnCl_2 \cdot 2H_2O$ (12.7 mmol, 2.5 eq) in hydrochloric acid (12 N solution, 10 ml) is then added and the solution is stirred for 1 hour at room temperature. The solid formed is filtered and then washed twice with 20 ml of water. The solid is suspended in 100 ml and the pH is adjusted to 10 by adding 30% soda solution. The organic phase is separated and then dried on anhydrous sodium sulfate before being concentrated under vacuum. A light yellow solid is obtained after recrystallization in ethyl acetate (470 mg, 34%).

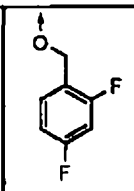
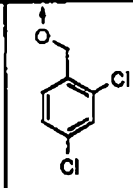
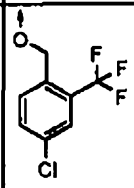
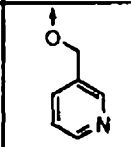
LCMS m/z 311 ($M+H^+$).

^1H NMR: δH ppm (400 MHz, DMSO): 11.91 (1H, bs, NH), 7.79 (1H, d, CH_{arom}), 7.55 (1H, s, CH_{arom}), 7.36 (2H, s, CH_{arom}), 7.33 (1H, m, CH_{arom}), 5.42 (2H, s, NH_2).

The following compounds are obtained by a similar method:



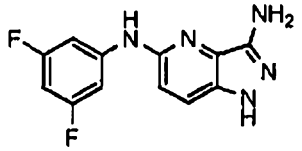
Ex.**	ArX	Y_4	W	R_j	Compound names	Yield	Mass MH^+
7-1		CH	H	H	5-(3,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-amine	28%	277
7-2		CH	H	H	5-(3,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine	33% 3 steps	278,9
7-3		CH	H	H	5-(2,4-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine	24% 3 steps	279,0
7-4		CH	H	H	5-(2,4-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine	24% 3 steps	311,0
7-5		CH	H	H	5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[4,3-b]pyridin-3-amine	17% 3 steps	311,0
7-6		N	H	H	5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-amine	6% 7 steps	279,9
7-7		N	H	H	5-(2,4-dichlorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-amine	4% 7 steps	311,9
7-8		N	H	H	5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-amine	6% 7 steps	311.9
7-9		CH	H	H	5-(3,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-amine	6% 3 steps	277.0

7-10		CH	H	H	5-(2,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-amine	3% 3 steps	277.0
7-11		CH	H	H	5-(2,5-dichlorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-amine	32% 3 steps	309.0
7-12		CH	H	H	5-(5-chloro-2-(trifluoromethyl)benzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-amine	8% 3 steps	343.1
7-13		CH	H	H	5-(pyridin-3-ylmethoxy)-1H-pyrazolo[4,3-b]pyridin-3-amine	6% 3 steps	342.1

** ^{1}H NMR: δH ppm (400 MHz, DMSO): **7-1**: 11,61 (1H, s large, NH), 7,73 (1H, d, CHarom), 7,24 (2H; m, CHarom), 7,18 (1H, m, CHarom), 6,86 (1H, d, CHarom). **7-2**: 11.95 (1H, sl, NH), 7.78 (1H, d, CHarom, J=11.6Hz), 7.33 (1H, d, CHarom, J=11.6Hz), 7.19 (1H, t, CHarom), 7.04 (2H, 2d, CHarom, J=8.8Hz), 5.51 (2H, s, NH_2). **7-3**: 11.80 (1H, sl, NH), 7.70 (1H, d, CHarom, J=8.8Hz), 7.60 (1H, t, CHarom), 7.49 (1H, q, CHarom), 7.27-7.33 (1H, m, CHarom), 7.11 (1H, d, CHarom, J=8.8Hz), 5.41 (2H, s, NH_2). **7-4**: 11.93 (1H, sl, NH), 7.80 (1H, d, CHarom, J=11.6Hz), 7.62 (1H, d, CHarom, J=11.6Hz), 7.40 (1H, dd, CHarom, J=11.2Hz), 7.29 (1H, d, CHarom, J=11.6Hz), 7.1 (1H, s, CHarom), 5.51 (2H, s, NH_2). **7-5**: 11.86 (1H, sl, NH), 7.87 (1H, d, CHarom, J=9.6Hz), 7.73 (1H, d, CHarom, J=11.6), 7.50-7.68 (2H, m, CHarom), 7.44 (1H, d, CHarom, J=10.4Hz), 7.11 (1H, d, CHarom, J=11.6Hz), 5.46 (2H, s, NH_2). **7-6**: 12.66 (1H, sl, NH), 8.52 (1H, s, CHarom), 7.12-7.20 (1H, m, CHarom), 7.02-7.10 (2H, m, CHarom), 5.90 (2H, s, NH_2). **7-7**: 12.70 (1H, s, NH), 8.52 (1H, s, CHarom), 7.60 (1H, d, CHarom, J=8.8Hz), 7.38 (1H, dd, CHarom, J=8.4Hz), 7.12 (1H, s, CHarom), 5.92 (2H, s, NH_2). **7-8**: 12.66 (1H, s, NH), 8.39 (1H, s, CHarom), 7.84 (1H, d, CHarom, J=7.6Hz), 7.58 (1H, t, CHarom), 7.50 (1H, t, CHarom), 7.34 (1H, d, CHarom, J=7.6Hz), 5.87 (2H, s, NH_2). **7-9**: 11,57 (1H, s, NH), 7,74 (1H, d, Charom, J=9Hz), 7,25 (3H, m, CHarom), 6,88 (1H, d, Charom, J=9Hz), 5,44 (2H, s), 5,08 (2H, s). **7-10**: 11.58 (1H, s,

NH), 7.73 (1H, d, CHarom, J=12.0Hz), 7.48-7.58 (1H, m, CHarom), 7.21-7.37 (2H, m, CHarom), 6.85 (1H, d, CHarom, J=12.0Hz), 5.44 (2H, s, CH), 5.10 (2H, sl, NH_2). **7-11**: 11.60 (1H, sl, NH), 7.70-7.77 (2H, m, CHarom), 7.57 (1H, d, CHarom, J=11.2Hz), 7.40-7.50 (1H, m, CHarom), 6.89 (1H, d, CHarom, J=12.0Hz), 5.48 (2H, s, CH), 5.06 (2H, sl, NH_2). **7-12**: 11.60 (1H, sl, NH), 7.91 (1H, s, CHarom), 7.83 (1H, d, CHarom, J=11.2Hz), 7.75 (1H, d, CHarom, J=12.0Hz), 7.66 (1H, d, CHarom, J=9.6Hz), 6.88 (1H, d, CHarom, J=12.0Hz), 5.58 (2H, s, CH), 5.01 (2H, sl, NH_2). **7-13**: 11.56 (1H, sl, NH), 8.77 (1H, s, CHarom), 8.55 (1H, s, CHarom), 7.96 (1H, d, CHarom, J=10.4Hz), 7.72 (1H, d, CHarom, J=12.0Hz), 7.42 (1H, dd, CHarom, J=10.0Hz), 6.83 (1H, d, CHarom, J=11.6Hz), 5.45 (2H, s, CH), 5.15 (2H, sl, NH_2).

Example 8: N5-(3,5-difluorophenyl)-1H-pyrazolo[4,3-b]pyridine-3,5-diamine



Example 8a: 6-(3,5-difluorophenylamino)-3-nitropicolinonitrile

A mixture of 6.5 g of 6-chloro-3-nitropicolinonitrile (0.065 mol) and 6.2 g of 3,5-difluoroaniline (0.048 mol) in 100 ml of toluene is heated at 70°C for 5 hours. The crude reaction product is diluted in an ethyl acetate fraction and washed using saturated NaCl solution. The organic phase is dried with sodium sulfate and the residue purified by silica gel chromatography (AcOEt/petroleum ether) to yield 3.9 g (33%) of a yellow solid.

Example 8b: 3-amino-6-(3,5-difluorophenylamino)picolinonitrile

10 ml of concentrated HCl is added to a solution of 6-(3,5-dichlorophenylthio)-3-nitropicolinonitrile (3.9 g, 0.0141 mol) in 150 ml of ethanol under stirring. The reaction medium is refluxed, added together with 2.4 g of iron (0.0423 mol) and stirred at 80°C for 1 hour. After returning to 0°C the pH is adjusted to 8 using 1 N soda solution and the reaction medium is filtered on Celite. The reaction mixture is added together with 100 ml of ethyl acetate and 50 ml of methanol. The organic phase is extracted and the aqueous phase is extracted several times by ethyl acetate fractions. The organic phases are combined and then dried on anhydrous sodium sulfate before being concentrated to yield, after concentration, 2.3 g (66%) of a brown solid.

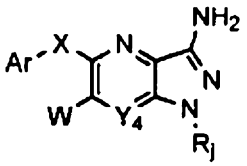
Example 8: 5-(3,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-amine

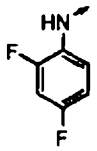
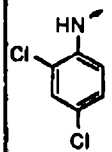
A solution of 713 mg of $NaNO_2$ (10.3 mmol) in water (5 ml) is added, drop by drop, to a stirring solution of 2.3 g of 3-amino-6-(3,5-difluorophenylamino)picolinonitrile (9.4 mmol) in 100 ml of 6 N hydrochloric acid at 0°C. The mixture is stirred for 20 minutes at 0-5°C. A solution of 5.3 g of $SnCl_2 \cdot 2H_2O$ (23.5 mmol, 2.5 eq) in hydrochloric acid (12 N solution, 30 ml) is then added drop by drop and the solution is stirred for 1 hour at room temperature. The reaction medium is then cooled at 0°C and basified to pH 8 using 30% soda solution. The mixture is extracted with ethyl acetate and washed using saturated NaCl solution and the organic phase is dried on anhydrous sodium sulfate before being concentrated under vacuum. The residue is purified by silica column chromatography (AcOEt). A light yellow solid is obtained (530 mg, 22%).

LCMS: m/z 262 ($M+H^+$).

^1H NMR: δH ppm (400 MHz, DMSO): 11.47 (s, 1H), 9.45 (s, 1H), 7.65 (m, 3H), 6.87 (d, 1H, J=7.8 Hz), 6.60 (m, 1H), 5.09 (s, 2H).

The following compounds are obtained by a similar method:



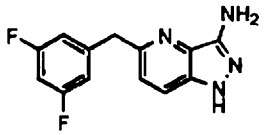
Ex.**	ArX	Y_4	W	R_j	Compound names	Yield	Mass MH^+
8-1		CH	H	H	N-(2,5-difluorophenyl)-1H-pyrazolo[4,3-b]pyridine-3,5-diamine	4% 4 steps	262.0
8-2		CH	H	H	N-(2,5-dichlorophenyl)-1H-pyrazolo[4,3-b]pyridine-3,5-diamine	9% 4 steps	294.0

** ^1H NMR: δH ppm (400 MHz, DMSO): **8-1**: 11.46 (1H, s, NH), 8.75-8.82 (2H, m, CHarom), 7.65 (1H, dd, CHarom, J=9.2Hz), 7.19-7.31 (2H, m, CHarom), 6.67-6.63 (1H, sl, CHarom), 5.06 (2H, s, NH_2). **8-2**: 11.58 (1H, sl, NH), 8.65 (1H, s, CHarom), 8.35 (1H, s, CHarom), 7.69 (1H, d, CHarom, J=12.0Hz), 7.45 (1H, d, CHarom,

J=11.6Hz), 7.24 (1H, d, CHarom, J=12.0Hz), 6.96 (1H, dd, CHarom, J=11.2Hz), 5.03 (2H, sl, NH_2).

Example of method B3

Example 9: 5-(3,5-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-amine



This compound can be prepared from the following intermediates, according to method B3.

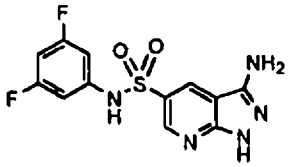
Example 9a: 2-(3,5-difluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Example 9b: 6-(3,5-difluorobenzyl)-3-nitropicolinonitrile

Example 9c: 3-amino-6-(3,5-difluorobenzyl)picolinonitrile

Example of method B4

Example 10: 3-amino-N-(3,5-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-sulfonamide



Example 10a: 5-(N-(3,5-difluorophenyl)sulfamoyl)nicotinic acid

2.74 g (9.64 mmol) of ethyl 2-chloro-5-(chlorosulfonyl)nicotinate in solution in 20 ml of anhydrous dichloromethane is added, drop by drop at 0°C, to a mixture of 623 mg (4.82 mmol) of 3,5-difluoroaniline and 1.68 ml (12.05 mmol) of triethylamine diluted in 10 ml of anhydrous dichloromethane. The solution is stirred at room temperature for 3 hours. The solvent is evaporated to yield a light brown solid. The solid is triturated in 20 ml of methanol, filtered and then rinsed with 3 ml of methanol to yield 2.85 g of a white solid.

This solid is redissolved in 25 ml of tetrahydrofuran and is added together with a solution of 0.421 g (10.04 mmol) of lithium monohydrate hydroxide in 10 ml of water.

The reaction mixture is left under stirring for 3 hours at 35°C and then diluted in water, acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic phase is collected, dried on sodium sulfate, filtered and concentrated to yield 1.12 g of 5-(N-(3,5-difluorophenyl)sulfamoyl)nicotinic acid in the form of an orange solid (yield=67%).

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.91 (1H, s, CH_{arom}), 8.51 (1H, s, CH_{arom}), 7.02 (1H, dd, CH_{arom}), 6.83 (2H, d, CH_{arom}).

Example 10b: 2-chloro-5-(N-(3,5-difluorophenyl)sulfamoyl)nicotinamide

0.288 ml (3.87 mmol) of thionyl chloride and a drop of DMF are added successively to 0.450 g (1.29 mmol) of 2-chloro-5-(N-(3,5-difluorophenyl)sulfamoyl)nicotinic acid in 5 ml of anhydrous toluene. The mixture is placed under stirring, at reflux of toluene, for 2 hours. The acid chloride reaction mixture is then added drop by drop to an iced solution, under stirring, of 4.5 ml of 25% ammonium hydroxide. A release of gas is observed. The reaction medium is left under stirring at room temperature for 30 minutes. The reaction medium is extracted several times with ethyl acetate. The combined organic phases are dried on anhydrous sodium sulfate and then concentrated. 0.315 g of 2-chloro-5-(N-(3,5-difluorophenyl)sulfamoyl)nicotinamide in the form of a light brown solid is obtained (yield=72%).

^{1}H NMR: δH ppm (400 MHz, DMSO): 11.18 (1H, bs, NH), 8.86 (1H, s, CH_{arom}), 8.22 (1H, s, CH_{arom}), 8.21 (1H, bs, NH), 7.98 (1H, bs, NH), 6.96 (1H, dd, CH_{arom}), 6.79 (2H, d, CH_{arom}).

Example 10c: 6-chloro-5-cyano-N-(3,5-difluorophenyl)pyridine-3-sulfonamide

3.4 ml (36.2 mmol) of phosphoryl chloride and a drop of concentrated sulfuric acid are added to 0.315 g (0.906 mmol) of 2-chloro-5-(N-(3,5-difluorophenyl) sulfamoyl)nicotinamide. The reaction mixture is stirred for 2 hours at 90°C and then added drop by drop to ice. The brown solid is filtered, rinsed with water and then dried under vacuum. 0.217 g of 6-chloro-5-cyano-N-(3,5-difluorophenyl)pyridine-3-sulfonamide is obtained in the form of a light brown solid (yield=72%).

^{1}H NMR: δH ppm (400 MHz, DMSO): 11.34 (1H, bs, NH), 9.04 (1H, s, CH_{arom}), 8.92 (1H, s, CH_{arom}), 7.03 (1H, dd, CH_{arom}), 6.85 (2H, d, CH_{arom}).

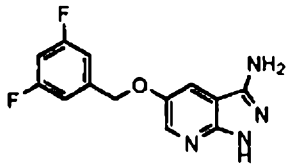
Example 10: 3-amino-N-(3,5-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-sulfonamide

0.377 ml (2.63 mmol) of 35% hydrazine is added to 0.217 g (0.658 mmol) of 6-chloro-5-cyano-N-(3,5-difluorophenyl)pyridine-3-sulfonamide diluted in 6 ml of isopropanol. The solution is heated at 75°C for 2 hours. The solvent is evaporated to yield 0.214 g of 3-amino-N-(3,5-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-sulfonamide in the form of a yellow solid (yield=100%).

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.74 (1H, d, CH_{arom}), 8.68 (1H, d, CH_{arom}), 6.88 (1H, dd, CH_{arom}), 6.80 (2H, d, CH_{arom}), 6.04 (2H, bs, NH).

Examples of method B5

Example 11: 5-(3,5-difluorobenzyloxy)-1H-pyrazolo[3,4-b]pyridin-3-amine



This compound can be prepared from the following intermediates, according to method B5.

Example 11a: 5-hydroxynicotinonitrile

A mixture of 1g of 5-methoxynicotinonitrile (7.46 mmol) and 8.62 g of pyridine hydrochloride is heated at 200°C for 2 hours. The crude reaction product is diluted in a water fraction several times with diethyl ether. The aqueous phase is basified by adding sodium bicarbonate and then extracted again with diethyl ether. The organic phase is dried and then concentrated to yield 850 mg of 5-hydroxynicotinonitrile (95%) in the form of a beige solid.

LCMS: m/z 120,94 ($M+H^+$).

^{1}H NMR: δH ppm (400 MHz, DMSO): 10,79 (s, 1H), 8,46 (s, 1H, CHarom.), 8,42 (s, 1H, CHarom.), 7,60 (s, 1H, CHarom.).

Example 11b: 5-(3,5-difluorobenzyloxy)nicotinonitrile

876 mg (2 eq) of sodium hydride is added gradually at 0°C under nitrogen to a solution of 865 mg of 5-hydroxynicotinonitrile (7.2 mmol) in 15 mL of dimethylacetamide. The mixture is stirred 10 min at 0°C before adding 2.24 g (1.5 aq) of 3,5-difluorobenzyl bromide. The mixture is placed under stirring for 2.5 additional hours before being diluted in an ethyl acetate fraction and being washed with aqueous fractions. The

organic phases are isolated, dried and concentrated. The solid residue obtained is recrystallized in methanol to yield 1.1 g (68 % of 5-(3,5-difluorobenzyloxy) nicotinonitrile in the form of a beige powder.

LCMS: m/z 247.11 ($M+H^+$).

^1H NMR: δH ppm (400 MHz, DMSO): 8,69 (s, 1H, CH), 8,65 (s, 1H, CH), 8,08 (s, 1H, CH), 7,26 (m, 3H, CH), 5,28 (d, 2H, CH_2).

Example 11c: 3-cyano-5-(3,5-difluorobenzyloxy)pyridine 1-oxide

224 mg of m-CPBA is added at 0°c to a solution in acetonitrile of 250 mg of 5-(3,5-difluorobenzyloxy)nicotinonitrile. The reaction medium is stirred for 20 hours while a precipitate is formed progressivelt. this solid is then filtered and washed to yield 200 mg (75%) of 3-cyano-5-(3,5-difluorobenzyloxy)pyridine 1-oxide in the form of a white powder.

LCMS: m/z 263,06 ($M+H^+$).

Example 11d: 2-chloro-5-(3,5-difluorobenzyloxy)nicotinonitrile

A mixture of 650 mg of 3-cyano-5-(3,5-difluorobenzyloxy)pyridine 1-oxide in 2.3 mL of $POCl_3$ added with few drops of H_2SO_4 is heated at 110°C for 1h30. The crude reaction medium is then poured in ice and the precipitate thus formed is isolated by filtration and dried under vacuum to yield 600 mg of a beige solid in the form of a mixture of regioisomers comprising mainly the desired 2-chloro-5-(3,5-difluorobenzyloxy)nicotinonitrile which is used without further purification.

LCMS: m/z 281,02 ($M+H^+$).

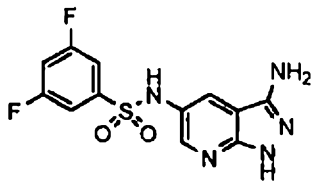
Example 11: 5-(3,5-difluorobenzyloxy)-1H-pyrazolo[3,4-b]pyridin-3-amine

313 mg of hydrazine hydrate (5 eq) is added to a solution of 1.6 g of 2-chloro-5-(3,5-difluorobenzyloxy)nicotinonitrile (450 µmol) in 10 mL of propan-2-ol. The reaction mixture is heated at 100°C for 6 hours. After return to room temperature leading to a precipitation, the crude reaction medium is filtered, the solid is removed and the filtrate is dry evaporated. It is then purified by chromatography on a silica column eluted with a gradient of ethyl acetate and methanol, whereas the more polar fraction is isolated, concentrated and suspended again in a small fraction of methanol under stirring. The solid thus obtained is isolated and dried to yield 221 mg of 5-(3,5-difluorobenzyloxy)-1H-pyrazolo[3,4-b]pyridin-3-amine in the form of a beige solid wich is used without further purification.

LCMS: m/z 277,07 ($M+H^+$).

Example of method B6

Example 11bis: N-(3-amino-1H-pyrazolo[3,4-b]pyridin-5-yl)-3,5-difluorobenzene sulfonamide



Example 11bis-a: N-(6-chloro-5-cyanopyridin-3-yl)-3,5-difluorobenzene-sulfonamide

1.132 g (5.32 mmol) of 3,5-difluorobenzene-1-sulfonyle chloride is added under argon to a solution of 545 mg (3.55 mmol) of 5-amino-2-chloronicotinotrile in 20 mL of an anhydrous 1:1 mixture of THF and pyridine. The reaction medium is heated to 70°C for 3 hours and let 12 additional hours under stirring at room temperature. The solvent is dry evaporated and the crude reaction product is redissolved in ethyl acetate and washed with several aqueous fractions. The organic phase is dried on magnesium sulfate, filtered, concentrated and then purified by silica gel chromatography to yield 784 mg (67%) of N-(6-chloro-5-cyanopyridin-3-yl)-3,5-difluorobenzene-sulfonamide.

^1H NMR: δH ppm (400 MHz, DMSO) : 11,39 (1H, sl, NH), 8. 34 (1H, m, CHarom), 8,10 (1H, m, CHarom), 7,67 (1H, m, CHarom), 7,59 (2H, m, CHarom).

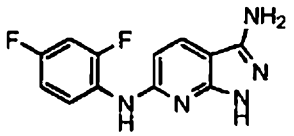
Example 11bis: N-(3-amino-1H-pyrazolo[3,4-b]pyridin-5-yl)-3,5-difluorobenzene-sulfonamide

1.786 g (35.7 mmol) of hydrazine hydrate is added under argon to a solution of 784 mg (2.38 mmol) of N-(6-chloro-5-cyanopyridin-3-yl)-3,5-difluorobenzene-sulfonamide in 6 mL of ethanol. The solution is heated to 100°C for 20 hours and then cooled to room temperature. The solvent is evaporated to yield 810 mg of N-(3-amino-1H-pyrazolo[3,4-b]pyridin-5-yl)-3,5-difluorobenzene-sulfonamide (100%) which is used without further purification in the following steps.

LCMS: m/z 326,07 ($M+H^+$).

Example of method C1

Example 12: N6-(2,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-3,6-diamine



This compound can be prepared from the following intermediates, according to method C1.

Example 12-a: 5-cyano-6-(methylthio)pyridin-2-yl trifluoromethanesulfonate

15.26 mL (1.2 eq) of potassium 2-methylpropan-2-olate and then 9.03 g (1.2 eq) of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide are added dropwise to a solution of 3.5 g (21.06 mmol) of 6-hydroxy-2-(methylthio)nicotinonitrile in 180 mL of tetrahydrofurane under nitrogen. The reaction mixture is stirred at room temperature for 2h45. Water is added and the product is extracted with ethyl acetate. The organic phase is dried on anhydrous magnesium sulfate, filtered and evaporated to yield an orange solid. The product is purified on a silica gel column (eluent: cyclohexane/dichloromethane 5:5) to yield 5.31 g (85%) of 5-cyano-6-(methylthio)pyridin-2-yl trifluoromethanesulfonate in the form of a yellow solid.

^{1}H NMR: δH ppm (400 MHz, DMSO): 8,57 (1H, d, CH), 7,52 (1H, d, CH), 2.59 (3H, s, CH_3).

Example 12-b: 6-(2,4-difluorophenylamino)-2-(methylthio)nicotinonitrile

0.81 mL (1.2 eq) of ,4-difluoroaniline and 1.53 g (1.4 eq) of cesium(I) carbonate are added under nitrogen to a solution of 2 g (6.71 mmol) of 5-cyano-6-(methylthio)pyridin-2-yl trifluoromethanesulfonate in 30 mL of 1,4-dioxane. The medium is degased for 5 minutes under argon before adding 0.25 g (0.06 eq) of de 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 0.08 g (0.04 eq) of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one, palladium(II) complex. The reaction medium is stirred at 100°C for 2 hours. After return to room temperature, ethyl acetate and brine are added. The organic phase is dried on anhydrous magnesium sulfate, fitered and evaporated. The residue obtained is purified on silica gel chromatography (eluent: cyclohexane/ethyl acetate 8:2 then 7:3) to yield 1.52 g (82%) of 6-(2,4-difluorophenylamino)-2-(methylthio)nicotinonitrile in the form of a white solid.

LCMS (IE, m/z): (M+1) 278,06.

^{1}H NMR: δH ppm (400 MHz, DMSO): 9,57 (1H, s, NH), 7,73-7,86 (2H, m, CH), 7,28-7,44 (1H, m, CH), 7,02-7,18 (1H, m, CH), 6,60 (1H, d, CH), 2.41 (3H, s, CH_3).

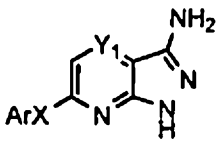
Example 12: N6-(2,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-3,6-diamine

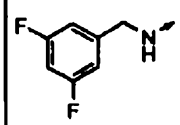
769 mg (3.12 mmol) of m-chloroperbenzoic acid (mCPBA) is added under argon to a stiring solution of 786 mg (2.83 mmol) of 6-(2,4-difluorophenylamino)-2-(methylthio)nicotinonitrile in 25 mL of dichloromethane. The reaction medium is stirred 1 hour at room temperature before adding a fraction of ethyl acetate and washed this organic phase with a $NaHCO_3$ saturated solution. The combined organic phases are dried on magnesium sulfate and dry evaporated. The crude reaction product is dissolved again in 10 mL of propanol and 2 equivalents of hydrazine hydrochloride in water are added. The mixture is heated at 90°C for 6 hours before being diluted in water and extracted with ethyl acetate. The organic phase is dried on magnesium sulfate and dry evaporated before being purified by silica gel chromatography to yield 495 mg of N6-(2,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-3,6-diamine in the form of a yellow-orange solid (67%).

LCMS (IE, m/z): (M+1) 262,14.

^{1}H NMR: δH ppm (400 MHz, DMSO): 11,40 (1H, s, NH), 8,76 (1H, s, NH), 8,15 (1H, m, CH), 7,81 (1H, d, CH), 7,28 (1H, m, CH), 7,06 (1H, m, CH), 6,55 (1H, d, CH), 5,24 (2H, s, NH_2).

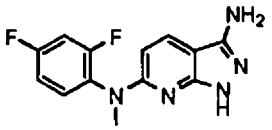
The following compound is obtained by a similar method:



Ex.**	ArX	Y_1	Compound names	Yield	Masse MH^+
12-1		CH	N6-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3,6-diamine	70%	276,15

** ^{1}H NMR, dmso-d_6, Ex.: 12-1: 11,17 (1H, s, NH), 7,66 (1H, d, CH), 7,37 (1H, s, NH), 7,04 (3H, m, CH), 6,24 (1H, d, CH), 5,11 (2H, s, NH_2), 4,52 (2H, s, CH_2).

Example 12bis: N6-(2,4-difluorophenyl)-N6-methyl-1H-pyrazolo[3,4-b]pyridine-3,6-diamine



Example 12bis-a: 6-((3,5-difluorophenyl)(methyl)amino)-2-(methylthio) nicotinonitrile

3.05 mL (5.04 mmol) of potassium 2-methylpropan-2-olate and then 286 µL (1.8 eq) of iodomethane are added dropwise under nitrogen to a solution of 700 mg (2.52 mmol) of 6-(2,4-difluorophenylamino)-2-(methylthio)nicotinonitrile in 20 mL of *N,N*-dimethyl formamide. The reaction medium is stirred at room temperature for 24 hours and then 126 µL (0.8 eq, 2.02 mmol) of iodomethane is added. The reaction medium is stirred at room temperature for 2 additional hours. Water is added and the product is extracted with ethyl acetate. The organic phase is dried on anhydrous magnesium sulfate, filtered, and evaporated to yield 660 mg (90%) of 6-((2,4-difluorophenyl)(methyl)amino)-2-(methylthio)nicotinonitrile in the form of a brown solid.

LCMS (IE, m/z): (M+1) 292,09.

^{1}H NMR: δH ppm (400 MHz, DMSO): 7,74-7,80 (1H, m, CH), 7,55-7,63 (1H, m, CH), 7,43-7,52 (1H, m, CH), 7,18-7,27 (1H, m, CH), 6,16-6,30 (1H, m, CH), 3,43 (3H, s, CH_3), 2.42 (3H, s, CH_3).

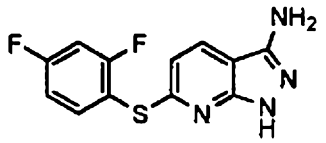
Example 12bis: N6-(2,4-difluorophenyl)-N6-methyl-1H-pyrazolo[3,4-b]pyridine-3,6-diamine

452 mg (1.84 mmol) of mCPBA is added under argon to a stirring solution of 486 mg (1.67 mmol) of 6-((2,4-difluorophenyl)(methyl)amino)-2-(methylthio)nicotinonitrile in 15 mL of dichloromethane. The reaction medium is stirred 30 min at room temperature before adding an ethyl acetate fraction. The organic phase is washed with a $NaHCO_3$ saturated solution, dried on magnesium sulfate and dry evaporated. The crude reaction product is dissolved again in 6 mL of propanol and 164 µL (3.38 mmol) of hydrazine hydrochloride in water is added. The mixture is heated at 90°C for 6 hours before being diluted in water and extracted with ethyl acetate. the organic phase is dried on magnesium sulfate and dry evaporated before being purified by silica gel

chromatography to yield 328 mg of N6-(2,4-difluorophenyl)-N6-methyl-1H-pyrazolo[3,4-b]pyridine-3,6-diamine in the form of a yellow-orange solid (70%).
LCMS (IE, m/z): (M+1) 276,15.
^{1}H NMR: δH ppm (400 MHz, DMSO): 11,41 (1H, s, NH), 7,75 (1H, d, CH), 7,51-7,55 (1H, m, CH), 7,40-7,43 (1H, m, CH), 7,17-7,22 (1H, m, CH), 6,03 (1H, d, CH), 5,23 (2H, s, NH_2), 3,28 (3H, s, CH_3).

