

INDOLIZINE DERIVATIVES AS PHOSHOINOSITIDE 3-KINASES INHIBITORS**FIELD OF THE INVENTION**

The present invention relates to compounds inhibiting Phosphoinositide 3-kinases (hereinafter PI3K); particularly the invention relates to compounds that are indolizine derivatives, methods of preparing such compounds, pharmaceutical compositions
5 containing them and therapeutic use thereof.

More particularly, the compounds of the invention are inhibitors of the activity or function of the Class I of PI3K and more specifically, they are inhibitors of the activity or function of PI3K α , PI3K β , PI3K δ and/or PI3K γ isoforms of the Class I PI3K.

Therefore, the compounds of the invention may be useful in the treatment of many
10 disorders associated with PI3K enzymes mechanisms, such as respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and cough; allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease;
15 cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; cystic fibrosis; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; organ transplantation and in particular in transplant rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain,
20 post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain, trigeminal neuralgia, central pain and respiratory infections, airways damage, treatment and/or prevention of airway injury in patients with PI3K δ mutations.

BACKGROUND OF THE INVENTION

In biochemistry, a kinase is a type of enzyme that transfers phosphate groups from
25 high-energy donor molecules, such as ATP, to specific substrates, a process referred to as phosphorylation. Specifically, PI3K enzymes are lipid enzyme kinases that can

phosphorylate Phosphoinositides (PIs) at the 3'-hydroxyl group of the inositol ring (Panayotou et al, Trends Cell Biol 2:358-60 (1992)). It is well known that PIs, localised in the plasma membranes, can act as second messengers in signaling cascades by docking proteins containing pleckstrin-homology (PH), FYVE, PX and other phospholipid-binding domains (Vanhaesebroeck B et al, Annu. Rev. Biochem 70, 535-602, 2001; Katso R et al, Annu. Rev. Cell Dev. Biol. 17, 615-675, 2001).

Therefore, PIs can act as second messengers in many cellular processes including signal transduction, regulation of membrane trafficking and transport, cytoskeleton organization, cell survival and death, and many other functions.

PIs may be bound to the lipid bilayer of the cell membrane via two fatty acids that are attached to the cytosolic inositol ring via a glycerol phosphate linker. PIs inositol ring can be phosphorylated by PI3K enzymes, leading to the regulation of cellular growth, survival and proliferation. For this reason, PIs phosphorylation by PI3K enzymes is one of the most relevant signal transduction events associated with mammalian cell surface receptor activation (Cantley LC, Science 296, 1655-7, 2002; Vanhaesebroeck B et al, Annu. Rev. Biochem 70, 535-602, 2001).

The PI3K enzymes have been divided into three classes: Class I PI3K, Class II PI3K and Class III PI3K, on the basis of sequence homology, structure, binding partners, mode of activation, and substrate preference (Vanhaesebroeck B et al, Exp. Cell Res. 253(1), 239-54, 1999; and Leslie NR et al, Chem. Rev. 101(8), 2365-80, 2001).

Class I PI3K convert phosphoinositide-(4,5)-diphosphate (PI(4,5)P₂) to phosphoinositide-(3,4,5)-triphosphate (PI(3,4,5)P₃), which functions as a second messenger. The signaling cascade activated by the increase in intracellular levels of PI(3,4,5)P₃ is negatively regulated through the action of 5'-specific and 3'-specific phosphatases (Vanhaesebroeck B et al., Trends Biochem. Sci. 22(7), 267-72, 1997; Katso R et al, Annu. Rev. Cell Dev. Biol. 17, 615-75, 2001; and Toker A, Cell. Mol. Life Sci. 59(5), 761-79, 2002).

Class II PI3K enzymes are the most recently identified class of PI3K and their exact

function is still unclear.

Class III PI3K enzymes consists of a single family member which is structurally related to Class I PI3K enzymes and appears to be important in endocytosis and vesicular trafficking. However, there are some evidences showing that Class III PI3K may be relevant in immune cell processes, such as phagocytosis and Toll-like receptor (TLR) signalling.

Class I PI3K enzymes can be further divided in class IA and class IB on the basis of their activation mechanisms.

In more detail, Class IA PI3K enzymes comprises three closely related isoforms: PI3K α , PI3K β and PI3K δ , while Class IB comprises only the PI3K γ isoform. These enzymes are heterodimers composed of a catalytic subunit known as p110, with four types: alpha (α), beta (β), delta (δ) and gamma (γ) isoforms, constitutively associated with a regulatory subunit. The first two p110 isoforms (α and β) are ubiquitously expressed and involved in cellular differentiation and proliferation. Consequently, PI3K α and PI3K β enzymes have been extensively studied as targets for the development of new chemotherapeutic agents.

Otherwise, p110 δ and p110 γ isoforms are mainly expressed in leukocytes and are important in the activation of the immune response, such as leukocytes migration, B and T cells activation and mast cells degranulation. Therefore, PI3K δ and PI3K γ isoforms are very relevant in inflammatory respiratory diseases and in cancer.

Presently, the inhibitors derivatives of PI3K enzymes known in the art could generally inhibit said isoforms (alpha α , beta β , delta δ and gamma γ isoforms) and they could act on the individual roles played in various diseases by said specific isoforms.

Many genetics variants of the PI3K δ isoform have been described in the literature (Angulo et al., Science 2013, 342, 866-871; Kracker et al. J. Clinic. Immunol. 2014, 134, 233-234; Lucas et al. Nature Immunology 2014, 15, 88-97). Some of them involve the catalytic domain (e.g. E1021K) whereas others take place in different enzyme regions (e.g. N334K of the C2 domain). Considering that PI3K activation seems to depend on domain-

domain interactions or interactions with other proteins, these mutations might lead to a change in the enzyme stability and affect enzyme activation. Furthermore, the role of PI3K mutations in immunodeficiency has been described (see references above. Patients with these mutations may develop respiratory infections, damage to the airway wall and lung parenchima.

Therefore, specific activity assays of Class IA inhibitors for one specific PI3K α , PI3K β , PI3K δ and PI3K γ isoform over another have been extensively developed in order to discern the suitable profile for the treatment of disorders associated with PI3K enzymes mechanisms. Such disorders could, for example, include respiratory diseases selected from idiopathic chronic cough, cough-variant asthma, cough associated with thoracic tumour or lung cancer, viral or post-viral cough, upper airways cough syndrome (UACS) or post nasal drip cough, or cough associated with gastro-oesophageal reflux disease both acid and non acid, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), interstitial lung disease, idiopathic pulmonary fibrosis (IPF), congestive heart disease, sarcoidosis, infections (such as whooping cough), viral infections including viral respiratory tract infections and viral exacerbation of respiratory diseases; non-viral respiratory infections including aspergillosis and leishmaniasis; allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia and central pain.

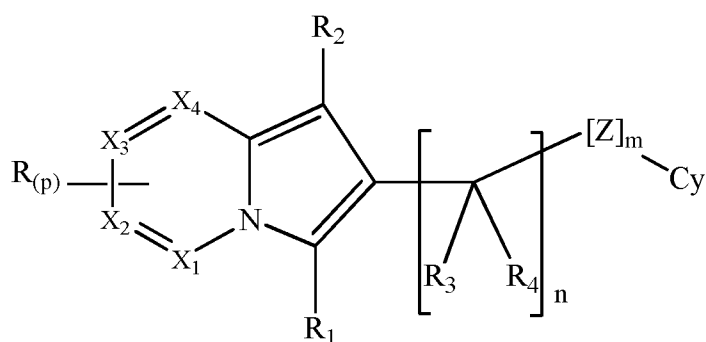
In view of the number of pathological responses which are mediated by PI3K enzymes, there is a continuing need for inhibitors of PI3K enzymes which can be useful in

the treatment of many disorders. Thus, the present invention relates to novel compounds which are inhibitors of PI3K α , PI3K β , PI3K δ and PI3K γ isoforms of Class I PI3K enzymes that, for the above reasons, may often have therapeutically desirable characteristics.

Particularly, compounds of the invention may have much more selectivity for the δ isoform or for both the γ and the δ isoforms of PI3K enzyme over other isoforms of the same enzyme.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of formula (I)



(I)

Wherein X₁, X₂, X₃ and X₄, R, R₁, R₂, R₃, R₄, Cy, Z, m, n and p are as reported below in the detailed description of the invention, acting as inhibitors of phosphoinositide 3- kinases, to processes for the preparation thereof, pharmaceutical compositions comprising them either alone or in combination with one or more active ingredient, in admixture with one or more pharmaceutically acceptable carrier.

In one aspect the present invention provides the use of a compound of the invention for the manufacture of a medicament.

In a further aspect the present invention provides the use of a compound of the invention for the preparation of a medicament for the prevention and/or treatment of any disease characterized by phosphoinositide-3-kinase (PI3K) enzyme overactivity and/or wherein an inhibition of PI3K activity is desirable and in particular through the selective inhibition of the delta or of both the delta and the gamma enzyme isoforms over the alpha and beta ones.

Moreover the present invention provides a method for prevention and/or treatment of any disease wherein a PI3K enzyme inhibition is desirable, said method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention.

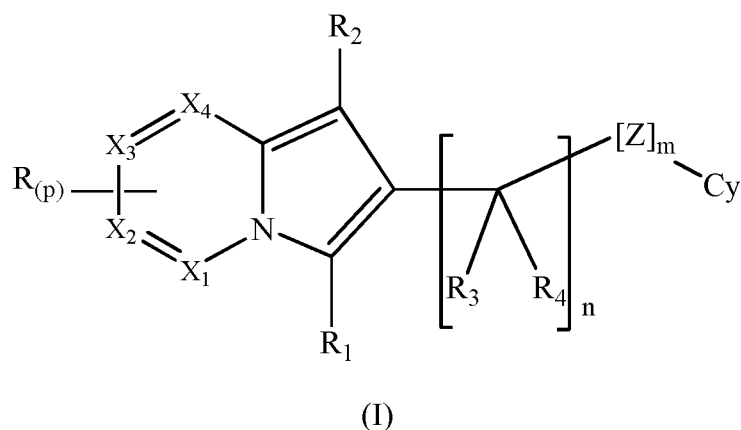
5 In particular the compounds of the invention alone or combined with other active ingredients may be administered for the prevention and/or treatment of a disease of the respiratory tract characterized by inflammatory airway obstruction such as, for example, cough, asthma, COPD and IPF.

DETAILED DESCRIPTION OF THE INVENTION

10 The invention is directed to a class of compounds acting as inhibitors of Phosphoinositide 3 Kinases (PI3K).

Said class of compounds inhibits the activity or function of the Class I of PI3K and more specifically, they are inhibitors derivatives of the activity or function of PI3K α , PI3K β , PI3K γ , and/or PI3K δ isoforms of the Class I PI3K. The present invention relates to

15 compounds of formula (I)



wherein

20 **X₁, X₂, X₃** and **X₄** are all CH groups or at least one of X₁, X₂, X₃ and X₄ is a nitrogen atom and the others are CH groups.

each **R**, when present, is selected from the group consisting of: -OR₅, -SR₅, -S(O)_q-R₇, halogen, -NR₁₀R₁₁, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-

C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₂-C₆) alkenyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl; each of which being in his turn optionally and independently substituted with one or more groups selected from halogen, -OH, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₂-C₆) alkenyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

R₁ is selected from the group consisting of -H, -OR₆, -SR₆, -S(O)_q-R₈, halogen, -NR₁₂R₁₃, -CN, -C(O)NR₁₂R₁₃, -C(O)OR₁₆, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₂-C₆) alkenyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, (C₂-C₆) aminoalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl; each of which being in his turn optionally and independently substituted with one or more groups selected from halogen, -NR₂₂R₂₃, -(CH₂)_nNR₂₂R₂₃, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, (C₁-C₆) aminoalkoxy, (C₃-C₆) heterocycloalkyloxy or (C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxy, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

R₂ is selected from the group consisting of -H, -OR₉, -SR₉, -S(O)_q-R₁₇, halogen, -NR₁₄R₁₅, -CN, -C(O)NR₁₄R₁₅, -C(O)OR₁₈, -(C₁-C₆) alkyl, -(C₁-C₆) haloalkyl, -(C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl; each of which being in his turn optionally and independently substituted with one or more groups selected from halogen; -NR₂₄R₂₅, -(CH₂)_nNR₂₄R₂₅, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

R₃ and **R₄**, the same or different, are selected from the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl;

Cy is selected from the group consisting of aryl, heteroaryl, and (C₃-C₆) heterocycloalkyl; each of which being optionally and independently substituted by one or more groups selected from halogen, -OH, -NR₁₉R₂₀, -CH₂NR₁₉R₂₀; -CN, -CH(O),

-CH=NOH, -C(O)NR₁₉R₂₀, -C(O)OR₂₁, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl, each of which being in his turn optionally and independently substituted with one or more groups selected from

5 -OH, halogen, -CN, -S(O)₂NR^IR^{III}, -NR^{III}S(O)₂R^{II}, -NR^IR^{III}, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆)alkoxy, aryl, heteroaryl, (C₃-C₆) heterocycloalkyl;

wherein R^I R^{II} and R^{III} the same or different, are independently selected from the group consisting of -H, (C₁-C₆) alkyl and alkanoyl;

R₅, R₆, R₉, R₁₆, R₁₈, and R₂₁ the same or different, are independently selected from

10 the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, alkanoyl, and aryl alkanoyl;

R₇, R₈ and R₁₇, the same or different, are independently selected from the group consisting of NR₁₂R₁₃, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, or by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl each

15 of which being in his turn optionally and independently substituted with one or more groups selected from halogen, -NR₂₂R₂₃, -CH₂NR₂₂R₂₃, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₉, R₂₀, R₂₂, R₂₃, R₂₄ and R₂₅, the same or different, are independently selected from the group consisting of -H, (C₁-C₆) alkyl (C₁-C₆) hydroxyalkyl and alkanoyl or, taken together with the nitrogen atom they are linked to, anyone of R₁₀

20 and R₁₁, R₁₂ and R₁₃, R₁₄ and R₁₅, R₁₉ and R₂₀, R₂₂ and R₂₃, R₂₄ and R₂₅ may form, a 5 to 6 membered heterocycle optionally containing one additional heteroatom or heteroatomic group selected from O, S, N, NH;

Z, when present, is an atom or a group selected from -O-, -NH-, -C(O)-, -NHC(O)-, -C(O)NH-, -S-, -S(O)-, and -S(O)₂-;

25

m is zero or 1;

n is 1 or 2,

p is zero or an integer ranging from 1 to 3

q is an integer ranging from 1 to 2

or pharmaceutically acceptable salts thereof.

DEFINITIONS

The term “pharmaceutically acceptable salts”, as used herein, refers to derivatives
5 of compounds of formula (I) wherein the parent compound is suitably modified by
converting any of the free acid or basic group, if present, into the corresponding addition
salt with any base or acid conventionally intended as being pharmaceutically acceptable.

Suitable examples of said salts may thus include mineral or organic acid addition
salts of basic residues such as amino groups, as well as mineral or organic basic addition
10 salts of acid residues such as carboxylic groups.

Cations of inorganic bases which can be suitably used to prepare salts within the
invention comprise ions of alkali or alkaline earth metals such as potassium, sodium,
calcium or magnesium.

Those obtained by reacting the main compound, functioning as a base, with an
15 inorganic or organic acid to form a salt comprise, for example, salts of hydrochloric acid,
hydrobromic acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic
acid, acetic acid, oxalic acid, maleic acid, fumaric acid, succinic acid and citric acid.

The term “halogen atoms” as used herein includes fluorine, chlorine, bromine, and
iodine, preferably chlorine or fluorine.

20 The term “(C₁-C₆) alkyl” refers to straight-chained or branched alkyl groups wherein
the number of constituent carbon atoms is in the range 1 to 6. Particular alkyl groups are
methyl, ethyl, n-propyl, isopropyl and t-butyl.

The expressions “(C₁-C₆) haloalkyl” refer to the above defined “(C₁-C₆)alkyl”
groups wherein one or more hydrogen atoms are replaced by one or more halogen atoms,
25 which can be the same or different from each other.

Examples of said (C₁-C₆) haloalkyl groups may thus include halogenated, poly-
halogenated and fully halogenated alkyl groups wherein all of the hydrogen atoms are
replaced by halogen atoms, e.g. trifluoromethyl or difluoro methyl groups.

By way of analogy, the terms “(C₁-C₆) hydroxyalkyl” or “(C₁-C₆) aminoalkyl” refer to the above defined “(C₁-C₆) alkyl” groups wherein one or more hydrogen atoms are replaced by one or more hydroxy (OH) or amino group respectively.

In the present description, unless otherwise provided, the definition of aminoalkyl
5 encompasses alkyl groups substituted by one or more (NR₁₀R₁₁).

With reference to the substituent R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₉, R₂₀, R₂₂, R₂₃, R₂₄ and R₂₅ as above defined, it is here further explained that when either R₁₀ and R₁₁ or R₁₂ and R₁₃ etc. are taken together with the nitrogen atom they are linked to form a 5 to 6
10 membered heterocyclic radical, at least one further ring carbon atom in the said heterocyclic radical may be replaced by at least one heteroatom or hetero-group (e.g. N, NH, S or O) and/or may bear an -oxo (=O) substituent group. The said heterocyclic radical might be further optionally substituted on the available points in the ring, namely on a carbon atom, or on an heteroatom or hetero-group available for substitution. Substitution on a carbon atom includes spiro disubstitution as well as substitution on two adjacent carbon atoms, in
15 both cases thus form an additional 5 to 6 membered heterocyclic ring. Thus, Examples of said heterocycle radicals are 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, piperazin-4-yl-2-one, 4-methylpiperazine-1-yl, 4-methylpiperazine-1-yl-2-one, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl, and (3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl.

20 The term “(C₃-C₇) cycloalkyl” refers to saturated cyclic hydrocarbon groups containing from 3 to 7 ring carbon atoms. Non limiting examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term “(C₂-C₆) alkenyl” refers to straight or branched carbon chains with one or more double bonds, conjugated or not conjugated, in cis or trans configuration, wherein the
25 number atoms is in the range 2 to 6.

By way of analogy, the terms “(C₅-C₇) cycloalkenyl” refers to cyclic hydrocarbon groups containing from 5 to 7 ring carbon atoms and one or two double bonds.

The term “(C₂-C₆) alkynyl” refers to straight or branched carbon chains with one or

more triple bonds wherein the number atoms is in the range 2 to 6.

The term “(C₂-C₆) hydroxyalkynyl” refers to the above defined “(C₁-C₆) alkynyl” groups wherein one or more hydrogen atoms are replaced by one or more hydroxy (OH) group.

5 The term “(C₂-C₆) aminoalkynyl” refers to the above defined “(C₁-C₆) alkynyl” groups wherein one or more hydrogen atoms are replaced by one or more (NR₁₀R₁₁) groups.

 The expression “aryl” refers to mono, bi- or tri-cyclic carbon ring systems which have 6 to 20, preferably from 6 to 15 ring atoms, wherein at least one ring is aromatic. The expression “heteroaryl” refers to mono-, bi- or tri-cyclic ring systems with 5 to 20,
10 preferably from 5 to 15 ring atoms, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom or heteroaromatic group (e.g. N, NH, S or O).

 Examples of suitable aryl or heteroaryl monocyclic ring systems include, for instance, phenyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl radicals and the like.

15 Examples of suitable aryl or heteroaryl bicyclic ring systems include naphthalenyl, biphenylenyl, purinyl, pteridinyl, pyrazolopyrimidinyl, benzotriazolyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, benzothiophenyl, benzodioxinyl, dihydrobenzodioxinyl, indenyl, dihydro-indenyl, dihydrobenzodioxepinyl, benzooxazinyl radicals and the like.

 Examples of suitable aryl or heteroaryl tricyclic ring systems include fluorenyl
20 radicals as well as benzocondensed derivatives of the aforementioned heteroaryl bicyclic ring systems.

 The derived expression “(C₃-C₆) heterocycloalkyl” refers to saturated or partially unsaturated monocyclic (C₃-C₆) cycloalkyl groups in which at least one ring carbon atom is replaced by at least one heteroatom or hetero-group (e.g. N, NH, S or O) or may bear an
25 -oxo (=O) substituent group. The said heterocyclic radical might be further optionally substituted on the available points in the ring, namely on a carbon atom, or on an heteroatom or hetero-group available for substitution. Substitution on a carbon atom includes spiro disubstitution as well as substitution on two adjacent carbon atoms, in both

cases thus form an additional 5 to 6 membered heterocyclic ring. Thus, examples of said heterocycle radicals are 1-pyrrolidinyl, 1-methyl-2-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, piperazin-4-yl-2-one, 4-methylpiperazine-1-yl, 1-methylpiperidin-4-yl, 4-methylpiperazine-1-yl-2-one, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl, and (3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl.

Non limiting examples of (C₃-C₆) heterocycloalkyl are represented by: pyrrolidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, dihydro- or tetrahydro-pyridinyl, tetrahydropyranyl, pyranal, 2H- or 4H-pyranal, dihydro- or tetrahydrofuranyl, dihydroisoxazolyl, pyrrolidin-2-one-yl radicals and the like.

The term “aryl (C₁-C₆) alkyl” refers to an aryl ring linked to a straight-chained or branched alkyl groups wherein the number of constituent carbon atoms is in the range from 1 to 6, e.g. phenylmethyl, phenylethyl or phenylpropyl.

The term “alkanoyl”, refers to HC(O)- or to alkylcarbonyl groups (e.g. (C₁-C₆)alkylC(O)- wherein the group “alkyl” has the meaning above defined. Non limiting examples include formyl, acetyl, propanoyl, butanoyl.

The term “alkoxy” refers to a straight or branched hydrocarbon of the indicated number of carbons, attached through an oxygen bridge.

By analogy, derived expressions (C₃-C₆) heterocycloalkyloxy and (C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxy refer to heterocycloalkyl groups attached through an oxygen bridge and chained heterocycloalkyl-alkoxy groups. Non-limiting examples of such (C₃-C₆) heterocycloalkyloxy and (C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxy groups are respectively (piperidin-4-yl)oxy, 1-methylpiperidin-4-yl)oxy, 2-(piperidin-4-yl)ethoxy, 2-(1-methylpiperidin-4-yl)ethoxy, and 2-(4-morpholino)ethoxy.

Likewise derived expression “(C₁-C₆) aminoalkoxy” refers to (C₁-C₆) aminoalkyl groups as above defined attached through an oxygen bridge, non limiting example is (2-(dimethylamino)ethoxy).

The term “aryl alkanoyl” refers to an arylC(O) or arylalkylcarbonyl group [e.g.

Aryl(C₁-C₆)alkylC(O)-] wherein aryl and alkyl have the meaning above defined. Non limiting examples are represented by benzoyl, phenylacetyl, phenylpropanoyl or phenylbutanoyl radicals.

The expression “saturated, partially unsaturated or aromatic, five or six membered
5 cycloalkane-diyl, arylene-diyl or heterocycle-diyl” refers to suitable vicinal disubstituted cycloalkane or heterocycle residue with five or six elements including 1,2-phenylene-diyl; 2,3-, 3,4-, 4,5- or 5,6- pyridine-diyl; 3,4-, 4,5- or 5,6- pyridazine-diyl; 4,5- or 5,6- pyrimidine-diyl; 2,3- pyrazinediyl; 2,3-, 3,4- or 4,5- thiophene-diyl / furane-diyl / pyrrole-diyl; 4,5-imidazole-diyl / oxazole-diyl / thiazole-diyl; 3,4- or 4,5- pyrazole-diyl /
10 isoxazolidiyl / isothiazole-diyl their saturated or partially unsaturated analogues and the like.

As used herein, the expression “ring system” refers to mono- or bicyclic ring systems which may be saturated, partially unsaturated or unsaturated, such as aryl, (C₃-C₇) cycloalkyl, (C₃-C₆) heterocycloalkyl or heteroaryl.

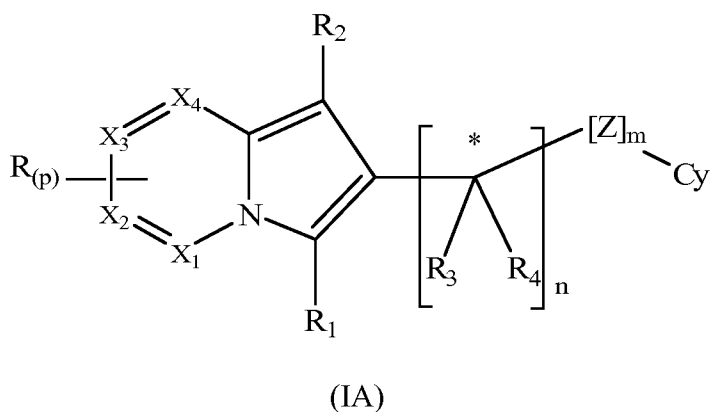
15 As used herein the terms “group”, “radical” or “fragment” or “substituent” are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments or molecules. A dash (“-”) that is not between two letters or symbols is meant to represent the point of attachment for a substituent. When graphically represented the point of attachment in a cyclic functional group (e.g. formulae
20 I-1 to I-9) is indicated with a dot (“•”) localized in one of the available ring atom where the functional group is attachable to a bond or other fragment of molecules.

As used herein an oxo moiety is represented by (O) as an alternative to the other common representation, e.g. (=O). Thus, in terms of general formula, the carbonyl group is herein preferably represented as -C(O)- as an alternative to the other common
25 representations such as -CO-, -(CO)- or -C(=O)-. In general the bracketed group is a lateral group, not included into the chain, and brackets are used, when deemed useful, to help disambiguating linear chemical formulas; e.g. the sulfonyl group -SO₂- might be also represented as -S(O)₂- to disambiguate e.g. with respect to the sulfinic group

–S(O)O–.

Whenever basic amino or quaternary ammonium groups are present in the compounds of formula I, physiological acceptable anions, selected among chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, p-toluenesulfonate, pamoate and naphthalene disulfonate may be present. Likewise, in the presence of acidic groups such as COOH groups, corresponding physiological cation salts may be present as well, for instance including alkaline or alkaline earth metal ions.

It will be apparent to those skilled in the art that compounds of formula (I) can at least contain one stereogenic center, namely represented in formula (IA) by the carbon atom (*) with an asterisk, and therefore may exist as optical stereoisomers.



Where the compounds according to the invention have at least one stereogenic center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more stereogenic centers, they may additionally exist as diastereoisomers. It is to be understood that all such single enantiomers, diastereoisomers and mixtures thereof in any proportion are encompassed within the scope of the present invention. The absolute configuration (R) or (S) for carbon (*) is assigned on the basis of Cahn-Ingold-Prelog nomenclature rules based on groups' priorities.

Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the

conformers (Bringmann G et al, Angew. Chemie Int. Ed. 44 (34), 5384-5427, 2005. doi:10.1002/anie.200462661).

Oki defined atropisomers as conformers that interconvert with a half-life of more than 1000 seconds at a given temperature (Oki M, Topics in Stereochemistry 14, 1-82, 5 1983).

Atropisomers differ from other chiral compounds in that in many cases they can be equilibrated thermally whereas in the other forms of chirality isomerization is usually only possible chemically.

Separation of atropisomers is possible by chiral resolution methods such as selective 10 crystallization. In an atropo-enantioselective or atroposelective synthesis one atropisomer is formed at the expense of the other. Atroposelective synthesis may be carried out by use of chiral auxiliaries like a Corey Bakshi Shibata (CBS) catalyst, an asymmetric catalyst derived from proline, or by approaches based on thermodynamic equilibration when an isomerization reaction favors one atropisomer over the other.

15 Racemic forms of compounds of formula (I) as well as the individual atropisomers (substantially free of its corresponding enantiomer) and stereoisomer-enriched atropisomers mixtures are included in the scope of the present invention.

It is to be understood that all preferred groups or embodiments described herebelow for compounds of formula I may be combined among each other and apply as well *mutatis* 20 *mutandis*.

In a preferred embodiment, the present invention is directed to compounds of formula (I) as above defined wherein $n=1$, R_3 has the same significance as above except H, R_4 is H and the absolute configuration of the chiral carbon (*) is (R).