Example of method C3

Example 12ter: 6-(2,4-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine

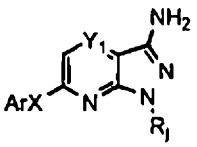


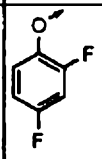
Example 12ter-a: 2-chloro-6-(2,4-difluorophenylthio)nicotinonitrile
A solution of 362 mg (1.05 eq) of potassium hydroxide in 10 mL of ethanol is added, under nitrogen, to a solution of 698 µL (6.16 mmol) of 2,4-difluorobenzenethiol in 30 mL of ethanol. The reaction medium is stirred at room temperature for 15 minutes and then cooled in ice before adding a solution of 1.015 g (0.95 eq) of 2,6-dichloronicotinonitrile in 30 mL of ethanol. The reaction medium is stirred for 2 hours at 0-5°C. 63 mL of a 0.1N HCl solution is added to stop the reaction. Water is added and the producted is extracted with ethyl acetate. The organic phase is dried on anhydrous magnesium sulfate, filtered and evaporated. The residue is purified by silica gel chromatography (eluent: cyclohexane/ethyl acetate 94:6) to yield 1.09 g (66%) of 2-chloro-6-(2,4-difluorophenylthio)-nicotinonitrile in the form of a white solid.
LCMS (IE, m/z): (M+1) 282,98.
^{1}H NMR: δH ppm (400 MHz, DMSO): 8,24 (1H, d, CH), 7,77-7,85 (1H, m, CH), 7,52-7,63 (1H, m, CH), 7,25-7,35 (2H, m, CH), 2,41 (3H, s, CH_3).
Example 12ter: 6-(2,4-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine
0.561 mL (11.57 mmol) of hydrazine monohydrate is added under nitrogen to a stirring solution of 1.09 g (3.86 mmol) of 2-chloro-6-(2,4-difluorophenylthio)nicotinonitrile in 15 mL of propanol. The reaction medium is heated at 80°C for 4 hours. A precipitate is obtained when the reaction medium is returned to room temperature. This precipitate is

filtered and rinced with ethanol. The solid is dissolved in an ethyl acetate fraction and washed with a 1N HCl solution. The organic phase is dried on magnesium sulfate and dry evaporated to yield 420 mg (39%) of 6-(2,4-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine in the form of a yellow solid.

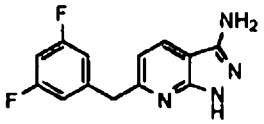
^{1}H NMR: δH ppm (400 MHz, DMSO): 12,10 (1H, s, NH), 8,11 (1H, d, CH), 7,82-7,89(1H, m, CH), 7,58-7,63 (1H, m, CH), 7,32-7,36 (1H, m, CH), 6,86 (1H, d, CH), 4,59 (2H, s, NH_2).

The following compound is obtained by a similar method:



Ex.**	ArX	Y_1	R_1	Compound names	Yield	Mass MH^+
12ter-1		CH	H	6-(2,4-difluorophenoxy)-1H-pyrazolo[3,4-b]pyridin-3-amine	ND	263,06

Example 12quater: 6-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-amine



17.35 mL of a 0.5M solution in THF of (3,5-difluorobenzyl)zinc chloride (8.58 mmol) is added under argon to a solution of 416 mg of palladium(II) chloride (510 mmol) and 883 mg of 2,6-dichloronicotinonitrile (5.1 mmol) in 2 mL of anhydrous THF. The reaction is refluxed for 7 hours, then cooled to room temperature. A 1N soda aqueous solution is added and the product is extracted with several successive ethyl acetate fractions. The organic phases are dried on magnesium sulfate and dry evaporated before being purified by silica gel chromatography to yield 680 mg of a mixture of 2-chloro-6-(3,5-difluorobenzyl)-nicotinonitrile and by-products wich is used without further purification in the following step.

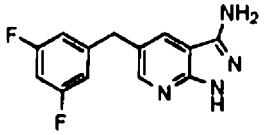
The previous mixture is dissolved in 10 mL of isopropanol under stirring and 750 µL of 35% hydrazine hydrate is added. The solution is heated at 80°C for 4 hours. The solvent is dry evaporated and the product is purified by silica gel chromatography (dichloromethane/methanol 9:1) to yield 290 mg of 6-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-amine (64%).

LCMS (IE, m/z): (M+1) 261.16.

^{1}H NMR: δH ppm (400 MHz, DMSO): 11,82 (1H, s, NH), 8,01 (1H, d, CH), 6,99-7,04 (3H, m, CH), 6,91 (1H, d, CH), 5,49 (2H, s, NH_2), 4,12 (2H, s, CH_2).

Example of method D1:

Example 13: 5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-amine

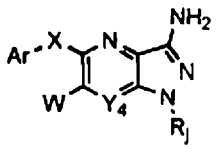


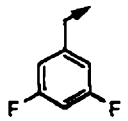
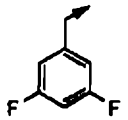
0.575 g (0.704 mmol) of $(dppf)_2PdCl_2 \cdot CH_2Cl_2$ and 28 ml (14.08 mmol) of 3,5-difluorobenzyl zinc (II) chloride are added to 1.5 g (7.04 mmol) of a solution of 5-bromo-1H-pyrazolo[3,4-b]pyridin-3-amine in 10 ml of tetrahydrofuran. The reaction medium is heated at 90°C for 18 hours. After returning to room temperature, the reaction is hydrolyzed by slowly adding water at 0°C. After filtration of the precipitate formed, the solid is rinsed with tetrahydrofuran and the aqueous filtrate is extracted several times with ethyl acetate. The organic phases are combined, dried on magnesium sulfate and concentrated. The residue is purified by silica chromatography (95:4.5:0.5 and then 95:4:1 dichloromethane/methanol/ammonium as eluent) to yield 1.7 g (93%) of 5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-amine in the form of a beige solid.

LCMS (EI, m/z): (M+1) 261.41.

^{1}H NMR: δH ppm (400 MHz, DMSO): 11.87 (1H, s, NH), 8.31 (1H, d, CH_{arom}), 7.92 (1H, d, CH_{arom}), 6.98-7.08 (3H, m, CH_{arom}), 5.47 (2H, s, NH), 4.04 (2H, s, CH_2).

The following compounds are obtained by a similar method:

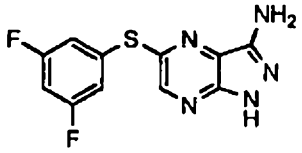


Ex.**	ArX	Y_4	W	R_j	Compound names	Yield	Mass MH^+
13-1		CH	H	H	5-(3,5-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	8% 4 steps	261.1
13-2		N	H	H	5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	21% 3 steps	262.1

** ^{1}H NMR: δH ppm (400 MHz, DMSO): **13-1**: 11.61 (1H, sl, NH), 7.65 (1H, d, CHarom, J=11.6Hz), 7.20 (1H, d, CHarom, J=11.2Hz), 6.95-7.10 (3H, m, CHarom), 5.32 (2H, sl, NH_2), 4.18 (2H, s, CH_2). **13-2**: 12.31 (1H, sl, NH), 8.44 (1H, s, CHarom), 7.03-7.08 (3H, m, CHarom), 5.61 (2H, sl, NH_2), 4.25 (2H, s, CH_2).

Examples of method D2

Example 14: 5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-amine

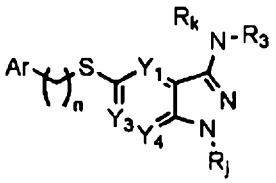


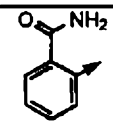
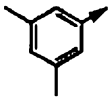
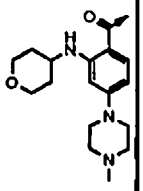
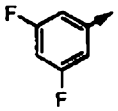
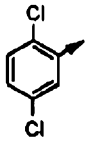
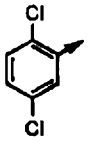
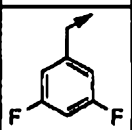
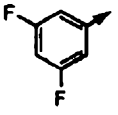
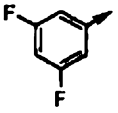
0.7 g (2.68 mmol) of 5-iodo-1H-pyrazolo[3,4-b]pyridine-3-amine, 0.74 g (5.36 mmol) of anhydrous potassium carbonate and 0.10 g of copper iodide (0.536 mmol) are mixed in a 50 ml round-bottom flask. 15 ml of propan-2-ol, 0.01 g (0.2 mmol) of polyethylene glycol and 0.43 g (2.95 mmol) of 3,5-difluorothiophenol are then added. The reaction mixture is heated at 80°C for 2 hours. The solvent is evaporated and the solid formed is filtered, rinsed with water and then with pentane and dried in an oven at 50°C to yield 0.75 g (100%) of 5-(3,5-diflurophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-amine in the form of a brown solid.

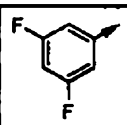
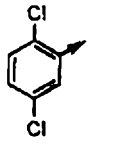
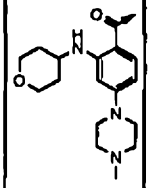
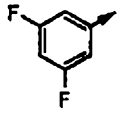
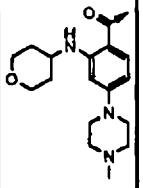
LCMS (EI, m/z): (M+1) 280.03.

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.65 (1H, bs, NH), 8.52 (1H, s, CH_{arom}), 7.18 (1H, t, CH_{arom}), 7.05-7.18 (2H, m, CH_{arom}), 5.89 (2H, s, NH).

The following derivatives were obtained according to the same method:

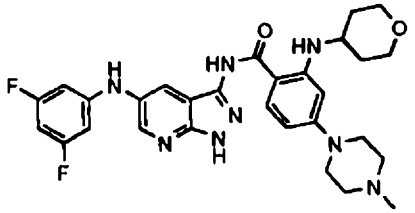


Ex.**	Ar	R_k	n	Y_1,Y_3,Y_4	R_3	R_j	Compound name	Yield	Mass MH^+
14-1		H	0	CH, CH, N	H	H	2-(3-amino-1H-pyrazolo[3,4-b]pyridin-5-ylthio)benzamide	ND	ND
14-2			0	CH, CH, N	H	H	N-(5-(3,5-dimethylphenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	ND
14-3		H	0	CH, CH, N	H	H	5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine	45%	(M+1) 279.28
14-4		H	0	CH, C-OMe, N	H	H	5-(2.5-dichlorophenylthio)-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-amine	80%	ND
14-5		H	0	CH, C-NH_2, N	H	H	5-(2.5-dichlorophenylthio)-1H-pyrazolo[3,4-b]pyridine-3,6-diamine	35%	ND
14-6		H	0	CH, CH, N	H	^{t}Bu	1-*tert*-butyl-5-(3,5-difluorobenzylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine	ND	(M+1) 293.08
14-7		H	0	CH, CMe, N	H	H	5-(3,5-difluorophenylthio)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-amine	ND	(M+1) 293.06
14-8		H	0	CH, C-OMe, N	H	H	5-(3,5-difluorophenylthio)-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-amine	28%	(M+1) 610.30

14-9		H	0	CH, CH, N	H	^{t}Bu	1-*tert*-butyl-5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine	79%	(M+1) 335.26
14-10			0	CH, CH, N	H	H	N-(5-(2.5-dichlorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	31%	(M+1) 612.37
14-11			0	CH, C-NH_2, N	H	H	N-(6-amino-5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	68%	ND

** ^{1}H NMR, DMSO-d_6, Ex.: **14-3:** 12.65 (1H, bs, NH), 8.52 (1H, s, CH_{arom}), 7.18 (1H, t, CH_{arom}), 7.05-7.18 (2H, m, CH_{arom}), 5.89 (2H, s, NH). **14-6:** 8.21 (2H, bs, CH_{arom}), 7.07 (1H, m, CH_{arom}), 6.90 (2H, m, CH_{arom}), 6.27 (2H, bs, NH), 4.03 (2H, s, CH), 1.63 (9H, s, CH). **14-7:** 12.16 (1H, bs, NH), 8.39 (1H, s, CH_{arom}), 7.00-7.08 (1H, m, CH_{arom}), 6.64-6.72 (2H, m, CH_{arom}), 5.73 (2H, bs, NH_2), 2.54 (3H, s, CH_3). **14-9:** 8.51 (1H, bs, CH_{arom}), 8.35 (1H, bs, CH_{arom}), 7.02 (1H, m, CH_{arom}), 6.72 (2H, bs, CH_{arom}), 6.52 (2H, bs, NH), 1.67 (9H, s, CH). (ND: not determined).

Example 14bis: N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide.



A solution of 225 mg of N-(5-iodo-1-trityl-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide (0.25 mmol), 36 mg of difluoroaniline (0.275 mmol), 19 mg of R-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyle (0.030 mmol), 11 mg (0.013 mmol) of tris(dibenzylideneacetone) dipalladium(0) and 75 mg (0.75 mmol) of sodium tert-butoxide in 10 mL of THF is

refluxed under argon overnight. The crude reaction medium is cooled, extracted with ethyl acetate and washed with water. The organic phase is dried on magnesium sulfate and purified by silica gel chromatography to yield N-(5-(3,5-difluorophenylamino)-1-trityl-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide which is used in the following step without further purification.

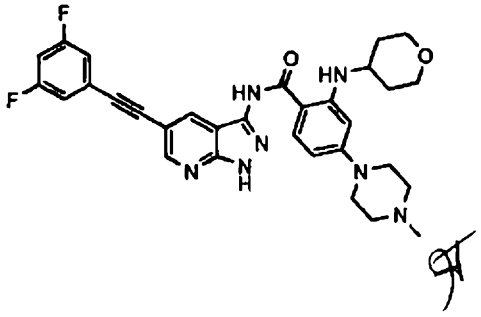
The product thus obtained is dissolved in 10 mL of dichloromethane at 0°C and 56 mg (0.5 mmol) of TFA is added. The reaction medium is stirred for 4 hours. Water is added and the pH of the reaction medium is adjusted to 7 with a $NaHCO_3$ solution. The aqueous phase is collected, basified (pH 9-10) with a concentrated K_2CO_3 solution and extracted with dichloromethane. The organic phase is collected, dried on magnesium sulfate and dry ccentrated to yield 40 mg of N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide.

LCMS (IE, m/z): (M+1) 562.12.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13,45 (1H, sl, NH), 10,47 (1H, sl, NH), 8,65 (1H, s, CH_{arom}), 8,55 (1H, s, CH_{arom}), 8,14 (1H, d, NH), 7,77 (1H, d, CH_{arom}), 7,26 (2H, m, CH_{arom}), 7,05 (1H, m, CH_{arom}), 6,25 (1H, d, CH_{arom}), 6,14 (1H, s, NH), 6,77 (1H, s, NH), 3,82-3,84 (2H, dt, CH), 3,72 (1H, m, CH), 3,47-3,52 (2H, m, CH), 3,28-3,34 (4H, m, CH), 2,43 (4H, m, CH), 2,23 (3H, s, CH_3), 1,94 -1,97 (2H, m, CH), 1,37-1,39 (2H, m, CH).

Examples of method D3:

<u>Example 15</u>: N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide

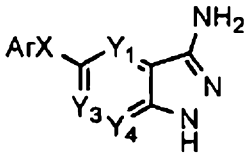


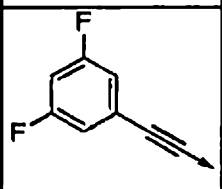
0.94 mg (0.926 mmol) of triethylamine is added to 400 mg (0.712 mmol) of N-(5-iodo-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide, 67.8 mg (0.356 mmol) of CuI, and 50 mg (0.071 mmol) of $Pd(PPh_3)_2Cl_2$ under argon in 12 ml of anhydrous dioxane under stirring. The reaction is heated for 3.5 hours at 100°C. The reaction mixture is diluted with 30 ml of water and extracted with ethyl acetate. The organic phase is dried on sodium sulfate, filtered and concentrated. The residue obtained is purified by silica gel chromatography (dichloromethane/methanol) to yield 152 mg of N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide in the form of a yellow solid (yield=37%).

LCMS (EI, m/z): (M+1) 572.17.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.57 (1H, bs, NH), 10.56 (1H, bs, NH), 8.68 (1H, s, CH_{arom}), 8.43 (1H, s, CH_{arom}), 8.13 (1H, d, NH), 7.80 (1H, d, CH_{arom}), 7.38 (2H, m, CH_{arom}), 6.27 (1H, d, CH_{arom}), 6.15 (1H, d, CH_{arom}), 3.84-3.82 (2H, dt, CH), 3.70 (1H, m, CH), 3.45-3.50 (2H, m, CH), 3.21-3.33 (4H, m, CH), 2.42-2.46 (4H, m, CH), 2.28 (3H, s, CH_3), 1.94-1.97 (2H, m, CH), 1.37-1.39 (2H, m, CH).

The following derivative was obtained according to the same method:



Ex.**	ArX	Y_1,Y_3,Y_4	Compound name	Yield	Mass MH+
15-1		N,CH,N	5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyrazin-3-amine	6% 6 steps	272.1

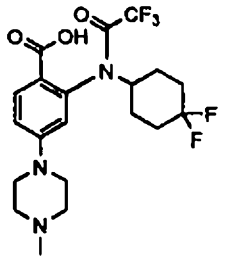
** ^{1}H NMR, dmso-d_6, Ex.: 15-1: 12.71 (1H, sl, NH), 8.66 (1H, s, CHarom), 7.40-7.47 (3H, m, CHarom), 6.01 (2H, sl, NH_2).

Examples of method E

The protocols comprising method E aim at functionalizing the exocyclic amine of the aminopyrazole rings by their reaction with an intermediate featuring an electrophilic function, optionally generated *in situ*, such as acid chloride, isocyanate, isothiocyanate or aldehyde.

Preparation of the reaction intermediates

Example 16: 2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-4-(4-methyl piperazin-1-yl)benzoic acid



Example 16a: *tert*-butyl 4-(4-methylpiperazin-1-yl)-2-nitrobenzoate

This compound was previously described in WO 2008/74749.

5.28 ml (47.6 mmol) of 1-methylpiperazine is added to 4.1 g (17 mmol) of *tert*-butyl 4-fluoro-2-nitrobenzoate. The reaction mixture is stirred without solvent for 5 hours. 150 ml of water is added to the reaction mixture and it is stirred for 24 hours. The precipitate formed is filtered, rinsed with water and dried under vacuum to yield 4.9 g (90%) of *tert*-butyl 4-(4-methylpiperazin-1-yl)-2-nitrobenzoate in the form of a yellow solid.

LCMS (EI, m/z): (M+1) 322.37.

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.69 (1H, d, CH_{arom}), 7.30 (1H, d, CH_{arom}), 7.20 (1H, dd, CH_{arom}), 3.38 (4H, m, CH), 2.40 (4H, m, CH), 2.22 (3H, s, CH_3), 1.45 (9H, s, CH_3).

Example 16b: *tert*-butyl 2-amino-4-(4-methylpiperazin-1-yl)benzoate

This compound was previously described in WO 2008/74749.

0.160 g (1.500 mmol) of palladium on carbon (10%) and 15.19 ml (150 mmol) of cyclohexene are added to a solution of 4.82 g (15 mmol) of *tert*-butyl 4-(4-

methylpiperazin-1-yl)-2-nitrobenzoate in 100 ml of ethanol. The reaction mixture is heated at a temperature of 80°C for 8 hours. The reaction mixture is filtered and then rinsed with ethanol to yield 4.2 g (yield=96%) of *tert*-butyl 2-amino-4-(4-methylpiperazin-1-yl)benzoate in the form of a yellow solid.

LCMS (EI, m/z): (M+1) 292.39.

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.44 (1H, d, CH_{arom}), 6.40 (2H, bs, NH_2), 6.19 (1H, dd, CH_{arom}), 6.12 (1H, d, CH_{arom}), 3.17 (4H, m, CH), 2.40 (4H, m, CH), 2.22 (3H, s, CH_3), 1.49 (9H, s, CH_3).

Example 16c: *tert*-butyl 2-(4,4-difluorocyclohexylamino)-4-(4-methylpiperazin-1-yl)benzoate

1.045 ml (13.57 mmol) of trifluoroacetic acid, 1 g (7.46 mmol) of 4,4-difluorocyclohexanone and 2.158 g (8.20 mmol) of tetramethylammonium triacetoxyborohydride are added to 1.521 g (5.22 mmol) of *tert*-butyl 2-amino-4-(4-methylpiperazin-1-yl)benzoate dissolved in 60 ml of dichloromethane. The reaction is left under stirring at room temperature for 24 hours. The solvent is evaporated and then the crude reaction product is redissolved in 30 ml of ethyl acetate. The solution is successively washed with 0.5 M HCl solution, 0.5 M soda solution and finally with saturated $NaHCO_3$ solution. The organic phase is dried on sodium sulfate, filtered and concentrated to obtain 2.2 g of *tert*-butyl 2-(4,4-difluorocyclohexylamino)-4-(4-methylpiperazin-1-yl)benzoate in the form of a light brown gum (yield=72%).

LCMS (EI, m/z): (M+1) 410.3.

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.73 (1H, bs, NH), 7.58 (1H, m, CH_{arom}), 7.77 (1H, m, CH_{arom}), 6.09 (1H, bs, CH_{arom}), 3.37 (4H, m, CH), 3.27 (4H, m, CH), 2.47 (4H, m, CH), 2.25 (3H, s, CH), 1.99 (4H, s, CH), 1.40 (9H, s, CH).

Example 16d: *tert*-butyl 2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-4-(4-methylpiperazin-1-yl)benzoate

0.99 ml (6.98 mmol) of trifluoroacetic anhydride and 1.12 ml (8.06 mmol) of triethylamine are added to 2.2 g (5.3 mmol) of *tert*-butyl 2-(4,4-difluorocyclohexylamino)-4-(4-methylpiperazin-1-yl)benzoate dissolved in 40 ml of dichloromethane. The reaction is left under stirring at room temperature for 3 hours. The solvent is evaporated and then the crude reaction product is taken up in 30 ml of ethyl acetate. The solution is washed with saturated $NaHCO_3$ solution. The organic

phase is dried on sodium sulfate, filtered and concentrated to obtain 2.5 g of *tert*-butyl 2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-4-(4-methylpiperazin-1-yl) benzoate in the form of a light brown gum (yield=92%).

LCMS (EI, m/z): (M+1) 506.26.

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.84 (1H, m, CH_{arom}), 7.09(1H, m, CH_{arom}), 6.89 (1H, bs, CH_{arom}), 3.45-3.39 (8H, m, CH), 2.83 (4H, m, CH), 2.20 (4H, m, CH), 2.05 (3H, s, CH), 1.46 (9H, s, CH).

Example 16: 2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-4-(4-methyl piperazin-1-yl)benzoic acid

7.62 ml (99 mmol) of trifluoroacetic acid is added to 2.5 g (4.95 mmol) of *tert*-butyl 2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-4-(4-methylpiperazin-1-yl) benzoate dissolved in 30 ml of dichloromethane. The reaction is left under stirring at room temperature overnight. The solvent is evaporated and then the crude reaction product is redissolved in 30 ml of ethyl acetate. The solvents are evaporated, the solid formed is redissolved in ethyl ether and the solvent is evaporated again. This operation is repeated three times until a light brown solid is obtained. 2.2 g of 2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-4-(4-methylpiperazin-1-yl)benzoic acid in the form of a trifluoroacetic salt is obtained (yield=79%).

LCMS (EI, m/z): (M+1) 450.1.

^{1}H NMR: δH ppm (400 MHz, DMSO): 10.01 (1H, bs, OH), 7.92 (1H, m, CH_{arom}), 7.13 (1H, m, CH_{arom}), 7.01 (1H, bs, CH_{arom}), 4.39 (1H, m, CH), 3.12-3.52 (8H, m, CH), 2.86 (3H, s, CH), 1.75-2.0 (8H, m, CH).

The following compounds are also obtained by this method:

4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl) acetamido)benzoic acid.

This compound was previously described in WO 2008/74749, WO 2009/13126 and WO 2010/69966.

LCMS (EI, m/z): (M+1) 416.40.

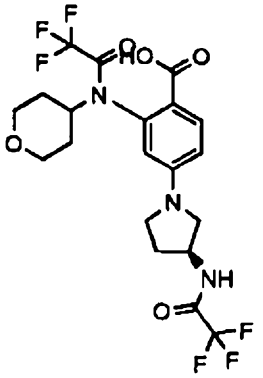
^{1}H NMR: δH ppm (400 MHz, DMSO): 12.60 (1H, bs, OH), 10.08 (1H, bs, OH), 7.90 (1H, d, CH_{arom}), 7.13 (1H, dd, CH_{arom}), 6.90 (1H, d, CH_{arom}), 4.40 (1H, m, CH), 4.10 (2H, m, CH), 3.70-3.90 (2H, m, CH), 3.59-3.62 (4H, m, CH), 3.30-3.32 (4H, m, CH),

2.87 (3H, s, CH_3), 1.87-1.98 (1H, m, CH), 1.59-1.60 (1H, m, CH), 1.00-1.54 (2H, m, CH).

4-((3-(dimethylamino)propyl)(methyl)amino)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid.

This compound was previously described in WO 2009/13126 and WO 2008/74749.

Example 17: (S)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-4-(3-(2,2,2-trifluoroacetamido)pyrrolidin-1-yl)benzoic acid



Example 17a: *tert*-butyl (S)-4-(3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl)-2-(tetrahydro-2*H*-pyran-4ylamino)benzoate

This compound was obtained by reproducing example 16d using *tert*-butyl (S)-pyrrolidin-3-ylcarbamate.

Example 17b: (S)-4-(3-aminopyrrolidin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzoic acid

19.7 ml (25 eq) of trifluoroacetic acid is added to a solution of 4.72 g (10.23 mmol) of *tert*-butyl (S)-4-(3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl)-2-(tetrahydro-2*H*-pyran-4-ylamino)benzoate in 100 ml of dichloromethane. The reaction medium is stirred at room temperature for 30 hours. The solvents are evaporated and the residue is redissolved in diethyl ether and triturated until a solid is obtained. The solid formed is filtered and dried under vacuum to yield 4.3 g (100%) of a yellow powder of (S)-4-(3-aminopyrrolidin-1-yl)-2-(tetrahydro-2*H*-pyran-4-ylamino)benzoic acid in the form of a trifluoroacetic acid salt.

LCMS (EI, m/z): (M+1) 306.22.

Example 17: (S)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-4-(3-(2,2,2-trifluoroacetamido)pyrrolidin-1-yl)benzoic acid

1.74 ml (3.5 eq) of triethylamine and 1.6 ml (2.1 eq) of trifluoroacetic anhydride are added to a solution of 1.5 g (3.58 mmol) of (S)-4-(3-aminopyrrolidin-1-yl)-2-(tetrahydro-2*H*-pyran-4-ylamino)benzoic acid in the form of a trifluoroacetic acid salt in 40 ml of dichloromethane at 0°C. The reaction medium is stirred at room temperature for 24 hours. Water (10 ml) is added drop by drop and then the organic phase is washed with saturated sodium chloride solution, dried on magnesium sulfate, filtered and evaporated. The residue is purified by silica gel chromatography (96:4 dichloromethane/methanol as eluent) to yield 250 mg (14%) of (S)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-4-(3-(2,2,2-trifluoroacetamido)pyrrolidin-1-yl) benzoic acid in the form of a yellow powder.

LCMS (EI, m/z): (M+1) 498.07.

Example 18: 2-(2-fluoroethoxy)-4-(4-methylpiperazin-1-yl)benzoic acid

This compound can be prepared from the following intermediates.

Example 18a: *tert*-butyl 4-fluoro-2-(2-fluoroethoxy)benzoate

Example 18b: *tert*-butyl 2-(2-fluoroethoxy)-4-(4-methylpiperazin-1-yl)benzoate

The following compound was also obtained by this method:

2-(2-fluoroethoxy)-4-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)benzoic acid.

Example 19: 4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(2-fluoroethyl)-acetamido)-benzoic acid

This compound can be prepared from the following intermediates.

Example 19a: *tert*-butyl 4-fluoro-2-(2-fluoroethylamino)benzoate

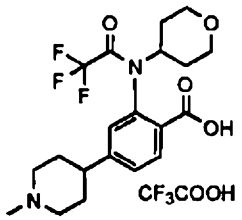
Example 19b: *tert*-butyl 4-fluoro-2-(2,2,2-trifluoro-N-(2-fluoroethyl)acetamido) benzoate

Example 19c: *tert*-butyl 4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(2-fluoroethyl)-acetamido)-benzoate

The following compound was also obtained by this method:

4-((3-(dimethylamino)propyl)(methyl)amino)-2-(2,2,2-trifluoro-N-(2-fluoroethyl) acetamido)benzoic acid.

Example 20: 4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid hydrotrifloroacetate



This compound can be prepared from the following intermediates.

Example 20a: *tert*-butyl 2-nitro-4-(pyridin-4-yl)benzoate

1.67 g of bis(triphenylphosphine)palladium(II)chloride (2.38 mmol) and 15.8 g of sodium carbonate (149 mmol) are added to a solution of 18 g of tert-butyl 4-bromo-2-nitrobenzoate (59.6 mmol) and 10.98 g of pyridine-4-ylboronic acid (89 mmol) in a mixture of 200 ml of dimethoxyethane and 100 mL of water. The reaction medium is heated at 100°C for 24 hours and then concentrated under reduced pressure. The residue obtained is purified by flash chromatography (CH_2Cl_2/AcOEt: 100:0 to 70:30, 30 min). The product is isolated in the form of an oil which crystallizes to yield 14.64 g (82%) of crystals.

MS (m/z): (M+1) 301.0.

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.73 (2H, d, CHarom, J=6.0Hz), 8.44 (1H, s, CHarom), 8.24 (1H, dd, CHarom, J=8.0Hz), 7.97 (1H, d, CHarom, J=8.0Hz), 7.85 (2H, dd, CHarom, J=4.4Hz), 1.54 (9H, s).

Example 20b: 4-(4-(*tert*-butoxycarbonyl)-3-nitrophenyl)-1-methylpyridinium iodide

7.55 mL od iodomethane (121 mmol) is added to a solution of 16.2 g of tert-butyl 2-nitro-4-(pyridin-4-yl)benzoate (60.6 mmol) in 20 mL of acetone. The reaction medium is heated at 60°C for 4 hours and then at room temperature overnight. After dry concentration, 27 g of orange crystals are isolated (100%).

MS (m/z): (M+1) 315.0.

^{1}H NMR: δH ppm (400 MHz, DMSO): 9.14 (2H, d, CHarom, J=6.4Hz), 8.71 (1H, s, CHarom), 8.63 (2H, d, CHarom, J=6.4Hz), 8.47 (1H, dd, CHarom, J=8.0Hz), 8.08 (1H, d, CHarom, J=8.0Hz), 4.37 (3H, s, CH), 1.54 (9H, s).

Example 20c: ***tert*-butyl 2-amino-4-(1-methylpiperidin-4-yl)benzoate**

0.48 g of platine (IV) oxide (2.12 mmol) is added to a solution of 26.8 g of 4-(4-(tert-butoxycarbonyl)-3-nitrophenyl)-1-methylpyridinium iodide (60.6 mmol) in 200 mL of methanol placed in a reactor made in stainless steel. The reaction medium is brought under 5 bar of hydrogen for 24h. The catalyst is filtered and the filtrate is concentrated under reduced pressure to yield 24.8 g (98%) of white crystals.

MS (m/z): (M+1) 291.1.

^{1}H NMR: δH ppm (400 MHz, DMSO): 9.18 (1H, s, HI), 7.60 (1H, d, CHarom, J=8.4Hz), 6.54-6.40 (3H, m, CHarom), 6.39 (1H, d, CHarom, J=8.0Hz), 3.48-3.53 (2H, m, CH), 3.06 (2H, t, CH), 2.81 (3H, s, CH), 2.60-2.70 (1H, m, CH), 1.89-1.97 (2H, m, CH), 1.70-1.80 (2H, m, CH), 1.52 (9H, s).

Example 20d: ***tert*-butyl 4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzoate**

7.18 mL of 2,2,2-trifluoroacetic acid (93 mmol), 4.11 mg of dihydro-2H-pyran-4(3H)-one (44.5 mmol) and then 14.5 g of tetramethylammonium triacetoxyborohydride (53.8 mmol) are successively added to a solution of 15 g of tert-butyl 2-amino-4-(1-methylpiperidin-4-yl)benzoate in 200 mL of dichloromethane under stirring. The reaction medium is stirred at room temperature for 2 h and then taklen up with a 1N soda solution. The organic phase is isolated, dried on magnesium sulfate and then dried concentrated. The residue contained always HI. It is thus taken up in dichloromethane and washed with 100 mL of a 1H soda solution. The organic phase is decanted, dried on magnesium sulfate and dry concentrated to yield 14.6 g of a yellow solid (quantitative yield).

MS (m/z): (M+1) 375.2.

^{1}H NMR: δH ppm (400 MHz, DMSO): 7.69 (1H, d, CHarom, J=8.4Hz), 7.63 (1H, d, CHarom, J=7.6Hz), 6.65 (1H, s, CHarom), 6.44 (1H, dd, CHarom, J=8.4Hz), 3.74-3.86 (2H, m, CH), 3.66-3.71 (1H, m, CH), 3.51 (2H, t, CH), 3.05-3.12 (2H, m, CH), 2.6-2.5 (1H, m, CH), 2.42 (3H, s, CH), 2.30-2.40 (2H, m, CH), 1.89-1.97 (2H, m, CH), 1.64-1.77 (4H, m, CH), 1.52 (9H, s), 1.33-1.45 (2H, m, CH).

Example 20e: ***tert*-butyl 4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoate**

6.35 mL of triethylamine and 5.50 mL of 2,2,2-trifluoroacetic anhydride (39.6 mmol) are added at 0°C to a solution of 11.4 g of tert-butyl 4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzoate (30.4 mmol) in 240 mL of dichloromethane under stirring. The reaction medium is stirred at room temperature for 1h and then 100 mL of water is added dropwise. The organic phase is decanted, dried on magnesium sulfate and dry concentrated. The residue is taken up in a mixture of ethanol/diethyl ether to yield a solid which is filtered on a fritted disc and 12.06 g of white crystals is isolated. The filtrate is concentrated (4.5g) and then purified by flach chromatography on silica (CH_2Cl_2/meOH: 95:5 to 90:10, 20 min). The product obtained is recrysltallized in diethyl ether to yield 1.04 g of additional white crystals (global yield = 74%).

MS (m/z): (M+1) 471.1.

^{1}H NMR: δH ppm (400 MHz, DMSO): 9.45 (1H, sl, NH^+), 7. 96 (1H, d, CHarom, J=8Hz), 7.51 (1H, d, CHarom, J=8Hz), 7.31 (1H, s, CHarom), 4.6-4.5 (1H, m, CH), 3. 90-3.75 (2H, m, CH), 3.5-3.35 (4H, m, CH), 3.1-2.85 (3H, m, CH), 2.79 (3H, s, CH_3), 2.1-1.95 (3H, 3, CH), 1.9-1.75 (2H, m, CH), 1.55-1.40 (11H, m), 1.0-0.85 (1H, m, CH).

Example 20: 4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid hydrotrifluoroacetate.

6.33 mL of 2,2,2-trifluoroacetic acid (82 mmol) is added under stirring to a solution of 3.2 g of tert-butyl 4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoate (5.47 mmol) (in the form of a salt of trifluoroacetic acid) in 30 mL of dichloromethane. The reaction medium is stirred at room temperature for 16h, and then evaporated under reduced pressure. The residue is taken up in ethanol, and the white solid formed is filtered on a fritted disc to yield 1.61 g (53%) of white crystals.

MS (m/z): (M+1) 415.1.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.39 (1H, sl, COOH), 9.46 (1H, sl, COOH du TFA), 7.99 (1H, d, CHarom, J=8.4Hz), 7.49 (1H, d, CHarom, J=8.4Hz), 7.30 (1H, s, CHarom), 4.53 (1H, m, CH), 3.74-3.86 (2H, m, CH), 3.35-3.45 (5H, m, CH), 2.90-3.01 (3H, m, CH), 2.76 (3H, s, CH), 1.65-2.04 (5H, m, CH), 1.44-1.54 (2H, m, CH).

Example 21: 1-(4-isothiocyanatophenyl)-4-methylpiperazine

This compound was prepared by adapting the method described in EP1215208.

The following compound was also obtained by this method:

***tert*-butyl 2-isothiocyanato-5-(4-methylpiperazin-1-yl)phenylcarbamate.**

Example 22: *tert*-butyl 2-isocyanato-5-(4-methylpiperazin-1-yl)phenylcarbamate

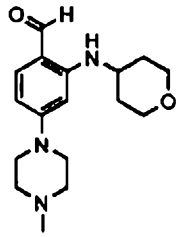
This compound can be prepared from the following intermediates.

Example 22a: *tert*-butyl 5-(4-methylpiperazin-1-yl)-2-nitrophenylcarbamate

Example 22b: *tert*-butyl 2-amino-5-(4-methylpiperazin-1-yl)phenylcarbamate

Example 22: *tert*-butyl 2-isocyanato-5-(4-methylpiperazin-1-yl)phenylcarbamate

Example 23: 4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzaldehyde



Example 23a: (4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) phenyl)methanol

500 mg (1.060 mmol) of 4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid dissolved in 5 ml of tetrahydrofuran is added at 0°C to a suspension of 201 mg (5.30 mmol) of $LiAlH_4$ in 9 ml of tetrahydrofuran. The reaction mixture is stirred at 0°C for 1 hour and then at room temperature for 3 hours. The reaction mixture is cooled at 0°C and then, drop by drop, 200 µl water, then 200 µl of soda solution (15% by weight) and finally 1 ml of water are added. The reaction mixture is stirred at room temperature for 2 hours and then filtered and rinsed with tetrahydrofuran. The filtrate is concentrated to yield 250 mg (yield=77%) of (4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)phenyl)methanol in the form of a white solid.

LCMS (EI, m/z): (M+1) 306.14.

^1H NMR: $\delta_{H\ ppm}$ (400 MHz, DMSO): 6.85 (1H, d, CH_{arom}), 6.20 (1H, d, CH_{arom}), 6.10 (1H, d, CH_{arom}), 4.95 (1H, bs, OH), 4.87 (1H, d, NH), 4.37 (2H, d, CH_2), 3.83-3.86 (2H,

m, CH), 3.56 (1H, m, CH), 3.46-3.56 (3H, m, CH), 3.45 (1H, m, CH), 3.05-3.07 (4H, m, CH), 2.41-2.44 (4H, m, CH), 2.21 (3H, s, CH_3), 1.89-1.92 (2H, m, CH).

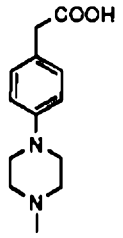
Example 23: 4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzaldehyde

85 mg (0.982 mmol) of manganese dioxide is added at room temperature to a solution of (4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)phenyl)methanol (100 mg, 0.327 mmol) in a mixture of ethyl acetate (10 ml) and dichloromethane (9 ml). The reaction mixture is placed in an ultrasonic bath for 5 hours. The reaction mixture is filtered, the solvents are evaporated and the crude product is purified by chromatography to yield 50.0 mg (yield=50.3%) of (4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzaldehyde in the form of a white solid.

LCMS (EI, m/z): (M+1) 304.19.

^{1}H NMR: $\delta_{H\ ppm}$ (400 MHz, DMSO): 9.43 (1H, d, CH), 7.32 (1H, d, CH_{arom}), 6.36 (1H, d, CH_{arom}), 6.08 (1H, d, CH_{arom}), 3.94-3.99 (2H, m, CH), 3.77 (1H, m, CH), 3.61-3.63 (2H, m, CH), 3.42-3.45 (4H, m, CH), 2.57-2.60 (4H, m, CH), 2.36 (3H, s, CH_3), 2.04-2.08 (2H, m, CH), 1.51-1.60 (2H, m, CH).

Example 24: 2-(4-(4-methylpiperazin-1-yl)phenyl)acetic acid



Example 24a: 2,2,2-trichloro-1-(4-(4-methylpiperazin-1-yl)phenyl)ethanol

1.0 ml (10.00 mmol) of trichloroacetic acid and, in small portions, 1.854 g (10 mmol) of sodium 2,2,2-trichloroacetate are added at room temperature to a solution of 1.362 g (6.67 mmol) of 4-(4-methylpiperazine-1-yl)benzaldehyde in 13.5 ml of dimethylformamide. The reaction mixture is stirred for 3 hours at room temperature. The solvent is concentrated and the crude reaction product extracted with ethyl acetate. The organic phase is washed using saturated sodium bicarbonate solution. The organic phases are combined, dried on magnesium sulfate and then concentrated to yield

1.760 g (yield=82%) of 2,2,2-trichloro-1-(4-(4-methylpiperazine-1-yl)phenyl)ethanol in the form of a white solid.

LCMS (EI, m/z): (M+1) 324.04.

^{1}H NMR: $\delta_{H\ ppm}$ (400 MHz, DMSO): 7.41 (2H, d, CH_{arom}), 7.02 (1H, bs, OH), 6.90 (2H, d, CH_{arom}), 5.08 (1H, bs, CH), 3.14-3.16 (4H, m, CH), 2.42-2.47 (4H, m, CH), 2.21 (3H, s, CH_3).

Example 24: 2-(4-(4-methylpiperazin-1-yl)phenyl)acetic acid

0.559 g (14.77 mmol) of sodium borohydride is added quickly to 2.294 g (7.35 mmol) of dibenzyl diselenide in 28 ml of ethanol. The reaction mixture is stirred at room temperature for 1 hour. 2.266 g (7 mmol) of 2,2,2-trichloro-1-(4-(4-methylpiperazine-1-yl)phenyl)ethanol and 1.680 g (42.0 mmol) of sodium hydroxide are then added. The reaction mixture is stirred at 35°C for 24 hours. The solvent is concentrated and the crude product extracted with ethyl acetate after adding a pH 5 aqueous phase. The organic phases are combined, dried on magnesium sulfate and then concentrated to yield 2-(4-(4-methylpiperazine-1-yl)phenyl)acetic acid which is used without additional purification.

LCMS (EI, m/z): (M+1) 235.294.

Example 25: 2-(4-(4-methylpiperazin-1-yl)-2-nitrophenyl) acetic acid

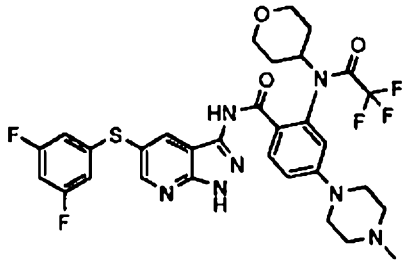
This compound can be prepared from the following intermediates.

Example 25a: diethyl 2-(4-fluoro-2-nitrophenyl)malonate

Example 25b: diethyl 2-(4-(4-methylpiperazin-1-yl)-2-nitrophenyl)malonate

Example of method E1:

Example 26: N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl) acetamido)benzamide

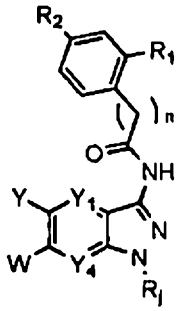


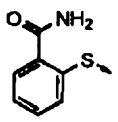
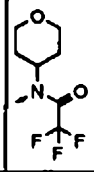
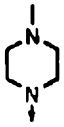
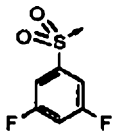
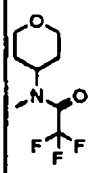
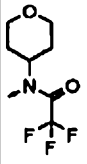
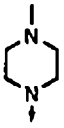
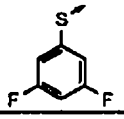
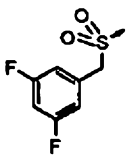
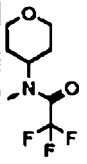
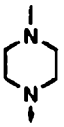
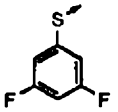
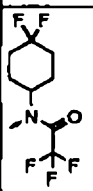
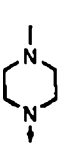
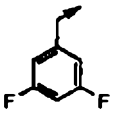
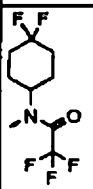
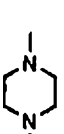
0.95 ml (11.21 mmol) of oxalyl chloride and 2 drops of anhydrous dimethylformamide are added to 2.97 g (5.61 mmol) of a solution of 4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid in 95 ml of dichloromethane. The reaction mixture is stirred for 2 hours at room temperature. The solvents are evaporated, the solid formed is taken up in toluene and the solvent evaporated. This operation is repeated three times until a white solid is obtained. The acid chloride is dissolved in 35 ml of anhydrous tetrahydrofuran at -20°C and then the solution formed is added to a solution containing 1.56 g (5.61 mmol) of 5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine and 3.71 ml (21.30 mmol) of N-ethyl-N-isopropylpropan-2-amine in 30 ml of anhydrous tetrahydrofuran. The reaction mixture is stirred for 3 hours at -20°C and then overnight at room temperature. The precipitate obtained is filtered and rinsed with tetrahydrofuran and water and then dried to yield 2 g (53%) of N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide.

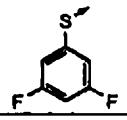
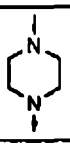
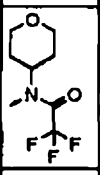
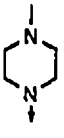
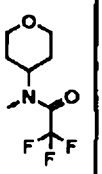
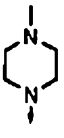
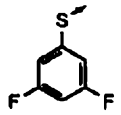
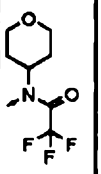
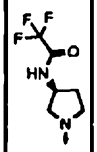
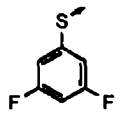
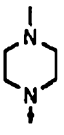
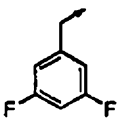
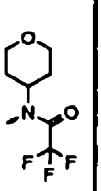
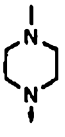
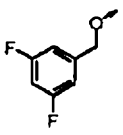
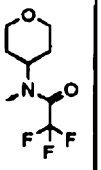
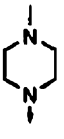
LCMS (EI, m/z): (M+1) 676.20.

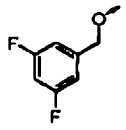
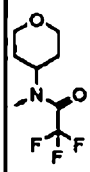
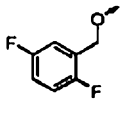
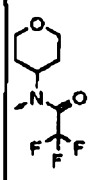
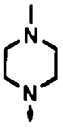
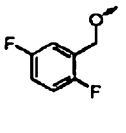
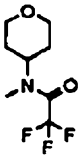
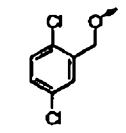
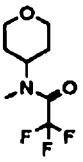
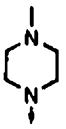
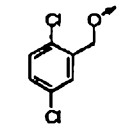
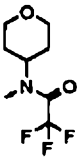
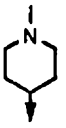
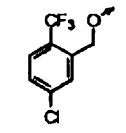
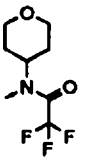
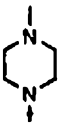
^{1}H NMR: δH ppm (400 MHz, DMSO): 13.66 (1H, bs, NH), 11.08 (1H, bs, NH), 8.61 (1H, s, CH_{arom}), 8.46 (1H, s, CH_{arom}), 7.83 (1H, d, CH_{arom}), 7.05-7.10 (2H, m, CH_{arom}), 6.83-6.89 (3H, m, CH_{arom}), 4.39-4.44 (1H, m, CH), 3.83-3.85 (1H, m, CH), 3.69-3.72 (1H, m, CH), 3.59-3.62 (1H, m, CH), 3.30-3.32 (4H, m, CH_2), 2.30-2.44 (4H, m, CH_2), 2.27 (3H, s, CH_3), 1.87-1.90 (1H, m, CH), 1.59-1.60 (1H, m, CH), 1.49-1.50 (1H, m, CH), 1.20-1.40 (1H, m, CH).

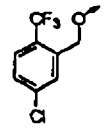
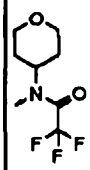
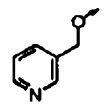
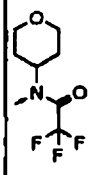
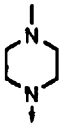
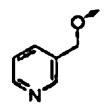
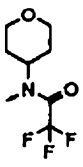
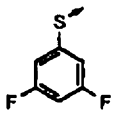
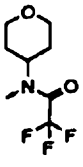
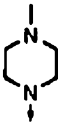
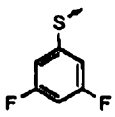
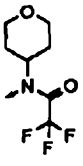
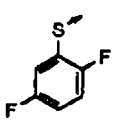
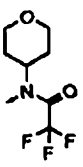
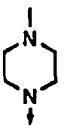
The following derivatives were obtained according to the same method:

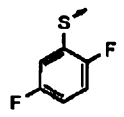
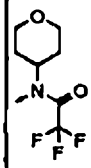
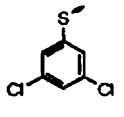
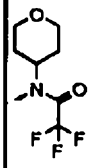
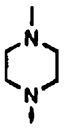
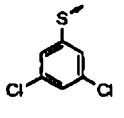
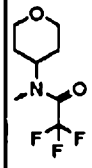
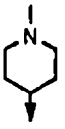
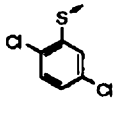
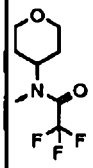
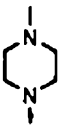
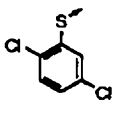
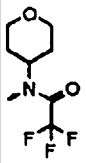
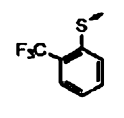
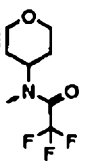
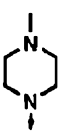


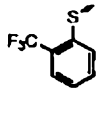
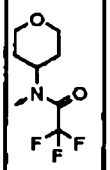
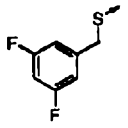
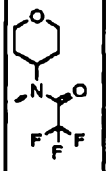
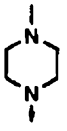
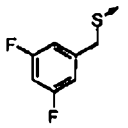
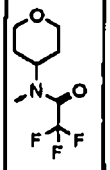
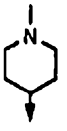
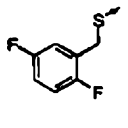
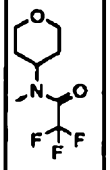
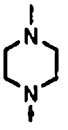
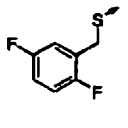
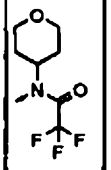
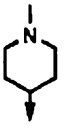
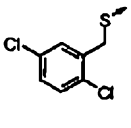
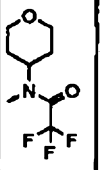
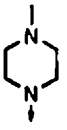
Ex.**	Y	R_1	R_2	n	W	R_j	Y_1, Y_4	Compound names	Yield	Mass MH^+
26-1				0	H	H	CH, N	N-(5-(2-carbamoylphenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-2				0	H	H	CH, N	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	ND
26-3	I			0	H	H	CH, N	N-(5-iodo-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-4		H	NO_2	1	H	H	CH, N	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-(4-nitrophenyl)acetamide	ND	442.21
26-5				0	H	H	CH, N	N-(5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-6				0	H	H	CH, N	2-(N-(4,4-difluorocyclohexyl)-2,2,2-trifluoroacetamido)-N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)benzamide	ND	ND
26-7				0	H	H	CH, N	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	22%	676.2

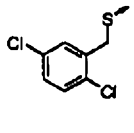
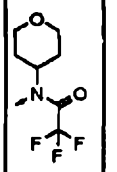
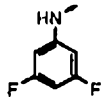
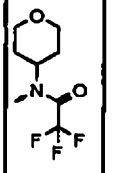
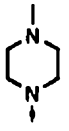
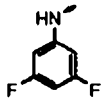
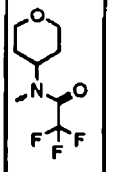
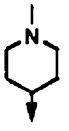
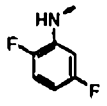
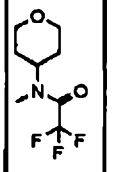
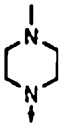
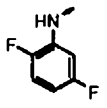
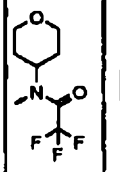
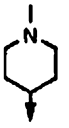
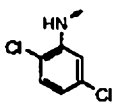
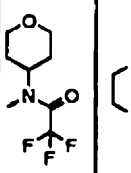
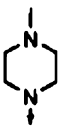
26-8		H		1	H	H	CH, N	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-(4-(4-methylpiperazin-1-yl)phenyl)acetamide	ND	495.17
26-9	I			0	OMe	H	CH, N	N-(5-iodo-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	688.18
26-10	I			0	NH_2	H	CH, N	N-(6-amino-5-iodo-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	673.06
26-11				1	H	H	CH, N	(S)-N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-4-(3-(2,2,2-trifluoroacetamido)pyrrolidin-1-yl)benzamide	ND	ND
26-12		H		0	H	H	CH, N	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)benzamide	46%	481.38
26-13				0	H	H	N, CH	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	35%	658.1
26-14				0	H	H	N, CH	N-(5-(3,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	63%	674.1

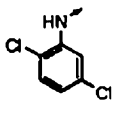
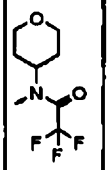
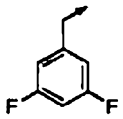
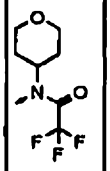
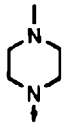
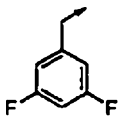
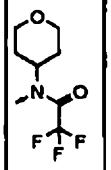
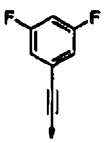
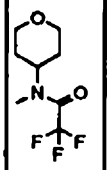
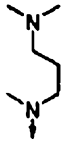
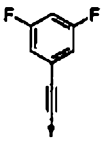
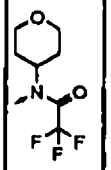
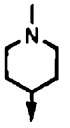
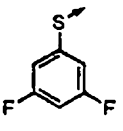
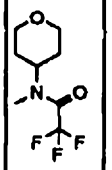
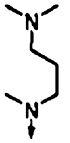
26-15				0	H	H	N, CH	N-(5-(3,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	673.1
26-16				0	H	H	N, CH	N-(5-(2,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	62%	674.2
26-17				0	H	H	N, CH	N-(5-(2,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	673.3
26-18				0	H	H	N, CH	N-(5-(2,5-dichlorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-19				0	H	H	N, CH	N-(5-(2,5-dichlorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-20				0	H	H	N, CH	N-(5-(5-chloro-2-(trifluoromethyl)benzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	55%	740.2

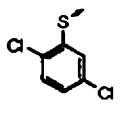
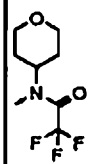
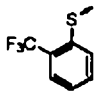
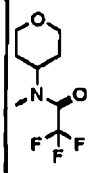
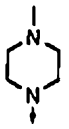
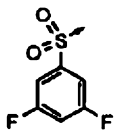
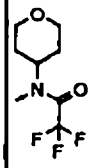
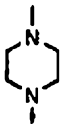
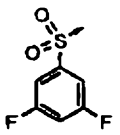
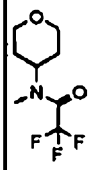
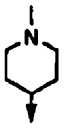
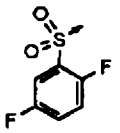
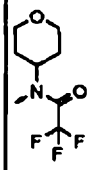
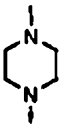
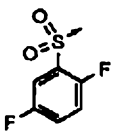
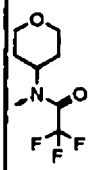
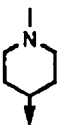
26-21				0	H	H	N, CH	N-(5-(5-chloro-2-(trifluoromethyl)benzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	739.3
26-22				0	H	H	N, CH	4-(4-methylpiperazin-1-yl)-N-(5-(pyridin-3-ylmethoxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	90%	639.2
26-23				0	H	H	N, CH	4-(1-methylpiperidin-4-yl)-N-(5-(pyridin-3-ylmethoxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	638.2
26-24				0	H	H	N, CH	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-25				0	H	H	N, CH	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	50%	ND
26-26				0	H	H	N, CH	N-(5-(2,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND

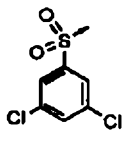
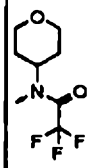
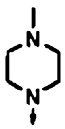
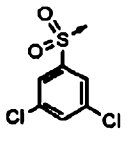
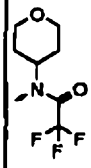
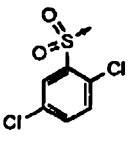
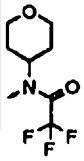
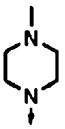
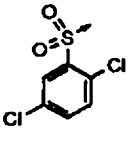
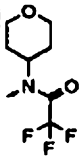
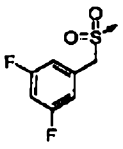
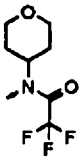
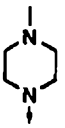
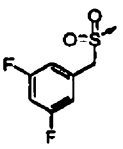
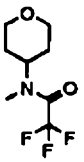
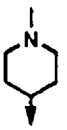
26-27				0	H	H	N, CH	N-(5-(2,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-28				0	H	H	N, CH	N-(5-(3,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-29				0	H	H	N, CH	N-(5-(3,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-30				0	H	H	N, CH	N-(5-(2,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-31				0	H	H	N, CH	N-(5-(2,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-32				0	H	H	N, CH	4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-N-(5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzamide	ND	ND

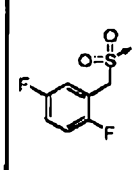
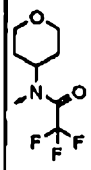
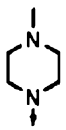
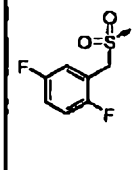
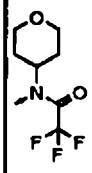
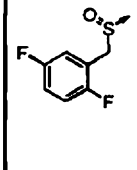
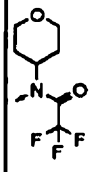
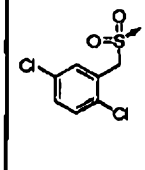
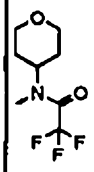
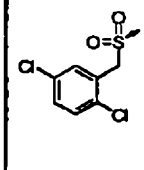
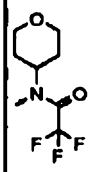
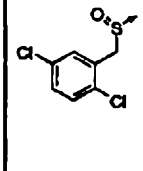
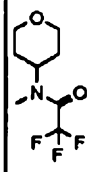
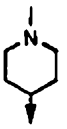
26-33				0	H	H	N, CH	4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-N-(5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzamide	ND	ND
26-34				0	H	H	N, CH	N-(5-(3,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-35				0	H	H	N, CH	N-(5-(3,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	73%	ND
26-36				0	H	H	N, CH	N-(5-(2,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-37				0	H	H	N, CH	N-(5-(2,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-38				0	H	H	N, CH	N-(5-(2,5-dichlorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND

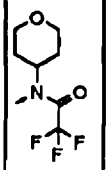
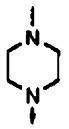
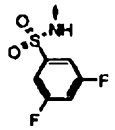
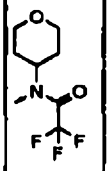
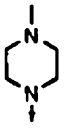
26-39				0	H	H	N, CH	N-(5-(2,5-dichlorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-40				0	H	H	N, CH	N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	79%	659.2
26-41				0	H	H	N, CH	N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	658.2
26-42				0	H	H	N, CH	N-(5-(2,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	659.2
26-43				0	H	H	N, CH	N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	658.2
26-44				0	H	H	N, CH	N-(5-(2,5-dichlorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	26%	691.2

26-45				0	H	H	N, CH	N-(5-(2,5-dichlorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	98%	692.2
26-46				0	H	H	N, N	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-47				0	H	H	N, N	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-48				0	H	H	N, N	N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-((3-(dimethylamino)propyl)(methyl)amino)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-49				0	H	H	N, N	N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-50				0	H	H	N, N	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-((3-(dimethylamino)propyl)(methyl)amino)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	43%	693.2

26-51				0	H	H	N, N	N-(5-(2,5-dichlorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-52				0	H	H	N, CH	4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)-N-(5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-yl)benzamide	66%	709.1
26-53				0	H	H	N, CH	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	28%	708.2
26-54				0	H	H	N, CH	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	74%	707.2
26-55				0	H	H	N, CH	N-(5-(2,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-56				0	H	H	N, CH	N-(5-(2,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND

26-57				0	H	H	N, CH	N-(5-(3,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-58				0	H	H	N, CH	N-(5-(3,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-59				0	H	H	N, CH	N-(5-(2,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-60				0	H	H	N, CH	N-(5-(2,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-61				0	H	H	N, CH	N-(5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	94%	ND
26-62				0	H	H	N, CH	N-(5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	99%	ND

26-63				0	H	H	N, CH	N-(5-(2,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	60%	ND
26-64				0	H	H	N, CH	N-(5-(2,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	36%	ND
26-65				0	H	H	N, CH	N-(5-(2,5-difluorobenzylsulfinyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	ND
26-66				0	H	H	N, CH	N-(5-(2,5-dichlorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	52%	ND
26-67				0	H	H	N, CH	N-(5-(2,5-dichlorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	90%	ND
26-68				0	H	H	N, CH	N-(5-(2,5-dichlorobenzylsulfinyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	50%	ND