In another embodiment the preferred configuration of the carbon (*) is (S).

25 In a preferred embodiment, the compounds of formula (I) described in the present invention are present as mixtures of diastereoisomers.

A first preferred group of compounds is that of formula (I) wherein:

R_3 is selected from H and (C₁-C₆) alkyl;

R₄ is H;

R, R₁, R₂, m, n, p, Z, Cy and X₁₋₄ are as defined above.

A more preferred group of compounds is that of formula (I) wherein:

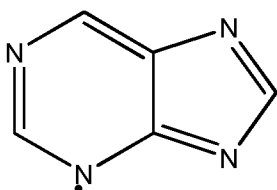
R₃ is selected from H and (C₁-C₆) alkyl;

5 R₄ is H;

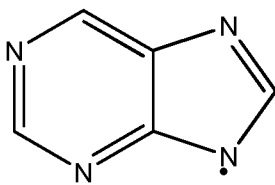
Cy is an heteroaryl selected from the group consisting of I-1 to I-9 wherein (I-1) is 3H-purin-3-yl, (I-2) is 9H-purin-9-yl, (I-3) is 9H-purin-6-yl, (I-4) is 1H-pyrazolo[3,4-d]pyrimidin-1-yl, (I-5) is 6-oxo-5H,6H,7H-pyrrolo[2,3-d]pyrimidin-4-yl, (I-6) is pyrimidin-4-yl, (I-7) is pyrimidin-2-yl, (I-8) is pyrazin-2-yl, (I-9) is 1,3,5-triazin-2-yl; each of which being optionally and independently substituted by one or more groups selected from halogen, -OH, -NR₁₉R₂₀, -CH₂NR₁₉R₂₀, -CN, -CH(O), -CH=NOH, -C(O)NR₁₉R₂₀, -C(O)OR₂₁, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl or by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl each of which being in his turn optionally and independently substituted with one or more groups selected from -OH, halogen, -CN, -S(O)₂NR^IR^{III}, -NR^{III}S(O)₂R^{II}, -NR^IR^{III}, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆)alkoxy, aryl, heteroaryl, (C₃-C₆) heterocycloalkyl; all the other variables being as defined above, and pharmaceutically acceptable salt thereof.

20 I-1 to I-9 can be graphically represented as follows

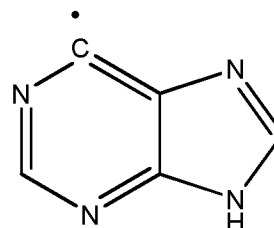
17



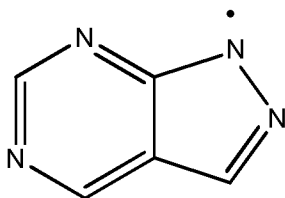
I-1



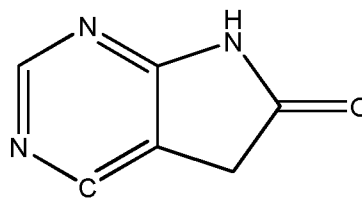
I-2



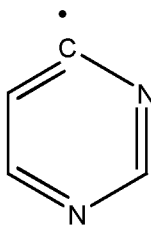
I-3



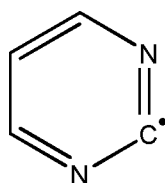
I-4



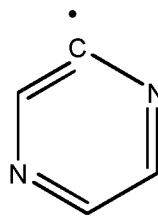
I-5



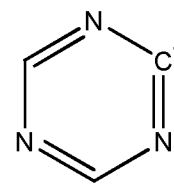
I-6



I-7



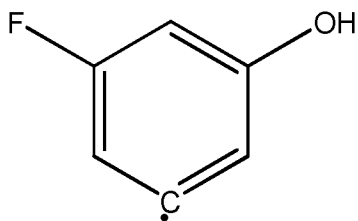
I-8



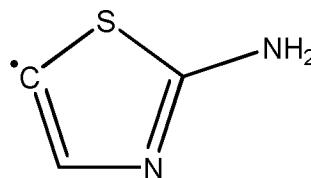
I-9

As above explained when graphically represented the monoradical symbol “•” is localized in one of the available ring atom indicating where the functional group is attachable to a bond or other fragment of molecules. This is not limiting the scope solely to the graphically represented structures; the invention is including also other chemically acceptable localization of the point of attachment in the functional group.

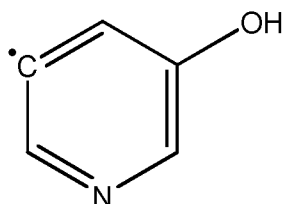
Examples of preferred aryl, heteroaryl, (C₃-C₆) heterocycloalkyl groups are phenyl, pyridinyl, thiazolyl and tetrazolyl groups, some particularly preferred are 3-fluoro-5-hydroxyphenyl, 2-amino-1,3-thiazol-5-yl, 5-hydroxypyridin-3yl, 1-methyl-1,2,3,6-tetrahydropyridin-4yl; corresponding to the below reported structures (CHEMAXON 6.0.4 name to structure tool).



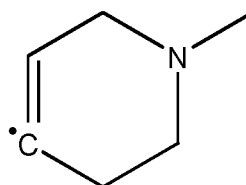
3-fluoro-5-hydroxyphenyl



2-amino-1,3-thiazol-5-yl



5-hydroxypyridin-3-yl



1-methyl-1,2,3,6-tetrahydropyridin-4-yl

In one embodiment:

X₁, X₂, X₃ and X₄ are all CH groups;

R is selected from the group consisting of C₁-C₆ alkyl, such as methyl, C₁-C₆ haloalkyl such as trifluoromethyl, and halogen, more preferably fluoro, chloro and bromo;

R₁ is selected in the group consisting of hydrogen, C₂-C₆ alkynyl such as 3-pent-1-yn-1-yl, C₂-C₆ aminoalkynyl such as 3-dimethylaminoprop-1-yn-1-yl, and C₂-C₆ hydroxyalkynyl such as 3-hydroxyprop-1-yn-1-yl, aryl, such as phenyl, heteroaryl, such as pyridyl, pyrazinyl, thienyl and thiazolyl, C₃-C₆ heterocycloalkyl such as 3,6-dihydro-2H-pyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, pyrrolidin-1-yl-2-one, and 4-methylpiperazin-1-yl-2-one, a group -(CH₂)_nN₂₂N₂₃ such as 4-morpholinomethyl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-ylmethyl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl}methyl, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl, and 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}methyl, wherein each aryl and heteroaryl may be optionally substituted by one or two groups independently selected from halogen such as chlorine and fluorine, cyano, (C₁-C₆) alkyl such as methyl, -C(O)NR₁₂R₁₃ such as 4-morpholinocarbonyl, (C₃-C₆) heterocycloalkyl such as 1-methylpyrrolidin-1-yl, -NR₂₂R₂₃ such as dimethylamino, -(CH₂)_nR₂₂R₂₃ such as 2-dimethylaminomethyl, N,N-bis(2-hydroxyethyl)amino, 4-morpholinomethyl, 2-(4-morpholino)ethyl, 1-pyrrolidinomethyl, and (4-methylpiperazin-

i-yl)methyl, (C₃-C₆) heterocycloalkoxyl such as 1-methylpiperidin-4-yl-oxyl, (C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxyl such as 2-(4-methylpiperazin-1-yl)ethoxyl, 2-(4-morpholino)ethoxyl, 2-dimethylaminoethoxyl and 2-(1-methylpiperidin-4-yl)ethoxyl;

R₂ is selected in the group consisting of hydrogen, cyano, (C₁-C₆) haloalkyl such as trifluoromethyl, aryl such as phenyl which is optionally substituted by halogen such as fluoro and methyl, heteroaryl such as pyridinyl;

R₃ is selected from the group consisting of H and (C₁-C₆) alkyl such as methyl and ethyl;

R₄ is H;

Cy is an heteroaryl selected from the following group: 9H-purine-6-amine-9-yl, 3H-purine-6-amine-3-yl, 9H-purin-6-yl, 4-amino-5-cyanopyrimidin-6-yl, 4-amino-5-formylpyrimidin-6-yl, 4-amino-5-bromopyrimidin-6-yl, 4-amino-5-trifluoromethylpyrimidin-6-yl, 4-amino-5-methylpyrimidin-6-yl, 4-amino-5-(N-methylcarbamoyl)pyrimidin-6-yl, 4-amino-5-carbamoylpyrimidin-6-yl, 4-amino-5-carboxypyrimidin-6-yl, 2-amino-3-pyrazinyl, 4-amino-5-hydroxymethylpyrimidin-6-yl, 4-amino-5-(4-morpholinomethyl)pyrimidin-6-yl, 4-amino-5-(hydroxyiminomethyl)pyrimidin-6-yl, 4-amino-5-(3-hydroxypropyn-1-yl)pyrimidin-6-yl, 4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-acetylaminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-hydroxymethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(5-hydroxy-3-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-methanesulphonylaminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(5-hydroxy-3-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(4-fluoro-3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-chloro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-aminosulphonylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-

sulphonylamino-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-aminosulphonyl-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-amino-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-cyano-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-5-(1H-1,2,3,4-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-hydroxypropyn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, and 4-amino-3-(2-aminothiazol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl.

m is 1;

10 n is 1;

p is 1;

Z is absent or is selected from -NH- or -NHC(O)-;

and all the other variables are as defined above.

A second preferred groups of compounds is that of formula (I) wherein:

15 R₃ is methyl;

R₄ is H;

Cy is 1H-pyrazolo[3,4-d]pyrimidin-1-yl, which is optionally and independently substituted by one or more groups selected from -NR₁₉R₂₀ and aryl which is optionally substituted by one or more groups selected from OH and halogen; and pharmaceutically acceptable salt thereof.

20

A more preferred group of compounds is that of formula (I) wherein:

R₁ is selected from the group consisting of 4-morpholinomethyl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl}methyl, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl, and 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}methyl;

25

R₃ is methyl;

R₄ is H;

Cy is 1H-pyrazolo[3,4-d]pyrimidin-1-yl (I-4), which is substituted in the position 4

by $-NH_2$ and in the position 3 by 3-fluoro-5-hydroxyphenyl; and a pharmaceutically acceptable salt thereof.

According to specific embodiments, the present invention provides the compounds listed in the table below: and pharmaceutical acceptable salts thereof.

5

Example	Chemical name - Chemaxon
1	9-[(3-phenylindolizin-2-yl)methyl]-9H-purin-6-amine
2	3-[(3-phenylindolizin-2-yl)methyl]-3H-purin-6-amine
3	9-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine
4	9-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
5	3-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-3H-purin-6-amine
6	9-{[3-(2-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
7	9-{[3-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
8	3-{[3-(2-methylphenyl)indolizin-2-yl]methyl}-3H-purin-6-amine
9	9-(indolizin-2-ylmethyl)-9H-purin-6-amine
10	9-[(1-phenylindolizin-2-yl)methyl]-9H-purin-6-amine
11	9-{[1-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
12	9-{[1-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
13	N-[(3-phenylindolizin-2-yl)methyl]-9H-purin-6-amine
14	N-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine
15	N-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
16	N-{[3-(2-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
17	N-[(1-phenylindolizin-2-yl)methyl]-9H-purin-6-amine
18	N-{[1-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
19	N-{[1-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine
20	N-{[1-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine
21	N-(indolizin-2-ylmethyl)-9H-purin-6-amine

(continued)

22	4-amino-6- {[3-(phenylindolizin-2-yl)methyl]amino} pyrimidine-5-carbonitrile
23	4-amino-6-([3-(pyridin-2-yl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
24	4-amino-6-([3-(3-fluorophenyl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
25	4-amino-6-([3-(2-fluorophenyl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
26	4-amino-6-([3-(2-methylphenyl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
27	4-amino-6- {[1-(phenylindolizin-2-yl)methyl]amino} pyrimidine-5-carbonitrile
28	4-amino-6-([1-(3-fluorophenyl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
29	4-amino-6-([1-(2-methylphenyl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
30	4-amino-6-([1-(pyridin-2-yl)indolizin-2-yl]methyl} amino)pyrimidine-5-carbonitrile
31	4-amino-6-[(indolizin-2-ylmethyl)amino]pyrimidine-5-carbonitrile
32	4-amino-6- {[1-(3-phenylindolizin-2-yl)ethyl]amino} pyrimidine-5-carbonitrile
33	4-amino-6-([1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile
34	4-amino-6-([1-[3-(pyridin-3-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile
35	4-amino-6-([1-[3-(pyrazin-2-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile
36	4-amino-6-([1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile
37	4-amino-6-([1-[3-(thiophen-2-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile
38	4-amino-6-([1-[3-(thiophen-3-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile
39	4-amino-6-([1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethyl} amino)pyrimidine-5-carbonitrile

(continued)

40	4-amino-6-({1-[5-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile
41	4-amino-6-({1-[8-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile
42	4-amino-6-({1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile
43	4-amino-6-({1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile
44	4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]propyl}amino)pyrimidine-5-carbonitrile
45	4-amino-6-({1-[3-(1,2,3,6-tetrahydropyridin-4-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile
46	4-amino-6-({1-[3-(3-hydroxyprop-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile
47	4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbaldehyde (A/1106/33/1)
48	5-bromo-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrimidine-4,6-diamine
49	4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-5-(trifluoromethyl)pyrimidine-4,6-diamine
50	5-methyl-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrimidine-4,6-diamine
51	4-amino-N-methyl-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxamide
52	4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxamide
53	4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxylic acid
54	3-amino-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrazine-2-carboxamide
55	3-amino-N-{[1-(pyridin-2-yl)indolizin-2-yl]methyl}pyrazine-2-carboxamide
56	[4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidin-5-yl]methanol

(continued)

57	5-(morpholin-4-ylmethyl)-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrimidine-4,6-diamine
58	5-[(1E)-(hydroxyimino)methyl]-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrimidine-4,6-diamine
59	3-[4-amino-6-(1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl)amino]pyrimidin-5-yl]prop-2-yn-1-ol
60	3-phenyl-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine
61	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol
62	3-(3-fluoro-5-methoxyphenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine
63	N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]acetamide
64	[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]methanol
65	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-(trifluoromethyl)phenol
66	3-(3-fluorophenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine
67	N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]methanesulfonamide
68	1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine
69	5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-3-ol
70	4-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol
71	5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol
72	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-chlorophenol
73	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzene-1-sulfonamide

(continued)

74	N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl]methanesulfonamide
75	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorobenzene-1-sulfonamide
76	3-(3-amino-5-fluorophenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine
77	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-hydroxybenzonitrile
78	3-[3-fluoro-5-(1H-1,2,3,4-tetrazol-5-yl)phenyl]-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine
79	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
80 (enantiomer 1) and 81 (enantiomer 2)	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol single enantiomers
82	3-(4-amino-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
83 (enantiomer 1) and 84 (enantiomer 2)	3-(4-amino-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol single enantiomers
85	3-{4-amino-1-[1-(3-phenylindolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
86	3-(4-amino-1-{1-[3-(2-fluorophenyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
87	3-(4-amino-1-{1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
88	3-(4-amino-1-{1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
89	3-(4-amino-1-{1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
90	3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
91	3-[4-amino-1-(1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
92	3-{4-amino-1-[1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol

(continued)

93	3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
93a (enantiomer 1) and 93b (enantiomer 2)	3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
94	3-(4-amino-1-{1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
95	1-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)pyrrolidin-2-one
96	3-(4-amino-1-{1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
97	3-(4-amino-1-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
98	3-(4-amino-1-{[3-(pyridin-3-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
99	3-(4-amino-1-{[3-(pyridin-4-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
100	3-(4-amino-1-{[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
101	3-(4-amino-1-{1-[3-(1,2,3,6-tetrahydropyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
102	3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)prop-2-yn-1-ol
103	5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3-thiazol-2-amine
104	3-(4-amino-1-{1-[7-chloro-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
105	3-(4-amino-1-{1-[7-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
106	3-(4-amino-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
107	5-(4-amino-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-3-ol
108	3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
108a (enantiomer 1) and 108b (enantiomer 2)	3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol

(continued)

109	3-{4-amino-1-[1-(3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
110	3-[4-amino-1-(1-{3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
111	3-[4-amino-1-(1-{3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
112	3-{4-amino-1-[1-(3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
113	3-[4-amino-1-(1-{3-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
114	3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
114a (enantiomer 1) and 114b (enantiomer 2)	3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
115	3-{4-amino-1-[1-(3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
116	3-{4-amino-1-[1-(3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
117	3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
117a (enantiomer 1) and 117b (enantiomer 2)	3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
118	3-[4-amino-1-(1-{3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol

(continued)

119	3-{4-amino-1-[1-(3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
120	5-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one
121	4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one
121a (enantiomer 1) and 121b (enantiomer 2)	4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one
122	4-(2-{1-[4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one
123	2-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)benzonitrile
124	3-(4-amino-1-{1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
125	3-[4-amino-1-(1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
126	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-(pyridin-2-yl)indolizine-1-carbonitrile
127	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile
127a (enantiomer 1) and 127b (enantiomer 2)	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile
128	3-{4-amino-1-[1-(7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazin-6-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
129	3-(4-amino-1-{1-[3-(1,3-thiazol-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

(continued)

130	3-[4-amino-1-(1-{3-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
131	3-[4-amino-1-(1-{3-[3-(dimethylamino)prop-1-yn-1-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol
132	1-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-4-methylpiperazin-2-one
133	4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one
133a (enantiomer 1) and 133b (enantiomer 2)	4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one
134	6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(pyrrolidin-1-yl)ethyl]-2,3-dihydropyridazin-3-one
135	6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(4-methylpiperazin-1-yl)ethyl]-2,3-dihydropyridazin-3-one
136	6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(morpholin-4-yl)ethyl]-2,3-dihydropyridazin-3-one
137	3-{4-amino-1-[1-(3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
138	3-{4-amino-1-[1-(3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
139	3-{4-amino-1-[1-(3-{6-[(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
140	3-{4-amino-1-[1-(3-{6-[2-(1-methylpiperidin-4-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
141	3-(4-amino-1-{1-[3-(morpholin-4-ylmethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

(continued)

142	3-(4-amino-1-{1-[3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
143	3-(4-amino-1-{1-[3-({9-methyl-3,9-diazaspiro[5.5]undecan-3-yl}methyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
144	3-(4-amino-1-{1-[3-({7-methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
145	3-{1-[1-(3-{[(3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl]methyl}indolizin-2-yl)ethyl]-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
146	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-(morpholin-4-ylmethyl)indolizine-1-carbonitrile
147	3-{4-amino-1-[1-(3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
148	3-{4-amino-1-[1-(3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol
149	3-(4-amino-1-{1-[3-(1-{2-[bis(2-hydroxyethyl)amino]ethyl}-1H-pyrazol-3-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
150	3-{4-amino-1-[1-(3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol

The compounds of formula (I) including all the compounds here above listed can be generally prepared according to the procedure outlined in the following Schemes shown below using generally known methods or following slightly modified procedures that the skilled person can easily apply.

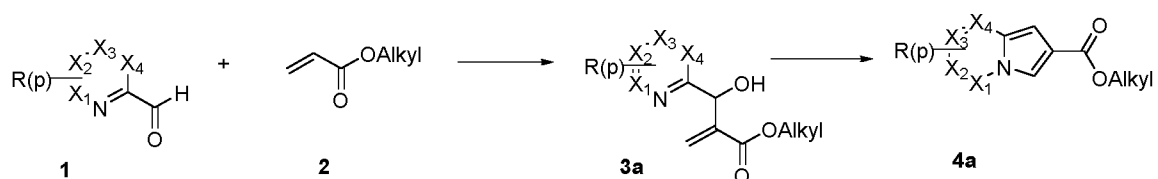
Processes of preparation described below and reported in the following Schemes should not be viewed as limiting the scope of the synthetic methods available for the preparation of the compounds of the invention.

Scheme 1-4 together with scheme 5-11 hereinbelow covers the synthetic procedure for the compounds according to the invention in general terms The processes described are particularly advantageous as they are susceptible of being properly modulated, through any proper variant known to the skilled person, so as to obtain any of the desired compounds

of the invention. Such variants are comprised within the scope of the present invention. Where a specific detail or step differs from the general Schemes it has been detailed in the specific examples and/or in additional schemes.

SCHEME 1

- 5 This scheme provides a synthetic route for the preparation of a compound of formula (4a), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, R(p) is variable as defined herein above and Alkyl is a (C₁-C₆) alkyl.

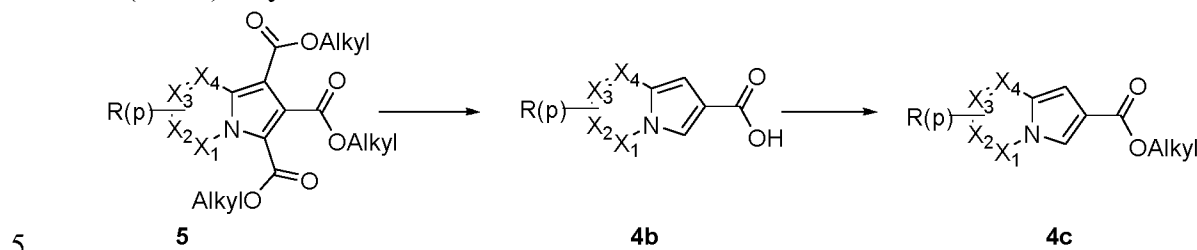


- 10 A compound of formula (3a), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, may be prepared according to Scheme 1 by reaction of a compound of formula (1) with an alkyl acrylate (2). Typical reaction conditions comprise reacting a pyridine-2-carbaldehyde of formula (1), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, with an alkyl acrylate (2), such as ethyl acrylate, in the presence of a base, such as DABCO, in a mixture of solvents, such as dioxane and water, at an appropriate temperature, for example, at RT. Aldehydes of formula (1) are commercially available or prepared following the well known procedures described in the literature.

- 20 A compound of formula (4a), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, may be prepared according to Scheme 1 by reaction of a compound of formula (3a) with acetic anhydride. Typical reaction conditions comprise reacting a compound of formula (3a), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, in acetic anhydride heating at an appropriate temperature, for example at 130°C, under thermal or microwave heating conditions.

SCHEME 2

This scheme provides a synthetic route for the preparation of compound of formula (4c), wherein $X_1 = N$, $X_2 = X_3 = X_4 = CH$, R(p) is variable as defined herein above and Alkyl is a (C₁-C₆) alkyl.

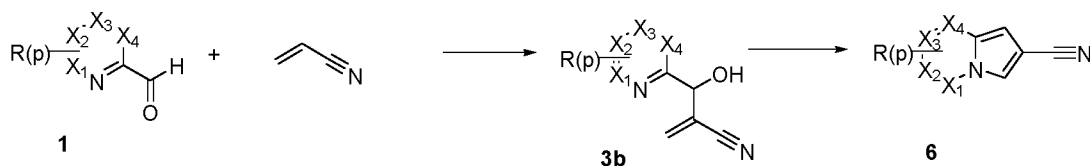


A compound of formula (4b), where $X_1 = N$, $X_2 = X_3 = X_4 = CH$, may be prepared by hydrolysis of a compound of formula (5), where $X_1 = N$, $X_2 = X_3 = X_4 = CH$. Typical hydrolysis conditions comprise reacting a compound of formula (5), with a solution of a metal hydroxide, such as KOH in water at an appropriate temperature, such as, for example, at 60°C, and then addition of HCl heating at an appropriate temperature, such as at 80°C. A compound of formula 5 could be prepared accordingly to the procedure reported in *J. Mat. Chem.*, 1999, 9, 2183-2188.

A compound of formula (4c), where $X_1 = N$, $X_2 = X_3 = X_4 = CH$ could be prepared by reaction of a compound of formula (4b) with a suitable alcohol. Typical reaction conditions comprise reacting a compound of formula (4b) with an alcohol such as MeOH, in the presence of a catalytic amount of sulfuric acid, at an appropriate temperature, such as heating at 80°C.

SCHEME 3

This scheme provides a synthetic route for the preparation of a compound of formula (6) wherein $X_1 = X_2 = X_3 = X_4 = CH$, and R(p) is variable as defined herein above.



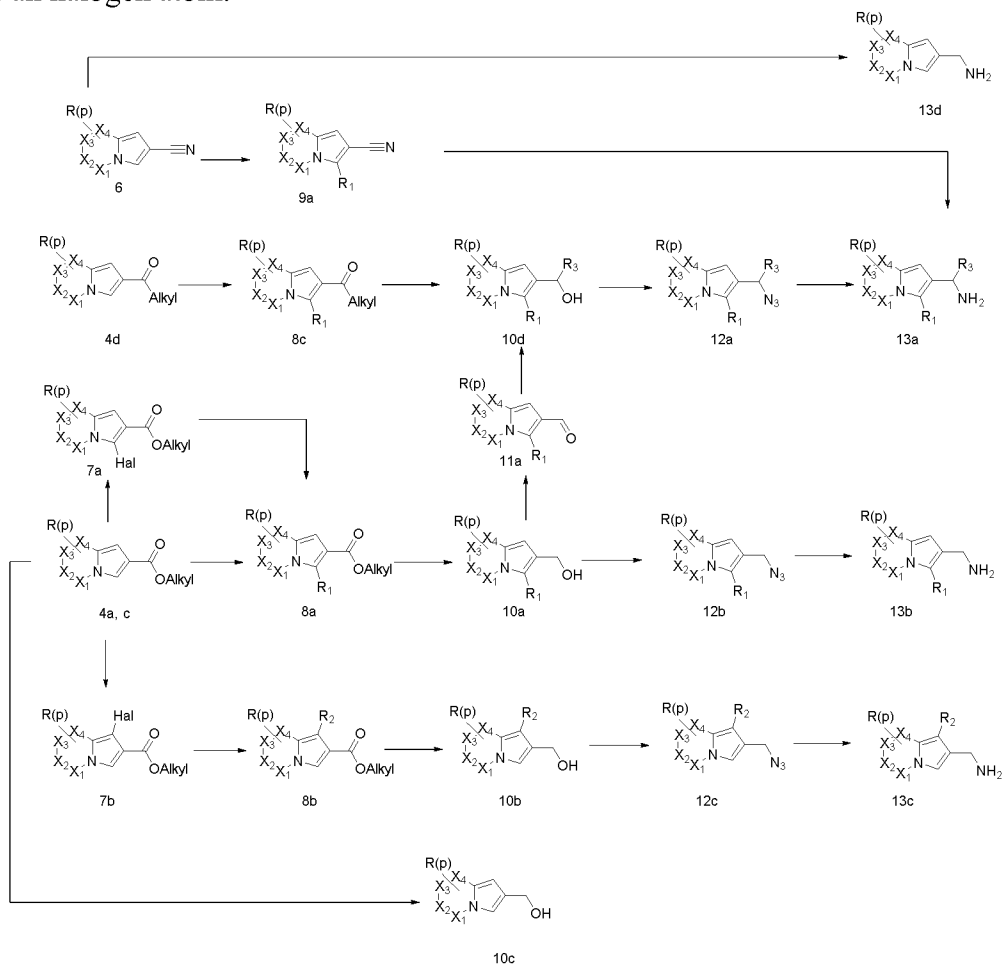
A compound of formula (3b), where $X_1 = X_2 = X_3 = X_4 = CH$, may be prepared

according to Scheme 3 by reaction of a compound of formula (1), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, with acrylonitrile. Typical reaction conditions comprise reacting a pyridine-2-carbaldehyde of formula (1) with acrylonitrile in the presence of a base, such as DABCO, at an appropriate temperature, for example, at 0 °C. Aldehydes of formula (1) are commercially available or prepared following the well known procedures described in the literature. A compound of formula (6), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, may be prepared according to Scheme 3 by reaction of a compound of formula (3b) with acetic anhydride. Typical reaction conditions comprise reacting a compound of formula (3b) in acetic anhydride heating at an appropriate temperature, for example at 130°C, under microwave heating conditions.

10

SCHEME 4

This scheme provides a synthetic route for the preparation of a compound of formula (10a,b,c,d) and (13a,b,c,d) wherein all the variables are described herein above and Hal is an halogen atom.



A compound of formula (4a), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$, or (4c), where $X_1 = \text{N}$, $X_2 = X_3 = X_4 = \text{CH}$, may be converted into a compound of formula (7a) by reaction with an appropriate N-halo succinimide, such as N-chlorosuccinimide, or N-iodosuccinimide, or N-bromosuccinimide in a polar solvent, such as acetonitrile, at an appropriate temperature, such as, for example, ranging from 0°C to RT.

A compound of formula (4a) may be converted into a compound of formula (7b) for example by reaction with bromine in a polar aprotic solvent, such as DCM, at an appropriate temperature, such as, for example, at -78°C.

A compound of formula (8a) may be prepared reacting a compound of formula (4a), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$ or (4c), where $X_1 = \text{N}$, $X_2 = X_3 = X_4 = \text{CH}$, with a suitable aryl halide or heteroaryl halide under Heck cross coupling conditions. Typical Heck reaction conditions comprise reacting a compound of formula (4a) with an aryl halide or heteroaryl halide in the presence of a Pd catalyst, such as $\text{Pd}(\text{OAc})_2$ with a trialkyl phosphine ligand, for example tricyclopentylphosphine tetrafluoroborate, or $\text{PdCl}_2(\text{PPh}_3)_2$, using a base, such as Cs_2CO_3 or potassium acetate, in a suitable solvent, such as toluene or NMP with water, at an appropriate temperature, such as, for example, ranging from 100°C to 130°C.

Alternatively a compound of formula (8a) may be prepared reacting a compound of formula (7a) in a cross coupling reaction, such as a Suzuki cross coupling, or a Stille cross coupling, or an Ullmann cross coupling, or a Sonogashira cross coupling. Typical Suzuki cross coupling conditions comprise reacting a compound of formula (7a) with a suitable boronic acid, or boronic ester, in the presence of a Pd catalyst, such as [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II), using a base, such as potassium phosphate monobasic and potassium phosphate tribasic, in a mixture of water and an organic solvent, such as dioxane, at an appropriate temperature, such as, for example, at 65°C. Typical Stille cross-coupling conditions comprise reacting a compound of formula (7a) with a suitable organo-tin reagent, in the presence of Pd catalyst, such as $\text{PdCl}_2(\text{PPh}_3)_2$, in a polar solvent, such as dioxane, at an appropriate temperature, such as, for example, ranging from 65°C to 90°C. Typical Ullmann conditions comprise reacting a compound of

formula (7a) with a suitable amide in the presence of CuI, with a ligand, such as N,N'-dimethylethylenediamine, and a base, such as cesium carbonate or K₃PO₄, in a polar solvent, such as DMF, at an appropriate temperature, such as, for example, at 65°C. Typical Sonogashira cross coupling conditions comprise reacting a compound of formula (7a) with
5 an appropriate terminal alkyne in the presence of CuI and a Pd catalyst such as PdCl₂(PPh₃)₂, in a mixture of a polar solvent, such as DMF, with an alkyl amine, such as diethylamine, at an appropriate temperature, such as at RT. A further protection step could be performed to introduce a protective group on OH or NH or NH₂ moieties following the general protocols reported in *Greene's Protective Groups in Organic Synthesis*.

10 A compound of formula (8b) may be prepared reacting a compound of formula (7b) in a cross coupling reaction, such as a Suzuki cross coupling or a Stille cross-coupling. Typical Suzuki cross coupling conditions comprise reacting a compound of formula (7b) with a suitable boronic acid, or boronic ester, or boroxine, in the presence of a Pd catalyst, such as [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II),
15 or Pd(PPh₃)₄, using a base, such as potassium phosphate monobasic and potassium phosphate tribasic, or potassium carbonate, in a mixture of water and an organic solvent, such as dioxane, at an appropriate temperature, such as ranging from 65°C to 110°C. Typical Stille cross-coupling conditions comprise reacting a compound of formula (7b) with a suitable organo-tin reagent in the presence of a Pd catalyst, such as Pd(PPh₃)₄, in a
20 suitable solvent or a mixture of solvents, such as toluene and methanol, at an appropriate temperature, such as, for example, ranging from 80°C to 110°C.

A compound of formula (8c) may be prepared reacting commercially available compound of formula (4d) where X₁= X₂= X₃= X₄= CH, with a suitable aryl halide or heteroaryl halide under Heck cross coupling conditions. Typical Heck reaction conditions
25 comprise reacting a compound of formula (4d) with an aryl halide or heteroaryl halide in the presence of a Pd catalyst, such as Pd(OAc)₂ with a trialkyl phosphine ligand, for example tricyclopentylphosphine tetrafluoroborate, using a base, such as Cs₂CO₃, in a suitable solvent, such as toluene, at an appropriate temperature, such as, for example, at

130°C.

A compound of formula (9a) may be prepared reacting a compound of formula (6) with a suitable aryl halide or heteroaryl halide under Heck cross coupling conditions. Typical Heck reaction conditions comprise reacting a compound of formula (6) with an aryl halide or heteroaryl halide in the presence of a Pd(II) catalyst, such as Pd(OAc)₂ with a trialkyl phosphine ligand, for example tricyclopentylphosphine tetrafluoroborate, using a base, such as Cs₂CO₃, in a suitable solvent, such as toluene, at an appropriate temperature, such as, for example, at 130°C.

A compound of formula (10a,b,c,d) may be prepared by reduction a compound of formula (8a,b,c) and (4a) respectively. Typical reduction conditions comprise reacting a compound of formula (8a,b,c) or (4a) with DIBAL in a suitable polar aprotic solvent, such as DCM, at an appropriate temperature, such as at -78°C, or with LiBH₄ in a suitable solvent, such as THF with MeOH, at an appropriate temperature, such as at 50°C, or with NaBH₄ in a protic solvent such as MeOH, at an appropriate temperature, such as at 0°C.

A compound of formula (10d) may be prepared alternatively by reaction of a compound of formula (11a) with a suitable Grignard reagent. Typical reaction conditions comprise reacting a compound of formula (11a) with a suitable alkylmagnesium halide, such as methylmagnesium bromide in a polar aprotic solvent, such as THF, at an appropriate temperature, such as at 0°C. A compound of formula (11a) may be prepared by oxidation of a compound of formula (10a). Typical oxidation conditions comprise reacting a compound of formula (10a) with an oxidizing system, such as MnO₂ in DCM at an appropriate temperature, such as at 50°C.

A compound of formula (12a,b,c) may be prepared by reaction of a compound of formula (10a,b,d) respectively with diphenylphosphoryl azide. Typical reaction conditions comprise reacting a compound of formula (10a,b,d) with diphenylphosphorylazide in the presence of a base, such as DBU, in a polar aprotic solvent, such as THF, at an appropriate temperature, such as ranging from 0°C to RT.

A compound of formula (13a,b,c) may be prepared by reduction of a compound of

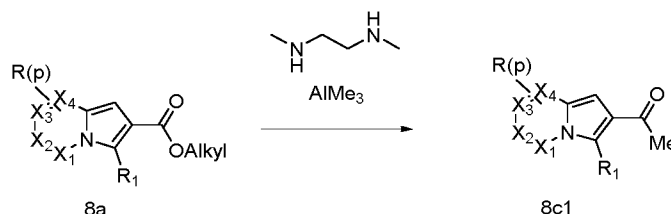
formula (12a,b,c) respectively under Staudinger reduction conditions. Typical reaction conditions comprise reacting a compound of formula (12a,b,c) with a triaryl phosphine, such as triphenylphosphine, in a suitable polar aprotic solvent, such as THF, at an appropriate temperature, such as, for example, at RT, and subsequently adding water and stirring at an appropriate temperature, such as, for example, ranging from RT to 50°C.

A compound of formula (13a) could alternatively be prepared by reaction of a compound of formula (9a) with an appropriate Grignard reagent and reduction of the obtained adduct. Typically a compound of formula (9a) may be reacted with an alkyl magnesium halide, such as MeMgBr, or EtMgBr, in a polar aprotic solvent, such as THF, at an appropriate temperature, such as at 100°C under microwave heating, then the obtained adduct could be reduced with a suitable hydride, such as NaBH₄ in a suitable solvent, such as MeOH, at an appropriate temperature, such as, for example, ranging from 0°C to RT.

A compound of formula (13d) may be prepared by reduction of a compound of formula (6). Typical reaction conditions comprise reduction of a compound of formula (6) with a hydride reagent, such as LiAlH₄, in a polar aprotic solvent, such as THF, at an appropriate temperature.

SCHEME 4a

This scheme provides a synthetic route for the preparation of a compound of formula (8c1) where X₁= X₂= X₃= X₄= CH and alkyl= Methyl, wherein all the variables are described herein above.



In some cases, a compound of formula (8c1) may be prepared reacting a compound of formula (8a) where X₁= X₂= X₃= X₄= CH and alkyl= Methyl with trimethylaluminum and N,N'-dimethylethylenediamine in a suitable solvent, such as toluene, at an appropriate

temperature, such as heating to reflux.

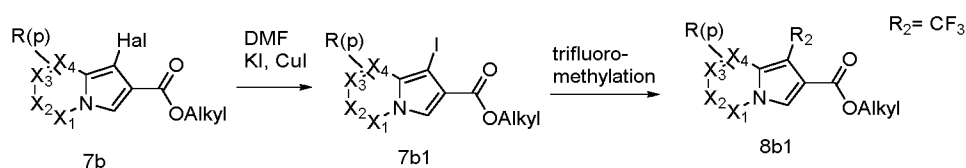
According to Scheme 4, compound of general formula 8c, such as 8c1, may be converted into alcohol 10d by mean of reduction step.

Scheme 4a has been used for the preparation of compounds of example 125.

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SCHEME 4b

This scheme provides a synthetic route for the preparation of a compound of formula (8b1) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_2 = \text{CF}_3$ and all the variables are described herein above.



10

In some cases, a compound of formula (7b), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $\text{Hal} = \text{Br}$ may be converted into a compound of formula (7b1), where $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $\text{Hal} = \text{I}$ for example by reaction with KI and CuI in a polar aprotic solvent, such as DMF, at an appropriate temperature, such as, for example, at 130°C (step 1).

15

A compound of formula (8b1), wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_2 = \text{CF}_3$, may be prepared by trifluoromethylation reaction of a compound of formula (7b1) with trimethyl(trifluoromethyl)silane in the presence of KF and CuI in a mixture of suitable polar aprotic solvents, such as DMF and NMP, at an appropriate temperature, such as at RT (step 2). According to Scheme 5, compound 8b1, a specific example of general formula 8b, may be converted into alcohol 10f by mean of Heck step to 8d, reduction step to alcohol 10e, oxidation step to aldehyde 11b, and finally conversion into alcohol 10f, by mean of reaction with a suitable Grignard reagent.

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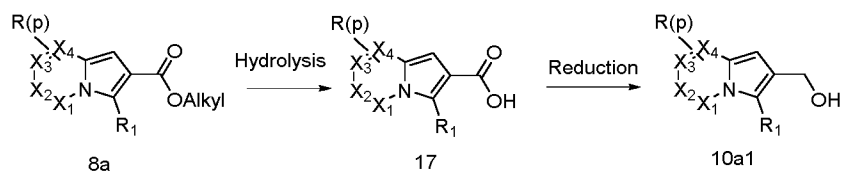
Scheme 4b has been used for the preparation of compounds of example 124.

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SCHEME 4c

This scheme provides a synthetic route for the preparation of a compound of formula (10a1) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_1 = -\text{NR}_{12}\text{R}_{13}$ where R_{12} and R_{13} can be linked to form a ring as above explained, all the other variables are as described above.

5



A compound of formula (17) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_1 = \text{NR}_{12}\text{R}_{13}$ may be prepared by hydrolysis of a compound of formula (8a). Typical hydrolysis conditions comprise reacting a compound of formula (8a) with a metal hydroxide, such as LiOH, in a mixture of water and a suitable solvent, such as THF, at an appropriate temperature, such as, for example, at 60°C (step 2).

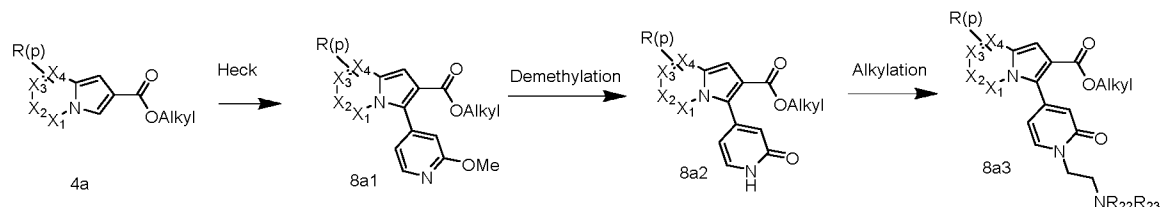
A compound of formula (10a1) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_1 = \text{NR}_{12}\text{R}_{13}$ may be prepared by reduction of a compound of formula (17). Typical reduction conditions comprise reacting a compound of formula (17) with a suitable reductive system, such as NaBH_4 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, in a suitable polar aprotic solvent, such as THF, at an appropriate temperature, such as ranging for 10°C to RT (step 3).

According to Scheme 4, compound of general formula 10a, such as 10a1, may be converted into alcohol 10d by mean of oxidation to aldehyde 11a, and finally conversion into alcohol 10d, by mean reaction with a suitable Grignard reagent

Scheme 4c has been used for the preparation of compounds of example 132.

SCHEME 4d

This scheme provides a synthetic route for the preparation of a compound of formula (8a3) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_1 = \text{heteroaryl}$ is 1,2-dihydropyridin-4-yl-2-one N-substituted with, $-(\text{CH}_2)_2\text{NR}_{22}\text{R}_{23}$ and all the variables are described herein above.



A compound of formula (8a1) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared from a compound of formula (4a) by means of a Heck cross coupling. Typical conditions comprise reacting a compound of formula (4a) with a suitable aryl or heteroaryl halide like 4-chloro-2-methoxypyridine in the presence of a Pd catalyst, such as $\text{Pd}(\text{OAc})_2$ with a trialkyl phosphine ligand, for example tricyclopentylphosphine tetrafluoroborate, using a base, such as Cs_2CO_3 , in a suitable solvent, such as toluene, at an appropriate temperature, such as, for example, at 130°C (step 1). A compound of formula (8a2) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared from a compound of formula (8a1) with a demethylation reaction. Typical reaction conditions for demethylation step comprise reacting a compound of formula (8a1) with Me_3SiI in a suitable polar aprotic solvent, such as acetonitrile, at an appropriate temperature, such as at 60°C (step 2). A compound of formula (8a3) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared from a compound of formula (8a2) with an alkylation reaction. Typical reaction conditions for alkylation step comprise reacting a compound of formula (8a2) with suitable aminoalkyl halide, such as 2-chloro-N,N-dimethylethylamine hydrochloride, in the presence of a base, such as K_2CO_3 in a suitable polar aprotic solvent, such as acetone, at an appropriate temperature, such as at 50°C to give compound 8a3 (step 3). According to Scheme 4, compound of general formula 8a, such as 8a3, may be converted into alcohol 10d by mean of reduction step to alcohol 10a, oxidation

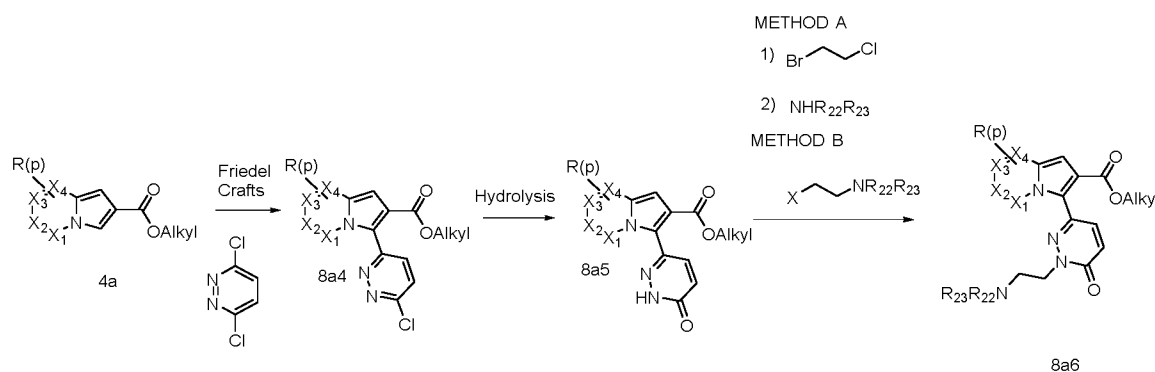
step to aldehyde 11a, and finally conversion into alcohol 10d, by mean of reaction with a suitable Grignard reagent.

Scheme 4d has been used for the preparation of compounds of examples 121, 122 and 133.

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SCHEME 4e

This scheme provides a synthetic route for the preparation of a compound of formula (8a6) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $R_1 = \text{heteroaryl}$ is 2,3-dihydropyridazin-6-yl-3-one N-substituted with $-(\text{CH}_2)_2\text{NR}_{22}\text{R}_{23}$, all the variables are described herein above.



10

A compound of formula (8a4) where $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared by compound of formula (4a) under Friedel Crafts reaction conditions. Typical reaction conditions comprise reacting a compound of formula (4a) with 3,6-dichloropyridazine, in the presence of AlCl_3 , in a suitable polar aprotic solvent, such as dichloroethane, at an appropriate temperature, such as, for example, at 80°C (step 1).

15

A compound of formula (8a5) where $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared by hydrolysis of a compound of formula (8a4) with acetic acid and sodium acetate at an appropriate temperature, such as, for example, heating to reflux (step 2).

A compound of formula (8a6) where $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared (step 3, method A) by alkylation of a compound of formula (8a5) with 1-bromo-2-chloroethane in the presence of a base, such as for example K_2CO_3 , in a suitable polar aprotic solvent, such as DMF, at an appropriate temperature, such as, for example, at 60°C followed by reaction with a suitable secondary amine such as, for example, pyrrolidine or 1-methyl

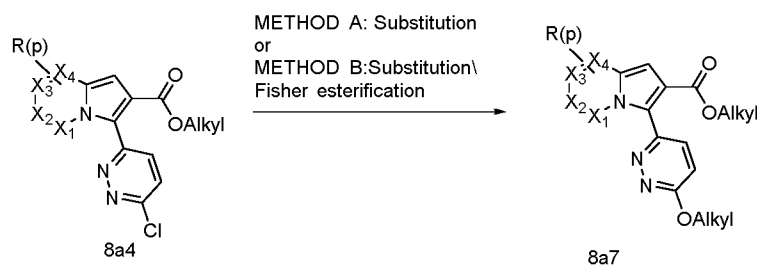
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piperazine in the presence of a base, such as for example K_2CO_3 , and KI, in a suitable polar aprotic solvent, such as acetonitrile, at an appropriate temperature, such as, for example, at $85^\circ C$. Alternatively a compound of formula (8a6) may also be prepared (step 3, method B) by alkylation of a compound of formula (8a5) with a suitable aminoalkyl halide such as for example 4-(2-chloroethyl)morpholine hydrochloride, in the presence of a base, such as for example K_2CO_3 , in a suitable polar aprotic solvent, such as DMF, at an appropriate temperature, such as, for example, at RT. According to Scheme 4, compound of general formula 8a, such as 8a6, may be converted into alcohol 10d by mean of reduction step to alcohol 10a, oxidation step to aldehyde 11a, and finally conversion into alcohol 10d, by mean reaction with a suitable Grignard reagent.

Scheme 4e has been used for the preparation of compounds of examples 134, 135 and 136.

SCHEME 4f

This scheme provides a synthetic route for the preparation of a compound of formula (8a7) wherein $X_1 = X_2 = X_3 = X_4 = CH$ and $R_1 =$ heteroaryl is pyridazine substituted by a group $-OAlkyl$ selected from (C_1-C_6) alkoxy, $(2-(dimethylamino)ethoxy)$, (C_3-C_6) heterocycloalkyloxy or (C_3-C_6) heterocycloalkyl (C_1-C_6) alkoxy further optionally substituted



A compound of formula (8a7) wherein $X_1 = X_2 = X_3 = X_4 = CH$ may be prepared (Method A) by nucleophilic aromatic substitution of a compound of formula (8a4) with a suitable alcohol in the presence of a base, such as potassium tert-butoxide, in a polar aprotic solvent, such as THF, at an appropriate temperature, such as, for example at RT.

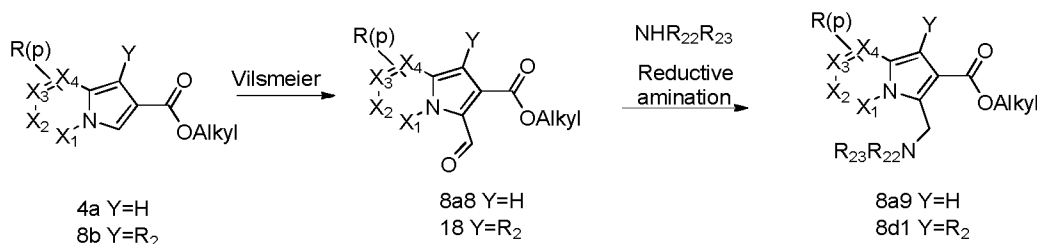
25 Alternatively a compound of formula (8a7) may be prepared (Method B) by

nucleophilic aromatic substitution of the carboxylic acid corresponding to a compound of formula (8a4) with a suitable alcohol followed by Fischer esterification with an alcohol, such as MeOH, in the presence of sulfuric acid, at an appropriate temperature, such as, for example, at 80°C. According to Scheme 4, compound of general formula 8a, such as 8a7, may be converted into alcohol 10d by mean of reduction step to alcohol 10a, oxidation step to aldehyde 11a, and finally conversion into alcohol 10d, by mean reaction with a suitable Grignard reagent.

Scheme 4f has been used for the preparation of compounds of examples 137, 138, 139 and 140.

SCHEME 4g

This scheme provides a synthetic route for the preparation of a compounds of formula (8a9) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $Y = \text{H}$ or compounds of formula (8d1) (specific example of a compound of formula 8d in scheme 5) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $Y = R_2$, all the variables are as described herein above.



A compound of formula (8a8) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $Y = \text{H}$ may be prepared by Vilsmeier formylation of a compound of formula (4a). Similarly a compound of formula (18) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $Y = R_2$ may be prepared by Vilsmeier formylation of a compound of formula (8b). Typical Vilsmeier reaction conditions comprise reacting a compound of formula (4a) or (8b) with DMF and POCl₃ in a suitable polar aprotic solvent, such as DCM, at an appropriate temperature, such ranging from 0 °C to RT (step 1).

A compound of formula (8a9) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $Y = \text{H}$ may be prepared by reductive amination of a compound of formula (8a8). Similarly a compound

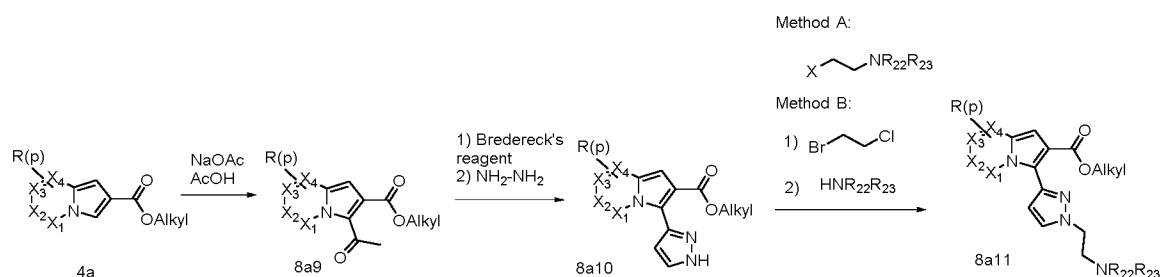
of formula (8d1) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and $Y = R_2$ may be prepared by reductive amination of a compound of formula (18). Typical reductive amination conditions comprise reacting of formula (8a8) or (18) with a suitable amine and acetic acid in the presence of a reducing reagent, such as sodium triacetoxy borohydride, in a polar solvent, such as DCM, at RT (step 2).

According to Scheme 4, compound of general formula 8a, such as 8a9 may be converted into alcohol 10d by mean of reduction step to alcohol 10a, oxidation step to aldehyde 11a, and finally conversion into alcohol 10d, by mean of reaction with a suitable Grignard reagent. According to Scheme 5, compound of general formula 8d, such as 8d1, may be converted into alcohol 10f by mean of reduction step to alcohol 10e, oxidation step to aldehyde 11b, and finally conversion into alcohol 10f, by mean of reaction with a suitable Grignard reagent.

Scheme 4g has been used for the preparation of compounds of examples 141, 142, 143, 144, 145 and 146.

SCHEME 4h

This scheme provides a synthetic route for the preparation of a compound of formula (8a-11) wherein $X_1 = X_2 = X_3 = X_4 = \text{H}$ and $R_1 = \text{heteroaryl like 1H-pyrazol-3-yl N1-substituted with } -(\text{CH}_2)_2\text{NR}_{22}\text{R}_{23}$, all the variables are described herein above.



A compound of formula (8a9) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared by acylation of a compound of formula (4a) with sodium acetate in acetic acid, at an appropriate temperature, such as at 140°C (step 1).

A compound of formula (8a10) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ may be prepared by

reaction of a compound of formula (8a9) with Brederick's reagent in a suitable solvent such as toluene, at an appropriate temperature, such as 110°C followed by reaction with hydrazine monohydrate, in a suitable solvent such as ethanol, at an appropriate temperature, such as 80°C (step 2).

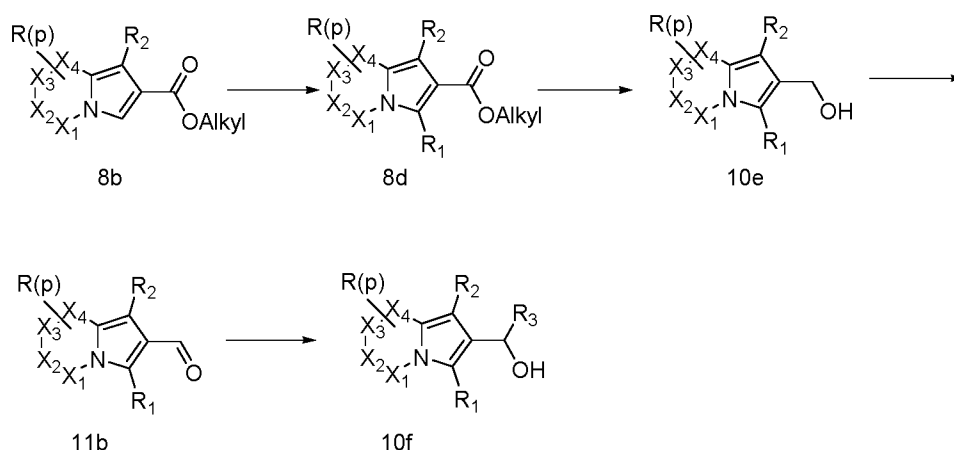
5 A compound of formula (8a11) may be prepared by (step 3, Method A) alkylation of a compound of formula (8a10) with 1-bromo-2-chloroethane in the presence of a base, such as for example K_2CO_3 , in a suitable polar aprotic solvent, such as DMF, at an appropriate temperature, such as, for example, at 60°C followed by reaction with a suitable secondary amine in the presence of a base, such as for example K_2CO_3 , and KI, in a suitable
10 polar aprotic solvent, such as acetonitrile, at an appropriate temperature, such as, for example, at 85°C. In some cases (example 149) a protection step of OH group as TBS was also required: for protection conditions see the general protocols reported in *Greene's Protective Groups in Organic Synthesis*, Peter G. M. Wuts, Theodora W. Greene; Editor Wiley&Sons, 4th Edition Dec.2006.