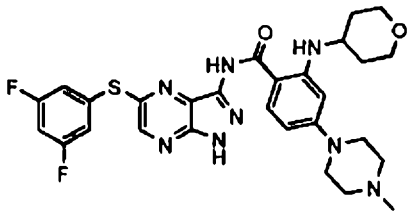
26-69	I			0	H	C(Ph)$_3$	CH, N	N-(5-iodo-1-trityl-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	67%	900.23
26-70				0	H	H	CH, N	N-(5-(3,5-difluorophenylsulfonamido)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	11%	ND

** ^{1}H NMR, dmso-d_6, Ex.: **26-4**: 13,64 (1H, sl, NH), 11,26 (1H, sl, NH), 8,68 (1H, d, CH_{arom}), 8,58 (1H, d, CH_{arom}), 8,20 (2H, d, CH_{arom}), 7,64 (2H, d, CH_{arom}), 7,03 (1H, m, CH_{arom}), 6,78 (2H, m, CH_{arom}), 3,95 (2H, m, CH_2). **26-8**: 13,59 (1H, sl, NH), 11,05 (1H, sl, NH), 8,68 (1H, d, CH_{arom}), 8,57 (1H, d, CH_{arom}), 7,19 (2H, d, CH_{arom}), 6,99-7,08 (1H, m, CH_{arom}), 6,88 (2H, d, CH_{arom}), 6,75-6,79 (2H, m, CH_{arom}), 3,61 (2H, m, CH_2), 3,07-3,09 (4H, m, CH), 2,41-2,44 (4H, m, CH), 2,20 (3H, s, CH_3). **26-9**: 13,17 (1H, sl, NH), 10,90 (1H, sl, NH), 8,55 (1H, s, CHarom), 7,79 (1H, d, CHarom), 7,07 (1H, dd, CHarom), 6,90 (1H, d, CHarom), 4,40-4,50 (1H, m, CH), 3,96 (3H, s, CH_3), 3,82-3,89 (1H, m, CH), 3,74-3,80 (1H, m, CH), 3,34-3,41 (2H, m, CH), 3,28-3,33 (4H, m, 2*CH_2), 2,43-2,47 (4H, m, 2*CH_2), 2,23 (3H, s, CH_3), 1,85-1,92 (1H, m, CH), 1,58-1,63 (1H, m, CH), 1,45-1,53 (1H, m, CH), 1,22-1,33 (1H, m, CH). **26-10**: 12,48 (1H, sl, NH), 10,72 (1H, sl, NH), 8,30 (1H, s, CHarom), 7,77 (1H, d, CHarom), 7,06 (1H, dd, CHarom), 6,88 (1H, d, CHarom), 6,40 (2H, sl, NH_2), 4,40-4,50 (1H, m, CH), 3,82-3,89 (1H, m, CH), 3,74-3,80 (1H, m, CH), 3,34-3,41 (2H, m, CH), 3,28-3,33 (4H, m, 2*CH_2), 2,43-2,47 (4H, m, 2*CH_2), 2,23 (3H, s, CH_3), 1,85-1,92 (1H, m, CH), 1,58-1,65 (1H, m, CH), 1,45-1,55 (1H, m, CH), 1,22-1,34 (1H, m, CH). (ND: not determined). **26-14**: 12.99 (1H, sl, NH), 10.25 (1H, s, NH), 7.96 (1H, d, CHarom, J=9.2Hz), 7.90-7.80 (1H, m, CHarom), 7.23-7.16 (3H, m, CHarom), 7.12-7.08 (1H, m, CHarom), 6.96 (1H, d, CHarom, J=8.8Hz), 6.87 (1H, s, CHarom), 5.31 (2H, s), 4.49-4.42 (1H ,m), 3.86-3.75 (2H, m), 3.45 (1H, m), 3.37 (1H,m), 3.35 (4H, s), 2.42 (4H, s), 2.22 (3H, s), 1.90-1.75 (2H, m), 1.53-1.49 (1H, m), 1.31-1.25 (1H, m). **26-16**: 13.00 (1H, s, NH), 10.27 (1H, s, NH), 7.95 (1H, d, CHarom, J=8.8Hz), 7.89-7.84 (1H, m,

CHarom), 7.50-7.40 (1H, m, CHarom), 7.35-7.20 (2H, m, CHarom), 7.12-7.09 (1H, m, CHarom), 6.94 (1H, d, CHarom, J=8.8Hz), 6.87 (1H, s, CHarom), 5.30 (2H, s), 4.52-4.43 (1H, m), 3.85-3.75 (2H, m), 3.46-3.43 (1H, m), 3.36 (5H, s), 2.45 (4H, s), 2.22 (3H, s), 1.92-1.82 (2H, m), 1.60-1.52 (1H, m), 1.33-1.26 (1H, m). **26-20**: 13.01 (1H, s, NH), 10.22 (1H, s, NH), 7.97 (1H, d, CHarom, J=8.8Hz), 7.90-7.78 (3H, m, CHarom), 7.68-7.64 (1H, m, CHarom), 7.12-7.08 (1H, m, CHarom), 6.97 (1H, d, CHarom, J=8.8Hz), 6.85 (1H, s, CHarom), 5.43 (2H, s), 4.45-4.40 (1H, m), 3.86-3.70 (2H, m), 3.46-3.42 (1H, m), 3.30-3.28 (5H, m), 2.46 (4H, s), 2.23 (3H, s), 1.90 (1H, d, J=11.2Hz), 1.77 (1H, d, J=11.2Hz), 1.58-1.50 (1H, m), 1.30-1.20 (1H, m).

In certain cases, the major product of these reactions corresponds to the disubstituted product characterized by the additional functionalization of the pyrazole ring. In these cases, this product is isolated and transformed into a monosubstituted product by treatment with a base as described below.

Example 27: N-(5-(3,5-difluorophenylthio)-1-H-pyrazolo[3,4-b]pyrazine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide



Example 27a: N-(5-(3,5-difluorophenylthio)-1-(4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoyl)-1H-pyrazolo[3,4-b]pyrazine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide

1.51 ml (17.90 mmol) of oxalyl chloride and 2 drops of anhydrous dimethylformamide are added to 4.74 g (8.95 mmol) of a solution of 4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid in 60 ml of dichloromethane. The reaction mixture is stirred for 2 hours at room temperature. The solvents are evaporated, the solid formed is taken up in toluene and the solvent is evaporated; this operation is repeated three times until a white solid is obtained.

The acid chloride is added at 0°C in small fractions to 1 g (3.58 mmol) of 5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyrazine-3-amine dissolved in 15 ml of pyridine. The reaction mixture is stirred at 25°C overnight at room temperature. After evaporation of the solvent, the residue is purified by silica gel chromatography (90:10 dichloromethane/methanol and then 90:9:1 and then 90:5:5 dichloromethane/methanol/ammonium as eluent) to yield N-(5-(3,5-difluorophenylthio)-1-(4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido) benzoyl)-1H-pyrazolo[3,4-b]pyrazine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide.

LCMS (EI, m/z): (M+1) 1074.64.

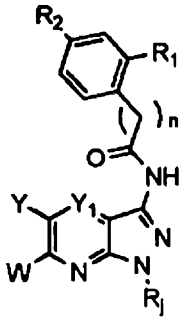
Example 27: N-(5-(3, 5-difluorophenylthio)-1-H-pyrazolo[3,4-b]pyrazine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide.

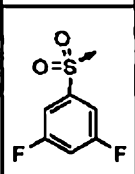
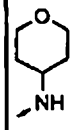
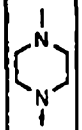
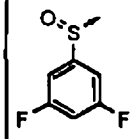
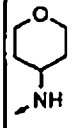
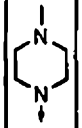
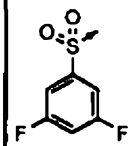
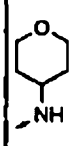
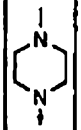
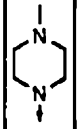
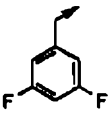
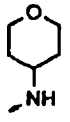
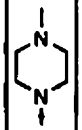
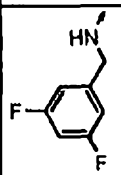
0.27 ml (1.95 mmol) of triethylamine is added to 0.21 g (0.19 mmol) of a solution of N-(5-(3,5-difluorophenylthio)-1-(4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoyl)-1H-pyrazolo[3,4-b]pyrazine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido) benzamide in 5 ml of methanol. The reaction medium is heated at 65°C for 4 hours, and then overnight at room temperature. After evaporation of the solvent, the product is extracted several times with ethyl acetate. The organic phases are combined, washed with saturated sodium bicarbonate solution, dried on magnesium sulfate and concentrated. The residue is purified by silica gel chromatography (95:4:1 dichloromethane/methanol/ammonium as eluent) to yield 0.065 g (57%) of N-(5-(3,5-difluorophenylthio)-1-H-pyrazolo[3,4-b]pyrazine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide in the form of a yellow solid.

LCMS (EI, m/z): (M-1) 579.21.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.95 (1H, bs, NH), 10.25 (1H, bs, NH), 8.62 (1H, s, CH_{arom}), 8.27 (1H, d, NH), 7.80 (1H, d, CH_{arom}), 7.17-7.27 (3H, m, CH_{arom}), 6.27 (1H, d, CH_{arom}), 6.12 (1H, d, CH_{arom}), 3.79-3.82 (2H, m, CH), 3.67 (1H, m, CH), 3.45-3.50 (2H, m, CH), 3.26-3.29 (4H, m, CH), 2.42-2.44 (4H, m, CH), 2.22 (3H, s, CH_3), 1.90-1.93 (2H, m, CH), 1.31-1.36 (2H, m, CH).

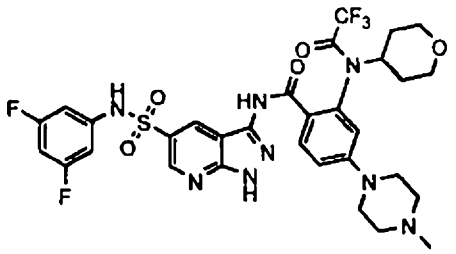
The following compounds were obtained by the same method:



Ex.**	Y	R_1	R_2	Y_1	n	W	R_j	Compound names	Yield	Mass
27-1				CH	0	H	H	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	18,6%	(M+H) 612.13
27-2				N	0	H	H	N-(5-(3,5-difluorophenylsulfinyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	(M+Na) 619.6
27-3				N	0	H	H	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	(M+H) 613.5
27-4	H			CH	0		H	N-(6-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	24%	(M+H) 562.00
27-5	H			CH	0		H	N-(6-(3,5-difluorobenzylamino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	(M-H) 275.1

Reactions carried out in pyridine often make it possible to modify the regioisomer distribution of the products. The following example is characteristic of a reaction of this type.

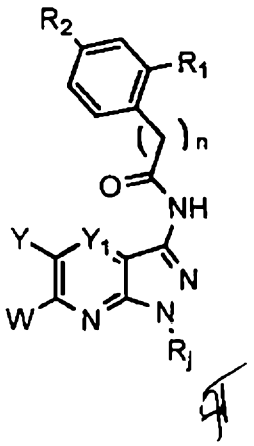
Example 27-bis: N-(5-(N-(3,5-difluorophenyl)sulfamoyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide

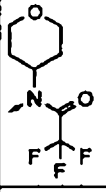
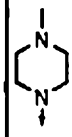
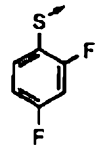
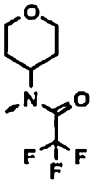
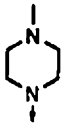
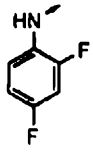
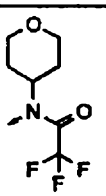
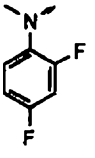


0.224 ml (2.63 mmol) of oxalyl chloride and 2 drops of anhydrous dimethylformamide are added to 0.697 g (1.316 mmol) of a solution of 4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzoic acid in 20 ml of dichloromethane. The reaction mixture is stirred for 2 hours at room temperature. The solvents are evaporated, the solid formed is redissolved in toluene and the solvent is evaporated. This operation is repeated three times until a white solid is obtained.

The acid chloride is dissolved in 5 ml of anhydrous pyridine and then the solution formed is added to a solution of 0.214 g (0.658 mmol) of 3-amino-N-(3,5-difluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-sulfonamide in 5 ml of pyridine at 0°C. The reaction mixture is stirred for 3 hours at 0°C, and then overnight at room temperature. The pyridine is evaporated and the crude reaction product is redissolved in toluene and then dry concentrated. The reaction mixture is diluted with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase is dried on $MgSO_4$, filtered and concentrated and the crude product is used directly in the deprotection reaction with no purification or characterization.

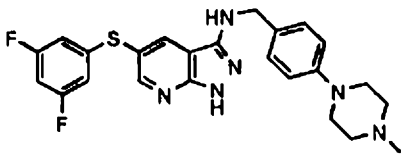
The following compounds were obtained by the same method:



Ex.**	Y	R_1	R_2	Y_1	n	W	R_3	Compound names	Yield	Mass
27bis-1	H			CH	0		H	N-(6-(2,4-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	676.18 (M+H)
27bis-2	H			CH	0		H	N-(6-(2,4-difluorophenylamino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	28%	657.13 (M-H)
27bis-3	H			CH	0		H	N-(6-((2,4-difluorophenyl)(methyl)amino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide	ND	671.05 (M-H)

Example of method E2:

Example 28: 5-(3,5-difluorophenylthio)-N-(4-(4-methylpiperazin-1-yl)benzyl)-1H-pyrazolo[3,4-b]pyridin-3-amine

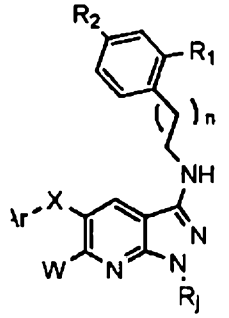


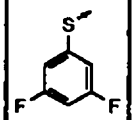
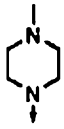
41.5 µl of trifluoroacetic acid (0.539 mmol) and, in small fractions, 129 mg (0.611 mmol) of sodium triacetoxyborohydride are added to a solution of 100 mg (0.35 mmol) of 5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine and 81 mg (0.395 mmol) of 4-(4-methylpiperazin-1-yl)benzaldehyde in 20 ml of a 1:1 mixture of dichloromethane and tetrahydrofuran. The reaction medium is stirred for 16 hours at room temperature. An additional fraction of 125 µl of trifluoroacetic acid and 388 mg of sodium triacetoxyborohydride are added and the reaction medium is stirred for an additional 24 hours. The solvent is then concentrated and the reaction medium extracted with ethyl acetate and washed using saturated sodium bicarbonate solution. The organic phases are combined, dried on magnesium sulfate and then concentrated to yield a yellow oil. A trituration of this oil in methanol leads to the isolation of 135 mg of a yellow solid.

LCMS (EI, m/z): (M+1) 467.57.

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.43 (1H, bs, NH), 8.49 (1H, d, CH_{arom}), 8.47 (1H, d, CH_{arom}), 7.25 (2H, d, CH_{arom}), 7.03-7.08 (1H, m, CH_{arom}), 6.89 (2H, d, CH_{arom}), 6.76-6.77 (3H, m, NH and CH_{arom}), 4.34 (2H, d, CH), 3.08 (4H, m, CH), 2.44 (4H, m, CH), 2.21 (3H, s, CH_3).

The following derivative was obtained according to the same method:

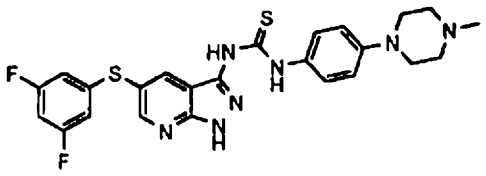


Ex.**	ArX	R_1	R_2	n	W	R_j	Compound name	Yield	Mass MH^+
28-1		NO_2		0	H	H	5-(3,5-difluorophenylthio)-N-(4-(4-methylpiperazin-1-yl)-2-nitrobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-amine	91%	512.16

**^{1}H NMR, DMSO-d_6, Ex.: 28-1: 12.43 (1H, bs, NH), 8.49 (1H, d, CH_{arom}), 8.47 (1H, d, CH_{arom}), 7.51 (1H, d, CH_{arom}), 7.45 (1H, m, CH_{arom}), 7.27 (1H, m, CH_{arom}), 7.03-7.08 (1H, m, CH_{arom}), 7.00 (1H, t, NH), 6.77-6.80 (2H, m, CH_{arom}), 4.63 (2H, d, CH), 3.19-3.21 (4H, m, CH), 2.42-2.45 (4H, m, CH), 2.21 (3H, s, CH_3).

Example of method E3

<u>Example 29</u>: 1-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)thiourea



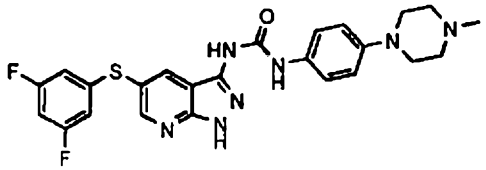
0.507 g (2.17 mmol) of 1-(4-isothiocyanatophenyl)-4-methylpiperazine is added at 25°C to 0.540 g (2.17 mmol) of 3,5-difluorophenylthio-1H-pyrazolo[3,4-b]pyridin-3-amine

dissolved in 12 ml of anhydrous dimethylacetamide. The mixture is left under stirring for 15 hours at 85°C. The reaction is treated by adding 20 ml of water and then is extracted with ethyl acetate. The organic phase is dried on sodium sulfate, filtered and concentrated. The product is purified by silica chromatography (15:1 dichloromethane/methanol as eluent) to yield 0.156 g (yield=15%) of 1-(1-*tert*-butyl-5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)thiourea in the form of a light brown solid.

LCMS (EI, m/z): (M+1) 512.08.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.69 (1H, bs, NH), 11.50 (1H, bs, NH), 11.19 (1H, bs, NH), 8.96 (1H, d, CH_{arom}), 8.66 (1H, d, CH_{arom}), 7.41 (2H, d, CH_{arom}), 7.10 (1H, ddd, CH_{arom}), 6.95 (2H, d, CH_{arom}), 6.89 (2H, bd, CH_{arom}), 3.13-3.16 (4H, m, CH), 2.45-2.47 (4H, m, CH), 2.23 (3H, s, CH).

Example 29-bis: 1-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)urea



0.048 g (1.19 mmol) of sodium hydride is added at 0°C to 0.200 g (0.598 mmol) of 1-*tert*-butyl-5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine dissolved in 10 ml of anhydrous dimethylacetamide. The reaction is left under stirring for 10 minutes. 0.130 g (0.598 mmol) of 1-(4-isocyanatophenyl)-4-methylpiperazine is then added at 0°C. The mixture is left under stirring for 3 hours at room temperature. The reaction is treated by adding 20 ml of water drop by drop at 0°C and then is extracted with ethyl acetate. The organic phase is dried on sodium sulfate, filtered and concentrated. The product is purified by silica chromatography to yield 0.150 g (yield=45%) of 1-(1-*tert*-butyl-5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)urea in the form of a light brown solid.

LCMS (EI, m/z): (M+1) 552.21.

^{1}H NMR: δH ppm (400 MHz, DMSO): 8.92 (1H, bs, NH), 8.58 (1H, bs, NH), 8.51 (1H, bs, CH_{arom}), 8.30 (1H, bs, CH_{arom}), 7.31 (2H, d, CH_{arom}), 7.05 (1H, m, CH_{arom}), 6.83-6.85

(2H, m, CH_{arom}), 3.03-3.08 (4H, m, CH), 2.45-2.48 (4H, m, CH), 2.21 (3H, s, CH), 1.76 (9H, s, CH).

A solution of 0.150 g (0.272 mmol) of 1-(1-*tert*-butyl-5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl)phenyl)urea dissolved in 20 ml of TFA (trifluoroacetic acid) is refluxed for 3 hours. The solvent is evaporated and the crude reaction product is diluted with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase is dried on $MgSO_4$, filtered and concentrated. The solid obtained is triturated in methanol, filtered and dried. 110 mg (82%) of 1-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-(4-(4-methylpiperazin-1-yl) phenyl)urea in the form of a beige solid is obtained.

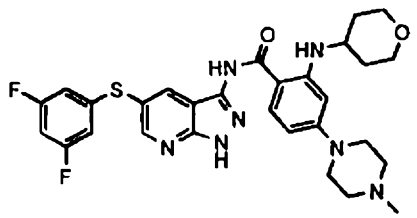
LCMS (EI, m/z): (M+1): 496.06.

^{1}H NMR: δH ppm (400 MHz, DMSO): 10.85 (1H, bs, NH), 9.57 (1H, bs, NH), 8.57 (1H, bs, CH_{arom}), 8.30 (1H, bs, CH_{arom}), 7.39 (2H, d, CH_{arom}), 6.99 (1H, m, CH_{arom}), 6.89 (2H, d, CH_{arom}), 6.70 (2H, bd, CH_{arom}), 3.03-3.08 (4H, m, CH), 2.45-2.48 (4H, m, CH), 2.21 (3H, s, CH).

Examples of method F

Examples of method F1: deprotection

<u>Example 30</u>: N-(5-(3, 5-difluorophenylthio)-1-H-pyrazolo[3, 4-b]pyridine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide



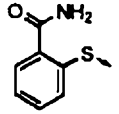
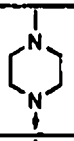
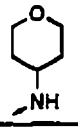
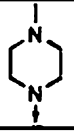
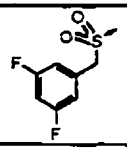
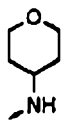
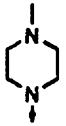
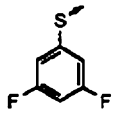
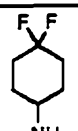
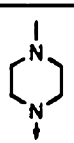
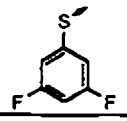
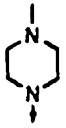
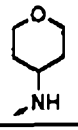
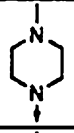
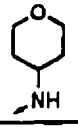
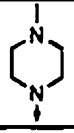
9.08 ml (65.1 mmol) of triethylamine is added to 2 g (2.96 mmol) of a solution of N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2H-pyran-4-yl)acetamido)benzamide in 65 ml of methanol. The reaction medium is heated at 65°C for 2 hours, and then overnight at room temperature. The precipitate formed is filtered, rinsed with pentane, with water and then with diethyl ether, and then is dried under vacuum to yield 0.73 g (43%) of (N-

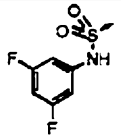
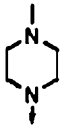
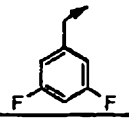
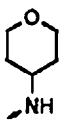
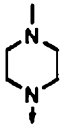
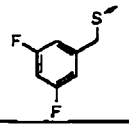
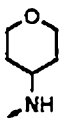
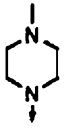
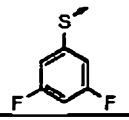
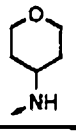
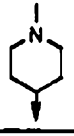
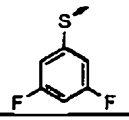
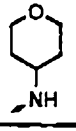
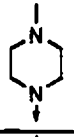
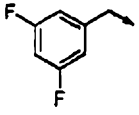
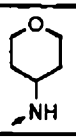
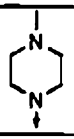
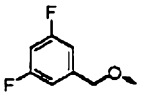
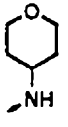
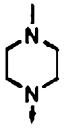
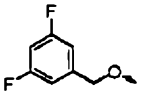
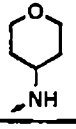
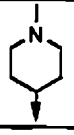
(5-(3,5-difluorophenylthio)-1-H-pyrazolo[3,4-b]pyridine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide in the form of a white solid.

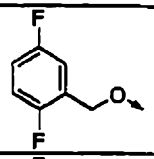
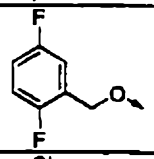
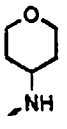
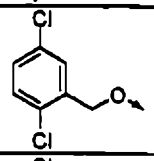
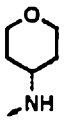
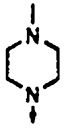
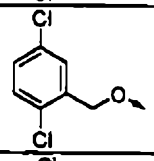
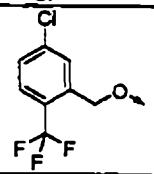
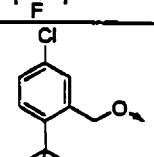
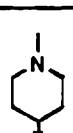
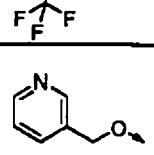
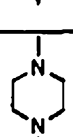
LCMS (EI, m/z): (M+1) 580.23.

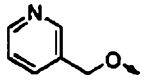
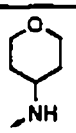
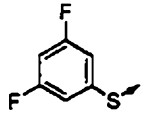
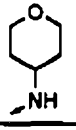
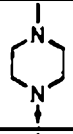
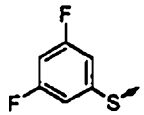
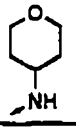
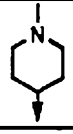
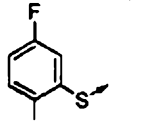
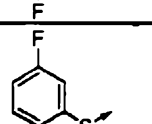
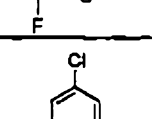
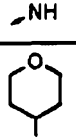
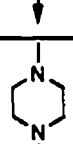
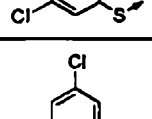
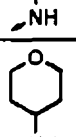
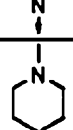
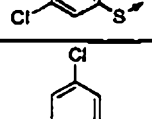
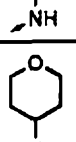
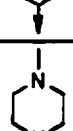
^{1}H NMR: δH ppm (400 MHz, DMSO): 13.59 (1H, bs, NH), 10.56 (1H, bs, NH), 8.61 (1H, s, CH_{arom}), 8.50 (1H, s, CH_{arom}), 8.17 (1H, d, NH), 7.80 (1H, d, CH_{arom}), 7.07 (1H, m, CH_{arom}), 6.86 (2H, m, CH_{arom}), 6.23 (1H, d, CH_{arom}), 6.13 (1H, d, CH_{arom}), 3.79-3.82 (2H, dt, CH), 3.60 (1H, m, CH), 3.45-3.50 (2H, m, CH), 3.21-3.33 (4H, m, CH), 2.42-2.46 (4H, m, CH), 2.22 (3H, s, CH_3), 1.91-1.94 (2H, m, CH), 1.35-1.38 (2H, m, CH).