15 Alternatively a compound of formula (8a11) may be prepared (step 3, Method B) by alkylation of a compound of formula (8a10) with a suitable aminoalkyl halide such as for example 4-(2-chloroethyl)morpholine hydrochloride, in the presence of a base, such as for example K_2CO_3 , in a suitable polar aprotic solvent, such as THF, at an appropriate temperature, such as, for example, at 60°C. According to Scheme 4, compound of general
20 formula 8a, such as 8a11 may be converted into alcohol 10d by mean of reduction step to alcohol 10a, oxidation step to aldehyde 11a, and finally conversion into alcohol 10d, by mean reaction with a suitable Grignard reagent.

Scheme 4h has been used for the preparation of compounds of examples 147, 148, 149 and 150.

SCHEME 5

This scheme provides a synthetic route for the preparation of a compound of formula (10f) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and R_1 , R_2 and R_3 and $R(p)$ and Alkyl are variable as defined herein above. The compound of formula (10f) can be converted to the desired compounds of the invention as provided in Scheme 6 and 10 below.



A compound of formula (8d) wherein R_1 is an heteroaryl group, may be prepared reacting a compound of formula (8b) with a suitable heteroaryl halide, such as 2-chloropyridine, under Heck cross coupling conditions. Typical Heck reaction conditions comprise reacting a compound of formula (8b) with (hetero)aryl halide in the presence of a Pd catalyst, such as $\text{Pd}(\text{OAc})_2$ with a trialkyl phosphine ligand, for example tricyclopentylphosphine tetrafluoroborate, using a base, such as Cs_2CO_3 , in a suitable solvent, such as toluene, at an appropriate temperature, such as, for example, at 130°C .

A compound of formula (10e) may be prepared by reduction of a compound of formula (8d). Typical reaction conditions comprise reacting a compound of formula (8d) with a reducing reagent, such as DIBAL, in a polar aprotic solvent, such as DCM, at an appropriate temperature, such as, for example, at -78°C .

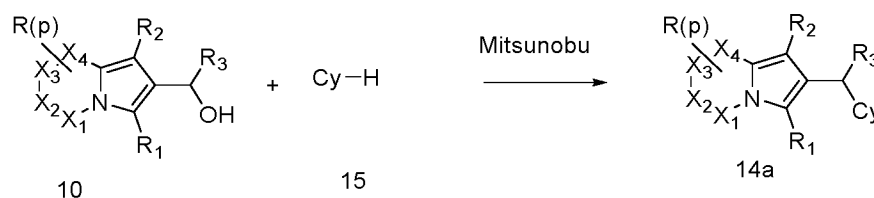
A compound of formula (11b) may be prepared by oxidation of a compound of formula (10e). Typical oxidation conditions comprise reacting a compound of formula (10e) under Swern oxidation conditions, such as with oxalyl chloride and DMSO in a

suitable solvent, such as DCM, at an appropriate temperature, for example at -78°C.

A compound of formula (10f) may be prepared by reaction of a compound of formula (11b) with a suitable Grignard reagent. Typical reaction conditions comprise reacting a compound of formula (11b) with an alkylmagnesium halide such as methylmagnesium bromide, in a polar aprotic solvent, such as THF, at an appropriate temperature, such as at 0°C.

SCHEME 6

This scheme provides a synthetic route for the preparation of a compound of formula (14a) from a compound of formula (10) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ or $X_1 = \text{N}$, $X_2 = X_3 = X_4 = \text{CH}$, and R_1 , R_2 and R_3 and $R(p)$ are variable as described herein above.

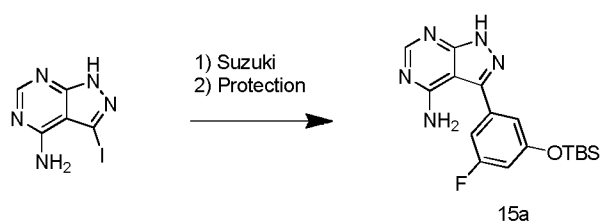


A compound of general formula (14a) may be prepared according to Scheme 6 by reaction of a compound of formula (10) with nitrogen based nucleophile CyH (15), such as adenine under Mitsunobu reaction conditions. Typical reaction conditions comprise reacting a compound of formula (10) with (15), such as adenine, in a polar aprotic solvent, such as THF, in the presence of a dialkyl azodicarboxylate, such as DIAD, and a triaryl phosphine, such as triphenylphosphine, at an appropriate temperature, such as, for example, ranging from RT to 50°C. This scheme provides a synthetic route for the preparation of the compound of example 1 to 12.

In some particular cases, where CyH is 3-(3-((tert-butyldimethylsilyl)oxy)-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (15a) compounds of formula (14a) may be prepared under Mitsunobu reaction conditions followed by deprotection of the TBS moiety. Typical reaction conditions comprise reacting a compound of formula (10) with 3-(3-((tert-butyldimethylsilyl)oxy)-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (15a) in an apolar aprotic solvent, such as THF, in the presence of a dialkyl

azodicarboxylate, such as DIAD and a triaryl phosphine, such as triphenylphosphine, at an appropriate temperature, such as, for example, at RT. Typical deprotection conditions to remove a TBS group comprise treatment with strong acid, such as HCl, in a suitable solvent, such as EtOH, at an appropriate temperature, such as at RT. For deprotection conditions see the general protocols reported in *Greene's Protective Groups in Organic Synthesis*, Peter G. M. Wuts, Theodora W. Greene; Editor Wiley&Sons, 4th Edition Dec.2006.

SCHEME 6a



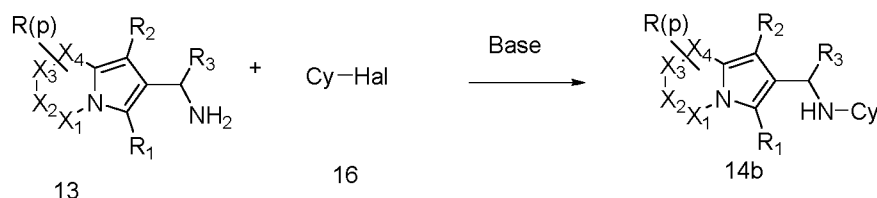
This scheme provides a synthetic route for the preparation of a compound of formula (15a).

A compound of formula (15a) may be prepared by a two-step Suzuki coupling\Protection sequence from commercially available 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine. Typical Suzuki cross coupling conditions comprise reacting commercially available 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine with a suitable boronic acid, or boronic ester like (3-fluoro-5-hydroxyphenyl)boronic acid, in the presence of a Pd catalyst, such as PdCl₂(dppf), using a base, such as aqueous potassium phosphate tribasic, in a polar solvent or in a mixture of polar solvents, such as DMF, at an appropriate temperature, such as at 120 °C. For protection conditions see the general protocols reported in *Greene's Protective Groups in Organic Synthesis*, Peter G. M. Wuts, Theodora W. Greene; Editor Wiley&Sons, 4th Edition Dec.2006.

Scheme 6a has been used for the preparation of compounds of example 124.

SCHEME 7

This scheme provides a synthetic route for the preparation of a compound of formula (14b) from a compound of formula (13) wherein all the variables are described herein above.

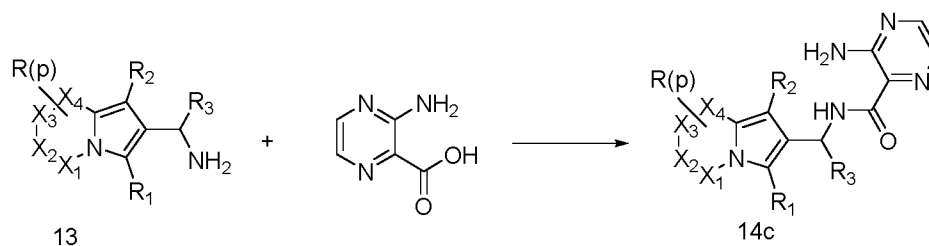


A compound of general formula (14b) may be prepared according to Scheme 7 by reaction of a compound of formula (13) with a suitable halide Cy-Hal (16), where “Cy” has the meaning above defined, such as for example 6-bromopurine, 4-amino-6-chloropyrimidine-5-carbonitrile, 4-amino-6-chloro-5-pyrimidinecarbaldehyde, 6-chloro-5-methylpyrimidin-4-amine. Typical reaction conditions comprise reacting a compound of formula (13) with 6-bromopurine in a polar solvent, such as t-BuOH, in the presence of a base, such as DIPEA, at an appropriate temperature, such as, for example, ranging from 80°C to 100°C.

This scheme provides a synthetic route for the preparation of the compound of examples 13 to 21 (where Cy-Hal is a purine derivative); and of examples 22 to 44 and 47 to 53 and 59 (where Cy-Hal is a pyrimidine derivative).

SCHEME 8

This scheme provides a synthetic route for the preparation of a compound of formula (14c) from a compound of formula (13) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$ and R_1 , R_2 and R_3 and $R(p)$ are variable as described herein above.

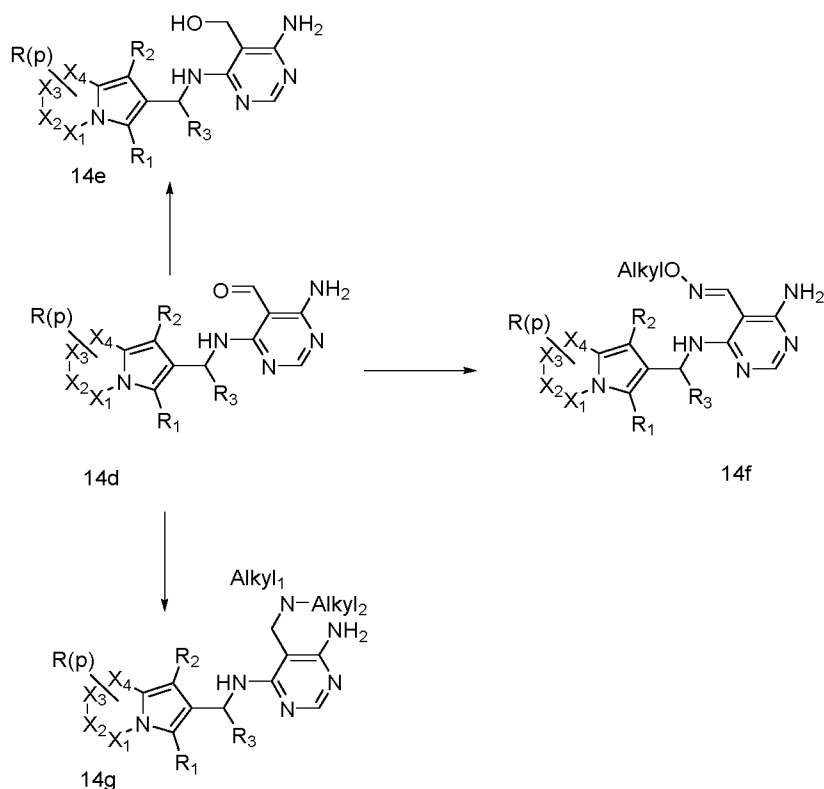


A compound of formula (14c) may be prepared according to Scheme 8 by condensation of a compound of formula (13) with 3-amino-2-pyrazinecarboxylic acid. Typical reaction conditions comprise reacting a compound of formula (13) with 3-amino-2-pyrazinecarboxylic acid in the presence of HOBt and a dialkyl carbodiimide, such as ECD HCl, in a polar aprotic solvent, such as DMF, at an appropriate temperature, such as at RT.

This scheme provides a synthetic route for the preparation of the compound of example 54 and 55.

SCHEME 9

This scheme provides a synthetic route for the preparation of a compound of formula (14e, f, g) from a compound of formula 14d wherein all the variables are described herein above (e.g. starting from the compound of example 47). Particularly Alkyl may also be H or is a (C₁-C₆) alkyl, and Alkyl₁ and Alkyl₂ may form, taken together with the nitrogen atom they are linked to, a 5 to 6 membered heterocyclic radical such as 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl;



A compound of formula (14e) (e.g. compound of example 56) may be prepared according to Scheme 9 by reduction of a compound of formula (14d). Typical reaction conditions comprise reacting (14d), with a reducing reagent, such as NaBH₄, in a polar protic solvent, such as MeOH, at an appropriate temperature, such as at 0°C. Compound of formula (14d) may be prepared as reported in scheme 7, from 13 and CyHal= 4-amino-6-chloro-5-pyrimidinecarbaldehyde.

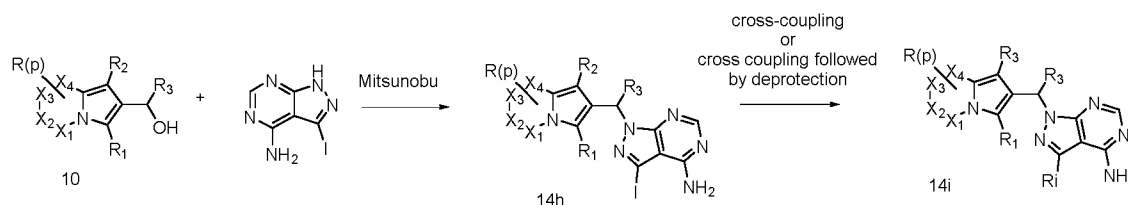
A compound of formula (14g) may be prepared according to Scheme 9 reacting a compound of formula (14d), under reductive amination conditions. Typical reaction conditions comprise reacting a compound of formula (14d), with a secondary amine, such as morpholine (e.g. in example 57) in the presence of a reducing reagent, such as sodium triacetoxy borohydride, in a polar solvent, such as DCM, at pH~5-6, at an appropriate temperature, such as at RT.

A compound of formula (14f) (e.g. compound of example 58) may be prepared according to scheme 9 by reaction of a compound of formula (14d), with an hydroxylamine salt. Typical reaction conditions comprise reacting a compound of formula (14d), with hydroxylamine salt such as hydroxylamine hydrochloride in the presence of pyridine, in a

polar solvent, such as ethanol, at an appropriate temperature, such as at RT.

SCHEME 10

This scheme provides a synthetic route for the preparation of a compound of formula 14h and 14i from a compound of formula (10) and 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine wherein all the variables are described herein above.



A compound of general formula (14h) may be prepared according to Scheme 10 by reaction of a compound of formula (10) with 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine under Mitsunobu reaction conditions. Typical reaction conditions comprise reacting a compound of formula (10) with 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine in an apolar aprotic solvent, such as THF, in the presence of a dialkyl azodicarboxylate, such as DIAD and a triaryl phosphine, such as triphenylphosphine, at an appropriate temperature, such as, for example, at RT.

A compound of general formula (14i) may be prepared according to Scheme 10 by reaction of a compound of formula (14h) in a cross-coupling reaction, such as for example Suzuki cross-coupling, or Sonogashira cross-coupling, or Stille cross-coupling with suitable reagents. Typical Suzuki cross coupling conditions comprise reacting a compound of formula (14h) with a suitable boronic acid, or boronic ester, in the presence of a Pd catalyst, such as Pd(PPh₃)₄, using a base, such as aqueous sodium bicarbonate, in a polar solvent or in a mixture of polar solvents, such as DME and EtOH, at an appropriate temperature, such as 80°C. Typical Sonogashira cross coupling conditions comprise reacting a compound of formula (14i) with an appropriate terminal alkyne in the presence of CuI and using a catalyst such as PdCl₂(PPh₃)₂, in a mixture of a polar solvent, such as DMF, and an alkyl amine, such as diethylamine, at an appropriate temperature, such as at

RT. Typical Stille cross-coupling conditions comprise reacting a compound of formula (14i) with a suitable organo-tin reagent, in the presence of LiCl and a catalyst, such as Pd(PPh₃)₄, in a polar aprotic solvent, such as dioxane, at an appropriate temperature, such as at 100°C.

5 This scheme provides a synthetic route for the preparation of the compound of examples 60 to 102.

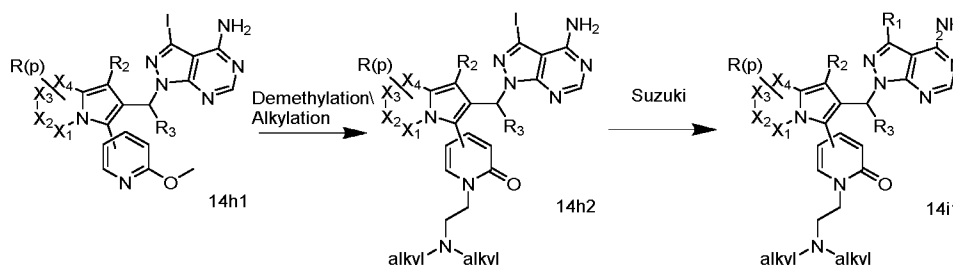
An additional deprotection step could be required to remove protection group from OH or NH or NH₂ moieties. Typical deprotection conditions to remove Boc protecting group comprise treatment with strong acid, such as TFA in a polar solvent, such as DCM, at an
10 appropriate temperature, such as ranging from 0° to RT. Typical deprotection conditions to remove TIPS protecting group comprise treatment with a fluoride salt, such as TBAF, in an apolar solvent, such as THF, at an appropriate temperature, such as, for example, at RT. Typical deprotection conditions to remove a TBS group comprise treatment with strong acid, such as HCl, in a suitable solvent, such as EtOH, at an appropriate temperature, such
15 as at RT. For deprotection conditions see the general protocols reported in *Greene's Protective Groups in Organic Synthesis*, Peter G. M. Wuts, Theodora W. Greene; Editor Wiley&Sons, 4th Edition Dec.2006. This deprotection step was used for the preparation of example 45, 46 and 103. And 117, 149

In some other particular cases an additional step was required to transform a Boc protecting
20 group into a methyl group. Typical condition comprise treatment with a reducing agent such as LiAlH₄ in a polar solvent or in a mixture of polar solvents like THF at an appropriate temperature such as 65 °C.

SCHEME 11

This scheme provides a synthetic route for the preparation of a compound of formula (14i1) wherein $X_1 = X_2 = X_3 = X_4 = \text{CH}$, $R_1 =$ heteroaryl like 2,3-dihydropyridinyl-2-one N-substituted with $-(\text{CH}_2)_2\text{NR}_{22}\text{R}_{23}$,

5



A compound of formula (14h2) may be prepared from a compound of formula (14h1) wherein $X_1 = X_2 = X_3 = X_4 = \text{C}$ with a demethylation/alkylation sequence. Typical reaction conditions for demethylation step comprise reacting a compound of formula (14h1) with Me₃SiI in a suitable polar aprotic solvent, such as acetonitrile, at an appropriate temperature, such as ranging from 50°C to 60°C. Typical reaction conditions for alkylation step comprise reacting the obtained material with suitable aminoalkyl halide, such as 4-(2-chloroethyl)morpholine hydrochloride, in the presence of a base, such as K₂CO₃ in a suitable polar aprotic solvent, such as acetone, at an appropriate temperature, such as at 60°C to give compound (14h2).

A compound of general formula (14i1) may be prepared according to Scheme 11 by reaction of a compound of formula (14h) in a cross-coupling reaction, such as for example Suzuki cross-coupling. Typical Suzuki cross coupling conditions comprise reacting a compound of formula (14h2) with a suitable boronic acid, or boronic ester, in the presence of a Pd catalyst, such as Pd(PPh₃)₄, using a base, such as aqueous sodium bicarbonate, in a polar solvent or in a mixture of polar solvents, such as DME and EtOH, at an appropriate temperature, such as 80°C.

The compounds of the invention are inhibitors of kinase activity, in particular PI3-kinase activity. Generally speaking, compounds which are PI3K inhibitors may be

useful in the treatment of many disorders associated with PI3K enzymes mechanisms.

In one embodiment, the disorders that can be treated by the compounds of the present invention include respiratory diseases selected from idiopathic chronic cough, cough-variant asthma, cough associated with thoracic tumour or lung cancer, viral or post-viral cough, upper airways cough syndrome (UACS), or post nasal drip cough, or cough associated with gastro- oesophageal reflux disease (both acid and non acid reflux), asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), interstitial lung disease, (such as idiopathic pulmonary fibrosis (IPF)), congestive heart disease, sarcoidosis, infections (such as whooping cough); viral infections (including viral respiratory tract infections and viral exacerbation of respiratory diseases; non-viral respiratory infections including aspergillosis and leishmaniasis; allergic diseases including allergic rhinitis and atopic dermatitis; autoimmune diseases including rheumatoid arthritis and multiple sclerosis; inflammatory disorders including inflammatory bowel disease; cardiovascular diseases including thrombosis and atherosclerosis; hematologic malignancies; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility; transplantation rejection; graft rejection; lung injuries; and pain including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia and central pain.

In another embodiment, the disorder that can be treated by the compound of the present invention is selected from the group consisting of idiopathic chronic cough, cough-variant asthma, cough associated with thoracic tumour or lung cancer, viral or post-viral cough, upper airways cough syndrome (UACS), post nasal drip cough, cough associated gastro- oesophageal reflux disease (both acid and non acid reflux), asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD) and interstitial lung disease (such as idiopathic pulmonary fibrosis (IPF)).

In a further embodiment, the disorder is selected from the group of asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cough and

chronic cough.

The methods of treatment of the invention comprise administering a safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to a patient in need thereof. As used herein, "safe and effective amount" in reference to a
5 compound of formula (I) or a pharmaceutically acceptable salt thereof or other pharmaceutically-active agent means an amount of the compound sufficient to treat the patient's condition but low enough to avoid serious side effects and it can nevertheless be routinely determined by the skilled artisan. The compounds of formula (I) or pharmaceutically acceptable salts thereof may be administered once or according to a
10 dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. Typical daily dosages may vary depending upon the particular route of administration chosen.

The invention also provides pharmaceutical compositions of compounds of formula (I) in admixture with one or more pharmaceutically acceptable carrier or excipient, for
15 example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A.

Administration of the compounds of the present invention and their pharmaceutical compositions may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by
20 infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration.

Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered
25 alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and known excipients, including suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in

administering the compounds of the present invention.

Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable known inert diluents such as water and suitable known excipients such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

Suppositories for rectal administration of the compounds of the invention can be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols.

Formulations for vaginal administration can be in the form of cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such as suitable carriers, are also known.

For topical administration the pharmaceutical composition can be in the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

For the treatment of the diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation.

Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

For administration as a dry powder, single- or multi-dose inhalers known from the prior art may be utilized. In that case the powder may be filled in gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir.

A diluent or carrier, generally non-toxic and chemically inert to the compounds of

the invention, e.g. lactose or any other additive suitable for improving the respirable fraction may be added to the powdered compounds of the invention.

Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of the invention either in solution or in dispersed form. The
5 propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known
10 from the prior art or by soft-mist nebulizers such as Respimat®.

The compounds of the invention can be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, e.g. beta₂-agonists, antimuscarinic agents, corticosteroids, mitogen-activated kinases (P38 MAP kinases) inhibitors,, human
15 neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs) and mucus regulators.

The dosages of the compounds of the invention depend upon a variety of factors including the particular disease to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the
20 efficacy, toxicology profile, and pharmacokinetic profile of the compound.

Advantageously, the compounds of formula (I) can be administered for example, at a dosage comprised between 0.001 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

When the compounds of formula (I) are administered by inhalation route, they are
25 preferably given at a dosage comprised between 0.001 and 500 mg/day, preferably between 0.1 and 200 mg/day.

The following examples illustrate the invention without limiting its scope.

PREPARATIONS OF INTERMEDIATES AND EXAMPLES

Chemical Names of the compounds were generated with CHEMAXON 6.0.4 tool.

solutions of common inorganic salts used in workups are aqueous solutions.

Abbreviations:

5

Et ₂ O	Diethyl ether
EtOAc	Ethyl acetate
DCM	Dichloromethane
MeOH	Methanol
DMF	N,N-Dimethylformamide
MeCN	Acetonitrile
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
NMP	1-Methyl-2-pyrrolidinone
<i>t</i> -BuOH	<i>tert</i> -Butanol
n-BuOH	1-Butanol
EtOH	Ethanol
DME	1,2-Dimethoxyethane
DABCO	1,4-Diazabicyclo[2.2.2]octane
TEA	Triethylamine
KOAc	Potassium acetate
PdCl ₂ (PPh ₃) ₂	Bis(triphenylphosphine)palladium(II) dichloride

(continued)

Pd(OAc) ₂	Palladium(II) acetate
PdCl ₂ (dtbpf)	[1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene]dichloropalladium(II)
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
DIBAL	Diisobutylaluminum hydride
PPH ₃	Triphenylphosphine
DPPA	Diphenyl phosphoryl azide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(Dimethylamino)pyridine
DIPEA	N,N-Diisopropylethylamine
MeMgBr	Methylmagnesium bromide
EtMgBr	Ethylmagnesium bromide
DIAD	Diisopropyl azodicarboxylate
HOBt	1-Hydroxybenzotriazole hydrate
EDC HCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
TFA	Trifluoroacetic acid
MW	microwave
SCX	Strong cation exchanger
Silica-NH	Secondary amine functionalized silica cartridge
r.t./RT	Room temperature
Rt	Retention time
H	hour
Min	minutes
Conc	concentrated
Eq	equivalent
Sat	saturated
MDAP	mass directed autopurification
TBS	<i>tert</i> -butyl-dimethylsilyl group

General Experimental details

NMR characterization:

Proton Magnetic Resonance (^1H NMR) spectra were collected using deuterated solvents ($\text{DMSO-}d_6$, CDCl_3) at 25°C on Agilent VNMRS-500, Agilent VNMRS-400 and
5 Bruker Avance 400.

Chemical shifts are expressed in parts per million (ppm) downfield of tetramethylsilane (δ units). Multiplicity is indicated as follows: (s) singlet, (d) doublet, (dd) double doublet, (ddd) triple doublet, (t) triplet, (dt) double triplet, (q) quartet, (m) multiplet, (br s) broad signal. Coupling constants J are expressed in unit of hertz (Hz).

LC/UV/MS Analytical Methods

LCMS may be recorded under the following conditions: diode array detector DAD chromatographic traces, mass chromatograms and mass spectra may be taken on UPLC/PDA/MS AcquityTM system coupled with Micromass ZQTM or Waters SQD single quadrupole mass spectrometer operated in positive and/or negative electron spray
15 ES ionisation mode and/ or Fractionlynx system used in analytical mode coupled with ZQTM single quadrupole operated in positive and/or negative ES ionisation mode.

Quality Control) methods used were four, two operated under low pH conditions and the other ones operated under high pH conditions:

Method A, low pH conditions: column: Acquity CSH C18, $1.7\ \mu\text{m}$, $2.1 \times 50\ \text{mm}$,
20 the column temperature was 40°C ; mobile phase solvent A was milliQ water + 0.1% HCOOH , mobile phase solvent B MeCN + 0.1% HCOOH . The flow rate was 1 ml/min. The gradient table was $t = 0\ \text{min}$ 97% A – 3% B, $t = 1.5\ \text{min}$ 0.1% A – 99.9% B, $t = 1.9\ \text{min}$ 0.1% A – 99.9% B and $t = 2\ \text{min}$ 97% A – 3% B. The UV detection range was 210 – 350 nm and the ES⁺/ES⁻ range was 100 – 1000 amu.

25 Method B, low pH conditions: column: Acquity UPLC BEH C18, $1.7\ \mu\text{m}$, $50\ \text{mm} \times 2.1\ \text{mm}$, the column temperature was 40°C ; mobile phase solvent A was milliQ water + 0.1% HCOOH , mobile phase solvent B MeCN + 0.1% HCOOH . The flow rate was 1 ml/min. The gradient table was $t = 0\ \text{min}$ 97% A – 3% B, $t = 1.5\ \text{min}$ 0.1% A – 99.9% B, $t =$

1.9 min 0.1% A – 99.9% B and t= 2 min 97% A – 3% B. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 1000 amu.

Method C, high pH conditions: column: Acquity BEH C18, 1.7 μ m, 2.1 x 50 mm the column temperature was 40°C; mobile phase solvent A was 10 mM aqueous solution of NH_4HCO_3 adjusted to pH= 10 with ammonia, mobile phase solvent B MeCN. The flow rate was 1 ml/min. The gradient table was t= 0 min 97% A – 3% B, t= 1.5 min 0.1% A – 99.9% B, t= 1.9 min 0.1% A – 99.9% B and t= 2 min 97% A – 3% B. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 1000 amu.

Method D, high pH conditions: column: XBridge C18, 5 μ m, 50mm x 4.6 mm, the column temperature was 40°C; mobile phase solvent A was 10 mM aqueous solution of NH_4HCO_3 adjusted to pH= 10 with ammonia, mobile phase solvent B MeCN. The flow rate was 2 ml/min. The gradient table was t= 0 min 97% A – 3% B, t= 6.5 min 0.1% A – 99.9% B, t= 8.5 min 0.1% A – 99.9% B and t= 8.6 min 97% A – 3% B. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 1000 amu.

Method J, high pH conditions: column: Acquity BEH C18, 1.7 μ m, 2.1 x 50 mm the column temperature was 40 °C; mobile phase solvent A was 0.1% v/v ammonia aqueous solution at pH 10, mobile phase solvent B MeCN. The flow rate was 1 ml/min. The gradient table was t= 0 min 97% A – 3% B, t= 1.5 min 0.1% A – 99.9% B, t= 1.9 min 0.1% A – 99.9% B and t= 2 min 97% A – 3% B. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 1000 amu.

Semipreparative mass directed autopurifications (MDAP) were carried out using Waters FractionlynxTM systems operating under low or high pH chromatographic conditions under the following conditions. The trigger for the collection of the target species was the presence of the target m/z ratio value in the TIC MS signal. All the purifications were carried out with the column kept at room T.

The semi-preparative set of conditions used were three:

Method E, low pH conditions: Stationery phase: XSelect CSH Prep. C18, 5 μ m, OBD 30 x 100 mm, at room temperature; mobile phase solvent A was milliQ water + 0.1%

HCOOH, mobile phase solvent B MeCN; the flow rate was 43 ml/min; the gradient timetables were customised on the Rt behaviour of the target species. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 900 amu.

Method F, high pH conditions: Stationary phase: Gemini 5 um C18 110A AXIA
5 (100 x 30 mm); mobile phase solvent A was 10 mM aqueous solution of NH_4HCO_3 adjusted to pH= 10 with ammonia, the flow rate was 43 ml/min; mobile phase solvent B MeCN; the gradient timetables were customised on the Rt behaviour of the target species. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 900 amu.

Method G, high pH conditions: Stationary phase: Gemini 5 um C18 110A AXIA
10 (100 x 30 mm); mobile phase solvent A was 10 mM aqueous solution of NH_4HCO_3 adjusted to pH= 10 with ammonia, the flow rate was 40 ml/min; mobile phase solvent B MeCN; the gradient timetable was customised on the Rt behaviour of the target species. The UV detection range was 210 – 350 nm and the ES+/ES- range was 100 – 900 amu.

Chiral resolutions were performed using a Semipreparative Waters 600 system or a
15 Semipreparative HPLC Agilent 1100 for semipreparative separations. The conditions are reported in the Examples.

The enantiomeric excess are determined by chiral HPLC analysis on a HPLC Agilent 1100 equipped with 6-position switching valve. It is equipped with DA, and CD detectors. The following methods were used:

20 Method H: Chiralpak AD-H (25 x 0.46 cm), 5 um; Mobile phase: n-Hexane/ (Ethanol+0.1% isopropylamine) 80/20 v/v; UV detection: 220 nM; Flow Rate: 0.8 mL/min; Loop: 10 uL.

Method I: Column: Chiralpak IC (25 x 0.46 cm), 5 um; Mobile phase: n-Hexane/(2-Propanol+0.1% isopropylamine) 60/40% v/v; UV detection: 220 nM; Flow
25 Rate: 1.0 mL/min; Loop: 20 uL.

Method K: Column: Chiralpak AD-H (25 x 0.46 cm), 5 um; Mobile phase: n-Hexane / (Ethanol+0.1% isopropylamine) 85/15 % v/v; UV detection: 220 nM; Flow Rate: 0.8 mL/min; Loop: 15 uL.

Method L: Column: Chiralpak AD-H (25 x 0.46 cm), 5 μ m; Mobile phase: n-Hexane / (Ethanol+0.1% isopropylamine) 70/30 % v/v; UV detection: 220 nM; CD: 240 nM; Flow Rate: 0.8 mL/min; Loop: 3 μ L.

Method M: Column: Chiralpak AD-H (25 x 0.46 cm), 5 μ m; Mobile phase: n-Hexane / (Ethanol+0.1% isopropylamine) 80/20 % v/v; UV detection: 220 nM; Flow Rate: 1.0 mL/min; Loop: 20 μ L.

Method N: Column: Chiralpak AD-H (25 x 0.46 cm), 5 μ m; Mobile phase: n-Hexane/(Ethanol/Methanol 1/1 + 0.1 % isopropylamine) 75/25 % v/v; UV detection: 220 nM; Flow Rate: 1.0 mL/min; Loop: 20 μ L.

Method O: Column: Chiralpak IC (25 x 0.46 cm), 5 μ m; Mobile phase: n-Hexane / (Ethanol+0.1% isopropylamine) 75/25 % v/v; UV detection: 220 nM; Flow Rate: 1.0 mL/min; Loop: 15 μ L.

Method P: Column: Chiralpak AD-H (25 x 0.46 cm), 5 μ m; Mobile phase: n-Hexane/(Ethanol+0.1% isopropylamine) 75/25 % v/v; UV detection: 220 nM; Flow Rate: 1.0 mL/min; Loop: 20 μ L.

Method Q: Column: Chiralpak IC (25 x 0.46 cm), 5 μ m; Mobile phase: n-Hexane / (Ethanol + 0.1 % isopropylamine) 70/30 % v/v; UV detection: 220 nM; Flow Rate: 1.0 mL/min; Loop: 15 μ L.

The experiment performed under microwave irradiation were carried out using a Biotage Initiator 2.0 system.

Flash chromatography purifications were performed using Biotage Isolera or Biotage SP1 flash chromatography systems, both instruments working with Biotage KP-SIL cartridges and Biotage KP-NH cartridges, or were manually performed using Isolute Flash silica gel pre-packed cartridges, or Varian Bond Elut pre-packed cartridges.

Reverse phase flash chromatography were carried out over pre-packed Biotage C18 SNAP cartridges or Varian Bond Elut C18 cartridges.

SPE-SCX cartridges are ion exchange solid phase extraction columns supplied by Varian.

Many of the compounds described in the following Examples have been prepared from stereochemically pure starting materials, for example 95% ee.

Brine refers to a saturated aqueous solution of NaCl. Unless otherwise specified.

Where the preparation of starting materials is not described, these are commercially available, known in the literature, or readily obtainable by those skilled in the art using standard procedures.

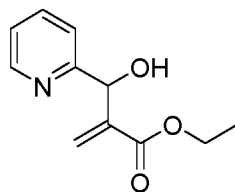
The stereochemistry of the compounds in the Examples, where indicated, has been assigned on the assumption that absolute configuration at resolved stereogenic centers of starting materials is maintained throughout any subsequent reaction conditions.

In the procedures that follow, after each starting material, reference to a compound number is sometimes provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.

When reference is made to the use of a “similar” or “analogous” procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variations, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

PREPARATION OF INTERMEDIATES:

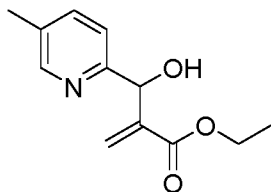
Intermediate A1: of ethyl 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enoate



To a solution of pyridine-2-carbaldehyde (commercially available from Sigma Aldrich, 9.0 g, 84 mmol) and ethyl acrylate (27.42 mL, 252 mmol) in a mixture of dioxane/water $\approx$ 1/1 (840 mL), DABCO (9.42 g, 84 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The mixture was partitioned between Et₂O and water and the aqueous phase was extracted with Et₂O. The combined organic layers

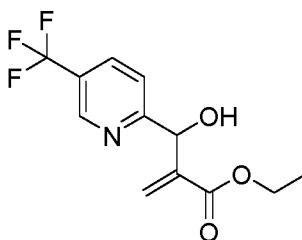
were washed with brine and dried over sodium sulfate. The solvent was removed and the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (340 g) (cyclohexane to cyclohexane: EtOAc = 50 : 50) yielding title compound as a pale yellow oil (17.9 g, 86.4 mmol, 91.2% yield). MS/ESI⁺ 208.1.[MH]⁺, Rt = 0.35 min (Method A).

5 **Intermediate A2: ethyl 2-[hydroxy(5-methylpyridin-2-yl)methyl]prop-2-enoate**



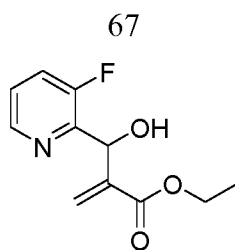
Prepared similarly to intermediate A1 starting from 5-methylpyridine-2-carbaldehyde (1.0 g, 8.25 mmol) in a mixture of dioxane/water 1/1 (70 mL), stirring at RT
10 for 3 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane: EtOAc = 80 : 20 to 50 : 50) yielding title compound as a pale yellow solid (0.862 g, 3.89 mmol, 47% yield). MS/ESI⁺ 222.1 [MH]⁺, Rt = 0.39 min (Method A).

15 **Intermediate A3: ethyl 2-[hydroxy[5-(trifluoromethyl)pyridin-2-yl]methyl]prop-2-enoate**



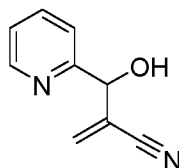
Prepared similarly to intermediate A1, starting from 5-(trifluoromethyl)pyridine-2-carbaldehyde (3.66 mmol), and stirring at RT overnight, and purified by flash chromatography on silica gel Biotage cartridge (cyclohexane to cyclohexane: EtOAc =
20 70 : 30) yielding title compound as a pale yellow oil (0.450 g, 1.64 mmol, 45% yield). MS/ESI⁺ 276.1 [MH]⁺, Rt = 0.88 min (Method A).

Intermediate A4: ethyl 2-[(3-fluoropyridin-2-yl)(hydroxy)methyl]prop-2-enoate



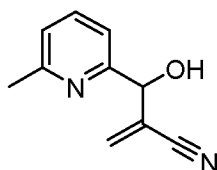
Prepared similarly to intermediate A1 starting from 3-fluoropyridine-2-carbaldehyde (0.5 g, 4.0 mmol) stirring at r.t. for 1.5 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane: EtOAc = 70 : 30 to 50 : 50) to afford title compound (0.900 g, 4.00 mmol, quantitative yield). MS/ESI⁺ 226.0 [MH]⁺, Rt = 0.62 min (Method A).

Intermediate A5: 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enitrile



To a solution of pyridine-2-carbaldehyde (4.72 g, 44 mmol) in acrylonitrile (17.4 mL, 264 mmol), DABCO (4.95 g, 44 mmol) was added and the resulting mixture was stirred at 0°C for 30 minutes. The mixture was partitioned between Et₂O and water and the aqueous phase was extracted with Et₂O. The combined organic layers were dried over sodium sulfate, the solvent was removed and the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane: EtOAc = 50 : 50) yielding title compound as a white solid (5.88 g, 4.7 mmol, 83% yield). MS/ESI⁺ 161.0 [MH]⁺, Rt = 0.35 min (Method A).

Intermediate A6: 2-[hydroxy(6-methylpyridin-2-yl)methyl]prop-2-enitrile

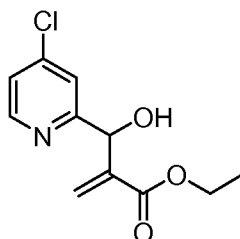


Prepared similarly to intermediate A5, starting from 6-methylpyridine-2-carbaldehyde (1.211 g, 10 mmol), and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane: EtOAc = 80 : 20 to 50 : 50) yielding title compound

as a white solid (1.0 g, 5.75 mmol, 57% yield). MS/ESI⁺ 175.0 [MH]⁺, Rt = 0.33 min (Method A).

Intermediate A8: ethyl 2-[(4-chloropyridin-2-yl)(hydroxy)methyl]prop-2-enoate

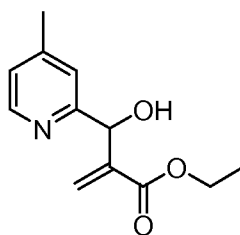
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Prepared similarly to intermediate A1 starting from 4-chloropyridine-2-carbaldehyde (1.0 g, 7.06 mmol) stirring at r.t. for 2 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as a colorless oil (1.75 g, quantitative yield). MS/ESI⁺ 242.1 [MH]⁺, Rt = 0.74 min (Method A).

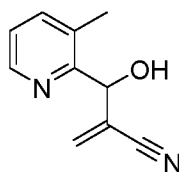
Intermediate A9: ethyl 2-[hydroxy(4-methylpyridin-2-yl)methyl]prop-2-enoate

15

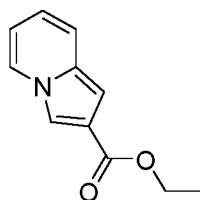


Prepared similarly to intermediate A1 starting from 4-methylpyridine-2-carbaldehyde (1.0 g, 8.26 mmol) stirring at r.t. overnight, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.970 g, 4.38 mmol, 53% yield). MS/ESI⁺ 222.2 [MH]⁺, Rt = 0.39 min (Method A).

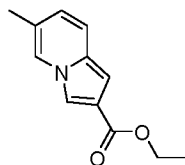
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Intermediate A7: 2-[hydroxy(3-methylpyridin-2-yl)methyl]prop-2-enitrile

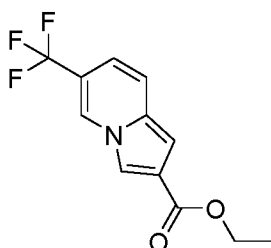
Prepared similarly to intermediate A5, starting from 3-methylpyridine-2-carbaldehyde (0.500 g, 4.12 mmol), and purified by flash chromatography on silica gel Biotage cartridge SNAP (cyclohexane: EtOAc = 80 : 20 to 70:30) yielding title compound as a white solid (0.380 g, 2.18 mmol, 53% yield). MS/ESI⁺ 175.0 [MH]⁺, Rt = 0.31 min (Method A).

Intermediate B1: ethyl indolizine-2-carboxylate

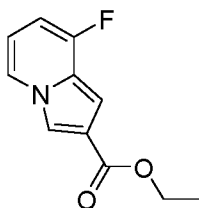
A solution of ethyl 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enoate A1 (17.9 g, 86.4 mmol) in acetic anhydride (150 mL) was split in ten vials and heated under MW irradiation at 130°C for 45 minutes (each one). The batches were combined, the volatiles were removed under reduced pressure and the crude was partitioned between EtOAc and aqueous sat. NaHCO₃. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography on silica gel (340 g) Biotage SNAP column (cyclohexane to cyclohexane: EtOAc = 90 : 10) to afford title compound as a white-yellow solid (10.91 g, 57.6 mmol, 67% yield). MS/ESI⁺ 190.1 [MH]⁺, Rt = 0.99 min (Method A).

Intermediate B2: ethyl 6-methylindolizine-2-carboxylate

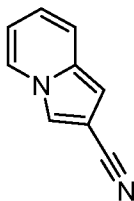
Prepared similarly to intermediate B1, starting from ethyl 2-[hydroxy(5-methylpyridin-2-yl)methyl]prop-2-enoate A2 (0.860 g, 3.88 mmol) and acetic anhydride (6.6 mL), heating under MW irradiation at 130°C for 1 h. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane: EtOAc = 95 : 5 to 80 : 20) affording title compound as a light-yellow solid (0.410 g, 2.01 mmol, 52% yield). MS/ESI⁺ 204.1 [MH]⁺, Rt = 1.12 min (Method A).

Intermediate B3: ethyl 6-(trifluoromethyl)indolizine-2-carboxylate

A solution of ethyl 2-{hydroxy[5-(trifluoromethyl)pyridin-2-yl]methyl}prop-2-enoate A3 (0.450 g, 1.64 mmol) in acetic anhydride (5 mL) was heated at 130°C overnight. The volatiles were removed under reduced pressure and the crude was partitioned between EtOAc and aqueous sat. NaHCO₃; the aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure. The crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane: EtOAc = 85 : 15) to afford title compound (0.240 g, 0.933 mmol, 60% yield). MS/ESI⁺ 258.1 [MH]⁺, Rt = 1.19 min (Method A).

Intermediate B4: ethyl 8-fluoroindolizine-2-carboxylate

A solution of ethyl 2-[(3-fluoropyridin-2-yl)(hydroxy)methyl]prop-2-enoate A4
5 (0.900 g, 4.00 mmol) in acetic anhydride (7 mL) was heated under MW irradiation at 130°C for 45 min. The volatiles were removed under reduced pressure and the crude was partitioned between EtOAc and sat. NaHCO₃. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography
10 on silica gel Biotage SNAP cartridge (cyclohexane: EtOAc = 90 : 10 to 80 : 20) affording title compound (0.228 g, 1.10 mmol). Crude starting intermediate A4 was recovered and further reacted in acetic anhydride (3 mL) heating under MW irradiation at 130°C for 45 min. The solvent was removed and the residue was purified by flash chromatography on silica gel (25 g) Biotage SNAP cartridge (cyclohexane: EtOAc = 90 : 10 to 80 : 20) to afford
15 title compound (0.230 g, 1.11 mmol). The two batches were combined to give the title compound (0.458 g, 2.21 mmol, 55% yield overall). MS/ESI⁺ 208.0 [MH]⁺, Rt = 1.05 min (Method A).

Intermediate B5: indolizine-2-carbonitrile

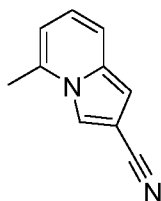
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Prepared similarly to intermediate B1, starting from 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enenitrile A5 (5.88 g, 36.7 mmol) in acetic anhydride (62.5 mL), heating under MW irradiation at 130°C for 1.5 h, and purified by flash chromatography on silica

gel Biotage SNAP cartridge (cyclohexane to cyclohexane: EtOAc = 90 : 10) affording title compound as a yellow solid (2.588 g, 18.2 mmol, 50% yield). MS/ESI⁺ 143.0 [MH]⁺, Rt = 0.88 min (Method A).

Intermediate B6: 5-methylindolizine-2-carbonitrile

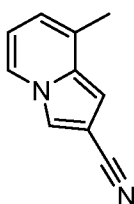
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Prepared similarly to intermediate B1, starting from 2-[hydroxy(6-methylpyridin-2-yl)methyl]prop-2-enenitrile A6 (1.0 g, 5.74 mmol) and acetic anhydride (8 mL), heating under MW irradiation at 130°C for 2.5 h. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 95 : 5) to afford title compound as a white solid (0.567 g, 3.63 mmol, 63% yield). MS/ESI⁺ 157.0 [MH]⁺, Rt = 0.98 min (Method A).

10

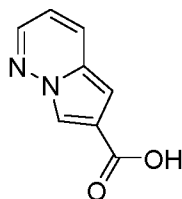
Intermediate B7: 8-methylindolizine-2-carbonitrile



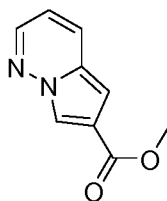
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Prepared similarly to intermediate B1, starting from 2-[hydroxy(3-methylpyridin-2-yl)methyl]prop-2-enenitrile A7 (0.380 g, 2.18 mmol) and acetic anhydride (3.8 mL), heating under MW irradiation at 130°C for 1 h. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 95 : 5) affording title compound as a white solid (0.245 g, 1.56 mmol, 72% yield). MS/ESI⁺ 157.0 [MH]⁺, Rt = 0.99 min (Method A).

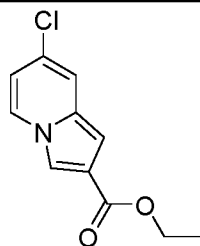
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Intermediate B8: pyrrolo[1,2-b]pyridazine-6-carboxylic acid

7-tert-butyl 5,6-dimethyl pyrrolo[1,2-b]pyridazine-5,6,7-tricarboxylate, prepared
5 accordingly to the procedure reported in *J. Mat. Chem.*, 1999, 9, 2183 - 2188, (3.25 g, 9.72
mmol) was suspended in a solution of KOH (2.727 g, 48.6 mmol) in water (12 mL) and the
reaction was heated at 60°C overnight. The mixture was acidified by addition of aqueous
conc. HCl (9.41 mL) until pH = 1 and stirred at 80 °C overnight. After cooling to room
temperature the precipitated was collected by filtration to afford title compound (1.52 g,
10 9.37 mmol, 96% yield). MS/ESI⁺ 163.1 [MH]⁺, Rt = 0.61 min (Method A).

Intermediate B9: methyl pyrrolo[1,2-b]pyridazine-6-carboxylate

To a solution of pyrrolo[1,2-b]pyridazine-6-carboxylic acid B8 (1.52 g, 9.37 mmol)
15 in MeOH (110 mL), concentrated sulfuric acid (6 drops) was added and the mixture was
stirred at 80°C for 6 h. The solvent was evaporated under reduced pressure and the residue
was dissolved in DCM and washed with aqueous sat. NaHCO₃. The organic phase was
dried over sodium sulfate, the solvent was removed and the crude was purified by flash
chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 85 : 15 to
20 80 : 20) to afford title compound (1.0 g, 5.67 mmol, 61% yield). MS/ESI⁺ 177.1 [MH]⁺, Rt
= 0.81 min (Method A).

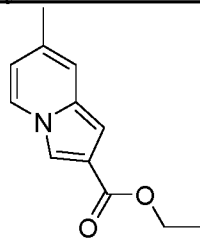
Intermediate B10: ethyl 7-chloroindolizine-2-carboxylate

Here and in the following examples when the title compound was obtained combining crude obtained from more than 1 synthetic batch (e.g. 2 batches), the amount of
5 any precursor in each batch was sometimes indicated as a sum in parenthesis (e.g. amount precursor in batch 1+ amount precursor in batch 2).

The crudes from the individual batches were finally mixed in a “combined crude” and a total yield over the two (or more) batches was reported.

A solution of ethyl 2-[(4-chloropyridin-2-yl)(hydroxy)methyl]prop-2-enoate A8
10 (0.500 g+1.25 g) in acetic anhydride (5 mL+7 mL) was heated at 120°C for 1 h. The volatiles were removed under reduced pressure and the crude was partitioned between EtOAc and aqueous sat. NaHCO₃; the aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure.

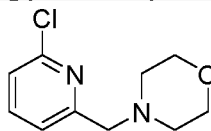
15 Combined crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound (1.07 g, 4.78 mmol). MS/ESI⁺ 224.2 [MH]⁺, Rt = 1.15 min (Method A).

Intermediate B11: ethyl 7-methylindolizine-2-carboxylate

20 Prepared similarly to intermediate B10 starting from ethyl 2-[hydroxy(4-methylpyridin-2-yl)methyl]prop-2-enoate A9 (0.7500.850 g, 3.393.842 mmol + 0.100 g, 0.452 mmol) in acetic anhydride (98 mL + 1 mL) and purified by flash chromatography on

Biotage silica gel cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a white solid (0.280 g, 1.38 mmol, 36% yield). MS/ESI⁺ 204.1 [MH]⁺, Rt = 1.12 min (Method A).

Intermediate BA1: 4-[(6-chloropyridin-2-yl)methyl]morpholine



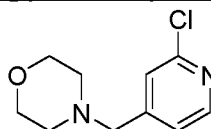
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To a solution of 6-chloropyridine-2-carbaldehyde (1.0 g, 7.06 mmol) in DCM (28 mL), morpholine (0.93 mL, 10.59 mmol) and 30 drops of AcOH were added. The mixture was stirred overnight at room temperature and then Na(OAc)₃BH (2.24 g, 10.59 mmol) was added and the mixture was stirred for 6 h. The reaction was quenched with sat. NaHCO₃, the organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to afford title compound as a pale yellow oil (1.45 g, 6.82 mmol, 97%).

10

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.60 - 7.76 (m, 1 H), 7.41 (d, 1 H), 7.22 (d, 1 H), 3.70 - 3.79 (m, 4 H), 3.65 (s, 2 H), 2.49 - 2.58 (m, 4 H).

Intermediate BA2: 4-[(2-chloropyridin-4-yl)methyl]morpholine



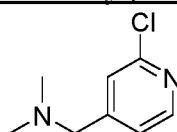
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Prepared similarly to intermediate BA1 starting from 2-chloropyridine-4-carbaldehyde (1.0 g, 7.06 mmol) and morpholine (0.93 mL, 10.59 mmol) to afford title compound as a pale yellow oil (1.4 g, 6.58 mmol, 93 % yield).

20

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.32 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.22 (d, 1 H), 3.70 - 7.77 (m, 4 H), 3.49 (s, 2 H), 2.42 - 2.50 (m, 4 H)

Intermediate BA3: [(2-chloropyridin-4-yl)methyl]dimethylamine

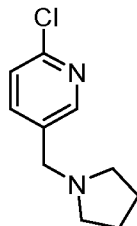


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Prepared similarly to intermediate BA1 starting from 2-chloropyridine-4-carbaldehyde (1.0 g, 7.06 mmol) and 2M dimethylamine in THF (5.30 mL, 10.59 mmol) to afford title compound as a pale yellow oil (1.20 g, 7.03 mmol, 99% yield).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.68 (d, 1 H), 7.75 (s, 1 H), 7.66 - 7.70 (m, 1 H), 3.78 (s, 2 H), 2.50 (s, 6 H)

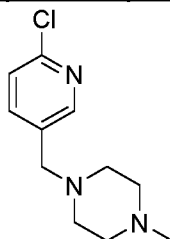
Intermediate BA4: 2-chloro-5-(pyrrolidin-1-ylmethyl)pyridine



5 Prepared similarly to intermediate BA1 starting from 6-chloropyridine-3-carbaldehyde (1.0 g, 7.06 mmol) and pyrrolidine (0.88 mL, 10.59 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound as a colorless oil (0.972 g, 4.94 mmol, 70 % yield).

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.32 (d, 1 H), 7.70 - 7.79 (m, 1 H),
10 7.30 (d, 1 H), 3.65 (s, 2 H), 2.49 - 2.62 (m, 4 H), 1.77 - 1.89 (m, 4 H).

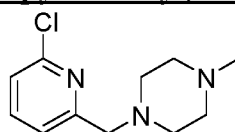
Intermediate BA5: 1-[(6-chloropyridin-3-yl)methyl]-4-methylpiperazine



Prepared similarly to intermediate BA1 starting from 6-chloropyridine-3-carbaldehyde (3.0 g, 21.19 mmol) and 1-methylpiperazine (4.7 mL, 42.38 mmol) to afford
15 title compound as an orange oil (4.8 g) which was used without purification.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.30 (d, 1 H), 7.76 (dd, 1 H), 7.47 (d, 1 H), 3.48 (s, 2 H), 2.21 - 2.44 (m, 8 H), 2.14 (s, 3 H).

Intermediate BA6: 1-[(6-chloropyridin-2-yl)methyl]-4-methylpiperazine

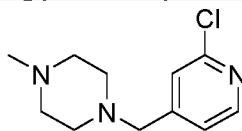


20 Prepared similarly to intermediate BA1 starting from 6-chloropyridine-2-carbaldehyde (1.0 g, 7.06 mmol) and 1-methylpiperazine (1.18 mL, 10.6 mmol) to afford

title compound as a pale yellow oil (1.54 g, 6.82 mmol, 97 % yield).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.80 - 7.85 (m, 1 H), 7.42 (d, 1 H), 7.38 (d, 1 H), 3.54 (s, 2 H), 2.20 - 2.48 (m, 8 H), 2.15 (s, 3 H).

Intermediate BA7: 1-[(2-chloropyridin-4-yl)methyl]-4-methylpiperazine



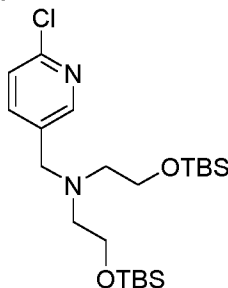
5

Prepared similarly to intermediate BA1 starting from 2-chloropyridine-4-carbaldehyde (1.0 g, 7.06 mmol) and 1-methylpiperazine (1.18 mL, 10.6 mmol) to afford title compound as a pale yellow oil (1.37 g, 6.07 mmol, 86 % yield).