The following derivatives were obtained according to the same method:

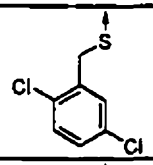
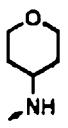
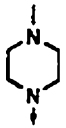
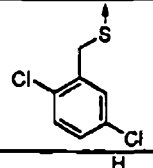
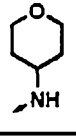
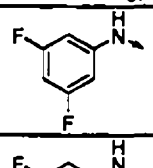
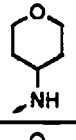
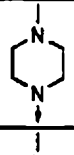
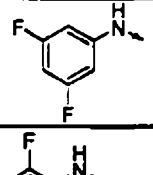
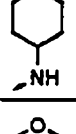
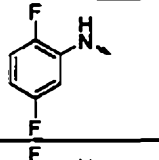
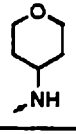
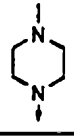
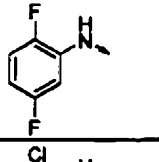
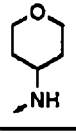
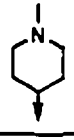
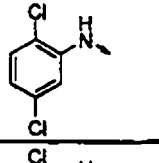
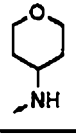
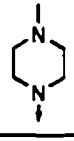
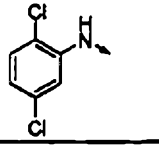
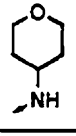
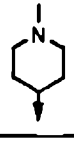
Ex.**	ArX	R_1	R_2	$(U)_n$	V	Y_1,Y_2,Y_3,Y_4	R_3	Compound name	Yield	Mass
30-1				n=0	CO	CH,CXAr,CH,N	H	N-(5-(2-carbamoylphenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	ND
30-2	I			n=0	CO	CH,CXAr,CH,N	H	N-(5-iodo-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	ND
30-3				n=0	CO	CH,CXAr,CH,N	H	N-(5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	(M+1) 626.14
30-4				n=0	CO	CH,CXAr,CH,N	H	2-(4,4-difluorocyclohexylamino)-N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)benzamide	ND	ND
30-5				n=0	CO	CH,CXAr,COMe,N	H	N-(5-(3,5-difluorophenylthio)-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	610.20
30-6	I			n=0	CO	CH,CXAr,COMe,N	H	N-(5-iodo-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	592.12
30-7	I			n=0	CO	CH,CXAr,CNH_2,N	H	N-(6-amino-5-iodo-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	(M-1) 574.87

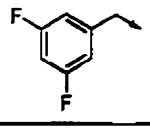
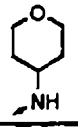
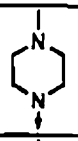
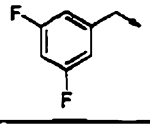
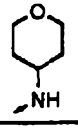
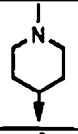
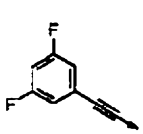
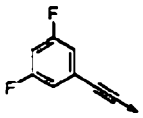
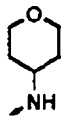
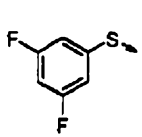
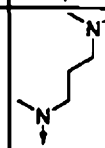
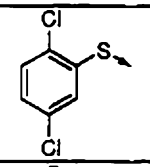
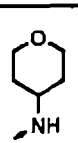
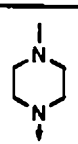
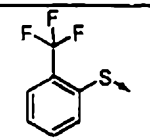
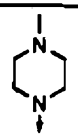
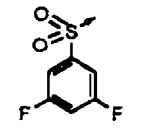
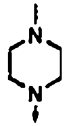
30-8				n=0	CO	CH,CXAr,CH,N	H	N-(5-(N-(3,5-difluorophenyl)sulfamoyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	30% (2 steps)	(M+1) 627.20
30-9				n=0	CO	CH,CXAr,CH,N	H	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	20%	(M+1) 562.42
30-10				n=0	CO	CH,CXAr,CH,N	H	N-(5-(3,5-difluorobenzylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	20.6%	(M+1) 594.11
30-11				n=0	CO	CH,CXAr,CH,N	H	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	59.4 % (2 steps	(M+1) 579.11
30-12				n=0	CO	CH,CXAr,CCH_3,N	H	N-(5-(3,5-difluorophenylthio)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	45%	(M+1) 579.11
30-13				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	70%	562.27
30-14				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	55%	578.27
30-15				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	49% 2 steps	577.27

30-16				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	61%	578.27
30-17				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	54% 2 steps	577.27
30-18				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	10% 2 steps	610.01
30-19				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	40% 2 steps	609.03
30-20				n=0	CO	N, ArXC, CH, CH	H	N-(5-(5-chloro-2-(trifluoromethyl)benzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	64%	644.24
30-21				n=0	CO	N, ArXC, CH, CH	H	N-(5-(5-chloro-2-(trifluoromethyl)benzyloxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	39% 2 steps	643.24
30-22				n=0	CO	N, ArXC, CH, CH	H	4-(4-methylpiperazin-1-yl)-N-(5-(pyridin-3-ylmethoxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	30%	543.28

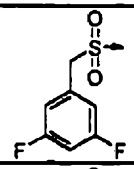
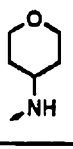
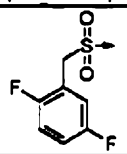
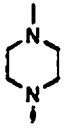
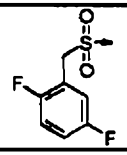
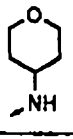
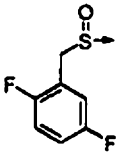
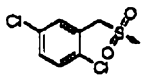
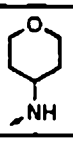
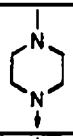
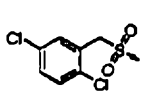
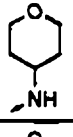
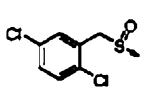
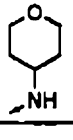
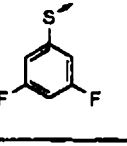
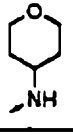
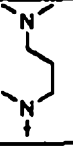
30-23				n=0	CO	N, ArXC, CH, CH	H	4-(1-methylpiperidin-4-yl)-N-(5-(pyridin-3-ylmethoxy)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	67% 2 steps	542.29
30-24				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	65% 2 steps	580.23
30-25				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	56% 2 steps	579.23
30-26				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	27% 2 steps	580.23
30-27				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	54% 2 steps	579.23
30-28				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	31% 2 steps	612.17
30-29				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	43% 2 steps	611.17
30-30				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	31% 2 steps	612.20

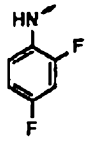
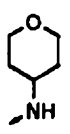
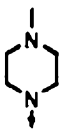
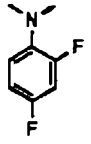
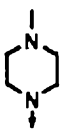
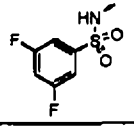
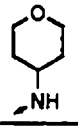
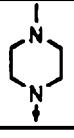
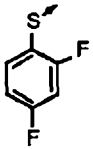
30-31				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorophenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	57% 2 steps 611.18
30-32				n=0	CO	N, ArXC, CH, CH	H	4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)-N-(5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzamide	38% 2 steps 612.24
30-33				n=0	CO	N, ArXC, CH, CH	H	4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)-N-(5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzamide	57% 2 steps 611.24
30-34				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	21% 2 steps 594.25
30-35				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	91% 593.25
30-36				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide 2,2,2-trifluoroacetate	86% 2 steps 594.25
30-37				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	55% 2 steps 593.25

30-38				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	24% 2 steps	626.19
30-39				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzylthio)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	50% 2 steps	625.19
30-40				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	70%	563.27
30-41				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	27% 2 steps	562.27
30-42				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	37% 2 steps	563.27
30-43				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	41% 2 steps	562.27
30-44				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	74%	595.21
30-45				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorophenylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	33%	594.21

30-46				n=0	CO	N, ArXC, CH, N	H	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	12% 2 steps	563.07
30-47				n=0	CO	N, ArXC, CH, N	H	N-(5-(3,5-difluorobenzyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	15% 2 steps	562.04
30-48				n=0	CO	N, ArXC, CH, N	H	N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-((3-(dimethylamino)propyl)(methyl)amino)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	12% 2 steps	589.24
30-49				n=0	CO	N, ArXC, CH, N	H	N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	16% 2 steps	572.07
30-50				n=0	CO	N, ArXC, CH, N	H	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-((3-(dimethylamino)propyl)(methyl)amino)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	27%	597.26
30-51				n=0	CO	N, ArXC, CH, N	H	N-(5-(2,5-dichlorophenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	23% 2 steps	613.16
30-52				n=0	CO	N, ArXC, CH, N	H	4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)-N-(5-(2-(trifluoromethyl)phenylthio)-1H-pyrazolo[3,4-b]pyrazin-3-yl)benzamide	64%	613.23
30-53				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	64%	612.22

30-54				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	48%	611.22
30-55				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	50% 2 steps	612.22
30-56				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	28% 2 steps	611.22
30-57				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	29% 2 steps	644.16
30-58				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	28% 2 steps	643.17
30-59				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	21% 2 steps	644.16
30-60				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	36% 2 steps	643.17
30-61				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	66%	626.24

30-62				n=0	CO	N, ArXC, CH, CH	H	N-(5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	67%	625.24
30-63				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	74%	626.24
30-64				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	58%	625.24
30-65				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-difluorobenzylsulfinyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide 2,2,2-trifluoroacetate	31% 2 steps	629.24
30-66				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	55%	658.18
30-67				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	57%	657.18
30-68				n=0	CO	N, ArXC, CH, CH	H	N-(5-(2,5-dichlorobenzylsulfinyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-4-(1-methylpiperidin-4-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	20%	641.19
30-69				n=0	CO	CH, ArXC, CH, N	H	N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-((3-(dimethylamino)propyl)(methyl)amino)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	57%	596.26

30-70				n=0	CO	CH, CH, ArXC, N	H	N-(6-(2,4-difluorophenylamino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	33%	561.19 (M-1)
30-71				n=0	CO	CH, CH, ArXC, N	H	N-(6-((2,4-difluorophenyl)(methyl)amino)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	ND	577.26 (M+1)
30-72				n=0	CO	CH, ArXC, CH, N	H	N-(5-(3,5-difluorophenylsulfonamido)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	74%	627.19 (M+1)
30-73				n=0	CO	CH, CH, ArXC, N	H	N-(6-(2,4-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	42 % (2 steps	(M+1) 580,23

** ^{1}H NMR, DMSO-d_6, Ex.: **30-3**: 13.86 (1H, bs, NH), 10.70 (1H, bs, NH), 8.67 (2H, bs, CH_{arom}), 8.10 (1H, d, NH), 7.77 (1H, d, CH_{arom}), 7.22 (1H, m, CH_{arom}), 6.95 (2H, d, CH_{arom}), 6.26 (1H, d, CH_{arom}), 6.16 (1H, bs, CH_{arom}), 4.85 (2H, bs, CH), 3.82-3.86 (2H, dt, CH), 3.70 (1H, m, CH), 3.47-3.53 (2H, m, CH), 3.28-3.32 (4H, m, CH), 2.42-2.46 (4H, m, CH), 2.20 (3H, s, CH_3), 1.94-1.98 (2H, m, CH), 1.34-1.41 (2H, m, CH).; **30-5**: 13.25 (1H, bs, NH), 10.48 (1H, bs, NH), 8.42 (1H, s, CH_{arom}), 8.11 (1H, d, NH), 7.76 (1H, d, CH_{arom}), 7.00-7.10 (1H, m, CH_{arom}), 6.79-6.87 (2H, m, CH_{arom}), 6.23 (1H, dd, CH_{arom}), 6.12 (1H, d, CH_{arom}), 3.94 (3H, s, CH_3), 3.75-3.83 (2H, m, CH), 3.63-3.71 (1H, m, CH), 3.42-3.52 (2H, m, CH), 3.22-3.32 (4H, m, 2*CH_2), 2.36-2.48 (4H, m, 2*CH_2), 2.22 (3H, s, CH_3), 1.88-1.97 (2H, m, CH), 1.32-1.42 (2H, m, CH). **30-6**: 13.10 (1H, bs, NH), 10.38 (1H, bs, NH), 8.56 (1H, s, CH_{arom}), 8.12 (1H, d, NH), 7.75 (1H, d, CH_{arom}), 6.23 (1H, dd, CH_{arom}), 6.14 (1H, d, CH_{arom}), 3.97 (3H, s, CH_3), 3.80-3.86 (2H, m, CH), 3.62-3.74 (1H, m, CH), 3.40-3.55 (2H, m, CH), 3.22-3.32 (4H, m, 2*CH_2), 2.36-2.48 (4H, m, 2*CH_2), 2.23 (3H, s, CH_3), 1.90-1.99 (2H, m, CH), 1.32-1.45 (2H, m, CH). **30-7**: 12.43 (1H, bs, NH), 10.22 (1H, bs, NH), 8.32(1H, s, CH_{arom}), 8.13(1H, d, NH), 7.73 (1H, d, CH_{arom}), 6.37 (2H, bs, NH_2), 6.22 (1H, dd, CH_{arom}), 6.13 (1H, d, CH_{arom}), 3.78-3.86 (2H, m, CH), 3.65-3.74 (1H, m, CH), 3.44-3.54 (2H, m, CH), 3.22-3.32 (4H, m, 2*CH_2), 2.36-2.48 (4H, m, 2*CH_2), 2.23 (3H, s, CH_3), 1.90-1.99 (2H, m, CH), 1.32-1.45 (2H, m, CH). **30-8**: 13.79 (1H, bs, NH), 10.91 (1H, bs, NH), 10.69 (1H, bs, NH), 8.83 (1H, s, CH_{arom}), 8.76 (1H, s, CH_{arom}), 8.18 (1H, d, NH), 7.80 (1H, d, CH_{arom}), 6.82-6.75 (3H, m, CH_{arom}), 6.26 (1H, d, CH_{arom}), 6.15 (1H, d, CH_{arom}), 3.87-3.82 (2H, dt, CH), 3.72 (1H, m, CH), 3.54-3.47 (2H, m, CH), 3.32-3.29 (4H, m, CH), 2.42-2.46 (4H, m, CH), 2.28 (3H, s, CH_3), 1.97-1.95 (2H, m, CH), 1.43-1.36 (2H, m, CH). **30-13**: 12.99 (1H, s, NH), 9.92 (1H, s, NH), 8.38 (1H, d, NH, J=7.6Hz), 7.92 (1H, d, CHarom, J=8.4Hz), 7.84 (1H, d, CHarom, J=9.2Hz), 7.32 (1H, d, CHarom, J=8.4Hz), 7.07-7.00 (3H, m, CHarom), 6.26 (1H, d, CHarom, J=8.8Hz), 6.14 (1H, s, CHarom), 4.21 (2H, s), 3.82-3.76 (2H, m), 3.69-3.63 (1H, m), 3.48 (2H, t), 3.28 (4H, s), 2.46 (4H, s), 2.25 (3H, s), 2.00-1.90 (2H, m), 1.37-1.26 (2H, m). **30-14**: 12.96 (1H, sl, NH), 9.84 (1H, s, NH), 8.34 (1H, d, NH, J=7.6Hz), 7.96 (1H, d, CHarom, J=9.2Hz), 7.81 (1H, d, CHarom, J=8.8Hz), 7.25 (1H, s, CHarom), 7.23 (1H, s, CHarom), 7.17 (1H, t, CHarom), 6.96 (1H, d, CHarom, J=9.2Hz), 6.25 (1H, d, CHarom, J=7.6Hz), 6.14 (1H, s, CHarom), 5.35 (2H, s), 3.82-3.77 (2H, m), 3.67 (1H, sl), 3.46 (2H, t), 3.29 (4H, s), 2.50 (4H, s), 2.29

(3H, s), 1.93-1.88 (2H, m), 1.35-1.25 (2H, m). **30-15**: 13.01 (1H, sl, NH), 10.11 (1H, sl, NH), 7.99 (1H, sl, NH), 7.97 (1H, d, CHarom, J=9.2Hz), 7.84 (1H, d, CHarom, J=8.4Hz), 7.25-7.14 (3H, m, CHarom), 6.97 (1H, d, CHarom, J=8.8Hz), 6.67 (1H, sl, CHarom), 6.51 (1H, d, CHarom, J=8.0Hz), 5.35 (2H, s, CHarom), 3.83-3.78 (2H, m), 3.68-3.63 (1H, m), 3.47 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.45-2.40 (1H, m), 2.19 (3H, s), 2.00-1.87 (4H, m), 1.75-1.65 (4H, m), 1.34-1.28 (2H, m). **30-16**: 12.95 (1H, sl, NH), 9.85 (1H, s, NH), 8.33 (1H, d, NH, J=7.6Hz), 7.95 (1H, d, CHarom, J=8.8Hz), 7.81 (1H, d, CHarom, J=8.8Hz), 7.48 (1H, q, CHarom), 7.31-7.20 (2H, m, CHarom), 6.93 (1H, d, CHarom, J=9.2Hz), 6.25 (1H, d, CHarom, J=9.2Hz), 6.14 (1H, s, CHarom), 5.35 (2H, s), 3.81-3.76 (2H, m), 3.68 (1H, sl), 3.47 (2H, t), 3.26 (4H, s), 2.44 (4H, s), 2.29 (3H, s), 1.94-1.88 (2H, m), 1.36-1.27 (2H, m). **30-17**: 13.06 (1H, sl, NH), 10.12 (1H, sl, NH), 7.93 (1H, sl, NH), 7.86 (2H, d, CHarom, J=8.4Hz), 7.51-7.44 (1H, m, CHarom), 7.30-7.20 (2H, m, CHarom), 6.90 (1H, sl, CHarom), 6.64 (1H, sl, CHarom), 6.49 (1H, sl, CHarom), 5.37 (2H, s, CHarom), 3.83-3.76 (2H, m), 3.68-3.63 (1H, m), 3.46 (2H, t), 2.86 (2H, d, J=10.4Hz), 2.44-2.38 (1H, m), 2.19 (3H, s), 1.99-1.90 (4H, m), 1.75-1.65 (4H, m), 1.40-1.30 (2H, m). **30-18**: 12.94 (1H, sl, NH), 9.81 (1H, s, NH), 8.32 (1H, d, CHarom, J=7.7Hz), 7.96 (1H, d, CHarom, J=9Hz), 7.81 (1H,d, CHarom, J=9Hz), 7.71 (1H, d, NH), 7.51 (1H, d, CHarom, J=8.6Hz), 7.43 (1H, dd, CHarom, J=8.6Hz), 6.97 (1H, d, CHarom, J=8.6Hz), 6.24 (1H, d, CHarom, J=8.9Hz), 6.13 (1H, s, CHarom), 5.39 (2H, s), 3.82-3.74 (2H, m), 3.72-3.62 (1H, m), 3.46 (2H, t), 3.28-3.22 (4H, m), 2.46-2.40 (4H, m), 2.22 (3H, s), 1.95-1.87 (2H, m), 1.37-1.26 (2H, m). **30-19**: 13.01 (1H, sl, NH), 10.09 (1H, s, NH), 7.97 (2H, d, CHarom, J=9Hz), 7.83 (1H,d, CHarom, J=8.2Hz), 7.71 (1H, dd, NH), 7.50 (1H, d, CHarom, J=7.4Hz), 7.43 (1H, dd, CHarom, J=8.6Hz), 6.98 (1H, d, CHarom, J=9Hz), 6.67 (1H, s, CHarom), 6.51 (1H, d, CHarom, J=8.2Hz), 5.38 (2H, s), 3.84-3.75 (2H, m), 3.72-3.62 (1H, m), 3.46 (2H, t), 2.86 (2H, d), 2.43 (1H, m), 2.19 (3H, s), 1.99-1.88 (4H, m), 1.74-1.64 (4H, m), 1.38-1.26 (2H, m). **30-20**: 12.97 (1H, sl, NH), 9.82 (1H, s, NH), 8.32 (1H, d, NH, J=8.0Hz), 7.97 (1H, d, CHarom, J=8.8Hz), 7.87 (1H, s, CHarom), 7.80-7.76 (2H, m, CHarom), 7.64 (1H, d, CHarom, J=8.4Hz), 6.96 (1H, d, CHarom, J=8.8Hz), 6.24 (1H, d, CHarom, J=8.8Hz), 6.13 (1H, s, CHarom), 5.47 (2H, s), 3.81-3.76 (2H, m), 3.66 (1H, sl), 3.46 (2H, t), 3.26 (4H, s), 2.43 (4H, s), 2.29 (3H, s), 1.93-1.88 (2H, m), 1.35-1.25 (2H, m). **30-21**: 13.03 (1H, s, NH), 10.08 (1H, s, NH), 8.00-7.95 (2H, m, CHarom), 7.87-7.75 (3H, m, CHarom), 7.63 (1H,

d, CHarom, J=8.4Hz), 6.97 (1H, d, CHarom, J=8.8Hz), 6.67 (1H, s, CHarom), 6.51 (1H, d, CHarom, J=8.0Hz), 5.47 (2H, s, CHarom), 3.83-3.76 (2H, m), 3.68-3.64 (1H, m), 3.47 (2H, t), 2.87 (2H, d, J=10.4Hz), 2.45-2.40 (1H, m), 2.20 (3H, s), 2.00-1.87 (4H, m), 1.74-1.65 (4H, m), 1.36-1.25 (2H, m). **30-22**: 12.93 (1H, s, NH), 9.86 (1H, s, NH), 8.70 (1H, s, CHarom), 8.51 (1H, dd, CHarom, J=5.2Hz), 8.38 (1H, d, NH, J=8.0Hz), 7.96-7.90 (2H, m, CHarom), 7.84 (1H, d, CHarom, J=8.8Hz), 7.73-7.33 (1H, m, CHarom), 6.91 (1H, d, CHarom, J=8.8Hz), 6.27 (1H, d, CHarom, J=8.8Hz), 6.15 (1H, s, CHarom), 5.35 (2H, s), 3.83-3.77 (2H, m), 3.70-3.64 (1H, m), 3.47 (2H, t), 3.59 (4H, s), 2.59 (4H, s), 2.34 (3H, s), 1.95-1.88 (2H, m), 1.40-1.28 (2H, m). **30-23**: 13.03 (1H, s, NH), 10.17 (1H, s, NH), 8.70 (1H, s, CHarom), 8.52 (1H, dd, CHarom, J=4.8Hz), 8.06 (1H, d, NH, J=7.6Hz), 7.96 (1H, d, CHarom, J=8.8Hz), 7.94-7.88 (2H, m, CHarom), 7.37-7.34 (1H, m, CHarom), 6.93 (1H, d, CHarom, J=9.2Hz), 6.69 (1H, s, CHarom), 6.52 (1H, d, CHarom, J=8.0Hz), 5.36 (2H, s, CHarom), 3.83-3.79 (2H, m), 3.68-3.64 (1H, m), 3.46 (2H, t), 3.25-3.15 (2H, m), 2.65-2.55 (3H, m), 2.54 (3H, s), 2.00-1.85 (6H, m), 1.41-1.28 (2H, m). **30-24**: 13.21 (1H, s, NH), 10.00 (1H, s, NH), 8.30 (1H, d, NH, J=7.6Hz), 8.00 (1H, d, CHarom, J=8.8Hz), 7.79 (1H, d, CHarom, J=9.2Hz), 7.33 (1H, d, CHarom, J=8.8Hz), 7.26-7.16 (3H, m, CHarom), 6.24 (1H, d, CHarom, J=8.8Hz), 6.13 (1H, s, CHarom), 4.06-3.99 (2H, m), 3.67 (1H, sl), 3.47 (2H, t), 3.28 (4H, s), 2.47 (4H, s), 2.25 (3H, s), 1.94-1.88 (2H, m), 1.37-1.26 (2H, m). **30-25**: 13.26 (1H, s, NH), 10.28 (1H, s, NH), 8.02 (1H, d, CHarom, J=8.8Hz), 7.97 (1H, d, NH, J=7.6Hz), 7.83 (1H, d, CHarom, J=8.0Hz), 7.34 (1H, d, CHarom, J=8.8Hz), 7.27-7.17 (3H, m, CHarom), 6.68 (1H, s, CHarom), 6.51 (1H, d, CHarom, J=8.0Hz), 3.85-3.78 (2H, m), 3.71-3.65 (1H, m), 3.47 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.48-2.40 (1H, m), 2.19 (3H, s), 1.98-1.88 (4H, m), 1.74-1.66 (4H, m), 1.36-1.27 (2H, m). **30-26**: 13.12 (1H, s, NH), 9.95 (1H, s, NH), 8.32 (1H, d, NH, J=7.6Hz), 7.93 (1H, d, CHarom, J=8.8Hz), 7.79 (1H, d, CHarom, J=8.8Hz), 7.73 (1H, t, CHarom), 7.52-7.40 (2H, m, CHarom), 7.12 (1H, d, CHarom, J=8.8Hz), 6.25 (1H, d, CHarom, J=8.8Hz), 6.13 (1H, s, CHarom), 3.83-3.77 (2H, m), 3.69 (1H, sl), 3.48 (2H, t), 3.28 (4H, s), 2.44 (4H, s), 2.27 (3H, s), 1.96-1.89 (2H, m), 1.37-1.27 (2H, m). **30-27**: 13.17 (1H, s, NH), 10.21 (1H, s, NH), 7.99-7.92 (2H, m, CHarom et NH), 7.81 (1H, d, CHarom, J=8.4Hz), 7.77-7.70 (1H, m, CHarom), 7.51-7.40 (2H, m, CHarom), 7.13 (1H, dd, CHarom, J=8.8Hz), 6.69 (1H, s, CHarom), 6.51 (1H, d, CHarom, J=8.4 Hz), 3.85-3.78 (2H, m), 3.72-3.67 (1H,

m), 3.48 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.47-2.40 (1H, m), 2.20 (3H, s), 1.96-1.87 (4H, m), 1.75-1.65 (4H, m), 1.38-1.28 (2H, m). **30-28**: 13.31 (1H, sl, NH), 9.95 (1H, sl, NH), 8.31 (1H, d, NH, J=7.6Hz), 7.99 (1H, d, CHarom, J=7.6Hz), 7.78 (1H, d, CHarom, J=9.2Hz), 7.58-7.49 (3H, m, CHarom), 7.31 (1H, d, CHarom, J=8.8Hz), 6.24 (1H, d, CHarom, J=8.8Hz), 6.10 (1H, s, CHarom), 3.83-3.76 (2H, m), 3.70-3.60 (1H, m), 3.45 (2H, t), 3.21 (4H, s), 2.43 (4H, s), 2.22 (3H, s), 1.94-1.86 (2H, m), 1.38-1.28 (2H, m). **30-29**: 13.26 (1H, s, NH), 10.25 (1H, s, NH), 8.01 (1H, d, CHarom, J=8.8Hz), 7.94 (1H, d, NH, J=7.6Hz), 7.82 (1H, d, CHarom, J=8.4Hz), 7.59-7.54 (3H, m, CHarom), 7.32 (1H, d, CHarom, J=8.8Hz), 6.67 (1H, s, CHarom), 6.54 (1H, d, CHarom, J=7.6Hz), 3.84-3.78 (2H, m), 3.71-3.62 (1H, m), 3.47 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.45-2.41 (1H, m), 2.19 (3H, s), 1.96-1.90 (4H, m), 1.74-1.68 (4H, m), 1.34-1.27 (2H, m). **30-30**: 13.23 (1H, s, NH), 9.98 (1H, s, NH), 8.29 (1H, d, NH, J=7.6Hz), 8.01 (1H, d, CHarom, J=8.8Hz), 7.79 (1H, d, CHarom, J=8.8Hz), 7.62 (1H, d, CHarom, J=8.4Hz), 7.52 (1H, s, CHarom), 7.44 (1H, d, CHarom, J=7.6Hz), 7.24 (1H, d, CHarom, J=8.4Hz), 6.25 (1H, d, CHarom, J=8.0Hz), 6.12 (1H, s, CHarom), 3.82-3.75 (2H, m), 3.73-3.67 (1H, m), 3.47 (2H, t), 3.27 (4H, s), 2.43 (4H, s), 2.22 (3H, s), 1.95-1.87 (2H, m), 1.35-1.28 (2H, m). **30-31**: 13.28 (1H, s, NH), 10.25 (1H, s, NH), 8.02 (1H, d, CHarom, J=8.8Hz), 7.95 (1H, d, NH, J=7.6Hz), 7.81 (1H, d, CHarom, J=8.0Hz), 7.61 (1H, d, CHarom, J=8.4Hz), 7.56 (1H, s, CHarom), 7.43 (1H, dd, CHarom, J=8.4Hz), 7.25 (1H, d, CHarom, J=8.8Hz), 6.68 (1H, s, CHarom), 6.51 (1H, d, CHarom, J=7.2 Hz), 3.84-3.78 (2H, m), 3.69-3.61 (1H, m), 3.47 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.47-2.41 (1H, m), 2.20 (3H, s), 2.00-1.90 (4H, m), 1.76-1.69 (4H, m), 1.40-1.30 (2H, m). **30-32**: 13.16 (1H, s, NH), 9.95 (1H, s, NH), 8.33 (1H, d, NH, J=8.0Hz), 7.93 (1H, d, CHarom, J=8.8Hz), 7.89 (1H, d, CHarom, J=9.2Hz), 7.79 (1H, d, CHarom, J=9.2Hz), 7.70-7.63 (2H, m, CHarom), 7.60 (1H, t, CHarom), 6.97 (1H, d, CHarom, J=8.8Hz), 6.25 (1H, d, CHarom, J=9.2Hz), 6.14 (1H, s, CHarom), 3.83-3.78 (2H, m), 3.68 (1H, sl), 3.48 (2H, t), 3.28 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.95-1.90 (2H, m), 1.38-1.28 (2H, m). **30-33**: 13.21 (1H, s, NH), 10.22 (1H, s, NH), 7.99 (1H, d, NH, J=7.6Hz), 7.94 (1H, d, CHarom, J=9.2Hz), 7.89 (1H, d, CHarom, J=7.2Hz), 7.82 (1H, d, CHarom, J=8.4Hz), 7.71-7.57 (3H, m, CHarom), 6.98 (1H, d, CHarom, J=8.8Hz), 6.69 (1H, s, CHarom), 6.52 (1H, d, CHarom, J=8.0 Hz), 3.85-3.79 (2H, m), 3.72-3.62 (1H, m), 3.48 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.47-2.41 (1H, m), 2.19 (3H, s), 2.00-1.90 (4H, m), 1.76-1.69 (4H, m), 1.40-

1.30 (2H, m). **30-34**: 13.07 (1H, s, NH), 10.11 (1H, s, NH), 8.32 (1H, d, NH, J=7.6Hz), 7.90-7.85 (2H, m, CHarom), 7.22 (1H, d, CHarom, J=8.8Hz), 7.19 (1H, s, CHarom), 7.17 (1H, s, CHarom), 7.03 (1H, t, CHarom), 6.30 (1H, d, CHarom, J=8.4Hz), 6.19 (1H, s, CHarom), 4.43 (2H, s), 4.02 (2H, sl), 3.80-3.74 (2H, m), 3.67 (1H, sl), 3.44 (2H, t), 3.10 (4H, s), 2.84 (3H, s), 1.89-1.84 (2H, m), 1.30-1.14 (4H, m). **30-35**: 13.08 (1H, s, NH), 10.28 (1H, s, NH), 7.96 (1H, d, NH, J=7.6Hz), 7.88 (1H, d, CHarom, J=8.8Hz), 7.86 (1H, d, CHarom, J=6.8Hz), 7.22 (1H, d, CHarom, J=8.8Hz), 7.18 (1H, s, CHarom), 7.17 (1H, s, CHarom), 7.02 (1H, t, CHarom), 6.66 (1H, s, CHarom), 6.51 (1H, d, CHarom, J=8.4Hz), 4.43 (2H, s), 3.80-3.74 (2H, m), 3.64 (1H, sl), 3.44 (2H, t), 2.89-2.84 (2H, m), 2.43 (1H, sl), 2.20 (3H, s), 1.98-1.95 (2H, m), 1.89-1.84 (2H, m), 1.72-1.69 (4H, m), 1.29-1.20 (2H, m). **30-36**: 13.10 (1H, sl, NH), 10.11 (1H, s, NH), 9.73 (1H, sl, COOH), 8.34 (1H, sl, NH), 7.92-7.86 (2H, m, CHarom), 7.47-7.40 (1H, m, CHarom), 7.23 (1H, d, CHarom, J=8.8Hz), 7.20-7.13 (1H, m, CHarom), 7.11-7.05 (1H, m, CHarom), 6.31 (1H, dd, CHarom, J=9.2Hz), 6.20 (1H, s, CHarom), 4.41 (2H, s), 4.04 (2H, d, J=8.8Hz), 3.81-3.75 (2H, m), 3.70-3.66 (1H, m), 3.51 (2H, d, J=11.2Hz), 3.44 (2H, t), 3.16-2.97 (4H, m), 2.87 (3H, s), 1.91-1.84 (2H, m), 1.34-1.22 (2H, m). **30-37**: 13.09 (1H, s, NH), 10.29 (1H, s, NH), 7.97 (1H, d, NH, J=7.6Hz), 7.90-7.86 (2H, m, CHarom), 7.47-7.41 (1H, m, CHarom), 7.23 (1H, d, CHarom, J=8.8Hz), 7.19-7.13 (1H, m, CHarom), 7.11-7.05 (1H, m, CHarom), 6.67 (1H, s, CHarom), 6.52 (1H, d, CHarom, J=8.0Hz), 4.41 (2H, s), 3.79-3.74 (2H, m), 3.66-3.62 (1H, m), 3.44 (2H, t), 2.86 (2H, d, J=11.2Hz), 2.45-2.40 (1H, m), 2.19 (3H, s), 2.00-1.85 (4H, m), 1.74-1.65 (4H, m), 1.33-1.23 (2H, m). **30-38**: 13.02 (1H, s, NH), 10.04 (1H, s, NH), 8.28 (1H, d, NH, J=8.0Hz), 7.88-7.84 (2H, m, CHarom), 7.74 (1H, s, CHarom), 7.43 (1H, d, CHarom, J=8.8Hz), 7.29 (1H, dd, CHarom, J=8.4Hz), 7.22 (1H, d, CHarom, J=8.8Hz), 6.25 (1H, dd, CHarom, J=9.2Hz), 6.12 (1H, s, CHarom), 4.50 (2H, s), 3.78-3.74 (2H, m), 3.66-3.62 (1H, m), 3.44 (2H, t), 3.26 (4H, s), 2.43 (4H, s), 2.22 (3H, s), 1.91-1.84 (2H, m), 1.35-1.23 (2H, m). **30-39**: 13.09 (1H, s, NH), 10.32 (1H, s, NH), 8.28 (1H, d, NH, J=8.0Hz), 7.90 (2H, D, CHarom), 7.74 (1H, s, CHarom), 7.43 (1H, d, CHarom, J=8.4Hz), 7.29 (1H, dd, CHarom, J=8.4Hz), 7.25 (1H, d, CHarom, J=8.8Hz), 6.67 (1H, s, CHarom), 6.54 (1H, dd, CHarom, J=8,4Hz), 4.51 (2H, s), 3.79-3.76 (2H, m), 3.70-3.64 (1H, m), 3.44 (2H, t), 2,95-2,92 (2H, m), 2,52-2,51 (1H, m), 2.27 (3H, s), 2.13-2,01 (2H, m), 1,90-1,87 (2H , m) 1.77-1.69 (4H, m), 1.32-1.24 (2H, m). **30-40**: 12.77