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.29 - 8.33 (m, 1 H), 7.33 - 7.36 (m, 1 H), 7.18 - 7.23 (m, 1 H), 3.50 (s, 2 H), 2.33 - 2.65 (m, 8 H), 2.31 (s, 3 H).

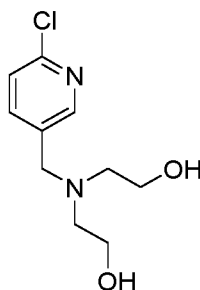
10

Intermediate BA8: 2-chloro-5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatriodecan-7-yl)methyl]pyridine



Step 1: 2-[(6-chloropyridin-3-yl)methyl]-(2-hydroxyethyl)amino}ethan-1-ol

15 **BA8a**



Prepared similarly to intermediate BA1 starting from 6-chloropyridine-3-carbaldehyde (1.2 g, 8.48 mmol) and 2-[(2-hydroxyethyl)amino]ethan-1-ol (1.22 mL, 12.72 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound as a colorless oil (0.680 g).

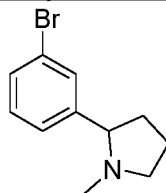
20

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.35 (d, 1 H), 7.83 (dd, 1 H), 7.45 (d, 1 H), 4.37 (t, 2 H), 3.67 (s, 2 H), 3.40 - 3.48 (m, 4 H), 2.52 (t, 4 H)

Step 2: 2-chloro-5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)methyl]pyridine BA8

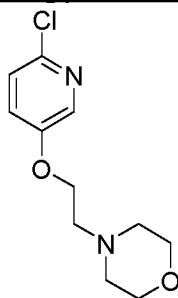
5 2-[[[(6-Chloropyridin-3-yl)methyl](2-hydroxyethyl)amino}ethan-1-ol BA8a (0.880 g) was dissolved in DCM (10 mL); imidazole (1.3 g, 19.05 mmol) and tert-butyl(chloro)dimethylsilane (1.44 g, 9.53 mmol) were added and the mixture was stirred at r.t. overnight. The mixture was washed with water, then with brine, the organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude
10 was purified by flash chromatography on silica-NH Biotage column (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a colorless oil (1.3 g). MS/ESI⁺ 459.5 [MH]⁺, Rt = 1.24 min (Method A).

Intermediate BA9: 2-(3-bromophenyl)-1-methylpyrrolidine

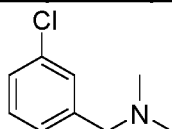


15 To a solution of 2-(3-bromophenyl)pyrrolidine (4.0 g, 17.69 mmol) in MeOH (120 mL), aqueous formaldehyde solution (37 wt. %) (2.63 mL, 35.38 mmol) and 20 drops of AcOH were added followed by Na(OAc)₃BH (7.5 g, 35.38 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was then quenched with aqueous sat. NaHCO₃ and extracted with DCM; the organic layer was washed with brine, dried over
20 Na₂SO₄ and concentrated to afford title compound as colorless oil (4.06 g, 16.91 mmol, 96 % Yield).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.49 - 7.51 (m, 1 H), 7.40 - 7.44 (m, 1 H), 7.25 - 7.34 (m, 2 H), 3.11 - 3.17 (m, 1 H), 3.07 (t, 1 H), 2.23 (q, 1 H), 2.10 - 2.20 (m, 1 H), 2.08 (s, 3 H), 1.68 - 1.88 (m, 2 H), 1.48 - 1.58 (m, 1 H).

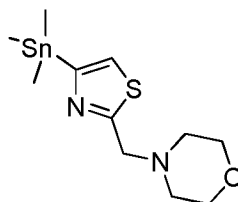
Intermediate BA10: 4-{2-[(6-chloropyridin-3-yl)oxy]ethyl}morpholine

To a stirred solution of PPh_3 (4.22 g, 16.1 mmol) in THF (55 mL) cooled at 0°C , DEAD 97% (3 mL, 16.1 mmol) was added and the mixture was stirred for 15 min. Then a solution of 4-(2-hydroxyethyl)morpholine (1.96 mL, 16.1 mmol) in THF (16 mL) was added followed by 2-chloro-5-hydroxypyridine (1.5 g, 11.5 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. The solvent was removed and the residue was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford a title compound a pink oil (2.722 g, 11.2 mmol, 97% yield). MS/ESI⁺ 243.3 [MH]⁺, Rt = 0.71 min (Method J).

Intermediate BA11: [(3-chlorophenyl)methyl]dimethylamine

Prepared similarly to intermediate BA1 starting from 3-chlorobenzaldehyde (4.0 mL, 35.28 mmol) and 2M dimethylamine solution in THF (35.28 mL, 70.56 mmol) to afford title compound as a pale yellow oil (5.8 g, 34.18 mmol, 97 % yield).

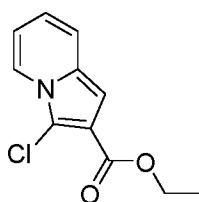
¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.28 - 7.37 (m, 3 H), 7.22 - 7.27 (m, 1 H), 3.38 (s, 2 H), 2.14 (s, 6 H).

Intermediate BB1: 4-{[4-(trimethylstannyl)-1,3-thiazol-2-yl]methyl}morpholine

A mixture of 4-[(4-bromo-1,3-thiazol-2-yl)methyl]morpholine (prepared

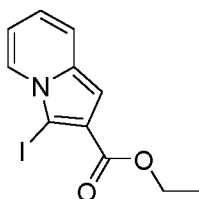
accordingly to the procedure reported in the patent **US2009/143372 A1**, 2.18 g, 8.28 mmol), hexamethylditin (17.2 mL, 82.8 mmol) and Pd(PPh₃)₄ (0.957 g, 0.828 mmol) in toluene (83 mL) was heated at 100°C for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica-NH Biotage cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound as a yellow oil (2.18 g, 6.28 mmol, 76% yield). MS/ESI⁺ 349.1 [MH]⁺, Rt = 0.59 min (Method A).

Intermediate C: ethyl 3-chloroindolizine-2-carboxylate



Ethyl indolizine-2-carboxylate B1 (2.00 g, 10.5 mmol) and N-chlorosuccinimide (1.69 g, 12.7 mmol) were dissolved in MeCN (320 mL) and the reaction was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure, the residue was diluted with water and extracted with EtOAc. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 :10); a further purification by reverse phase flash chromatography on 60 g Biotage C-18 cartridge. (H₂O + 0.1% HCOOH : CH₃CN + 0.1% HCOOH = 95 : 5 to 50 : 50) was required to afford title compound as a yellow green oil (1.642 g, 7.34 mmol, 70% yield). MS/ESI⁺ 224.1 [MH]⁺, Rt = 1.17 min (Method A).

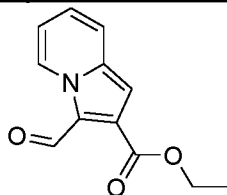
Intermediate D: ethyl 3-iodoindolizine-2-carboxylate



Ethyl indolizine-2-carboxylate B1 (0.400 g, 2.11 mmol) and N-iodosuccinimide (0.523 g, 2.3 mmol) were dissolved in MeCN (65 mL) and the reaction was stirred for 30

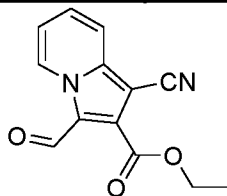
min at 0 °C. The reaction mixture was diluted with DCM and washed with aqueous sodium thiosulfate. The resulting organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford
5 title compound as a yellow oil (0.626 g, 1.98 mmol, 94% yield). MS/ESI⁺ 316.1 [MH]⁺, Rt = 1.21 min (Method A).

Intermediate DA1: ethyl 3-formylindolizine-2-carboxylate



A solution of POCl₃ (4.07 mL, 44.85 mmol) in DMF (146 mL) was stirred at 0°C
10 for 1 h. To a stirred solution of ethyl indolizine-2-carboxylate B1 (5.000 g, 26.4 mmol) in dry DCM (588 mL), 2/3 of the previously prepared POCl₃ solution in DMF (1.1 eq.) was added at 0°C. After being stirred at RT for 1 h, the reaction mixture was quenched with aqueous sat. NaHCO₃ (350 mL) and diluted with DCM (200 mL). The organic layer was washed with water (300 mL), dried over sodium sulfate and concentrated under reduced
15 pressure. The residue was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as a yellow-green solid (4.342 g, 19.99 mmol, 76% yield). MS/ESI⁺ 218.0 [MH]⁺, Rt = 0.99 min (Method A).

Intermediate DA2: ethyl 1-cyano-3-formylindolizine-2-carboxylate

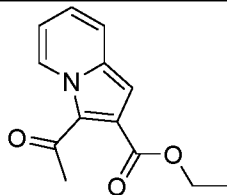


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Prepared similarly to intermediate DA1 starting from ethyl 1-cyanoindolizine-2-carboxylate (prepared as reported in Journal of the Chemical Society, 1965, 2948 - 2951, 1.4 g, 6.1 mmol), and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a

light-yellow solid (1.21 g, 4.99 mmol, 81% yield). MS/ESI⁺ 243.2 [MH]⁺, Rt = 0.97 min (Method A).

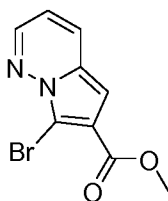
Intermediate DB: ethyl 3-acetylindolizine-2-carboxylate



5 A solution of ethyl indolizine-2-carboxylate B1 (2.0 g, 10.5 mmol) and sodium acetate (4.3 g, 52.5 mmol) in acetic anhydride (60 mL) was heated at 140°C overnight. Additional sodium acetate (1 eq) was added and the reaction was stirred at same temperature for further 4 h. The reaction was diluted with EtOAc and washed with water and brine. The aqueous phase was extracted with EtOAc and the combined organic layers
10 were dried over sodium sulphate. The solvent was evaporated and the crude was purified by flash chromatography on silica gel Biotage column (cyclohexane to cyclohexane : EtOAc = 90 : 10) affording title compound as a yellow solid (1.78 g, 7.7 mmol, 73 % yield). MS/ESI⁺ 232.2 [MH]⁺, Rt = 1.03 min (Method A).

Intermediate E: methyl 7-bromopyrrolo[1,2-b]pyridazine-6-carboxylate

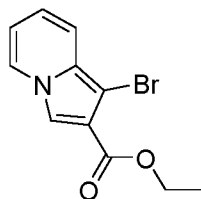
15



Methyl pyrrolo[1,2-b]pyridazine-6-carboxylate B9 (0.500 g, 2.83 mmol) and N-bromosuccinimide (0.606 g, 3.4 mmol) were dissolved in MeCN (85.5 mL) and the reaction was stirred for 30 min at RT. The mixture was concentrated under reduced
20 pressure, the residue was diluted with water and extracted with EtOAc. The organic layer was washed with a saturated solution of sodium thiosulfate, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by reverse phase flash chromatography on Biotage C18 cartridge (H₂O + 0.1% HCOOH : MeCN + 0.1% HCOOH = 90 : 10 to 50 : 50) to afford title compound as a pale yellow solid (0.425 g, 1.66 mmol,

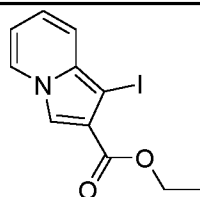
58% yield). MS/ESI⁺ 255.0 - 257.0 [MH]⁺, Rt = 0.91 min (Method A).

Intermediate F: ethyl 1-bromoindolizine-2-carboxylate

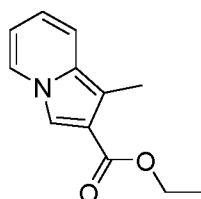


5 0.5 M Bromine in DCM (9.5 mL, 4.75 mmol) was slowly added to a solution of ethylindolizine-2-carboxylate B1 (1.00 g, 5.28 mmol) in DCM at -78 °C. After 0.5 h the reaction was quenched with water; the organic phase was separated, washed with aqueous 10% sodium thiosulfate and dried over sodium sulfate. The volatiles were removed under reduced pressure and the crude mixture was purified by flash chromatography on a silica
10 gel Biotage SNAP cartridge (cyclohexane : EtOAc = 95 : 5) affording title compound as a white-yellow solid (0.908 g, 3.38 mmol, 64% yield). This intermediate was stored at -20 °C under nitrogen atmosphere. MS/ESI⁺ 268.0 – 270.0 [MH]⁺, Rt = 1.13 min (Method A).

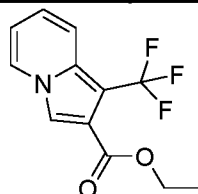
Intermediate FA: ethyl 1-iodoindolizine-2-carboxylate



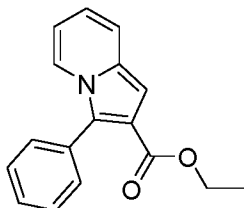
15 To a solution of ethyl 1-bromoindolizine-2-carboxylate F (0.700 g, 2.61 mmol) in anhydrous DMF (7 ml), KI (1.299 g, 7.84 mmol) and CuI (1.490 g, 7.84 mmol) were added and the mixture was stirred at 130 °C overnight. The mixture was cooled to RT, diluted with EtOAc and washed with aqueous 10% sodium thiosulfate. The organic phase was
20 washed with brine, dried over sodium sulfate and concentrated; the residue was purified by flash chromatography on silica gel Biotage column (cyclohexane : EtOAc = 98 : 2 to 95 : 5) affording title compound as a white-yellow solid (0.595 g) which was stored at -20°C under nitrogen atmosphere. MS/ESI⁺ 316.1 [MH]⁺, Rt = 1.24 min (Method A).

Intermediate G: ethyl 1-methylindolizine-2-carboxylate

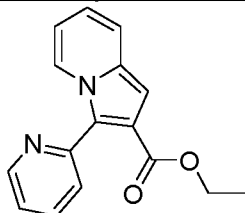
Ethyl 1-bromoindolizine-2-carboxylate F (1.156 g, 4.31 mmol) was split in three
5 vials; trimethylboroxine (0.390 ml, 2.87 mmol), potassium carbonate (0.597 g,
4.32 mmol), Pd(PPh₃)₄ (0.173 g 0.15 mmol) and 4.4 mL of dioxane/H₂O (10/1) were added
in each vial at RT, the mixtures were degassed and then heated at 110°C overnight. The
mixtures were combined and extracted with DCM; the organic phase was washed with
brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The
10 crude was purified by flash chromatography on silica gel Biotage SNAP cartridge
(cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound (0.396 g, 1.95
mmol, 45% yield). MS/ESI⁺ 204.1 [MH]⁺, Rt = 1.14 min (Method A).

Intermediate GA: ethyl 1-(trifluoromethyl)indolizine-2-carboxylate

15 KF (0.369 g, 6.38 mmol) and CuI (1.214 g, 6.38 mmol) were thoroughly mixed in
a Schlenk tube and flame heated under gentle shaking at reduced pressure until a greenish
color appeared. Ethyl 1-iodoindolizine-2-carboxylate FA (0.670 g), anhydrous DMF (2.7
mL) and NMP (2.7 ml) were added followed by trimethyl(trifluoromethyl)silane (0.943 ml,
6.38 mmol) and the slurry solution was stirred at RT overnight. The mixture was quenched
20 with water and extracted with Et₂O, the organic phase was washed with brine, dried over
sodium sulphate, filtered and concentrated under reduced pressure. The residue was
purified by flash chromatography on silica gel Biotage column (cyclohexane : EtOAc = 95
: 5 to 90 : 10) to afford title compound (0.360 g, 1.4 mmol). MS/ESI⁺ 258.2 [MH]⁺, Rt =
1.17 min (Method A).

Intermediate H1 ethyl 3-phenylindolizine-2-carboxylate

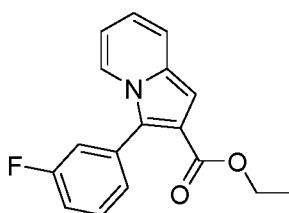
Ethyl indolizine-2-carboxylate B1 (0.500 g, 2.645 mmol), bromobenzene
5 (0.338 mL, 3.175 mmol), KOAc (0.519 g, 5.29 mmol) and Pd(PPh₃)₂Cl₂ (0.093 g, 0.132 mmol) in NMP (5.3 mL) were reacted under nitrogen at 100°C for 10 min, then water (0.095 mL, 5.29 mmol) was added and the reaction was further stirred for 6.5 h. Additional bromobenzene (0.170 mL, 1.59 mmol) was added followed by Pd(PPh₃)₂Cl₂ (0.045 g, 0.064 mmol) and the mixture was stirred at that temperature overnight. Further Pd(PPh₃)₂Cl₂
10 (0.045 g, 0.064 mmol) was added and the heating was continued for 3 h. The mixture was cooled to room temperature and then partitioned between EtOAc and brine. The organic phase was washed several times with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on Biotage silica gel SNAP column (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford
15 title compound as a yellow solid (0.477 g, 1.80 mmol, 68% yield). MS/ESI⁺ 266.1 [MH]⁺, Rt = 1.25 min (Method B).

Intermediate H2: ethyl 3-(pyridin-2-yl)indolizine-2-carboxylate

A mixture of ethyl indolizine-2-carboxylate B1 (0.567 g, 3.00 mmol), Pd(OAc)₂
20 (0.034 g, 0.15 mmol), tricyclopentylphosphine tetrafluoroborate (0.098 g, 0.30 mmol) and Cs₂CO₃ (2.932 g, 9.00 mmol) was flushed with nitrogen and toluene (5.5 mL) was added followed by 2-chloropyridine (0.568 mL, 6.00 mmol). The mixture was stirred at RT for 10 min and then heated at 130°C overnight. Additional Pd(OAc)₂ (0.034 g, 0.15 mmol)

and tricyclopentylphosphine tetrafluoroborate (0.098 g, 0.30 mmol) were added at RT followed by 2-chloropyridine (0.085 mL, 0.9 mmol) and the reaction was heated at 130°C for further 24 h. The mixture was diluted with DCM and filtered through a celite pad. The filtrate was evaporated to dryness and the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 85 : 15) yielding title compound as a yellow solid (0.555 g, 2.08 mmol, 69% yield). MS/ESI⁺ 267.1 [MH]⁺, Rt = 0.91 min (Method A).

Intermediate H3: ethyl 3-(3-fluorophenyl)indolizine-2-carboxylate

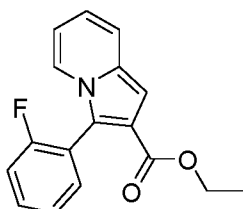


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Prepared similarly to intermediate H2 starting from ethyl indolizine-2-carboxylate B1 (0.200 g, 1.06 mmol), Pd(OAc)₂ (0.012 g, 0.053 mmol), tricyclopentylphosphine tetrafluoroborate (0.035 g, 0.106 mmol), Cs₂CO₃ (1.036 g, 3.18 mmol), toluene (3 mL) and 1-bromo-3-fluorobenzene (0.236 mL, 2.12 mmol), at 130°C for 20 h. Additional tricyclopentylphosphine tetrafluoroborate (0.035 g, 0.106 mmol), Pd(OAc)₂ (0.012 g, 0.053 mmol) and 1-bromo-3-fluorobenzene (0.080 mL, 0.716 mmol) were added and the reaction was heated at the same temperature for further 4 h. After work-up the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow oil (0.255 g, 0.900 mmol, 85% yield). MS/ESI⁺ 284.1 [MH]⁺, Rt = 1.26 min (Method B).

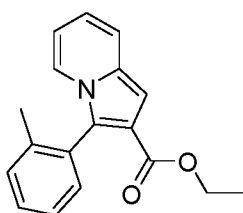
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Intermediate H4: ethyl 3-(2-fluorophenyl)indolizine-2-carboxylate



Prepared similarly to intermediate H2, using ethyl indolizine-2-carboxylate B1 (0.500 g, 2.643 mmol), Pd(OAc)₂ (0.030 g, 0.132 mmol), tricyclopentylphosphine tetrafluoroborate (0.086 g, 0.265 mmol), Cs₂CO₃ (2.583 g, 7.935 mmol), toluene (5.2 mL) and 1-chloro-2-fluorobenzene (0.555 mL, 5.29 mmol), at 130°C for 40 h. The crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to give title compound as a pale yellow oil (0.640 g, 2.26 mmol, 85% yield). MS/ESI⁺ 284.1 [MH]⁺, Rt = 1.22 min (Method A).

Intermediate H5: ethyl 3-(2-methylphenyl)indolizine-2-carboxylate

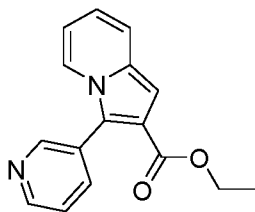


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Prepared similarly to intermediate H2, using ethyl indolizine-2-carboxylate B1 (0.500 g, 2.645 mmol), Pd(OAc)₂ (0.030 g, 0.132 mmol), tricyclopentylphosphine tetrafluoroborate (0.086 g, 0.265 mmol), Cs₂CO₃ (2.583 g, 7.935 mmol), toluene (5.2 mL) and 2-chlorotoluene (0.618 mL, 5.29 mmol), at 130°C overnight. After work-up the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to give title compound as a pale yellow oil (0.770 g). MS/ESI⁺ 280.2 [MH]⁺, Rt = 1.32 min (Method A).

15

Intermediate H6: ethyl 3-(pyridin-3-yl)indolizine-2-carboxylate

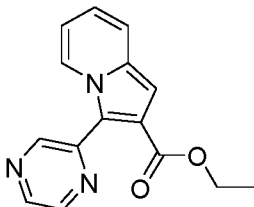


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Prepared similarly intermediate H2, using ethyl indolizine-2-carboxylate B1 (0.300 g, 1.585 mmol), Pd(OAc)₂ (0.018 g, 0.079 mmol), tricyclopentylphosphine tetrafluoroborate (0.052 g, 0.158 mmol), Cs₂CO₃ (1.549 g, 4.755 mmol), toluene (1.8 mL)

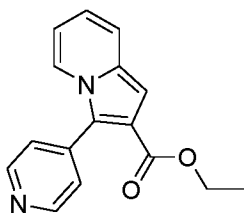
and 3-chloropyridine (0.302 mL, 3.171 mmol), at 130°C overnight. After work-up the crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane : EtOAc = 90 : 10 to 50 : 50) to afford title compound as a pale yellow oil (0.346 g, 1.299 mmol, 82% yield). MS/ESI⁺ 267.1 [MH]⁺, Rt = 0.81 min (Method A).

5 **Intermediate H7: ethyl 3-(pyrazin-2-yl)indolizine-2-carboxylate**



Prepared similarly to intermediate H2, using ethyl indolizine-2-carboxylate B1 (0.300 g, 1.585 mmol), Pd(OAc)₂ (0.018 g, 0.079 mmol), tricyclopentylphosphine tetrafluoroborate (0.052 g, 0.158 mmol), Cs₂CO₃ (1.549 g, 4.755 mmol), toluene (3 mL) and 2-chloropyrazine (0.283 mL, 3.171 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.018 g, 0.079 mmol), tricyclopentylphosphine tetrafluoroborate (0.052 g, 0.158 mmol) and 2-chloropyrazine (0.283 mL, 3.171 mmol) were added continuing the heating for further 24 h. Additional Pd(OAc)₂ (0.018 g, 0.079 mmol), tricyclopentylphosphine tetrafluoroborate (0.052 g, 0.158 mmol) and 2-chloropyrazine (0.283 mL, 3.171 mmol) were added heating at the same temperature for further 48 h. After work-up the crude was purified by flash chromatography on Biotage silica SNAP gel cartridge (cyclohexane : EtOAc = 90 : 10 to 70 : 30) to afford title compound as a yellow solid (0.100 g, 0.374 mmol, 24% yield). MS/ESI⁺ 268.1 [MH]⁺, Rt = 0.98 min (Method A).

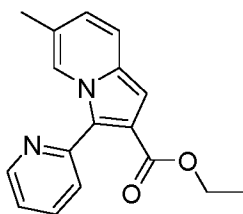
20 **Intermediate H8: ethyl 3-(pyridin-4-yl)indolizine-2-carboxylate**



Prepared similarly to intermediate H2, using ethyl indolizine-2-carboxylate B1

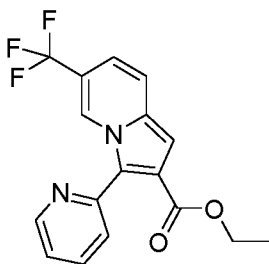
(0.250 g, 1.32 mmol), Pd(OAc)₂ (0.015 g, 0.066 mmol), tricyclopentylphosphine tetrafluoroborate (0.043 g, 0.132 mmol), Cs₂CO₃ (1.290 g, 3.96 mmol), toluene (2.5 mL) and 4-chloropyridine (0.300 g, 2.64 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.015 g, 0.066 mmol) and tricyclopentylphosphine tetrafluoroborate (0.043 g, 0.132 mmol) were added continuing the heating for further 24 h. After work-up the crude was purified by flash chromatography on Biotage silica SNAP gel cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow solid (0.250 g, 0.939 mmol, 71% yield). MS/ESI⁺ 267.2 [MH]⁺, Rt = 0.66 min (Method A).

Intermediate H9: ethyl 6-methyl-3-(pyridin-2-yl)indolizine-2-carboxylate



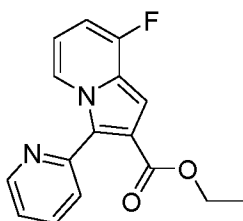
Prepared similarly to intermediate H2, using ethyl 6-methylindolizine-2-carboxylate B2 (0.410 g, 2.01 mmol), Pd(OAc)₂ (0.045 g, 0.201 mmol), tricyclopentylphosphine tetrafluoroborate (0.131 g, 0.402 mmol), Cs₂CO₃ (1.964 g, 6.03 mmol), toluene (3.5 mL) and 2-chloropyridine (0.380 mL, 4.02 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.045 g, 0.201 mmol) and tricyclopentylphosphine tetrafluoroborate (0.131 g, 0.402 mmol) were added at RT and the mixture was heated at 130°C for further 2 h. After work-up, the crude was purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane : EtOAc = 95 : 5 to 90 : 10) to afford title compound as a light-yellow solid (0.115 g, 0.41 mmol, 20% yield). MS/ESI⁺ 281.2 [MH]⁺, Rt = 1.00 min (Method A).

Intermediate H10: ethyl 3-(pyridin-2-yl)-6-(trifluoromethyl)indolizine-2-carboxylate



Prepared similarly to intermediate H2, using ethyl 6-(trifluoromethyl)indolizine-2-carboxylate B3 (0.240 g, 0.933 mmol), Pd(OAc)₂ (0.011 g, 0.047 mmol), tricyclopentylphosphine tetrafluoroborate (0.030 g, 0.093 mmol), Cs₂CO₃ (0.912 g, 2.800 mmol), toluene (1.5 mL) and 2-chloropyridine (0.177 mL, 1.866 mmol), at 130°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane: EtOAc = 90 : 10) to afford title compound as a yellow solid (0.255 g, 0.763 mmol, 82% yield). MS/ESI⁺ 335.2 [MH]⁺, Rt = 1.24 min (Method A).

Intermediate H11: ethyl 8-fluoro-3-(pyridin-2-yl)indolizine-2-carboxylate

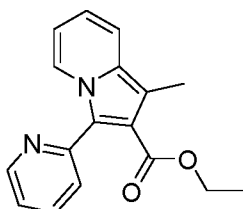


Prepared similarly to intermediate H2, using ethyl 8-fluoroindolizine-2-carboxylate B4 (0.458 g, 2.21 mmol), Pd(OAc)₂ (0.025 g, 0.11 mmol), tricyclopentylphosphine tetrafluoroborate (0.073 g, 0.22 mmol), Cs₂CO₃ (2.160 g, 6.63 mmol), toluene (3 mL) and 2-chloropyridine (0.418 mL, 4.42 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.050 g, 0.22 mmol) and tricyclopentylphosphine tetrafluoroborate (0.146 g, 0.44 mmol) were added at RT and the mixture was heated at 130°C for further 24 h. After work-up, the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 85 : 15); a further purification by flash chromatography on

Biotage silica gel SNAP cartridge (DCM : EtOAc = 98 : 2) was required to obtain title compound as a pale yellow solid (0.140 g, 0.49 mmol, 22% yield). MS/ESI⁺ 285.1 [MH]⁺, Rt = 1.05 min (Method A).

Intermediate H12: ethyl 1-methyl-3-(pyridin-2-yl)indolizine-2-carboxylate

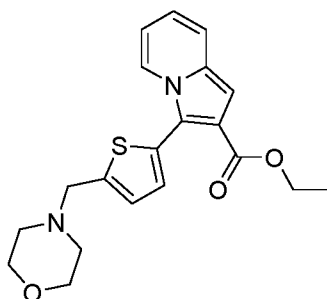
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Prepared similarly to intermediate H2, using ethyl 1-methylindolizine-2-carboxylate G (0.206 g, 0.96 mmol), Pd(OAc)₂ (0.011 g, 0.048 mmol), tricyclopentylphosphine tetrafluoroborate (0.031 g, 0.096 mmol), Cs₂CO₃ (0.938 g, 2.88 mmol), toluene (1.76 mL) and 2-chloropyridine (0.181 mL, 1.91 mmol), at 130°C for 48 h. Additional Pd(OAc)₂ (0.011 g, 0.048 mmol) and tricyclopentylphosphine tetrafluoroborate (0.031 g, 0.096 mmol) were added at RT and the mixture was heated at 130°C for further 48 h. After work-up, the crude was purified by flash chromatography on Biotage silica NH SNAP cartridge (cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow solid (0.088 g, 0.31 mmol, 32% yield). MS/ESI⁺ 281.2 [MH]⁺, Rt = 0.98 min (Method A).

15

Intermediate H13: ethyl 3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizine-2-carboxylate

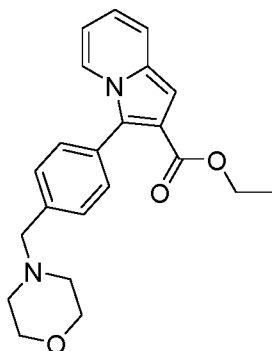


To a solution of ethyl 3-chloroindolizine-2-carboxylate C (0.400 g, 1.79 mmol) in dioxane (14 mL) and water (1.79 mL), (5-(morpholinomethyl)-2-thiopheneboronic acid pinacol ester (1.217 g 3.93 mmol), potassium phosphate monobasic (0.487 g, 3.58 mmol), potassium phosphate tribasic (0.759 g, 3.58 mmol) and PdCl₂(dtbpf), (0.233 g 0.358 mmol)

20

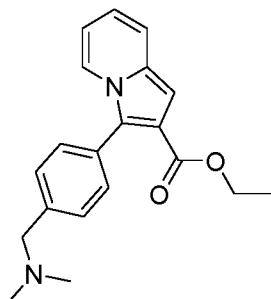
were added under nitrogen atmosphere at RT, the mixture was degassed and the reaction was heated at 65°C overnight. The mixture was extracted with DCM, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica-NH Biotage cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as an orange oil (0.569 g, 1.53 mmol, 86%). MS/ESI⁺ 371.2 [MH]⁺, Rt = 0.67 min (Method A).

Intermediate H14: ethyl 3-[4-(morpholin-4-ylmethyl)phenyl]indolizine-2-carboxylate



Prepared similarly to intermediate H13, starting from ethyl 3-chloroindolizine-2-carboxylate C (0.300 g, 1.34 mmol) and 4- (4-morpholinomethyl) phenylboronic acid pinacol ester (0.894 g, 2.95 mmol), at 65°C for 18 h. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a brown oil (0.488 g, 1.34 mmol, quantitative yield). MS/ESI⁺ 365.3 [MH]⁺, Rt = 0.66 min (Method A).

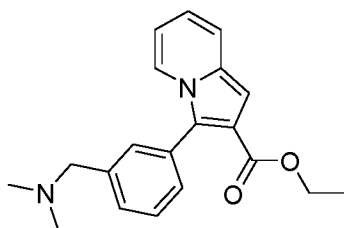
Intermediate H15: ethyl 3-[4-[(dimethylamino)methyl]phenyl]indolizine-2-carboxylate



Prepared similarly to intermediate H13, starting from ethyl 3-chloroindolizine-2-carboxylate C (0.300 g, 1.34 mmol) and dimethyl-[4-(4,4,5,5-tetramethyl-

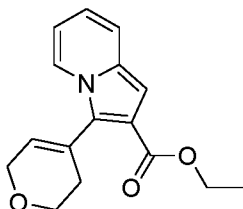
[1,3,2]dioxaborolan-2-yl)-benzyl]-amine (0.769 g, 2.95 mmol), at 65 °C overnight. The crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as an orange oil (0.421 g, 1.30 mmol, 97%). MS/ESI⁺ 323.3 [MH]⁺, Rt = 0.65 min (Method A).

5 **Intermediate H16: ethyl 3-{3-[(dimethylamino)methyl]phenyl}indolizine-2-carboxylate**



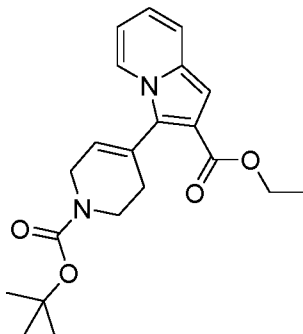
Prepared similarly to intermediate H13, starting from ethyl 3-chloroindolizine-2-carboxylate C (0.400 g, 1.79 mmol) and dimethyl({[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl})amine (1.027 g, 3.93 mmol), at 65°C overnight. The crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as an orange oil (0.457 g, 1.42 mmol, 79% yield). MS/ESI⁺ 323.3 [MH]⁺, Rt = 0.67 min (Method A).

15 **Intermediate H17: ethyl 3-(3,6-dihydro-2H-pyran-4-yl)indolizine-2-carboxylate**



Prepared similarly to intermediate H13 starting from ethyl 3-chloroindolizine-2-carboxylate C (0.150 g, 0.67 mmol) and 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (0.309 g 1.47 mmol), at 65°C overnight. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow oil (0.106 g, 0.39 mmol, 58%). MS/ESI⁺ 272.1 [MH]⁺, Rt = 1.10 min (Method A).

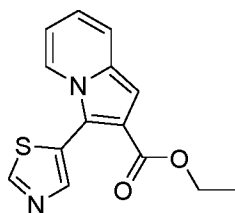
Intermediate H18: ethyl 3-{1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}indolizine-2-carboxylate



5 Prepared similarly to intermediate H13 starting from 3-chloroindolizine-2-carboxylate C (0.300 g, 1.34 mmol) and N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (0.912 g 2.95 mmol), at 65°C for 18 h. The crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound as a yellow oil (0.254 g, 0.68 mmol, 51%).

10 MS/ESI⁺ 371.3 [MH]⁺, Rt = 1.34 min (Method A).

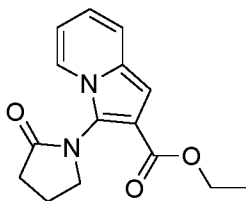
Intermediate H19: ethyl 3-(1,3-thiazol-5-yl)indolizine-2-carboxylate



To a solution of 3-iodoindolizine-2-carboxylate D (0.346 g, 1.1 mmol) in dioxane
15 (4.1 ml) Pd(PPh₃)₂Cl₂ (0.077 g, 0.11 mmol) and 5-(tributylstannyl)-1,3-thiazole (0.617 g, 1.65 mmol) were added under nitrogen atmosphere and the mixture was heated at 65°C overnight. Additional Pd(PPh₃)₂Cl₂ (0.077 g, 0.11 mmol) and 5-(tributylstannyl)-1,3-thiazole (0.205 g, 0.55 mmol) were added and the heating was continued at 65°C for further
20 6 h. The mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a Celite® pad. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane :

EtOAc = 80 : 20) affording title compound as a yellow oil (0.169 g, 0.62 mmol, 57%).
MS/ESI⁺ 273.1 [MH]⁺, Rt = 1.04 min (Method A).

Intermediate H20: ethyl 3-(2-oxopyrrolidin-1-yl)indolizine-2-carboxylate

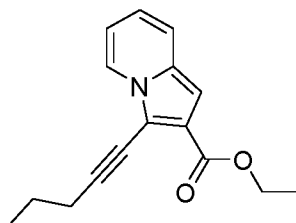


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A sealed tube was charged with CuI (0.010 g, 0.053 mmol), N,N'-dimethylethylenediamine (0.009 g 0.107 mmol), 2-pyrrolidinone (0.127 g 1.49 mmol) and Cs₂CO₃ (0.488 g, 1.49 mmol); ethyl 3-iodoindolizine-2-carboxylate D (0.337 g, 1.07 mmol) and anhydrous DMF (2.1 mL) were added and the reaction was heated at 65°C overnight.

10 Additional CuI iodide (0.010 g, 0.053 mmol) and N,N'-dimethylethylenediamine (0.009 g 0.107 mmol) were added and the reaction was heated at 65°C for further 24 h. The mixture was allowed to cool to room temperature and diluted with DCM and water. The phases were separated, the aqueous phase was extracted with DCM and the combined organic layers were washed with brine, dried over sodium sulfate and evaporated. The crude was
15 purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane EtOAc = 50 : 50) to afford title compound as a brown oil (0.127 g, 0.47 mmol, 43% yield). MS/ESI⁺ 273.2 [MH]⁺, Rt = 0.88 min (Method A).

Intermediate H21: ethyl 3-(pent-1-yn-1-yl)indolizine-2-carboxylate



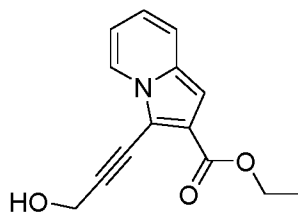
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A mixture of ethyl 3-iodoindolizine-2-carboxylate D (0.626 g, 1.98 mmol), 1-pentyne (0.674 g, 9.9 mmol), CuI (0.132 g, 0.693 mmol) and diethylamine (2.23 mL, 21.58 mmol) in DMF (7.9 mL) was degassed, Pd(PPh₃)₂Cl₂ (0.236 g, 0.336 mmol) was added

and the reaction was stirred at RT for 1 h. The mixture was diluted with EtOAc and filtered through a Celite® pad; the filtrate was washed with water and brine, then dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on Biotage silica SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5). A further
5 purification by reverse phase flash chromatography on Biotage C18 cartridge (H₂O + 0.1% HCOOH : CH₃CN + 0.1% HCOOH = 95 : 5 to 30 : 70) was required to afford title compound as a yellow oil (0.263 g, 1.03 mmol, 52% yield). MS/ESI⁺ 256.2 [MH]⁺, Rt = 1.34 min (Method A).

Intermediate H22: ethyl 3-(3-hydroxyprop-1-yn-1-yl)indolizine-2-carboxylate

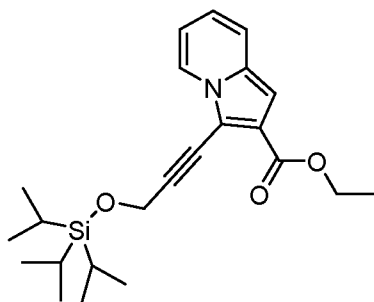
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Prepared similarly to intermediate H21, starting from ethyl 3-iodoindolizine-2-carboxylate D (0.688 g, 2.18 mmol) and propargyl alcohol (0.611 g, 10.9 mmol), stirring at RT for 30 minutes. After work-up the crude was purified by flash chromatography on
15 Biotage silica gel cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a brown oil (0.332 g, 1.36 mmol, 63% yield). MS/ESI⁺ 243.9 [MH]⁺, Rt = 0.90 min (Method A).

Intermediate H23: ethyl 3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizine-2-carboxylate

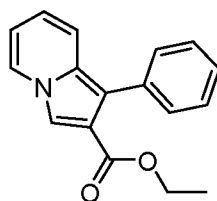
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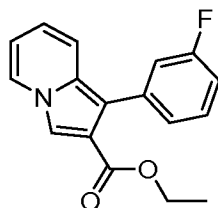
To a stirred mixture of ethyl 3-(3-hydroxyprop-1-yn-1-yl)indolizine-2-carboxylate

H22 (0.332 g, 1.36 mmol) and imidazole (0.231 g, 3.40 mmol) in DMF (1.6 mL), triisopropylsilyl chloride (0.270 g, 1.40 mmol) was added at r.t. and the reaction was stirred overnight. The mixture was diluted with EtOAc and washed with a saturated aqueous solution of NH_4Cl . The organic phase was dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound as a yellow oil (0.501 g, 1.25 mmol, 92% yield). MS/ESI⁺ 400.3 [MH]⁺, Rt = 1.71 min (Method C).

Intermediate H24: ethyl 1-phenylindolizine-2-carboxylate

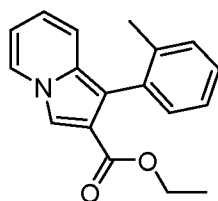


To a solution of ethyl 1-bromoindolizine-2-carboxylate F (0.780 g, 2.9 mmol) in dioxane/ H_2O = 10/1 (22.6 mL), phenylboronic acid (0.780 g, 6.38 mmol), potassium phosphate monobasic (0.790 g, 5.8 mmol), potassium phosphate tribasic (1.23 g, 5.8 mmol) and $\text{PdCl}_2(\text{dtbpf})$, (0.378 g 0.6 mmol) were added at RT, the mixture was degassed and the reaction was heated at 65°C for 18 h. The mixture was diluted with DCM, washed with brine and dried over sodium sulfate; the solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound which was used in the next step without any additional purification (0.475 g, 1.79 mmol, 62% yield). MS/ESI⁺ 266.1 [MH]⁺, Rt = 1.25 min (Method A).

Intermediate H25 ethyl 1-(3-fluorophenyl)indolizine-2-carboxylate

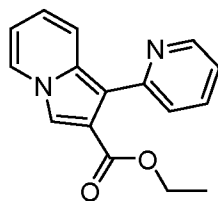
Prepared similarly to intermediate H24, using ethyl 1-bromoindolizine-2-carboxylate F (0.700 g, 2.6 mmol) and (3-fluorophenyl)boronic acid (0.400 g 2.86 mmol), at 65°C for 18 h. The crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 15) to give title compound which was used without any additional purification (0.585 g, 2.06 mmol, 70% yield). MS/ESI⁺ 284.1 [MH]⁺, Rt = 1.25 min (Method A).

10

Intermediate H26: ethyl 1-(2-methylphenyl)indolizine-2-carboxylate

Prepared similarly to intermediate H24, using ethyl 1-bromoindolizine-2-carboxylate F (0.500 g, 1.86 mmol of intermediate) and (2-methylphenyl)boronic acid (0.556 g 4.09 mmol), at 65°C for 18 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to yield title compound which was used without any additional purification (0.350 g, 1.25 mmol, 67% yield). MS/ESI⁺ 280.1 [MH]⁺, Rt = 1.30 min (Method A).

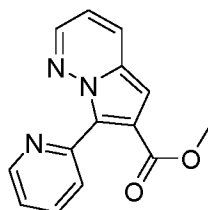
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Intermediate H27: ethyl 1-(pyridin-2-yl)indolizine-2-carboxylate

To a solution of ethyl 1-bromoindolizine-2-carboxylate F (1.4 g, 5.22 mmol) in toluene/MeOH = 20/1 (25.27 mL), Pd(PPh₃)₄ (0.090 g, 0.078 mmol) and 2-(tributylstannyl)pyridine (2.53 mL, 7.83 mmol) were added under nitrogen atmosphere and the reaction was refluxed for 24 h.

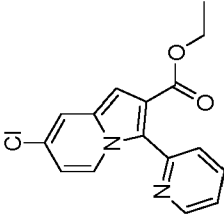
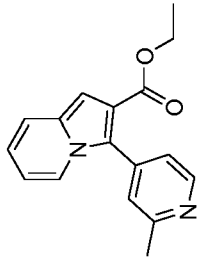
5 In a different flask, to a solution of ethyl 1-bromoindolizine-2-carboxylate F (0.100 g, 0.37 mmol) in toluene/MeOH = 20/1 (1.84 mL), Pd(PPh₃)₄ (0.0043 g, 0.0037 mmol) and 2-(tributylstannyl)pyridine (0.121 mL, 0.37 mmol) were added under nitrogen atmosphere and the reaction was heated to reflux for 24 h. The two mixtures were cooled to room temperature, diluted with EtOAc, combined and filtered through a Celite® pad. The filtrate
10 was concentrated and the resulting crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (DCM to DCM : MeOH = 96 : 4). A further purification by flash chromatography on silica gel-NH Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 60 : 40) was required to afford title compound (0.446 g, 1.67 mmol, 32% yield). MS/ESI⁺ 267.1 [MH]⁺, Rt = 0.49 min (Method A).

15 **Intermediate H28: methyl 7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazine-6-carboxylate**

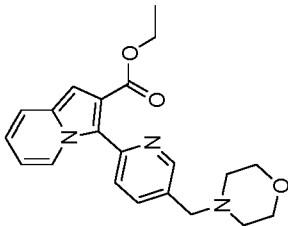
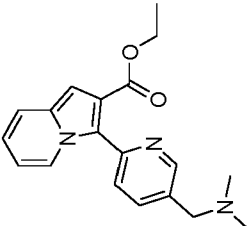
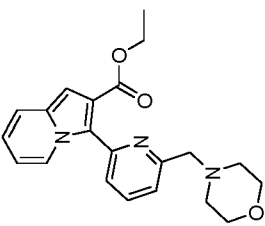
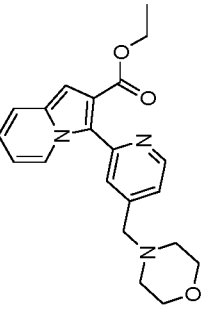


To a mixture of methyl 7-bromopyrrolo[1,2-b]pyridazine-6-carboxylate E (0.425 g, 1.66 mmol) in dioxane (6.15 mL), Pd(PPh₃)₂Cl₂ (0.116 g, 0.16 mmol) and 2-(tributylstannyl)pyridine (0.806 mL, 2.5 mmol) were added under nitrogen atmosphere and
20 the reaction was heated at 90°C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc and filtered through a Celite® pad. The filtrate was concentrated and the residue was purified by flash chromatography on silica-NH Biotage cartridge (cyclohexane : EtOAc = 80 : 20 to 50 : 50) to afford title compound (0.287 g, 1.13 mmol,
25 68% yield). MS/ESI⁺ 254.2 [MH]⁺, Rt = 0.52 min (Method A).

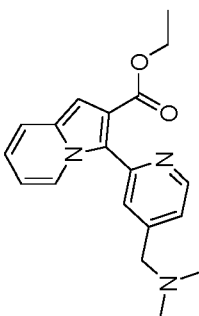
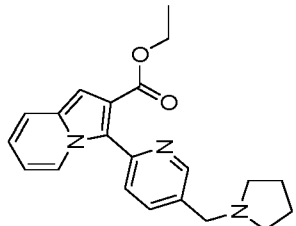
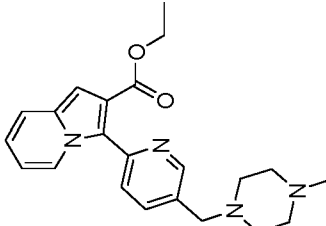
Intermediates H29-51 found in the table below may be prepared from suitable intermediates reported below following similar procedures as for compound H2.

Intermediate	Name and Molecular Structure		Reagent	Analytical data
H29	<u>ethyl 7-chloro-3-(pyridin-2-yl)indolizine-2-carboxylate</u>		B10 and 2-chloropyridine	MS/ESI ⁺ 301.1 [MH] ⁺ , Rt = 1.17 min (Method A).
H30	<u>ethyl 7-methyl-3-(pyridin-2-yl)indolizine-2-carboxylate</u>		B11 and 2-chloropyridine	MS/ESI ⁺ 281.2 [MH] ⁺ , Rt = 1.03 min (Method A)
H31	<u>ethyl 3-(2-methylpyridin-4-yl)indolizine-2-carboxylate</u>		B1 and 4-chloro-2-methylpyridine	MS/ESI ⁺ 281.2 [MH] ⁺ , Rt = 0.61 min (Method A)

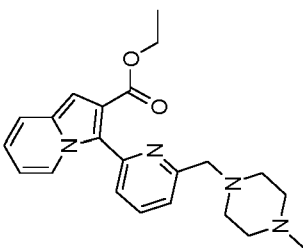
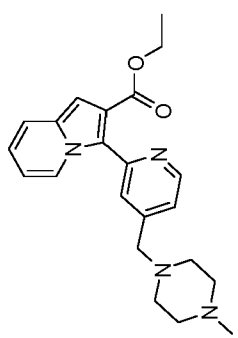
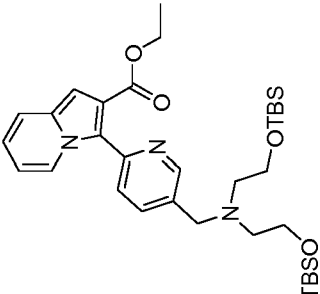
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H32	<u>ethyl</u> <u>3-[5-(morpholin-4-yl)methyl]pyridin-2-yl]indolizine-2-carboxylate</u>		B1 and 4-[(6-chloropyridin-3-yl)methyl]morpholine	MS/ESI ⁺ 366.3 [MH] ⁺ , Rt = 0.58 min (Method A)
H33	<u>ethyl</u> <u>3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and (6-chloropyridin-3-yl)methyl]dimethylamine	MS/ESI ⁺ 324.2 [MH] ⁺ , Rt = 0.56 min (Method A)
H34	<u>ethyl</u> <u>3-[6-(morpholin-4-yl)methyl]pyridin-2-yl]indolizine-2-carboxylate</u>		B1 and 4-[(6-chloropyridin-2-yl)methyl]morpholine BA1	MS/ESI ⁺ 366.4 [MH] ⁺ , Rt = 0.61 min (Method A)
H35	<u>ethyl</u> <u>3-[4-(morpholin-4-yl)methyl]pyridin-2-yl]indolizine-2-carboxylate</u>		B1 and 4-[(2-chloropyridin-4-yl)methyl]morpholine BA2	MS/ESI ⁺ 366.4 [MH] ⁺ , Rt = 0.59 min (Method A)

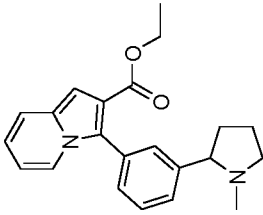
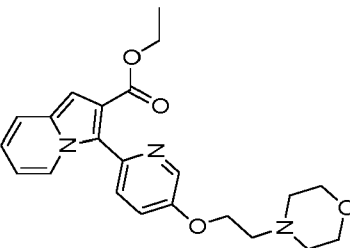
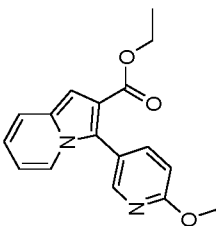
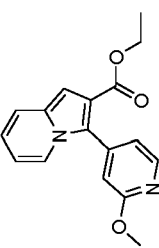
(continued)

H36	<u>ethyl</u> <u>3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and [(2-chloropyridin-4-yl)methyl]dimethylamine BA3	MS/ESI ⁺ 324.4 [MH] ⁺ , Rt = 0.55 min (Method A)
H37	<u>ethyl</u> <u>3-[5-(pyrrolidin-1-yl)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and 2-chloro-5-(pyrrolidin-1-yl)methylpyridine BA4	MS/ESI ⁺ 350.2 [MH] ⁺ , Rt = 0.59 min (Method A)
H38	<u>ethyl</u> <u>3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and 1-[(6-chloropyridin-3-yl)methyl]-4-methylpiperazine BA5	MS/ESI ⁺ 379.4 [MH] ⁺ , Rt = 0.57 min (Method A)

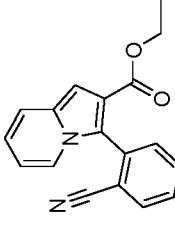
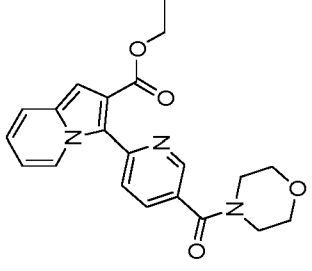
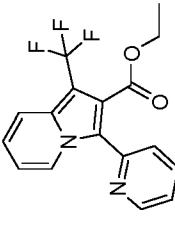
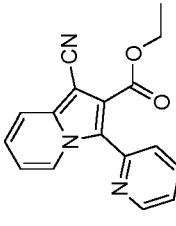
(continued)

H39	<u>ethyl 3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and 1-[(6-chloropyridin-2-yl)methyl]-4-methylpiperazine BA6	MS/ESI ⁺ 379.4 [MH] ⁺ , Rt = 0.59 min (Method A)
H40	<u>ethyl 3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and 1-[(2-chloropyridin-4-yl)methyl]-4-methylpiperazine BA7	MS/ESI ⁺ 379.4 [MH] ⁺ , Rt = 0.54 min (Method A)
H41	<u>ethyl 3-{5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-disilatridecan-7-yl)methyl]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and 2-chloro-5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)methyl]pyridine BA8	MS/ESI ⁺ 612.6 [MH] ⁺ , Rt = 1.29 min (Method A)

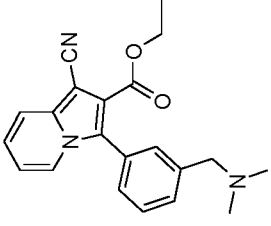
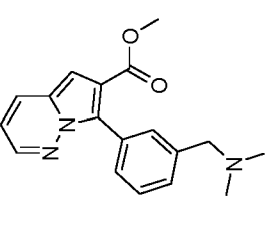
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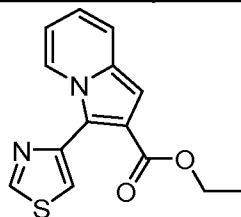
H42	<u>ethyl 3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizine-2-carboxylate</u>		B1 and 2-(3-bromophenyl)-1-methylpyrrolidine BA9	MS/ESI ⁺ 349.3 [MH] ⁺ , Rt = 0.68 min (Method A)
H43	<u>ethyl 3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizine-2-carboxylate</u>		B1 and 4-{2-[(6-chloropyridin-3-yl)oxy]ethyl}morpholine BA10	MS/ESI ⁺ 396.5 [MH] ⁺ , Rt = 1.08 min (Method J).
H44	<u>ethyl 3-(6-methoxypyridin-3-yl)indolizine-2-carboxylate</u>		B1 and 5-chloro-2-methoxypyridine	MS/ESI ⁺ 297.3 [MH] ⁺ , Rt = 1.17 min (Method A)
H45	<u>ethyl 3-(2-methoxypyridin-4-yl)indolizine-2-carboxylate</u>		B1 and 4-chloro-2-methoxypyridine	MS/ESI ⁺ 297.2 [MH] ⁺ , Rt = 1.15 min (Method A)

(continued)

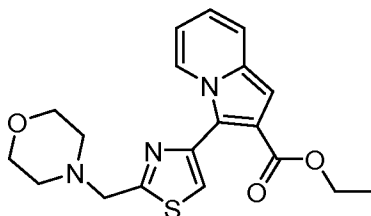
H46	<u>ethyl 3-(2-cyanophenyl)indolizine-2-carboxylate</u>		B1 and 2-bromobenzonitrile	MS/ESI ⁺ 291.2 [MH] ⁺ , Rt = 1.13 min (Method A)
H47	<u>ethyl 3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizine-2-carboxylate</u>		B1 and 4-(6-chloropyridine-3-carbonyl)morpholine	MS/ESI ⁺ 380.4 [MH] ⁺ , Rt = 0.93 min (Method A)
H48	<u>ethyl 3-(pyridin-2-yl)-1-(trifluoromethyl)indolizine-2-carboxylate</u>		GA and 2-chloropyridine	MS/ESI ⁺ 335.3 [MH] ⁺ , Rt = 1.22 min (Method A)
H49	<u>ethyl 1-cyano-3-(pyridin-2-yl)indolizine-2-carboxylate</u>		1-cyanoindolizine-2-carboxylate (prepared as reported in Journal of the Chemical Society, 1965, 2948-2951) and 2-chloropyridine	MS/ESI ⁺ 292.2 [MH] ⁺ , Rt = 0.95 min (Method A)

(continued)

H50	<u>ethyl</u> <u>[(dimethylamino)methyl]phenyl]indolizine-2-carboxylate</u>		1-cyanoindolizine-2-carboxylate (prepared as reported in Journal of the Chemical Society, 1965, 2948-2951) and [(3-chlorophenyl)methyl]dimethylamine BA11	¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.92 - 7.96 (m, 1 H), 7.73 - 7.77 (m, 1 H), 7.45 - 7.54 (m, 2 H), 7.37 - 7.41 (m, 2 H), 7.30 - 7.35 (m, 1 H), 6.95 - 7.00 (m, 1 H), 4.13 (q, 2 H), 3.46 (s, 2 H), 2.17 (s, 6 H), 1.06 (t, 3 H).
H51	<u>methyl</u> <u>[(dimethylamino)methyl]phenyl]pyrrolo[1,2-b]pyridazine-6-carboxylate</u>		B9 and [(3-chlorophenyl)methyl]dimethylamine BA11	MS/ESI⁺ 310.3 [MH]⁺, Rt = 0.54 min (Method A)

Intermediate H52: ethyl 3-(1,3-thiazol-4-yl)indolizine-2-carboxylate

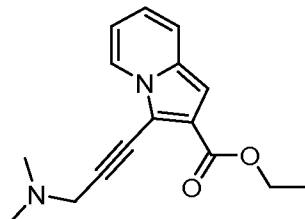
Prepared similarly to intermediate H19 starting from 3-iodoindolizine-2-carboxylate D (1.00 g) and 4-(tributylstannyl)-1,3-thiazole (1.78 g, 4.76 mmol) at 65°C overnight; additional Pd(PPh₃)₂Cl₂ and 4-(tributylstannyl)-1,3-thiazole (0.220 g) were added and the mixture was heated at 65°C overnight. The crude was purified by flash chromatography on silica-NH Biotage column (cyclohexane to cyclohexane : EtOAc = 85 : 15) to afford title compound (0.200 g, 0.734 mmol) as a brown solid. MS/ESI⁺ 273.3 [MH]⁺, Rt = 1.08 min (Method A).