(1H, s, NH), 9.86 (1H, s, NH), 9.60 (1H, s, NH), 8.40 (1H, d, NH, J=7.6Hz), 7.86 (1H, d, CHarom, J=8.8Hz), 7.83 (1H, d, CHarom, J=9.2Hz), 7.56 (2H, d, CHarom, J=8.8Hz), 6.93 (1H, d, CHarom, J=9.2Hz), 6.55 (1H, t, CHarom), 6.23 (1H, dd, CHarom, J=9.2Hz), 6.13 (1H, s, CHarom), 3.82-3.75 (2H, m), 3.69-3.61 (1H, m), 3.46 (2H, t), 3.27 (4H, s), 2.44 (4H, s), 2.29 (3H, s), 1.96-1.88 (2H, m), 1.38-1.26 (2H, m). **30-41**: 12.85 (1H, sl, NH), 10.13 (1H, s, NH), 9.62 (1H, s, NH), 8.03 (1H, d, NH, J=7.2Hz), 7.90-7.84 (2H, m, CHarom), 7.57 (2H, dd, CHarom, J=10.4Hz), 6.95 (1H, d, CHarom, J=8.8Hz), 6.68 (1H, s, CHarom), 6.60-6.50 (2H, m, CHarom), 3.83-3.78 (2H, m), 3.68-3.63 (1H, m), 3.46 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.45-2.40 (1H, m), 2.20 (3H, s), 2.00-1.92 (4H, m), 1.75-1.65 (4H, m), 1.37-1.27 (2H, m). **30-42**: 12.77 (1H, s, NH), 9.87 (1H, s, NH), 9.02 (1H, s, NH), 8.80-8.72 (1H, m, CHarom), 8.41(1H, d, NH, J=7.6Hz), 7.86 (1H, d, CHarom, J=8.8Hz), 7.83 (1H, d, CHarom, J=9.2Hz), 7.28 (1H, d, CHarom, J=9.2Hz), 7.22-7.15 (1H, m, CHarom), 6.63-6.57 (1H, m, CHarom), 6.23 (1H, d, CHarom, J=8.8Hz), 6.13 (1H, s, CHarom), 3.83-3.75 (2H, m), 3.70-3.64 (1H, m), 3.46 (2H, t), 3.27 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.95-1.88 (2H, m), 1.39-1.26 (2H, m). **30-43**: 12.84 (1H, s, NH), 10.13 (1H, s, NH), 9.05 (1H, sl, NH), 8.81-8.74 (1H, m, CHarom), 8.05 (1H, d, NH, J=7.2Hz), 7.89-7.84 (2H, m, CHarom), 7.30 (1H, d, CHarom, J=8.8Hz), 7.23-7.15 (1H, m, CHarom), 6.67 (1H, s, CHarom), 6.64-6.58 (1H, m, CHarom), 6.51 (1H, d, CHarom, J=8.4Hz), 3.83-3.76 (2H, m), 3.68-3.64 (1H, m), 3.47 (2H, t), 2.89 (2H, d, J=10.8Hz), 2.45-2.40 (1H, m), 2.21 (3H, s), 2.01-1.91 (4H, m), 1.74-1.66 (4H, m), 1.38-1.27 (2H, m). **30-44**: 12.80 (1H, s, NH), 10.16 (1H, s, NH), 8.89 (1H, s, CHarom), 8.52 (1H, s, NH), 8.34 (1H, d, NH, J=7.6Hz), 7.89 (1H, d, CHarom, J=9.2Hz), 7.81 (1H, d, CHarom, J=9.2Hz), 7.41 (1H, d, CHarom, J=8.8Hz), 7.35 (1H, d, CHarom, J=9.2Hz), 6.89 (1H, dd, CHarom, J=8.4Hz), 6.21 (1H, d, CHarom, J=9.2Hz), 6.11 (1H, s, CHarom), 3.83-3.75 (2H, m), 3.66-3.60 (1H, m), 3.46 (2H, t), 3.25 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.95-1.87 (2H, m), 1.37-1.26 (2H, m). **30-45**: 12.86 (1H, s, NH), 10.10 (1H, s, NH), 8.91 (1H, s, CHarom), 8.54 (1H, s, NH), 8.00 (1H, d, NH, J=7.6Hz), 7.90 (1H, d, CHarom, J=9.2Hz), 7.85 (1H, d, CHarom, J=8.0Hz), 7.41 (1H, d, CHarom, J=8.4Hz), 7.37 (1H, d, CHarom, J=9.2Hz), 6.88 (1H, dd, CHarom, J=8.4Hz), 6.64 (1H, s, CHarom), 6.48 (1H, d, CHarom, J=8.4Hz), 3.83-3.77 (2H, m), 3.67-3.60 (1H, m), 3.47 (2H, t), 2.88 (2H, d, J=11.2Hz), 2.45-2.38 (1H, m), 2.21 (3H, s), 2.00-1.87 (4H, m), 1.75-1.65 (4H, m), 1.37-1.26 (2H, m). **30-46**: 13.74

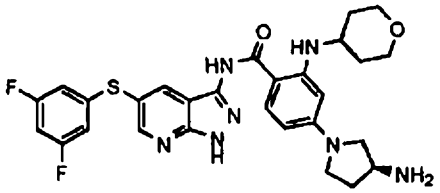
(1H, sl, NH), 10.14 (1H, s, NH), 8.62 (1H, s, CHarom), 8.33 (1H, d, NH), 7.81 (1H, d, CHarom, J=8.7Hz), 7.12-7.03 (3H, m, CHarom), 6.26 (1H, d, CHarom, J=8.8Hz), 6.13 (1H, s, CHarom), 4.31 (2H, s), 4.14-4.07 (4H, m), 3.68 (1H, sl), 3.28 (4H, s), 2.43 (4H, s), 2.23 (3H, s), 1.92 (2H, d, J=12.4Hz), 1.38-1.26 (2H, m). **30-47**: 13.80 (1H, sl, NH), 10.41 (1H, s, NH), 8.64 (1H, s, CHarom), 8.02 (1H, d, NH), 7.85 (1H, d, CHarom, J=8.1Hz), 7.12-7.03 (3H, m, CHarom), 6.69 (1H, s, CHarom), 6.52 (1H, d, CHarom, J=8.1Hz), 4.30 (2H, s), 3.81 (2H, d, J=11.1Hz), 3.68 (1H, sl), 3.48 (2H, t), 2.87 (2H, d, J=10.5Hz), 2.47-2.39 (1H, sl), 2.19 (3H, s), 2-1.88 (4H, m), 1.76-1.66 (4H, m), 1.39-1.27 (2H, m). **30-48**: 13.99 (1H, sl, NH), 10.17 (1H, s, NH), 8.34 (1H, s, CHarom), 8.29 (1H, dl, NH), 7.78 (1H, d, CHarom, J=8.9Hz), 7.54-7.41 (3H, m, CHarom), 6.07 (1H, d, CHarom, J=8.9Hz), 5.87 (1H, s, CHarom), 3.82 (2H, dl), 3.62 (1H, sl), 3.51-3.37 (4H, m), 2.97 (3H, s), 2.28-2.19 (2H, m), 2.15 (6H, s), 2-1.90 (2H, m), 1.71-1.61 (2H, m), 1.42-1.28 (2H, m). **30-49**: 14.06 (1H, sl, NH), 10.56 (1H, s, NH), 8.85 (1H, s, CHarom), 7.97 (1H, sl, NH), 7.85 (1H, d, CHarom, J=8.1Hz), 7.50-7.40 (3H, m, CHarom), 6.71 (1H, s, CHarom), 6.54 (1H, d, CHarom, J=8.1Hz), 3.83-3.76 (2H, m), 3.70 (1H, sl), 3.48 (2H, t), 2.88 (2H, d, J=10.6Hz), 2.48-2.40 (1H, m), 2.20 (3H, s), 2.01-1.89 (4H, m), 1.76-1.66 (4H, m), 1.40-1.28 (2H, m). **30-50**: 13.94 (1H, sl, NH), 10.11 (1H, sl, NH), 8.59 (1H, s, CHarom), 8.30 (1H, sl, NH), 7.76 (1H, d, CHarom, J=9.2Hz), 7.27-7.13 (3H, m, CHarom), 6.04 (1H, dd, CHarom, J=9.2Hz), 5.85 (1H, s, CHarom), 3.87-3.76 (2H, m), 3.66-3.55 (1H, m), 3.49-3.26 (4H, m), 2.96 (3H, s), 2.22 (2H, t), 2.14 (6H, s), 1.97-1.89 (2H, m), 1.69-1.60 (2H, q), 1.40-1.28 (2H, m). **30-51**: 13.95 (1H, sl, NH), 10.17 (1H, sl, NH), 8.54 (1H, s, CHarom), 8.28 (1H, sl, NH), 7.78 (1H, d, CHarom, J=8.8Hz), 7.59 (1H, d, CHarom, J=9.2Hz), 7.42-7.38 (2H, m, CHarom), 6.23 (1H, d, CHarom, J=8.0Hz), 6.11 (1H, s, CHarom), 3.82-3.77 (2H, m), 3.66 (1H, sl), 3.46 (2H, t), 3.26 (4H, s), 2.43 (4H, s), 2.22 (3H, s), 1.92-1.88 (2H, m), 1.34-1.24 (2H, m). **30-52**: 13.97 (1H, sl, NH), 10.20 (1H, s, NH), 8.38 (1H, s, CHarom), 8.27 (1H, d, NH), 7.88 (1H, d, CHarom, J=7.2Hz), 7.78 (1H, d, CHarom, J=9.2Hz), 7.66-7.55 (3H, m, CHarom), 6.26 (1H, dd, CHarom, J=9.2Hz), 6.13 (1H, s, CHarom), 3.85-3.76 (2H, m), 3.75-3.63 (1H, m), 3.48 (2H, t), 3.37-3.26 (4H, m), 2.61-2.52 (4H, m), 2.32 (3H, sl), 1.96-1.88 (2H, m), 1.39-1.26 (2H, m). **30-53**: 13.64 (1H, s, NH), 10.20 (1H, s, NH), 8.30 (1H, d, CHarom, J=8.8Hz), 8.23 (1H, d, CHarom, J=8.0Hz), 8.19 (1H, d, CHarom, J=8.8Hz), 7.81 (1H, d, CHarom, J=9.2Hz), 7.75-7.65 (3H, m, CHarom), 6.28 (1H, dd,

CHarom, J=8.8Hz), 6.14 (1H, s, CHarom), 3.83-3.77 (2H, m), 3.70-3.64 (1H, m), 3.48 (2H, t), 3.29 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.95-1.89 (2H, m), 1.38-1.26 (2H, m). **30-54**: 13.64 (1H, sl, NH), 10.48 (1H, sl, NH), 8.32 (1H, d, CHarom, J=8.8Hz), 8.19 (1H, d, CHarom, J=8.8Hz), 7.91 (1H, sl, NH), 7.85 (1H, d, CHarom, J=8.4Hz), 7.77-7.65 (3H, m, CHarom), 6.71 (1H, s, CHarom), 6.54 (1H, d, CHarom, J=8.4Hz), 3.86-3.80 (2H, m), 3.71-3.64 (1H, m), 3.48 (2H, t), 2.89 (2H, d, J=11.2Hz), 2.45-2.40 (1H, m), 2.21 (3H, s), 2.00-1.90 (4H, m), 1.75-1.65 (4H, m), 1.38-1.27 (2H, m). **30-55**: 13.64 (1H, s, NH), 10.16 (1H, s, NH), 8.29 (1H, d, CHarom, J=8.8Hz), 8.24 (1H, d, NH, J=7.6Hz), 8.17 (1H, d, CHarom, J=8.8Hz), 8.09 (1H, t, CHarom), 7.88-7.85 (1H, m, CHarom), 7.81 (1H, d, CHarom, J=9.2Hz), 7.67 (1H, q, CHarom), 6.28 (1H, d, CHarom, J=8.8Hz), 6.14 (1H, s, CHarom), 3.83-3.75 (2H, m), 3.72-3.67 (1H, m), 3.48 (2H, t), 3.29 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.96-1.89 (2H, m), 1.35-1.28 (2H, m). **30-56**: 13.67 (1H, s, NH), 10.43 (1H, s, NH), 8.31 (1H, d, CHarom, J=8.8Hz), 8.18 (1H, d, CHarom, J=8.8Hz), 8.13-8.05 (1H, m, CHarom), 7.92 (1H, d, NH, J=7.6Hz), 7.90-7.82 (2H, m, CHarom), 7.66 (1H, q, CHarom), 6.71 (1H, s, CHarom), 6.54 (1H, d, CHarom, J=8.4Hz), 3.85-3.80 (2H, m), 3.73-3.65 (1H, m), 3.49 (2H, t), 2.89 (2H, d, J=11.2Hz), 2.48-2.42 (1H, m), 2.21 (3H, s), 1.99-1.90 (4H, m), 1.76-1.68 (4H, m), 1.37-1.27 (2H, m). **30-57**: 13.66 (1H, s, NH), 10.17 (1H, s, NH), 8.30 (1H, d, CHarom, J=8.8Hz), 8.24-8.16 (2H, m, CHarom et NH), 8.03-7.97 (3H, m, CHarom), 7.81 (1H, d, CHarom, J=9.2Hz), 6.28 (1H, d, CHarom, J=7.2Hz), 6.14 (1H, s, CHarom), 3.83-3.77 (2H, m), 3.71-3.67 (1H, m), 3.48 (2H, t), 3.29 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.96-1.89 (2H, m), 1.34-1.28 (2H, m). **30-58**: 13.71 (1H, s, NH), 10.45 (1H, s, NH), 8.32 (1H, d, CHarom, J=9.2Hz), 8.22 (1H, d, CHarom, J=8.8Hz), 8.02-7.96 (3H, m, CHarom), 7.86-7.81 (1H, m, NH), 7.83 (1H, d, Charom), 6.71 (1H, s, CHarom), 6.54 (1H, d, CHarom, J=7.6Hz), 3.85-3.78 (2H, m), 3.72-3.65 (1H, m), 3.48 (2H, t), 2.88 (2H, d, J=11.2Hz), 2.48-2.44 (1H, m), 2.21 (3H, s), 1.97-1.87 (4H, m), 1.76-1.70 (4H, m), 1.36-1.28 (2H, m). **30-59**: 13.69 (1H, s, NH), 10.04 (1H, s, NH), 8.34 (1H, d, NH, J=8.8Hz), 8.26-8.16 (3H, m, CHarom), 7.81 (1H, dd, CHarom, J=8.4Hz), 7.74 (1H, d, CHarom, J=9.2Hz), 7.66 (1H, d, CHarom, J=8.4Hz), 6.24 (1H, dd, CHarom, J=9.2Hz), 6.10 (1H, s, CHarom), 3.82-3.76 (2H, m), 3.68-3.62 (1H, m), 3.48 (2H, t), 3.27 (4H, s), 2.43 (4H, s), 2.22 (3H, s), 1.93-1.86 (2H, m), 1.31-1.21 (2H, m). **30-60**: 13.74 (1H, s, NH), 10.31 (1H, s, NH), 8.35 (1H, d, CHarom, J=8.8Hz), 8.25 (1H, d, CHarom,

J=8.8Hz), 8.21 (1H, s, CHarom), 7.85 (1H, d, NH, J=7.2Hz), 7.81 (1H, dd, CHarom, J=8.8Hz), 7.76 (1H, d, CHarom, J=8.0Hz), 7.66 (1H, d, CHarom, J=8.8Hz), 6.67 (1H, s, CHarom), 6.50 (1H, d, CHarom, J=8.0Hz), 3.85-3.78 (2H, m), 3.68-3.62 (1H, m), 3.48 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.46-2.40 (1H, m), 2.20 (3H, s), 1.97-1.87 (4H, m), 1.75-1.67 (4H, m), 1.32-1.24 (2H, m). **30-61**: 13.61 (1H, s, NH), 10.32 (1H, s, NH), 8.71 (1H, d, NH, J=8.0Hz), 8.21 (1H, d, CHarom, J=8.8Hz), 7.87 (1H, d, CHarom, J=9.2Hz), 7.80 (1H, d, CHarom, J=8.8Hz), 7.17 (1H, t, CHarom), 7.05-7.02 (2H, m, CHarom), 6.29 (1H, d, CHarom, J=9.2Hz), 6.14 (1H, s, CHarom), 4.93 (2H, s), 3.74-3.68 (3H, m), 3.43 (2H, t), 3.29 (4H, s), 2.44 (4H, s), 2.28 (3H, s), 1.90-1.84 (2H, m), 1.28-1.20 (2H, m). **30-62**: 13.67 (1H, sl, NH), 10.59 (1H, s, NH), 8.23 (1H, d, CHarom, J=8.8Hz), 8.10 (1H, d, NH, J=7.6Hz), 7.92 (1H, d, CHarom, J=8.0Hz), 7.82 (1H, d, CHarom, J=8.8Hz), 7.17 (1H, t, CHarom), 7.05-7.02 (2H, m, CHarom), 6.71 (1H, s, CHarom), 6.56 (1H, d, CHarom, J=8.0Hz), 4.94 (2H, s), 3.77-3.70 (3H, m), 3.43 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.45-2.40 (1H, m), 2.20 (3H, s), 1.98-1.91 (2H, m), 1.89-1.95 (2H, m), 1.75-1.67 (4H, m), 1.30-1.20 (2H, m). **30-63**: 13.63 (1H, sl, NH), 10.28 (1H, s, NH), 8.37 (1H, d, NH, J=8.0Hz), 8.24 (1H, d, CHarom, J=8.8Hz), 7.88-7.82 (2H, m, CHarom), 7.24-7.17 (3H, m, CHarom), 6.29 (1H, d, CHarom, J=9.2Hz), 6.14 (1H, s, CHarom), 4.87 (2H, s), 3.75-3.70 (3H, m), 3.43 (2H, t), 3.28 (4H, s), 2.45 (4H, s), 2.23 (3H, s), 1.90-1.85 (2H, m), 1.32-1.20 (2H, m). **30-64**: 13.69 (1H, sl, NH), 10.55 (1H, s, NH), 8.26 (1H, d, CHarom, J=8.8Hz), 8.05 (1H, d, NH, J=7.6Hz), 7.90 (1H, d, CHarom, J=8.4Hz), 7.86 (1H, d, CHarom, J=8.8Hz), 7.24-7.15 (3H, m, CHarom), 6.70 (1H, s, CHarom), 6.56 (1H, d, CHarom, J=8.0Hz), 4.88 (2H, s), 3.80-3.65 (3H, m), 3.43 (2H, t), 2.87 (2H, d, J=11.2Hz), 2.46-2.40 (1H, m), 2.20 (3H, s), 2.00-1.86 (4H, m), 1.75-1.67 (4H, m), 1.29-1.23 (2H, m). **30-65**: 13.49 (1H, sl, NH), 10.45 (1H, s, NH), 9.31 (1H, sl, COOH), 8.21 (1H, d, CHarom, J=8.8Hz), 8.06 (1H, sl, NH), 7.92 (1H, d, CHarom, J=8.4Hz), 7.57 (1H, d, CHarom, J=8.8Hz), 7.17-7.11 (2H, m, CHarom), 6.96-6.91 (1H, m, CHarom), 6.67 (1H, s, CHarom), 6.53 (1H, d, CHarom, J=8.0Hz), 4.51 (1H, d, J=13.2Hz), 4.20 (1H, d, J=13.2Hz), 3.81-3.76 (2H, m), 3.71-3.62 (1H, m), 3.56-3.41 (4H, m), 3.08 (2H, t), 2.83 (3H, s), 2.45-2.40 (1H, m), 2.07-2.00 (2H, m), 1.95-1.86 (4H, m), 1.41-1.29 (2H, m). **30-66**: 13.62 (1H, sl, NH), 10.22 (1H, sl, NH), 8.36 (1H, d, NH, J=7.6Hz), 8.23 (1H, d, CHarom, J=8.8Hz), 7.85 (1H, d, CHarom, J=9.2Hz), 7.80 (1H, d, CHarom, J=8.8Hz), 7.48 (1H, s, CHarom), 7.45-7.37 (2H, m, CHarom), 6.29

(1H, d, CHarom, J=7.2Hz), 6.14 (1H, s, CHarom), 4.97 (2H, s), 3.76-3.70 (3H, m), 3.44 (2H, t), 3.28 (4H, s), 2.44 (4H, s), 2.23 (3H, s), 1.91-1.86 (2H, m), 1.30-1.24 (2H, m). **30-67**: 13.67 (1H, sl, NH), 10.49 (1H, s, NH), 8.25 (1H, d, CHarom, J=8.8Hz), 8.02 (1H, d, NH, J=7.2Hz), 7.89 (1H, d, CHarom, J=8.0Hz), 7.82 (1H, d, CHarom, J=8.8Hz), 7.49 (1H, t, CHarom), 7.45-7.35 (2H, m, CHarom), 6.70 (1H, s, CHarom), 6.56 (1H, d, CHarom, J=8.0Hz), 4.97 (2H, s), 3.78-3.64 (3H, m), 3.44 (2H, t), 2.88 (2H, d, J=11.2Hz), 2.45-2.40 (1H, m), 2.20 (3H, s), 1.98-1.86 (4H, m), 1.76-1.66 (4H, m), 1.32-1.22 (2H, m). **30-68**: 13.46 (1H, s, NH), 10.36 (1H, s, NH), 8.21 (1H, d, CHarom, J=8.8Hz), 8.00 (1H, d, NH, J=7.6Hz), 7.86 (1H, d, CHarom, J=8.4Hz), 7.59 (1H, d, CHarom, J=8.8Hz), 7.43-7.33 (2H, m, CHarom), 7.28 (1H, s, CHarom), 6.69 (1H, s, CHarom), 6.54 (1H, d, CHarom, J=7.6Hz), 4.58 (1H, d, J=12.8Hz), 4.30 (1H, d, J=12.8Hz), 3.78-3.75 (2H, m), 3.70-3.65 (1H, m), 3.46 (2H, t), 2.92-2.88 (2H, m), 2.45-2.40 (1H, m), 2.24 (3H, s), 2.05-1.95 (2H, m), 1.93-1.89 (2H, m), 1.77-1.70 (4H, m), 1.34-1.24 (2H, m). (ND: not determined).

<u>Example 30-bis</u>: (S)-4-(3-aminopyrrolidin-1-yl)-N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide



876 µl (20 eq) of triethylamine is added to a solution of 238 mg (0.314 mmol) of (S)-*N*-(5-(3,5-difluorophenylthio)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-2-(2,2,2-trifluoro-N-(tetrahydro-2*H*-pyran-4-yl)acetamido)-4-(3-(2,2,2-trifluoroacetamido)pyrrolidin-1-yl)benzamide in 6 ml of methanol. The reaction medium is stirred at 65°C for 4 hours. After returning to room temperature, 8 ml of n-butanol and 260 mg (6 eq) of potassium carbonate are added. The reaction medium is stirred at 80°C for 24 hours. After returning to room temperature, the solvents are evaporated, water is added and the product is extracted with dichloromethane. The organic phase is washed with saturated sodium chloride solution, dried on magnesium sulfate, filtered and evaporated. The residue is purified by silica gel chromatography (8:2 dichloromethane/methanol as eluent) to yield 87 mg (yield=49%) of (S)-4-(3-aminopyrrolidin-1-yl)-*N*-(5-(3,5-

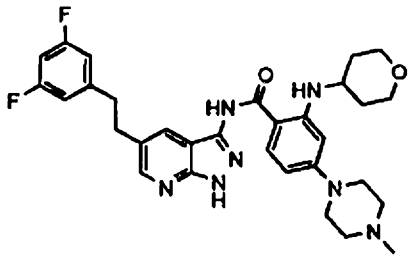
difluorophenylthio)-1*H*-pyrazolo[3,4-*b*]pyrazine-3-yl)-2-(tetrahydro-2*H*-pyran-4-ylamino)benzamide in the form of a brown powder.

LCMS (EI, m/z): (M+1) 566.24.

^{1}H NMR: δH ppm (400 MHz, DMSO): 10.46 (1H, bs, NH), 8.60 (1H, s, CH_{arom}), 8.50 (1H, s, CH_{arom}), 8.26 (1H, d, NH), 7.78 (1H, d, CH_{arom}), 7.08 (1H, t, CH_{arom}), 6.86 (2H, d, CH_{arom}), 5.86 (1H, dd, CH_{arom}), 5.71 (1H, d, CH_{arom}), 3.80-3.88 (2H, m, CH), 3.63-3.70 (2H, m, CH), 3.40-3.55 (5H, m, CH), 3.01-3.08 (1H, m, CH), 2.08-2.13 (1H, m, CH), 1.92-1.99 (2H, m, CH_3), 1.76-1.82 (1H, m, CH), 1.30-1.41 (2H, m, $CH_{pyranone}$).

Examples of method F2: reduction

<u>Example 31</u>: N-(5-(3,5-difluorophenethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide



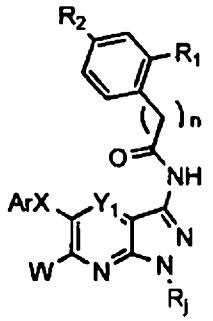
10 mg of 10% Pd/C is added to 100 mg (0.175 mmol) of N-(5-((3,5-difluorophenyl)ethynyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide in solution in a mixture of 10 ml of tetrahydrofuran and 5 ml of methanol before placing the reaction medium under an atmosphere of hydrogen. The reaction mixture is stirred for 12 hours at room temperature and then filtered on Celite and concentrated. 62 mg (yield=60%) of N-(5-(3,5-difluorophenethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide are isolated in the form of a white solid.

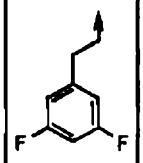
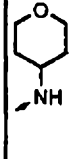
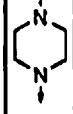
LCMS (EI, m/z): (M+1) 576.23.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.14 (1H, bs, NH), 10.32 (1H, bs, NH), 8.40 (1H, d, CH_{arom}), 8.22 (1H, d, NH), 7.96 (1H, d, CH_{arom}), 7.80 (1H, d, CH_{arom}), 7.03-6.98 (3H, m, CH_{arom}), 6.23 (1H, d, CH_{arom}), 6.16 (1H, bs, CH_{arom}), 3.84-3.81 (2H, dt, CH), 3.70 (1H, m, CH), 3.52-3.46 (2H, m, CH), 3.04-2.93 (4H, m, CH), 2.59-2.69 (4H, m,

CH), 2.42-2.46 (4H, m, CH), 2.38 (3H, s, CH_3), 1.96-1.93 (2H, m, CH), 1.40-1.33 (2H, m, CH).

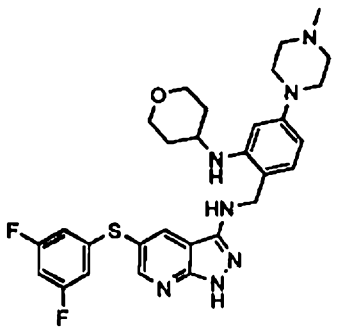
The following derivative was obtained according to the same method:



Ex.**	ArX	R_1	R_2	Y_1	n	W	R_j	Compound names	Yield	Mass
31-1				N	0	H	H	N-(5-(3,5-difluorophenethyl)-1H-pyrazolo[3,4-b]pyrazin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide	47%	577.07 (M+H)

** ^{1}H NMR, dmso-d_6, Ex. : **31-1**: 13.68 (1H, sl, NH), 10.11 (1H, s, NH), 8.52 (1H, s, CHarom), 8.35 (1H, dl, NH), 7.82 (1H, d, CHarom, J=9Hz), 7.05-6.97 (3H, m, CHarom), 6.27 (1H, dd, CHarom), 6.14 (1H, s, CHarom), 3.83-3.76 (2H, m), 3.74-3.64 (1H, m), 3.47 (2H, t), 3.32-3.20 (6H, m), 3.07 (2H, dd), 2.44 (4H, dd), 2.23 (3H, s), 1.91 (2H, d), 1.38-1.27 (2H, m).

Example 32: 5-(3,5-difluorophenylthio)-N-(4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzyl)-1H-pyrazolo[3,4-b]pyridin-3-amine



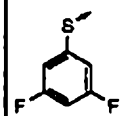
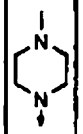
100 mg (0.173 mmol) of N-(5-(3,5-difluorophenylthio)-1-H-pyrazolo[3,4-b]pyridine-3-yl)-4-(4-methylpiperazine-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide is added, in small fractions, to a solution of 19.64 mg (0.518 mmol) of $LiAlH_4$ in 3 ml of

anhydrous tetrahydrofuran under argon at 0°C. The reaction mixture is heated at 90°C for 15 hours. An additional portion of 20 mg of $LiAlH_4$ is then added and the reaction medium stirred at 90°C for 5 hours. 45 µl of water at 0°C is then added to the reaction mixture, followed by 45 µl of sodium hydroxide (15% wt) and finally 120 µl of water. The reaction mixture is stirred at 25°C for 1 hour and then filtered on Dicalite. After evaporation of the solvents, the crude product is purified by chromatography. 16.80 mg (17%) of 5-(3,5-difluorophenylthio)-N-(4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzyl)-1H-pyrazolo[3,4-b]pyridin-3-amine in the form of a yellow solid is obtained.

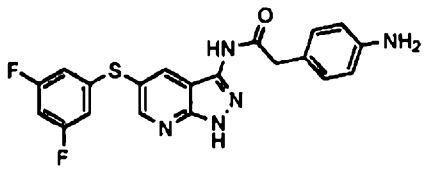
LCMS (EI, m/z): (M+1) 566.68.

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.57 (1H, bs, NH), 8.45 (2H, d, CH_{arom}), 6.97-7.06 (2H, m, CH_{arom}), 6.73-6.75 (2H, m, CH_{arom}), 6.65 (1H, t, NH), 6.13-6.19 (2H, m, CH_{arom}), 4.98 (1H, d, NH), 4.30 (2H, m, CH_2), 3.73-3.77 (2H, m, CH), 3.60 (1H, m, CH), 3.45-3.50 (2H, m, CH), 3.04 (4H, m, CH), 2.42 (4H, m, CH), 2.18 (3H, s, CH_3), 1.80-1.83 (2H, m, CH), 1.27-1.32 (2H, m, CH).

The following derivatives were obtained according to the same method:

Ex.**	ArX	R_1	R_2	$(U)_n$	V	Y_1,Y_2,Y_3,Y_4	R_3	Compound name	Yield	Mass
32-1				n=0	CH_2	N,ArXC,CH,N	H	5-(3,5-difluorophenylthio)-N-(4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzyl)-1H-pyrazolo[4,3-b]pyrazin-3-amine	1%	567.3

Example 33: 2-(4-aminophenyl)-N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)acetamide



A solution of 152 mg (2.72 mmol) of iron and 70 mg (1.3 mmol) of ammonium chloride in 100 µl of water is added to a solution of 0.24g (0.544 mmol) of N-(5-(3,5-

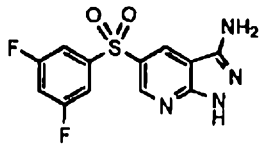
difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl)-2-(4-nitrophenyl)acetamide in 10 ml of a 2:1 ethanol/water mixture. Several drops of acetic acid are added to this mixture and it is heated at 60°C for 4 hours. After cooling and concentration of the solvents, the crude reaction product is extracted with ethyl acetate and is washed with saturated sodium bicarbonate solution. The organic phases are combined, dried on magnesium sulfate and then concentrated. The crude product is purified by silica gel chromatography (DCM/MeOH) to yield 11 mg (4%) of 2-(4-aminophenyl)-N-(5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-yl) acetamide in the form of a brown solid.

LCMS (EI, m/z): (M+1) 412.09.

^{1}H NMR: δH ppm (400 MHz, DMSO): 13.60 (1H, bs, NH), 10.96 (1H, bs, NH), 8.68 (1H, d, CH_{arom}), 8.55 (1H, d, CH_{arom}), 7.06 (1H, m, CH_{arom}), 6.98 (2H, d, CH_{arom}), 6.79 (2H, m, CH_{arom}), 6.50 (2H, m, CH_{arom}), 4.92 (2H, s, NH), 3.51 (2H, m, CH_2).

Examples of method F3: sulfide oxidation

Example 34: 5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-amine

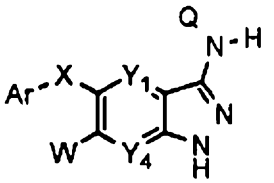


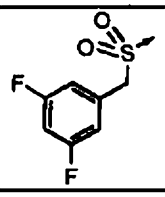
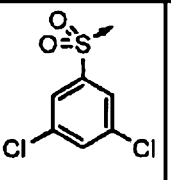
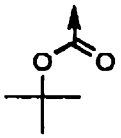
A solution of 663 mg (1.078 mmol) of oxone in 1.1 ml of water is added to a solution of 300 mg (1.078 mmol) of 5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-b]pyridin-3-amine in 10 ml of a 1:1 mixture of tetrahydrofuran and methanol at 0°C. The reaction mixture is stirred at room temperature for 16 hours. An additional portion of 663 mg of oxone at 0°C is then added and the reaction medium stirred at room temperature for 24 hours. The solvents are evaporated and the reaction medium is diluted with sodium bicarbonate solution, extracted with ethyl acetate, dried on $MgSO_4$ and then concentrated to yield 340 mg (81%) of 5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-amine in the form of a yellow solid.

LCMS (EI, m/z): (M+1) 311.03.

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.72 (1H, bs, NH), 8.92 (1H, d, CH_{arom}), 8.84 (1H, d, CH_{arom}), 7.89-8.01 (1H, d, CH_{arom}), 7.62-7.80 (2H, m, CH_{arom}), 6.06 (2H, bs, NH).

The following compounds were also obtained by this method:

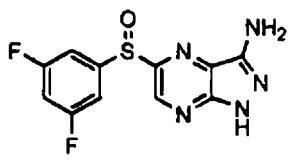


Ex.**	ArX	Q	Y_1, Y_4	W	Compound name	Yield	Mass MH^+
34-2		H	CH, N	H	5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[3,4-b]pyridin-3-amine	ND	(M+1) 325.07
34-3			N, CH	H	*tert*-butyl 5-(3,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-ylcarbamate	ND	ND

** ^{1}H NMR, DMSO-d_6, Ex.: 33-2: 12.64 (1H, bs, NH), 8.56 (1H, d, CH_{arom}), 8.49 (1H, d, CH_{arom}), 7.24 (1H, ddd, CH_{arom}), 6.94 (2H, bd, CH_{arom}), 6.03 (2H, bs, NH), 4.80 (2H, s, CH). (ND: not determined).

Alternatively, a protection step can be carried out before the oxidation reaction, followed by a deprotection step which can lead to the preparation of the corresponding sulfones or sulfoxides.

Example 34-bis: 5-(3,5-difluorophenylsulfinyl)-1H-pyrazolo[4,3-b]pyrazin-3-amine



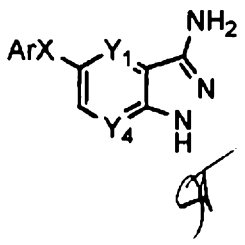
0.55 mL of triethylamine and 22 mg of 4-dimethylaminopyridine are added under argon to a solution of 500 mg (1.790 mmol) of 5-(3,5-difluorophenylthio)-1H-pyrazolo[3,4-

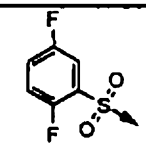
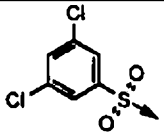
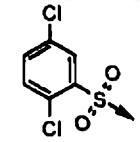
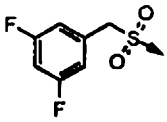
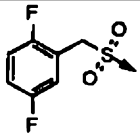
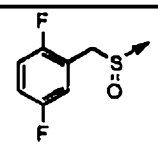
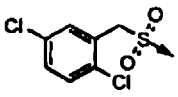
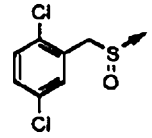
b]pyrazin-3-amine in 10 mL of tetrahydrofurane. The solution is stirred at 0°C and 0.915 mL of di-tert-butyl dicarbonate is added and the reaction medium is stirred overnight. An aqueous fraction is added to the reaction medium which is then extracted with ethyl acetate. The organic phases are dried on $MgSO_4$ and concentrated in vacuum to give a crude product which is used in the oxidation step without further purification.

The crude product obtained is dissolved in 10 mL of a 1:1 mixture of tetrahydrofurane and methanol at 0°C and then a solution of 1.103 g (1.794 mmol) of oxone in 2 mL of water is added. The reaction medium is stirred at room temperature for 16 hours. An additional portion of 550 mg of oxone is then added and the reaction medium is stirred at room temperature for 5 hours. The solvents are evaporated and the reaction medium is diluted with a sodium bicarbonate solution, extracted with ethyl acetate, dried on magnesium sulfate and concentrated to lead to a mixture of the corresponding sulfone and sulfoxide which are used without further purification in the deprotection step.

0.373 mL of TFA in 4 mL of anhydrous THF is added at 0°C to a solution of 600 mg of the previously obtained mixture in 6 mL of dichloromethane. The mixture is stirred 1 hour at room temperature and an additional portion of 4 equivalents of TFA in 4 mL of THF is added. After 1 hour of stirring, this operation is repeated and the reaction medium is stirred for a total time of 3h45. The solvents are evaporated and the reaction medium is diluted with a potassium carbonate solution, extracted with ethyl acetate, dried on magnesium sulfate and concentrated to yield a 1:1 mixture of 5-(3,5-difluorophenylsulfonyl)-1H-pyrazolo[3,4-b]pyrazin-3-amine and 5-(3,5-difluorophenyl sulfinyl)-1H-pyrazolo[3,4-b]pyrazin-3-amine. This mixture is used in the following steps without further purification.

The following compounds were also obtained by this method:



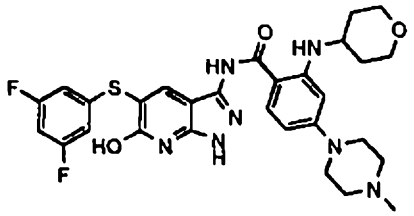
Ex.**	ArX	Y_1, Y_4	Compound names	Yield	Mass MH^+
34bis-1		CH, N	5-(2,5-difluorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	58% 3 steps	(M+1) 310.9
34bis-2		CH, N	5-(3,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	38% 3 steps	(M+1) 342.8
34bis-3		CH, N	5-(2,5-dichlorophenylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	41% 3 steps	(M+1) 342.9
34bis-4		CH, N	5-(3,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	58% 3 steps	(M+1) 325.0
34bis-5		CH, N	5-(2,5-difluorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	45% 3 steps	(M+1) 325.0
34bis-6		CH, N	5-(2,5-difluorobenzylsulfinyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	5% 3 steps	(M+1) 308.9
34bis-7		CH, N	5-(2,5-dichlorobenzylsulfonyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	3% 3 steps	ND
34bis-8		CH, N	5-(2,5-dichlorobenzylsulfinyl)-1H-pyrazolo[4,3-b]pyridin-3-amine	18% 3 steps	ND

** ^1H NMR, DMSO-d_6, Ex.: **34bis-1**: 12.31 (1H, sl, NH), 8.08-8.18 (1H, m, CHarom), 8.05 (1H, d, CHarom, J=11.6Hz), 7.97 (1H, d, CHarom, J=11.6Hz), 7.87-7.93 (1H, m, CHarom), 7.64-7.76 (1H, m, CHarom), 5.81 (2H, sl, NH_2). **34bis-2**: 12.32 (1H, sl, NH), 7.94-8.11 (5H, m, CHarom), 5.85 (2H, sl, NH_2). **34bis-3**: 12.34 (1H, sl, NH), 8.27 (1H, s, CHarom), 8.12 (1H, d, CHarom, J=11.6Hz), 8.01 (1H, d, CHarom, J=11.6Hz), 7.82-7.89 (1H, m, CHarom), 7.67 (1H, d, CHarom, J=11.2Hz), 5.70 (2H, sl, NH_2). **34bis-4**: 12.28 (1H, sl, NH), 7.89 (1H, d, CHarom, J=8.8Hz), 7.68 (1H, d, CHarom, J=8.8Hz),

7.21 (1H, m, CHarom), 6.91-6.97 (2H, m, CHarom), 5.87 (2H, s, NH2), 4.94 (2H, s, CH). **34bis-5**: 12.28 (1H, sl, NH), 7.89 (1H, d, CHarom, J=8.8Hz), 7.68 (1H, d, CHarom, J=8.8Hz), 7.20-7.25 (2H, m, CHarom), 7.10-7.15 (1H, m, CHarom), 5.84 (2H, s, NH2), 4.87 (2H, s, CH). **34bis-6**: 12.04 (1H, s, NH), 7.87 (1H, d, CHarom, J=8.8Hz), 7.40 (1H, d, CHarom, J=8.8Hz), 7.10-7.25 (2H, m, CHarom), 6.90-6.97 (1H, m, CHarom), 5.61 (2H, s, NH2), 4.47 (1H, d, CH, J=13.2Hz), 4.18 (1H, d, CH, J=13.2Hz). **34bis-7**: 12.28 (1H, s, NH), 7.89 (1H, d, CHarom, J=8.8Hz), 7.64 (1H, d, CHarom, J=8.8Hz), 7.40-7.50 (3H, m, CHarom), 5.81 (2H, s, NH2), 4.96 (2H, s, CH).

Example of method F4: demethylation

<u>Example 35</u>: N-(5-(3,5-difluorophenylthio)-6-hydroxy-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide



443 µl (3 eq) of a solution of 1 M boron tribromide in dichloromethane is added to a solution of 90 mg (0.148 mmol) of N-(5-(3,5-difluorophenylthio)-6-methoxy-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide (example 18) in 4 ml of 1,2-dichloroethane at 0°C. The reaction medium is stirred at 60°C for 3 hours and then cooled in an ice bath before adding methanol. The solvents are evaporated and the residue is redissolved in a mixture of methanol and ethyl acetate. The solid formed is filtered, redissolved in 3 ml of tetrahydrofuran and is added to 1 N soda solution. The reaction medium is stirred for 18 hours at room temperature. The pH of the solution is adjusted to 8-9 and the aqueous phase is extracted with ethyl acetate. The organic phase is dried on magnesium sulfate and the crude product is purified on a silica gel column (dichloromethane/methanol as eluent) to yield 21 mg (24%) of N-(5-(3,5-difluorophenylthio)-6-hydroxy-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide in the form of a yellow powder.

LCMS (EI, m/z): (M+1) 596.13.

^{1}H NMR: δH ppm (400 MHz, DMSO): 12.96 (1H, broad flat singlet), 12.02 (1H, broad flat singlet), 10.64 (1H, bs, NH), 8.46 (1H, bs), 8.09 (1H, bs), 7.72 (1H, d, CH_{arom}), 6.97-7.10 (1H, m, CH_{arom}), 6.60-6.74 (2H, m, CH_{arom}), 6.28 (1H, dd, CH_{arom}), 6.13 (1H, d, CH_{arom}), 3.80-3.90 (2H, m, $CH_{pyranone}$), 3.65-3.77 (1H, m, $CH_{pyranone}$), 3.50 (2H, t, $CH_{pyranone}$), 3.25-3.32 (4H, m, 2*CH_2), 2.37-2.45 (4H, m, 2*CH_2), 2.22 (3H, s, CH_3), 1.91-2.00 (2H, m, $CH_{pyranone}$), 1.28-1.43 (2H, m, $CH_{pyranone}$).

II. Biological tests of the compounds according to the invention

- **Test for measuring inhibition of ALK kinase:**

A ViewPlate microplate (Packard) is incubated with 0.1 mg/ml GST-PLCγ1 substrate (purified recombinant form) in phosphate buffer (PBS, pH 7.4) (100 µl/well) for one hour under stirring. The plate is then saturated with blocking solution comprising 5% bovine serum albumin (BSA) (Sigma) in PBS buffer, pH 7.4.

After having added a compound according to the invention to the desired final concentration (typical range between 30 µM and 10 nM), the reaction is carried out by adding 180 ng/ml ALK to a reaction buffer comprised of 13 mM Tris, pH 7.5 (Sigma); 6.5 mM $MgCl_2$ (Merck); 0.65 mM dithiothreitol (DTT) (Acros); 39 mM sodium β-glycerophosphate (TCI); 0.65 mM sodium orthovanadate (Sigma); and 250 µM ATP (Sigma). Incubation is carried out for 30 minutes at 30°C under stirring.

After three washings under stirring in 0.1% PBS/Tween-20 buffer (Sigma), an anti-phosphotyrosine antibody, coupled with HRP (UBI) diluted to 1/1000 in 5 mg/ml PBS/BSA buffer, is incubated for one hour with stirring. After three new washings in 0.1% PBS/Tween-20, the wells are incubated for two minutes with 100 µl of SuperSignal ELISA mixture (Pierce).

The signal is read in luminescence mode using a luminometer (SpectraMax M5e, Molecular Devices).

IC_{50}s are determined by nonlinear regression on the basis of a sigmoidal dose/response relationship model, wherein the Hill coefficient is left variable, carried out on the GraphPad software package according to the algorithm provided.

- **Test for measuring inhibition of cell (Karpas 299) proliferation:**

The antiproliferative activities of the compounds according to the invention were measured by the ATPlite technique (Perkin Elmer).

Nonadherent human anaplastic large-cell lymphoma cells (Karpas 299) are inoculated in 96-well plates (300,000 cells/ml) at day 1, at a concentration compatible with logarithmic growth for the 72 hours required for the evaluation of the compounds. All of the cells are treated at day 1 and then placed in an incubator at 37°C under an atmosphere of 5% CO_2. Cell viability is evaluated at day 4 by assaying released ATP, which is characteristic of viable cells. IC_{50}s are determined by nonlinear regression on the basis of a sigmoidal dose/response relationship model, wherein the Hill coefficient is left variable, carried out on the GraphPad software package according to the algorithm provided.

The results of these two tests obtained with the compounds of the invention are indicated below:

Molecule	Enzymatic inhibition of ALK (IC_{50}, μM)	Karpas 299 cell proliferation inhibition (IC_{50}, μM)
30-1	0.020	2.2
30	0.001	0.16
30-9	0.001	ND
28	0.036	ND
31	0.017	0.83
30-5	0.066	2.6

(ND: not determined)

- **Pharmacological activity *in vivo***

The molecules described and tested exhibit marked antitumor activity *in vivo* which is expressed, in an unexpected manner, by a particularly wide therapeutic index, thus suggesting that these compounds are particularly well tolerated. This was demonstrated by evaluating the effects *in vivo* of the compounds on a human anaplastic large-cell lymphoma (ALCL) tumor model. The compounds were administered orally at various doses on a daily schedule to mice with ALCL tumors grafted subcutaneously. Tumor size was measured regularly during the study and the animals were weighed several times per week in order to identify any adverse effects. A compound is declared active if it induces inhibition of ALCL tumor growth by at least 58%. Several

compounds of the present invention, in particular molecules 30 and 30-9, induced 100% inhibition of tumor growth, with no adverse effects, which corresponds to complete regression of the tumors.

Furthermore, the molecules described and tested have general pharmacological properties which seem quite favorable. Notably, they accumulate within the experimental tumors in a long-lasting manner, after their administration *in vivo*. To that end, ALCL tumors were grafted subcutaneously in the mice and then when the tumors reached a size of approximately 70-130 mm^3 the compounds were administered orally in a therapeutically-active dose. The tumors were removed at various times after the administration of the compounds and then ground. The presence of the compounds within the ALCL tumors sampled was then investigated by assays using chromatography with UV and mass.

- **Test for measuring inhibition of a panel of kinases:**

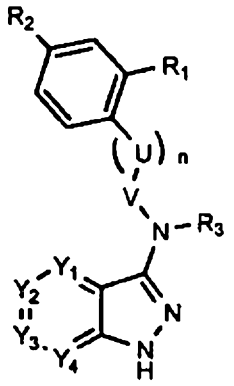
These kinases are produced by Millipore and are screened according to the manufacturer's protocols.

The results are presented in the table below:

Kinases	Enzyme inhibition (IC_{50}, nM)	
	30-9	30
ALK	15	7
Abl	38	18
c-Src	9	4

CLAIMS

1. A compound of following general formula (I):



(I)

or a pharmaceutically acceptable salt or solvate of same, a tautomer of same, or a stereoisomer or mixture of stereoisomers of same in any proportions, such as a mixture of enantiomers, notably a racemic mixture,

wherein:

- Y_1 and Y_4 each represent, independently of each other, a CH group or a nitrogen atom,
- Y_2 represents a nitrogen atom or a CH or C-X-Ar group,
- Y_3 represents a nitrogen atom or a C-X-Ar or C-W group,

on the condition that:

- at least one and at most two Y_1, Y_2, Y_3, and Y_4 groups represent a nitrogen atom,
- Y_2 and Y_4 cannot represent a nitrogen atom at the same time,
- when Y_2=C-X-Ar, then Y_3 represents a nitrogen atom or a C-W group, and
- when Y_3=C-X-Ar, then Y_2 represents a nitrogen atom or a CH group,

- **Ar** represents an aryl or heteroaryl group optionally substituted by one or more groups selected from a halogen atom, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$haloalkoxy, $(C_1\text{-}C_6)$halothioalkoxy, CN, NO_2, OR_{11}, SR_{12}, $NR_{13}R_{14}$, CO_2R_{15}, $CONR_{16}R_{17}$, SO_2R_{18}, $SO_2NR_{19}R_{20}$, COR_{21}, $NR_{22}COR_{23}$, $NR_{24}SO_2R_{25}$, and $R_{26}NR_{27}R_{28}$ and/or optionally fused to a heterocycle,

- **X** represents a divalent group selected from O, S, S(O), $S(O)_2$, NR_4, $S(NR_4)$, $S(O)(NR_4)$, $S(O)_2(NR_4)$, NR_4S, $NR_4S(O)$, $NR_4S(O)_2$, CH_2, CH_2S, $CH_2S(O)$, $CH_2S(O)_2$, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, CH_2CH_2, CH=CH, C≡C, CH_2O, OCH_2, NR_4CH_2, and CH_2NR_4,
- **W** represents an R_5, SR_5, OR_5 or NR_5R_6 group,
- **U** represents a CH_2 or NH group, one or more hydrogen atoms which may be replaced by a $(C_1$-$C_6)$alkyl group,
- **V** represents C(O), C(S) or CH_2,
- **n** represents 0 or 1,
- $\mathbf{R_1}$ represents a hydrogen atom, or an OR_7 or NR_7R_8 group,
- $\mathbf{R_2}$ represents a hydrogen atom, an optionally substituted heterocycle, NO_2, OR_9 or NR_9R_{10},
- $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_{11}}$ to $\mathbf{R_{25}}$ and $\mathbf{R_{27}}$ to $\mathbf{R_{28}}$ each represent, independently of each other, a hydrogen atom or a $(C_1$-$C_6)$alkyl group,
- $\mathbf{R_5}$ and $\mathbf{R_6}$ each represent, independently of each other, a hydrogen atom or a $(C_1$-$C_6)$alkyl, optionally substituted aryl or optionally substituted benzyl group,
- $\mathbf{R_7}$, $\mathbf{R_8}$, $\mathbf{R_9}$ and $\mathbf{R_{10}}$ each represent, independently of each other, a hydrogen atom or an optionally substituted $(C_1$-$C_6)$alkyl or $(C_3$-$C_{12})$cycloalkyl group or an optionally substituted heterocycle, and
- $\mathbf{R_{26}}$ represents a $(C_1$-$C_6)$alkyl group.

2. The compound according to claim 1, characterized in that:

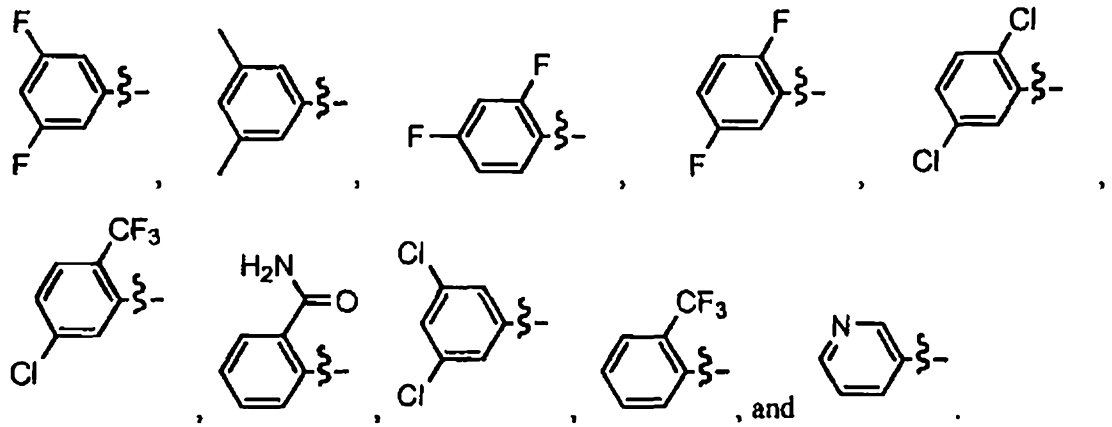
- $\mathbf{Y_1}$ and/or $\mathbf{Y_4}$ = N,
- $\mathbf{Y_2}$=CH or C-X-Ar, and
- $\mathbf{Y_3}$=C-W or C-X-Ar.

3. The compound according to either claim 1 or claim 2, characterized in that **X** represents a divalent group selected from S, S(O), $S(O)_2$, NR_4, CH_2, CH_2S, $CH_2S(O)$, $CH_2S(O)_2$, CH_2O, CH_2NR_4, $NHS(O)_2$, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, $S(O)_2NH$, OCH_2, NR_4CH_2, CH_2CH_2, CH=CH, and C≡C; notably from S, S(O), $S(O)_2$, NR_4, CH_2, SCH_2, $S(O)CH_2$, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, C≡C, OCH_2, and NR_4CH_2; in particular from

S, $S(O)_2$, CH_2, SCH_2, $S(O)_2CH_2$, $S(O)_2NH$, CH_2CH_2, and C≡C, wherein the first atom of these groups is bound to atom C of chain C-X-Ar.

4. The compound according to any one of claims 1 to 3, characterized in that **Ar** represents an aryl group, such as phenyl, optionally substituted by one or more groups selected from a halogen atom, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$haloalkoxy, $(C_1$-$C_6)$halothioalkoxy, CN, NO_2, OR_{11}, SR_{12}, $NR_{13}R_{14}$, CO_2R_{15}, and $CONR_{16}R_{17}$, SO_2R_{18}, $SO_2NR_{19}R_{20}$, COR_{21}, $NR_{22}COR_{23}$ or $NR_{24}SO_2R_{25}$; or a pyridine group.

5. The compound according to claim 4, characterized in that **Ar** represents a group selected from the following groups:



, and .

6. The compound according to any one of claims 1 to 5, characterized in that **W** represents an R_5, SR_5, OR_5 or NR_5R_6 group, with R_5 and R_6 representing, independently of each other, a hydrogen atom or a $(C_1$-$C_6)$alkyl group.

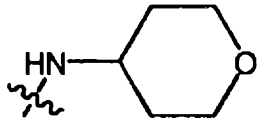
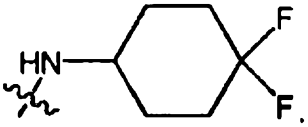
7. Compound according to any one of claims 1 to 6, characterized in that:

- R_3=H,
- U=CH_2 or NH,
- V=C(O) or C(S), and notably C(O), and
- n=0 or 1, and notably 0.

8. The compound according to any one of claims 1 to 7, characterized in that R_1 represents a hydrogen atom or an NR_7R_8 group, with R_7 representing a hydrogen atom

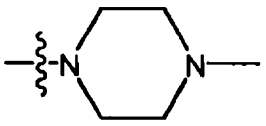
and R_8 representing an optionally substituted (C_3-C_{12})cycloalkyl group or an optionally substituted heterocycle.

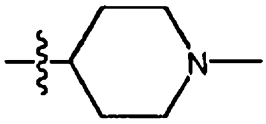
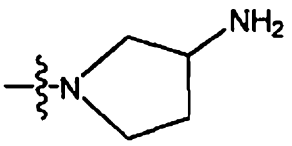
9. The compound according to claim 8, characterized in that R_1 represents one of the following groups:

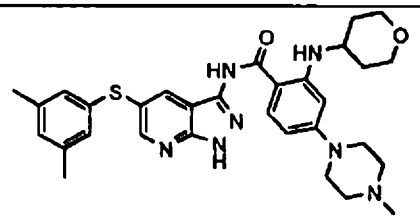
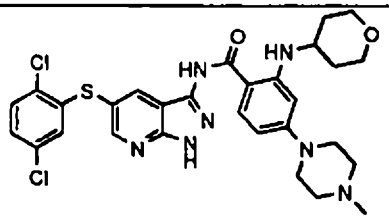
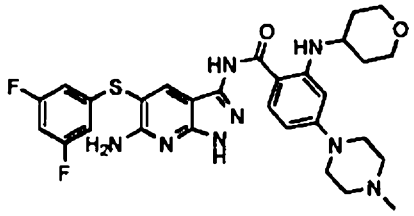
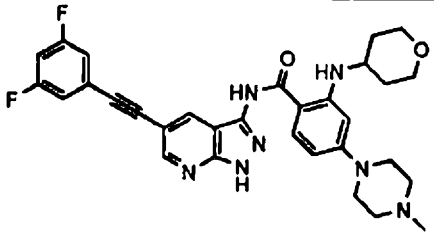
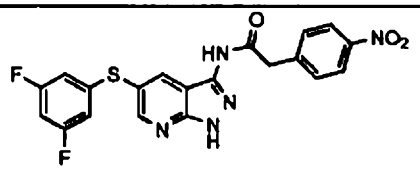
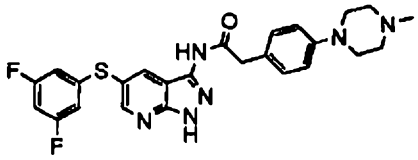
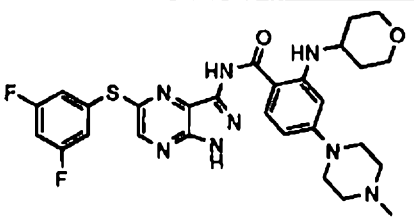
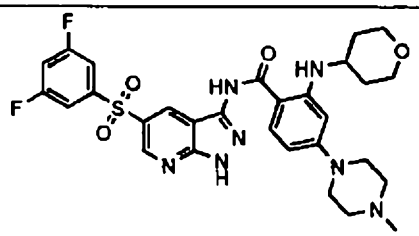
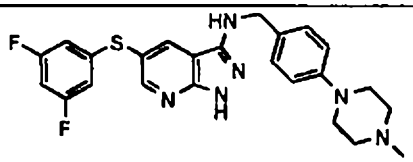
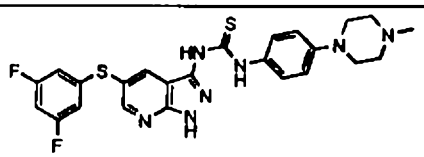
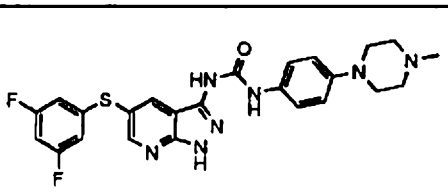
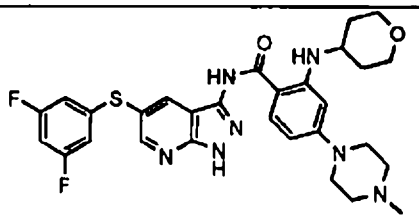
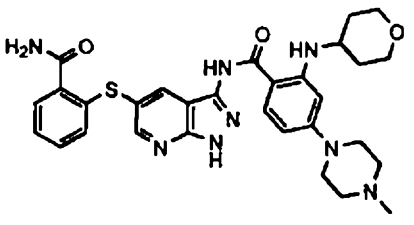
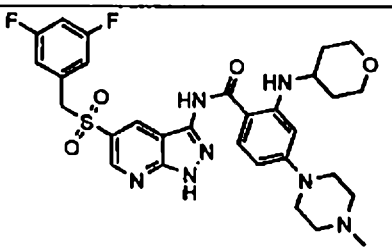
H,  and  .

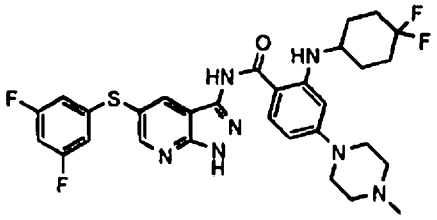
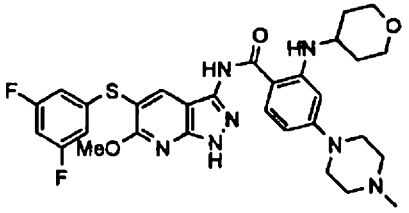
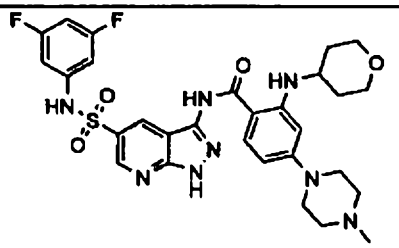
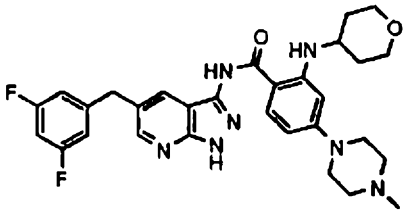
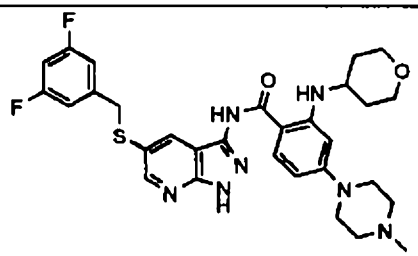
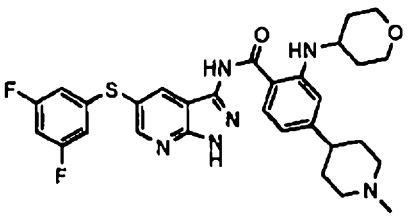
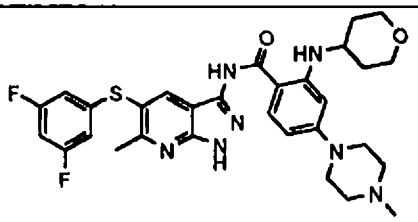
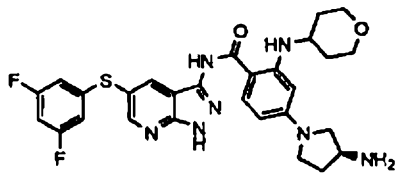
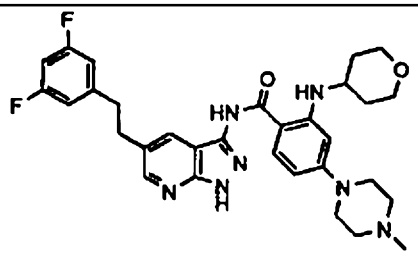
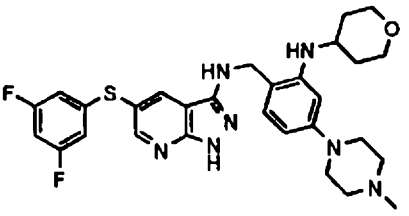
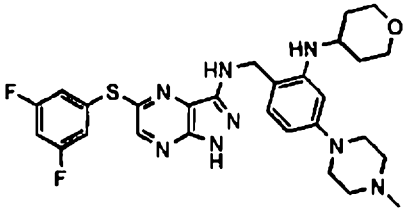
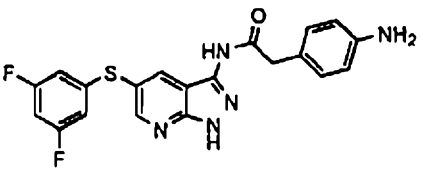
10. The compound according to any one of claims 1 to 9, characterized in that R_2 represents NO_2, NR_9R_{10} or a heterocycle optionally substituted by (C_1-C_6)alkyl or NH_2.

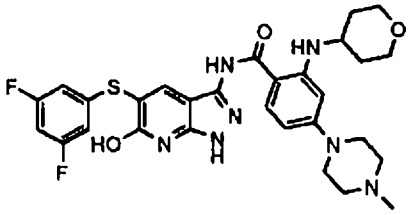
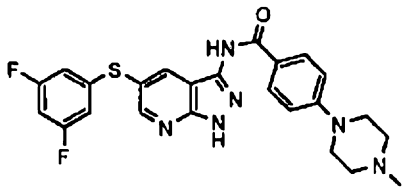
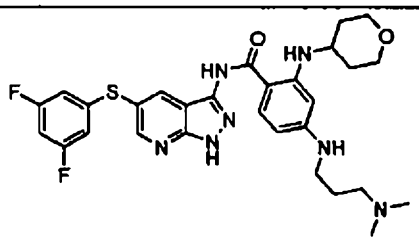
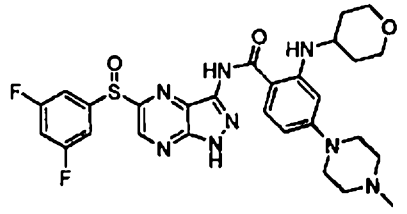
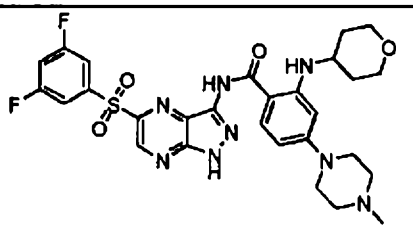
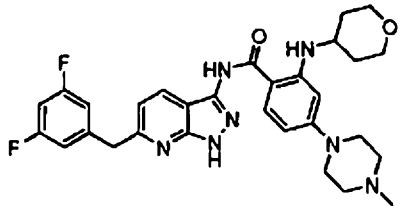
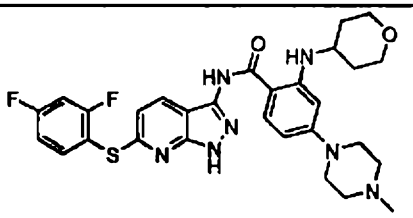
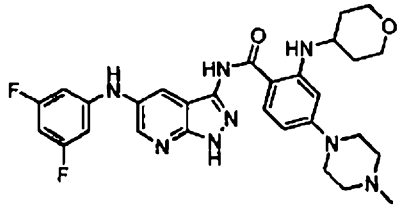
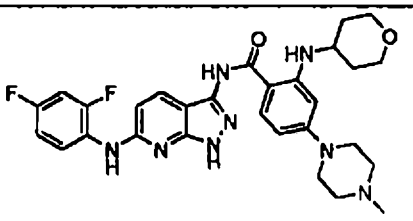
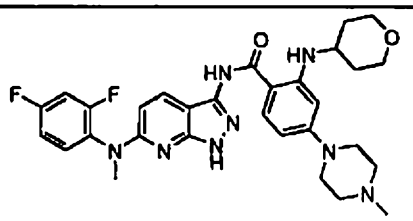
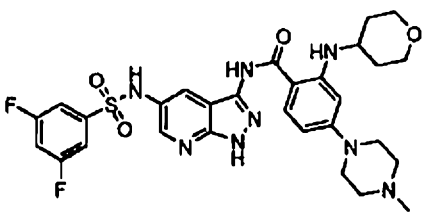
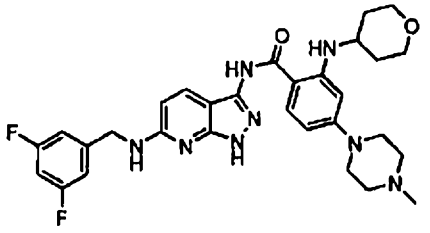
11. The compound according to claim 10, characterized in that R_2 represents one of the following groups:

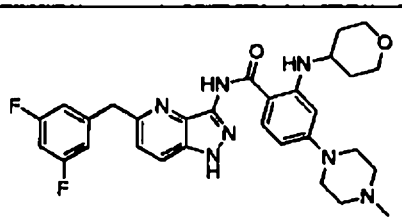
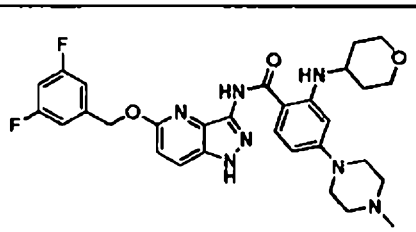
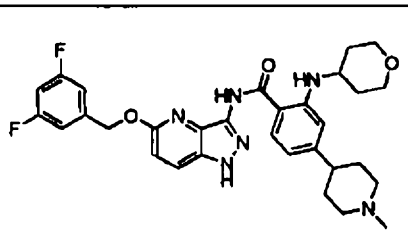
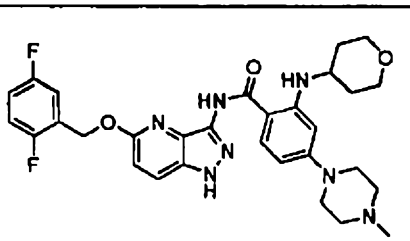
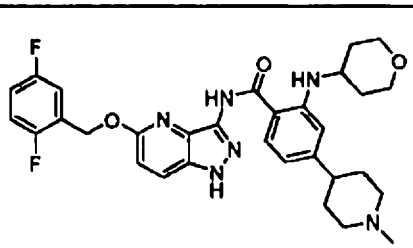
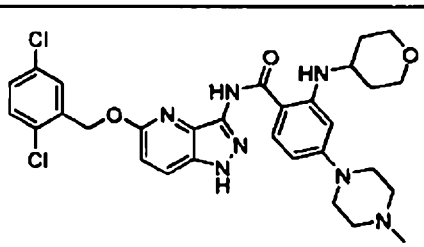
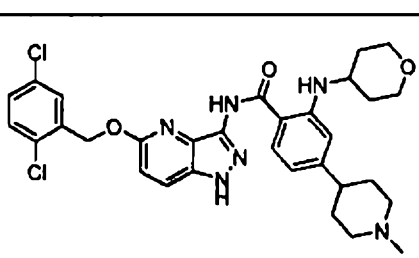
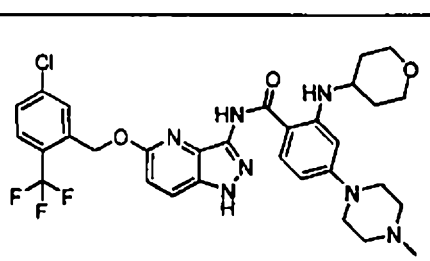
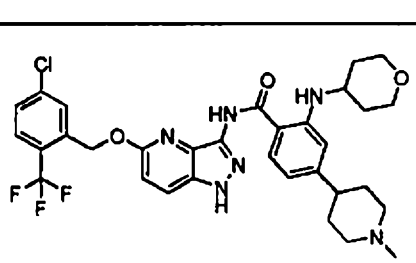
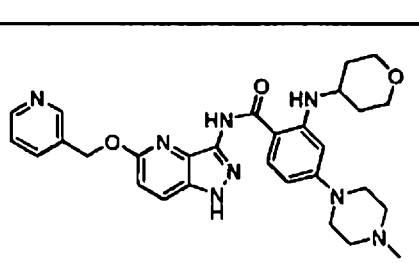
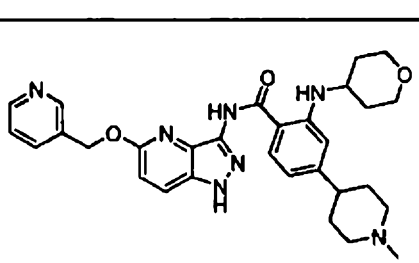
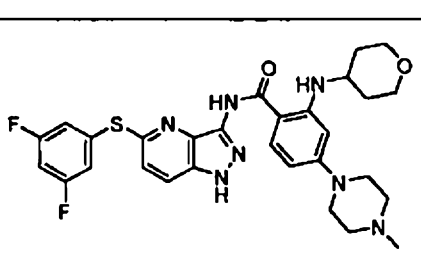
NH_2, $NH(CH_2)_3NMe_2$, $NMe(CH_2)_3NMe_2$, NO_2,  ,

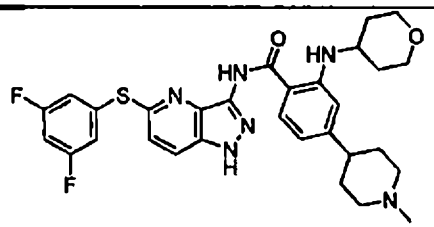
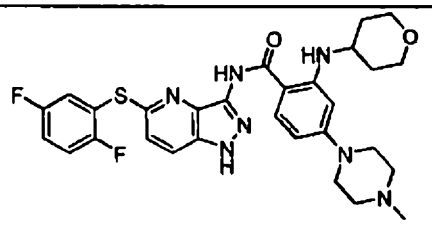
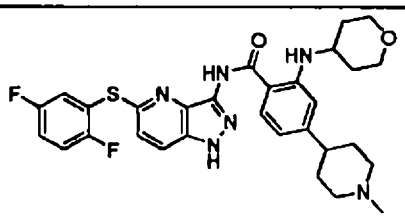
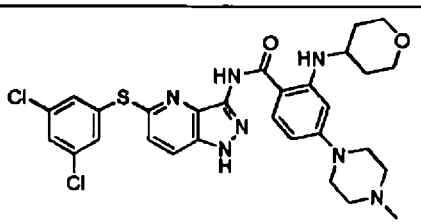
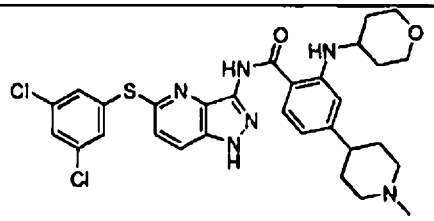
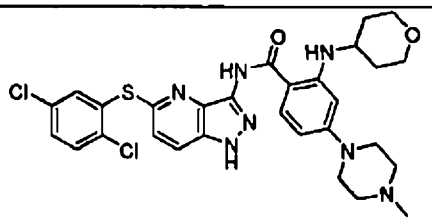
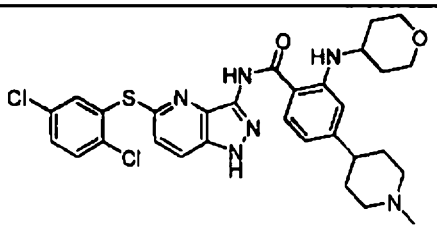
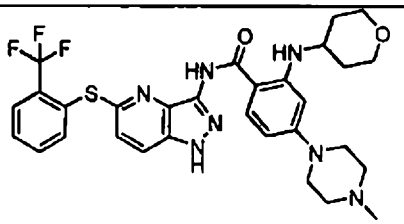
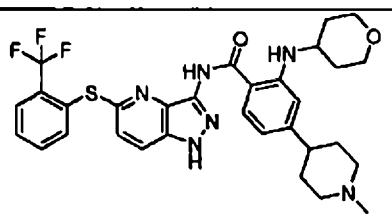
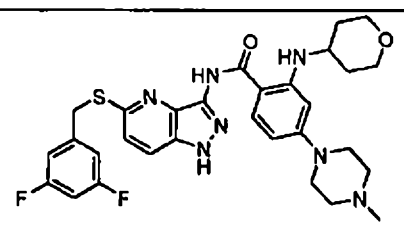
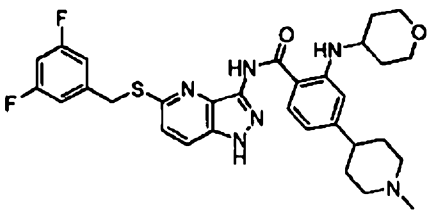
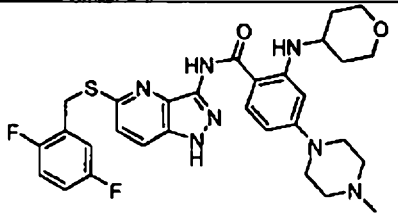
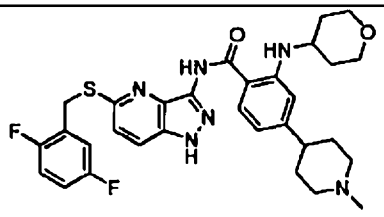
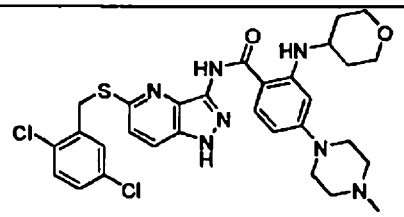
 , and  .

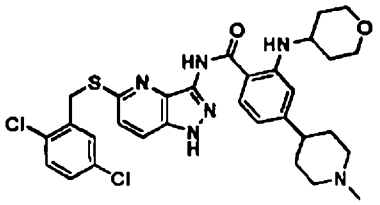
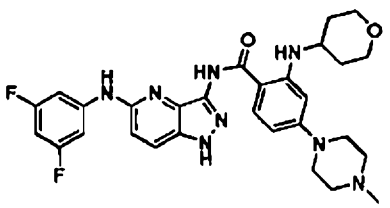
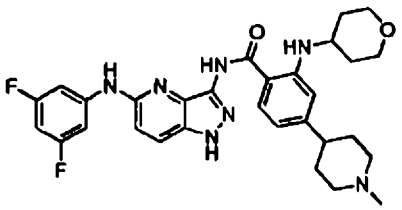
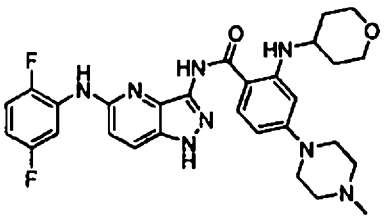
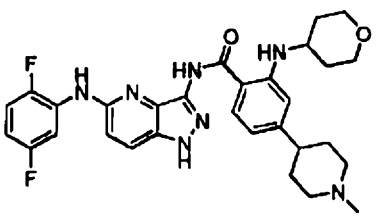
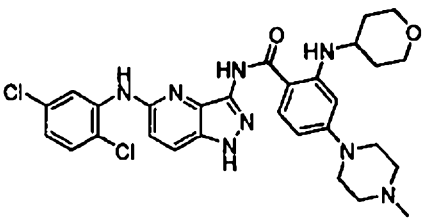
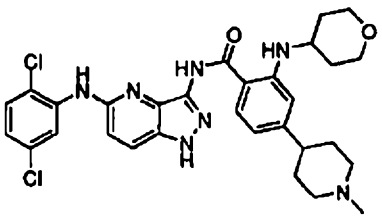
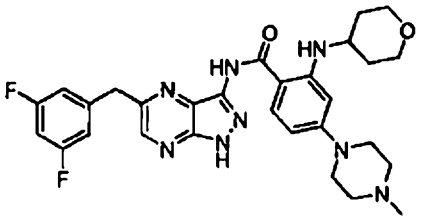
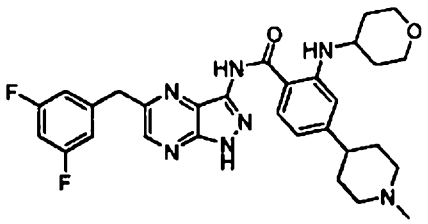
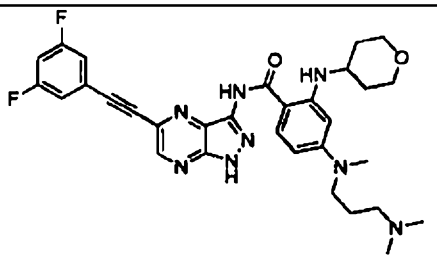
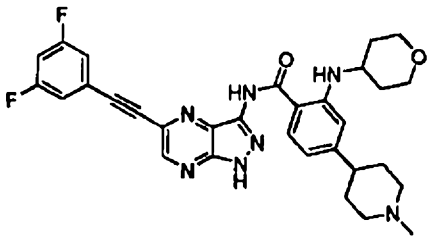
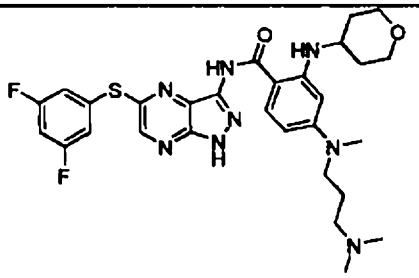
14-2		14-10	
14-11		15	
26-4		26-8	
27		27-1	
28		29	
29-a		30	
30-1		30-3	

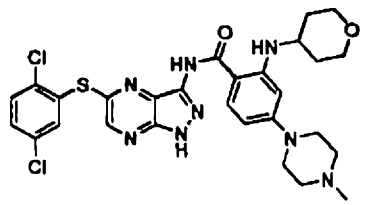
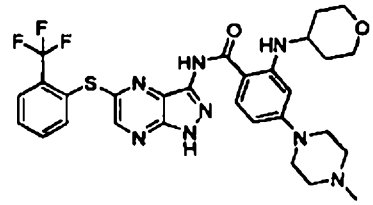
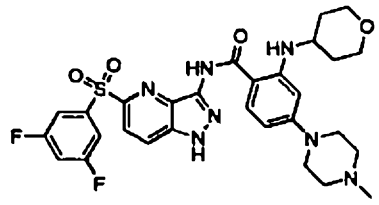
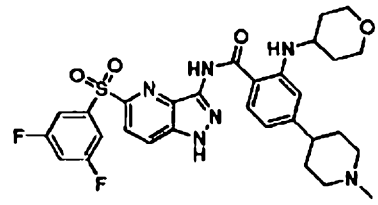
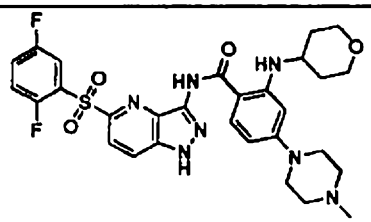
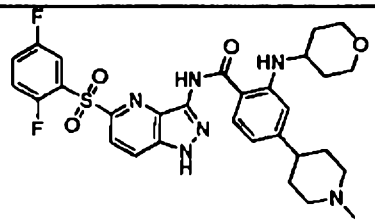
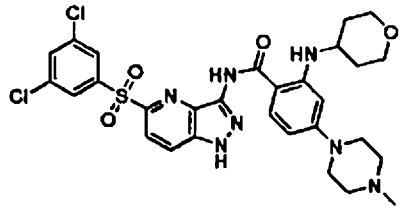
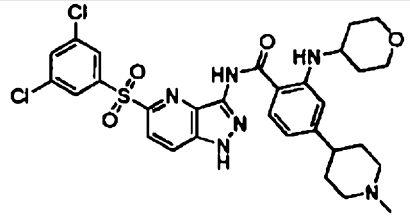
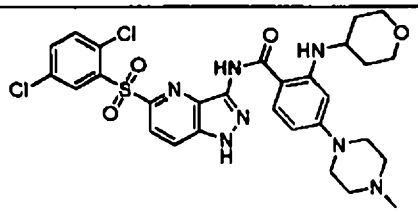
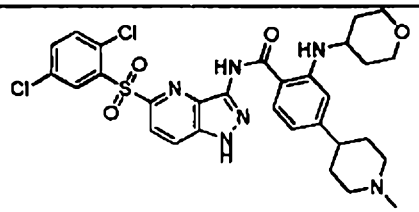
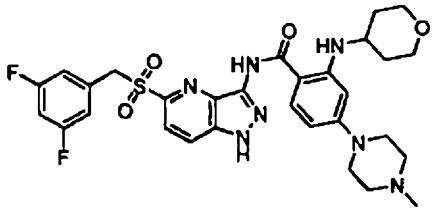
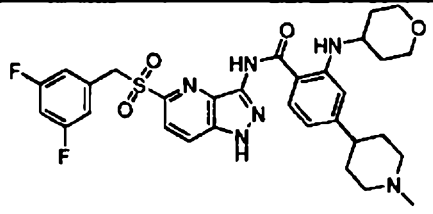
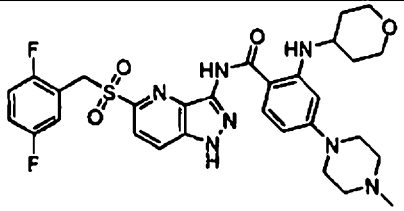
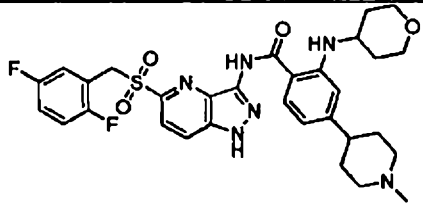
30-4		30-5	
30-8		30-9	
30-10		30-11	
30-12		30-a	
31		32	
32-1		33	

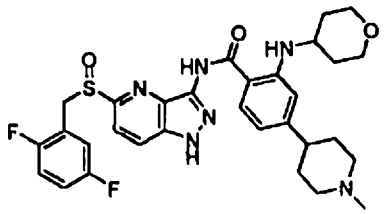
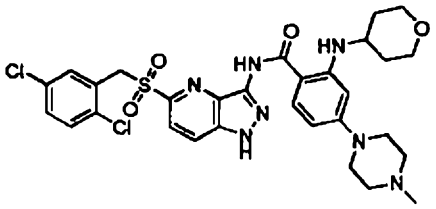
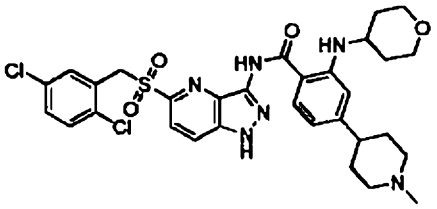
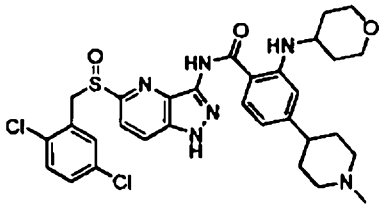
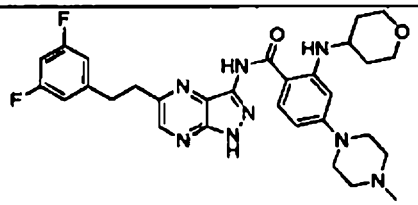
35		26-12	
30-69		27-2	
27-3		27-4	
30-73		14bis	
30-70		30-71	
30-72		27-5	

30-13		30-14	
30-15		30-16	
30-17		30-18	
30-19		30-20	
30-21		30-22	
30-23		30-24	

30-25		30-26	
30-27		30-28	
30-29		30-30	
30-31		30-32	
30-33		30-34	
30-35		30-36	
30-37		30-38	

30-39		30-40	
30-41		30-42	
30-43		30-44	
30-45		30-46	
30-47		30-48	
30-49		30-50	

30-51		30-52	
30-53		30-54	
30-55		30-56	
30-57		30-58	
30-59		30-60	
30-61		30-62	
30-63		30-64	

30-65		30-66	
30-67		30-68	
31-1			

13. A compound according to any one of claims 1 to 12, for use as a drug.

14. A compound according to any one of claims 1 to 12, for use as a drug intended for the treatment of cancer, inflammation and neurodegenerative diseases such as Alzheimer's disease, in particular cancer.

15. A compound according to any one of claims 1 to 12, for use as an inhibitor of kinases such as ALK, Abl and/or c-Src.

16. A compound according to any one of claims 1 to 12, for use as a drug intended for the treatment of a disease associated with a kinase such as ALK, Abl and/or c-Src.

17. A pharmaceutical composition comprising at least one compound of formula (I) according to any one of claims 1 to 12, and at least one pharmaceutically acceptable excipient.

18. The pharmaceutical composition according to claim 17, further comprising at least one other active ingredient such as an anticancer agent.

19. A pharmaceutical composition comprising:

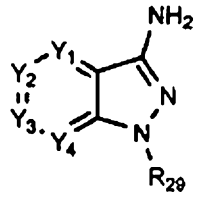
(i) at least one compound of formula (I) according to any one of claims 1 to 12, and

(ii) at least one other active ingredient, such as an anticancer agent,

as a combination product for simultaneous, separate or sequential use.

20. A method for the preparation of a compound of formula (I) according to any one of claims 1 to 12, wherein V=C(O) or C(S), preferably C(O), and notably U=CH_2, comprising the following successive steps:

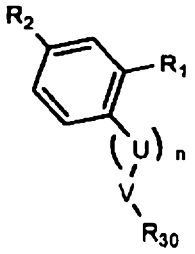
(a1) coupling between a compound of following formula (A):



(A)

wherein Y_1, Y_2, Y_3 and Y_4 are as defined in claim 1, and R_{29} represents a hydrogen atom or an N-protecting group,

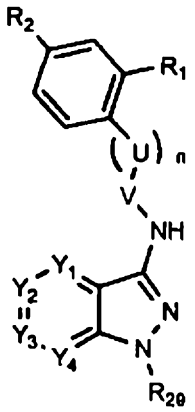
with a compound of following formula (B):



(B)

wherein R_1, R_2, U and n are as defined in claim 1, V=C(O) or C(S), and R_{30}=OH or a leaving group such as Cl,

to yield a compound of following formula (C):



(C)

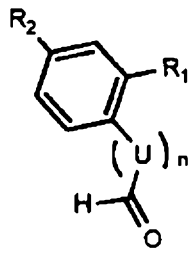
wherein Y_1, Y_2, Y_3, Y_4, R_1, R_2, U and n are as defined in claim 1, R_{29} is such as defined above and V=C(O) or C(S),

(b1) optionally substitution of the nitrogen atom bound to V of the compound of formula (C) obtained in the preceding step with an R_3 group other than H and/or deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group to yield a compound of formula (I) with V=C(O) or C(S),

(c1) optionally forming of a salt of the compound of formula (I) obtained in the preceding step to yield a pharmaceutically acceptable salt of same.

21. A method for the preparation of a compound of formula (I) according to any one of claims 1 to 12, wherein V=CH_2, and notably U=CH_2, comprising the following successive steps:

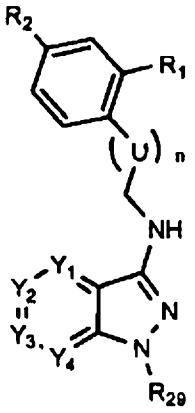
(a2) reducing amination reaction between a compound of formula (A) such as defined in claim 20 and an aldehyde of following formula (D):



(D)

wherein R_1, R_2, U and n are as defined in claim 1,

to yield a compound of following formula (E):



(E)

wherein Y_1, Y_2, Y_3, Y_4, R_1, R_2, U and n are as defined in claim 1 and R_{29} is such as defined in claim 20,

(b2) optionally deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group and/or substitution of the nitrogen atom bound to V with an R_3 group other than H of the compound of formula (E) obtained in the preceding step to yield a compound of formula (I) with V=CH_2, and

(c2) optionally forming of a salt of the compound of formula (I) obtained in the preceding step to yield a pharmaceutically acceptable salt of same.

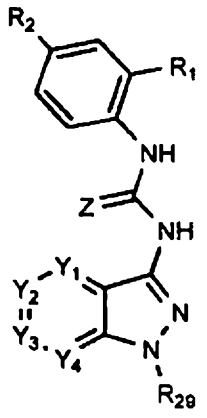
22. A method for the preparation of a compound of formula (I) according to any one of claims 1 to 12 wherein V=C(O) or C(S), n=1 and U=NH, comprising the following successive steps:

(a3) coupling between a compound of formula (A) such as defined in claim 1 and a compound of following formula (F):

(F)

wherein R_1 and R_2 are such as defined above and Z=O or S,

to yield a compound of following formula (G):



(G)

wherein Y_1, Y_2, Y_3, Y_4, R_1 and R_2 are as defined in claim 1, R_{29} is such as defined in claim 20 and Z is such as defined above,

(b3) optionally deprotection of the nitrogen atom carrying an R_{29} group representing an N-protecting group and/or substitution of the nitrogen atom bound to V with an R_3 group other than H of the compound of formula (G) obtained in the preceding step to yield a compound of formula (I) with V=C(O) or C(S), n=1 and U=NH, and

(c3) optionally forming of a salt of the compound of formula (I) obtained in the preceding step to yield a pharmaceutically acceptable salt of same.

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PAR PROCURATION

18 JUIL. 2013