Intermediate H53: ethyl 3-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]indolizine-2-carboxylate

Prepared similarly to intermediate H19 starting from 3-iodoindolizine-2-carboxylate D (1.097 g + 0.236 g) and 4-[[4-(trimethylstannyl)-1,3-thiazol-2-yl]methyl]morpholine BB1 (1.943 g, 5.6 mmol + 0.432 g, 1.24 mmol), at 65°C overnight. Additional Pd(PPh₃)₂Cl₂ and 4-[[4-(trimethylstannyl)-1,3-thiazol-2-yl]methyl]morpholine XX12 (0.230 g, 0.66 mmol) were added and the mixture was heated at 65°C for further 48 h. The crude was purified by flash chromatography on silica-NH Biotage cartridge (cyclohexane to cyclohexane: EtOAc = 90 : 10); the obtained product was dissolved in EtOAc, KF was added and the mixture was stirred at r.t. for 3 h. The mixture was filtered and the filtrate was concentrated under reduced pressure; the residue was further purified by flash chromatography on silica-NH Biotage cartridge (cyclohexane to cyclohexane: EtOAc = 90 : 10) to afford title compound as a yellow oil (0.485 g). MS/ESI⁺ 372.3 [MH]⁺,

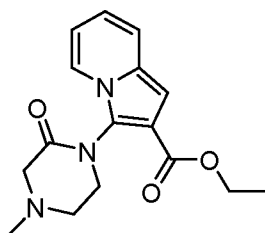
Rt = 0.76 min (Method A).

Intermediate H54: ethyl 3-[3-(dimethylamino)prop-1-yn-1-yl]indolizine-2-carboxylate



5 Prepared similarly to intermediate H21, starting from ethyl 3-iodoindolizine-2-carboxylate D (0.800 g, 2.54 mmol) and 3-dimethylamino-1-propyne (1.37 mL, 12.69 mmol), stirring at RT for 1 h. After work-up the crude was purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford crude title compound as a dark yellow oil (0.687 g) which was used without
10 any additional purification. MS/ESI⁺ 271.2 [MH]⁺, Rt = 0.61 min (Method A).

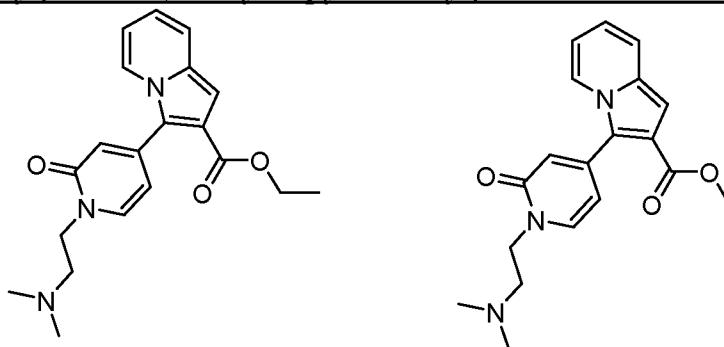
Intermediate H55: ethyl 3-(4-methyl-2-oxopiperazin-1-yl)indolizine-2-carboxylate



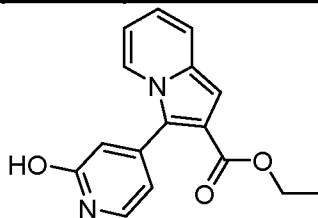
A flask was charged with 3-iodoindolizine-2-carboxylate D (1.641 g), 1-methyl-3-oxopiperazine (0.594 g, 5.2 mmol), K₃PO₄ (2.207 g, 10.4 mmol) and Copper (I) iodide (0.050 g, 0.26 mmol), and the flask was purged and back-filled with N₂. Anhydrous DMF (4.9 mL) was added, followed by N,N'-dimethylethylenediamine (0.056 mL, 0.52 mmol) and the suspension was heated at 65°C overnight. Additional Copper (I) iodide (0.050 g, 0.26 mmol), N,N'-dimethylethylenediamine (0.056 mL, 0.52 mmol) were added and the
15 reaction was heated at 65°C for further 24 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over sodium sulfate
20

and evaporated. The crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow solid (0.694 g). MS/ESI⁺ 302.2 [MH]⁺, Rt = 0.51 min (Method A).

Intermediate H56: ethyl 3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carboxylate and methyl 3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carboxylate



Step1: ethyl 3-(2-hydroxypyridin-4-yl)indolizine-2-carboxylate H56a



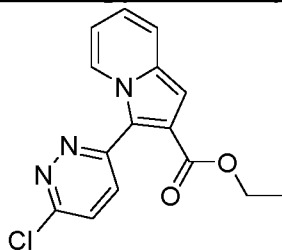
Iodotrimethylsilane (4.00 mL, 28.6 mmol) was added to a solution of ethyl 3-(2-methoxypyridin-4-yl)indolizine-2-carboxylate H45 (1.00 g, 3.37 mmol) in dry acetonitrile (59 mL) and the resulting mixture was heated at 60°C for 3 h. Then, at that temperature, MeOH (59 mL) was added and stirring was carried out for further 15 minutes. After cooling to RT, the mixture was diluted with DCM and washed with an aqueous solution of Na₂S₂O₅ and then with brine. The organic phase was concentrated under reduce pressure to afford title compound as a yellow solid (0.951 g, 3.37 mmol, 100% yield). MS/ESI⁺ 283.3 [MH]⁺, Rt = 0.85 min (Method A).

Step 2: ethyl 3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carboxylate and methyl 3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carboxylate H56

K₂CO₃ (1.78 g, 12.88 mmol) was added to a solution of ethyl 3-(2-hydroxypyridin-

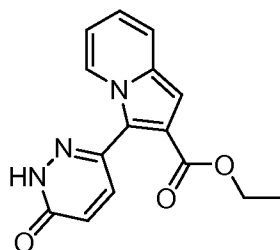
4-yl)indolizine-2-carboxylate H56a (0.800 g, 2.8 mmol) in acetone (42.0 mL) and the mixture was stirred at 50°C for 2 h under nitrogen atmosphere. 2-Chloro-N,N-dimethylethylamine hydrochloride (1.209 g, 8.4 mmol) was added and the resulting mixture was stirred overnight at 50°C. Additional K₂CO₃ (1.16 g, 8.4 mmol) and 2-chloro-N,N-dimethylethylamine hydrochloride (0.806 g, 5.6 mmol), were added and the reaction was allowed to stir at the same temperature for further 24 h. The reaction mixture was diluted with MeOH and the solvents were removed; water was added and the mixture was extracted with DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : EtOAc = 80 : 20) to afford a mixture of ethyl 3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carboxylate and methyl 3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carboxylate (≈ 1:1 ratio) (0.621 g) which was used without any additional purification. MS/ESI⁺ 354.3 and 340.3 [MH]⁺, Rt = 0.59 min and 0.53 min (Method A).

Intermediate H57: ethyl 3-(6-chloropyridazin-3-yl)indolizine-2-carboxylate



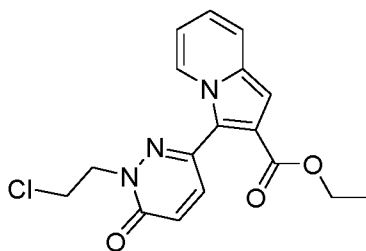
AlCl₃ (0.990 g, 7.42 mmol) was added to a solution of 3,6-dichloropyridazine (1.105 g, 7.42 mmol) in 1,2-dichloroethane (10 ml) and the mixture was stirred for 30 minutes at RT, then ethyl indolizine-2-carboxylate B1 (1.00 g, 5.3 mmol) was added and the mixture was stirred at 80°C for 24 h. The reaction mixture was poured into ice and extracted with DCM. The organic layers were dried over sodium sulfate, the solvent was removed and the crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane : EtOAc = 95 : 5 to 80 : 20) to afford title compound as a pale yellow solid (0.425 g, 1.41 mmol, 26% yield). MS/ESI⁺ 302.2 [MH]⁺, Rt = 1.09 min (Method A).

Intermediate H58: ethyl 3-(6-oxo-1,6-dihydropyridazin-3-yl)indolizine-2-carboxylate



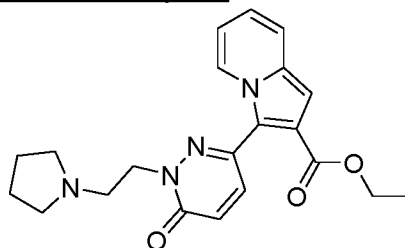
To a solution of ethyl 3-(6-chloropyridazin-3-yl)indolizine-2-carboxylate H57
5 (0.425 g, 1.4 mmol) in 22 ml of acetic acid, sodium acetate (0.231 g, 2.81 mmol) was added
and the mixture was heated to reflux under stirring for 3 h. The reaction mixture was poured
into cold water and extracted with DCM. The organic layers were dried over sodium sulfate
and the solvent was removed to afford title compound as a pale orange solid which was
used without any additional purification (0.395 g). MS/ESI⁺ 284.2 [MH]⁺, Rt = 0.85 min
10 (Method A).

Intermediate H59: ethyl 3-[1-(2-chloroethyl)-6-oxo-1,6-dihydropyridazin-3-yl]indolizine-2-carboxylate

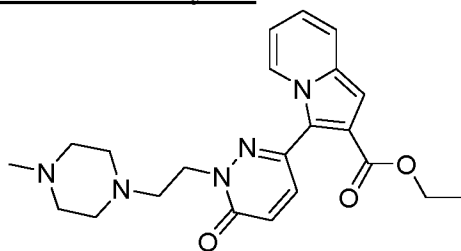


Ethyl 3-(6-oxo-1,6-dihydropyridazin-3-yl)indolizine-2-carboxylate H58 (0.175 g)
15 was dissolved in 2 ml of DMF, K₂CO₃ (0.389 g, 1.85 mmol) was added followed by 1-
bromo-2-chloroethane (0.154 ml, 1.85 mmol) and the mixture was stirred at 60 °C for 2 h.
The mixture was diluted with ethyl acetate, the solid was filtered-off and the filtrate was
washed with brine. The organic phase was then dried over sodium sulfate, the solvent was
removed and the crude was purified by flash chromatography on Biotage silica gel cartridge
20 (cyclohexane : EtOAc = 80 : 20 to 60 : 40) to afford title compound as a pale yellow solid
(0.134 g). MS/ESI⁺ 346.3 [MH]⁺, Rt = 1.08 min (Method A).

Intermediate H60: ethyl 3-{6-oxo-1-[2-(pyrrolidin-1-yl)ethyl]-1,6-

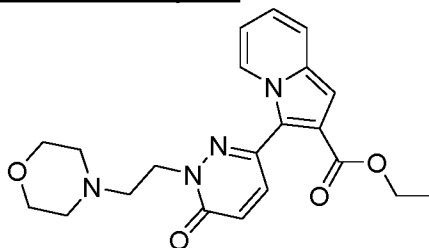
ethyl 3-[1-(2-chloroethyl)-6-oxo-1,6-dihydropyridazin-3-yl]indolizine-2-carboxylate

To a solution of ethyl 3-[1-(2-chloroethyl)-6-oxo-1,6-dihydropyridazin-3-yl]indolizine-2-carboxylate H59 (0.134 g) in acetonitrile (7 mL), KI (69.4 mg, 0.42 mmol) and K₂CO₃ (0.157 g, 1.14 mmol) were added followed by pyrrolidine (0.64 ml, 0.77 mmol) and the mixture was stirred at 85 °C for 4 h. The mixture was diluted with ethyl acetate, the solid was filtered-off and the filtrate was evaporated to dryness; the crude was purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow oil (0.114 g, 0.3 mmol). MS/ESI⁺ 381.2 [MH]⁺, Rt = 0.60 min (Method A).

Intermediate H61: ethyl 3-[1-[2-(4-methylpiperazin-1-yl)ethyl]-6-oxo-1,6-dihydropyridazin-3-yl]indolizine-2-carboxylate

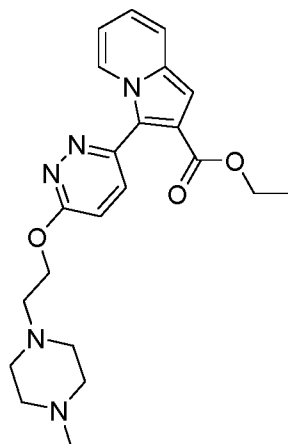
Prepared similarly to intermediate H60 starting from ethyl 3-[1-(2-chloroethyl)-6-oxo-1,6-dihydropyridazin-3-yl]indolizine-2-carboxylate H59 (0.193 g) and 1-methyl piperazine (0.125 ml, 1.12 mmol), at 85 °C for 5 h, and purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow oil (0.179 g, 0.43 mmol). MS/ESI⁺ 410.4 [MH]⁺, Rt = 0.59 min (Method A).

Intermediate H62: ethyl 3-{1-[2-(morpholin-4-yl)ethyl]-6-oxo-1,6-dihydropyridazin-3-yl}indolizine-2-carboxylate



Ethyl 3-(6-oxo-1,6-dihydropyridazin-3-yl)indolizine-2-carboxylate H58 (0.202 g +
5 0.043 g) was dissolved in 9.5 ml (+2 mL) of DMF, K₂CO₃ (0.3435 g, 2.48 mmol + 0.0725 g, 0.52 mmol) was added followed by 4-(2-chloroethyl)morpholine hydrochloride (0.1725 g, 0.92 mmol + 0.0335 g, 0.18 mmol) and the mixture was stirred at room temperature for 48 h. The mixture was diluted with ethyl acetate, the solid was filtered-off and the filtrate was washed with brine. The organic phase was dried over sodium sulfate, the solvent was
10 removed and the crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane : EtOAc = 70 : 30 to 30 : 70) to afford title compound as a pale yellow solid (0.265 g, 0.67 mmol over 2 batches). MS/ESI⁺ 397.3 [MH]⁺, Rt = 0.60 min (Method A).

Intermediate H63: ethyl 3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizine-2-carboxylate



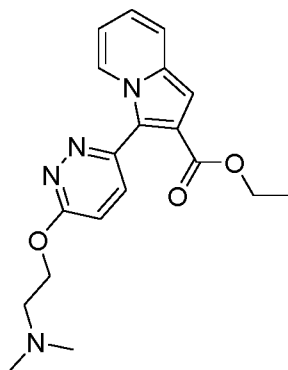
15

2-(4-Methylpiperazin-1-yl)ethan-1-ol (0.2676 g, 1.85 mmol) was dissolved in 5.5 ml of THF, potassium *tert*-butoxide (0.309 g, 2.76 mmol) was added and the mixture was stirred at room temperature for 30 min. Ethyl 3-(6-chloropyridazin-3-yl)indolizine-2-carboxylate H57 (0.280 g 0.92 mmol) was added and the mixture was stirred at RT for 5

min. The mixture was diluted with ethyl acetate and washed with brine, the phases were separated and the organic layer was dried over sodium sulphate. The solvent was removed and the residue was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound (0.187 g, 0.45 mmol, 49% yield).

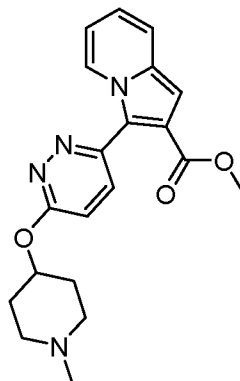
5 MS/ESI⁺ 410.4 [MH]⁺, Rt = 0.57 min (Method A).

Intermediate H64: ethyl 3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizine-2-carboxylate



Prepared similarly to intermediate H63 starting from ethyl 3-(6-chloropyridazin-3-yl)indolizine-2-carboxylate H57 (0.500 g 1.65 mmol) and 2-dimethylaminoethanol (0.333 ml, 3.30 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound (0.341 g). MS/ESI⁺ 355.3 [MH]⁺, Rt = 0.62 min (Method A).

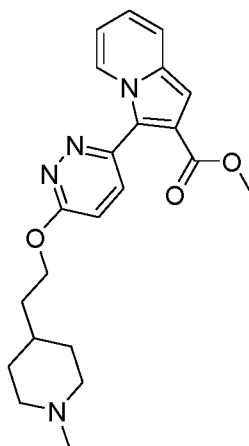
15 **Intermediate H65: methyl 3-{6-[(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizine-2-carboxylate**



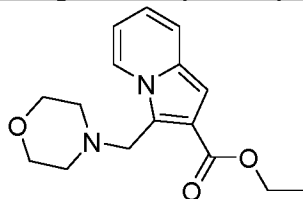
Ethyl 3-(6-chloropyridazin-3-yl)indolizine-2-carboxylate H57 (0.255 g, 0.84 mmol) and 1-methylpiperidin-4-ol (0.390 g 3.38 mmol) were dissolved in 10.5 ml of THF;

potassium *tert*-butoxide (0.380 g, 3.38 mmol) was added and the mixture was stirred at RT for 30 min. The mixture partitioned between ethyl acetate and water, the phases were separated and the aqueous layer was evaporated. The residue was dissolved in MeOH (25 mL), concentrated sulfuric acid (10 drops) was added and the mixture was stirred at 80 °C for 16 h. The solvent was evaporated and the residue was dissolved in DCM and basified with a saturated solution of NaHCO₃ (pH = 8). The phases were separated and the aqueous layers was extracted three times with a solution of DCM/MeOH = 9/1. The combined organic layers were dried over sodium sulfate, the solvent was evaporated and the residue was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (0.110 g, 0.3 mmol, 35% yield). MS/ESI⁺ 367.4 [MH]⁺, Rt = 0.58 min (Method A).

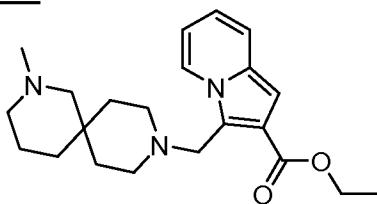
Intermediate H66: methyl 3-{6-[2-(1-methylpiperidin-4-yl)ethoxy]pyridazin-3-yl}indolizine-2-carboxylate



Prepared similarly to intermediate H65 starting from ethyl 3-(6-chloropyridazin-3-yl)indolizine-2-carboxylate H57 (0.510 g, 1.69 mmol) and 2-(1-methylpiperidin-4-yl)ethan-1-ol (0.970 g, 6.77 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (0.140 g). MS/ESI⁺ 395.4 [MH]⁺, Rt = 0.64 min (Method A).

Intermediate H67: ethyl 3-(morpholin-4-ylmethyl)indolizine-2-carboxylate

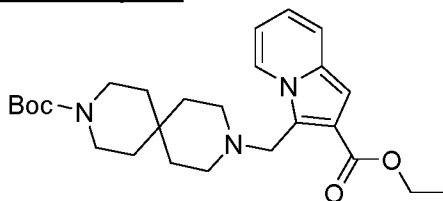
To a solution of ethyl 3-formylindolizine-2-carboxylate DA1 (1.05 g, 4.83 mmol + 0.100 g, 0.46 mmol) in DCM (19.3 mL + 1.84 mL), morpholine (0.63 mL, 7.25 mmol + 0.060 mL, 0.69 mmol) and 21 drops (+ 2) of AcOH were added. The mixture was stirred overnight at room temperature and then Na(OAc)₃BH (1.536 g, 7.25 mmol + 0.146 g, 0.69 mmol) was added. After 6 h the mixture was quenched with sat. NaHCO₃ (20 mL + 2 mL); the organic layer was separated, washed with brine, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title as a pale yellow oil (1.218 g, 4.2 mmol, 79% yield over two batches). MS/ESI⁺ 289.3 [MH]⁺, Rt = 0.51 min (Method A).

Intermediate H68: ethyl 3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl)indolizine-2-carboxylate

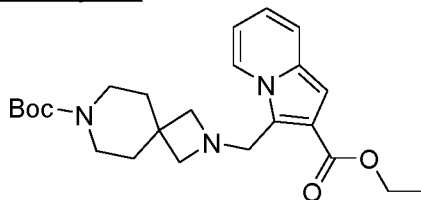
Prepared similarly to intermediate H67 starting from ethyl 3-formylindolizine-2-carboxylate DA1 (0.786 g, 3.62 mmol) and 2-methyl-2,9-diazaspiro[5.5]undecane (0.730 g, 4.34 mmol, obtained from commercially available dihydrochloride salt after SCX treatment and elution with aqueous ammonia) and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound (1.10 g, 2.98 mmol, 82 % yield). MS/ESI⁺ 370.4 [MH]⁺, Rt = 0.39 min (Method A).

Intermediate H69: tert-butyl 9-{[2-(ethoxycarbonyl)indolizin-3-yl]methyl}-

117

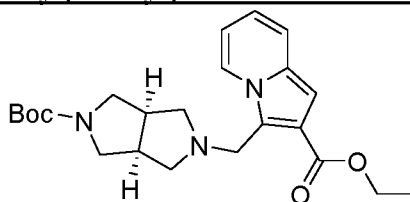
3,9-diazaspiro[5.5]undecane-3-carboxylate

Prepared similarly to intermediate H67 starting from ethyl 3-formylindolizine-2-carboxylate DA1 (0.610 g, 2.81 mmol) and tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (1 g, 3.93 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound (0.975 g, 2.14 mmol, 76% yield). MS/ESI⁺ 456.6 [MH]⁺, Rt = 0.79 min (Method A).

Intermediate H70: tert-butyl 2-{[2-(ethoxycarbonyl)indolizin-3-yl]methyl}-2,7-diazaspiro[3.5]nonane-7-carboxylate

10

Prepared similarly to intermediate H67 starting from ethyl 3-formylindolizine-2-carboxylate DA1 (0.600 g, 2.72 mmol) and tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (obtained from 1 g, 3.8 mmol of commercially available hydrochloride salt after filtration through PL-HCO₃ cartridges (3x1 g)) and purified by flash chromatography on Biotage silica cartridge (cyclohexane : EtOAc = 90 : 10 to 45 : 55) to afford title compound as an oil (0.537 g, 1.25 mmol, 46%). MS/ESI⁺ 428.2 [MH]⁺, Rt = 0.74 min (Method A).

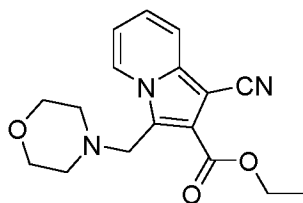
Intermediate H71: ethyl 3-{[(3aR,6aS)-5-[(tert-butoxy)carbonyl]-octahydropyrrolo[3,4-c]pyrrol-2-yl]methyl}indolizine-2-carboxylate

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Prepared similarly to intermediate H67 starting from ethyl 3-formylindolizine-2-

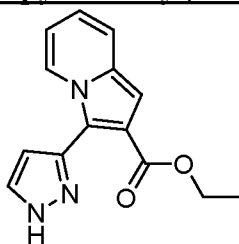
carboxylate DA1 (0.500 g, 2.3 mmol) and meso-tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (0.733 g, 3.45 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as a pale yellow oil (0.951 g, 2.3 mmol, 100%). MS/ESI⁺ 414.5 [MH]⁺, Rt = 0.71 min (Method A).

Intermediate H72: ethyl 1-cyano-3-(morpholin-4-ylmethyl)indolizine-2-carboxylate

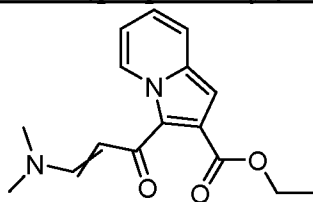


Prepared similarly to intermediate H67 starting from ethyl 1-cyano-3-formylindolizine-2-carboxylate DA2 (0.605 g, 2.49 mmol) and morpholine (0.436 ml, 4.98 mmol) and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 99 : 1) to afford title compound (0.750 g, 2.39 mmol, 96% yield). MS/ESI⁺ 314.3 [MH]⁺, Rt = 0.54 min (Method A).

Intermediate H73: ethyl 3-(1H-pyrazol-3-yl)indolizine-2-carboxylate



Step 1: ethyl 3-[3-(dimethylamino)prop-2-enoyl]indolizine-2-carboxylate H73a



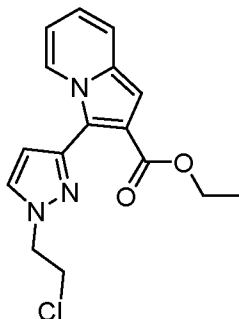
To a solution of ethyl 3-acetylindolizine-2-carboxylate DB (1.780 g, 7.7 mmol) in toluene (30 ml), tert-butoxy bis(dimethylamino)methane (3.18 ml, 15.4 mmol) was added and the mixture was stirred at 110 °C for 2 h. The solvent was removed and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane :

EtOAc = 60 : 40 to 40 : 60) to afford title compound as a pale yellow oil (2.120 g, 7.4 mmol, 96% yield). MS/ESI⁺ 287.3 [MH]⁺, Rt = 0.89 min (Method A).

Step 2: ethyl 3-(1H-pyrazol-3-yl)indolizine-2-carboxylate H73

To a solution of ethyl 3-[3-(dimethylamino)prop-2-enoyl]indolizine-2-carboxylate
5 H73a (1.580 g, 5.5 mmol) in ethanol (14 ml), hydrazine monohydrate (0.267 ml, 5.5 mmol) was added and the mixture was stirred at 80 °C for 1 h. The solvent was removed and the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound as a pale yellow solid (1.165 g, 4.5 mmol, 83%
10 yield). MS/ESI⁺ 256.2 [MH]⁺, Rt = 0.95 min (Method A).

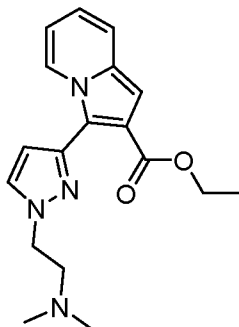
Intermediate H74: ethyl 3-[1-(2-chloroethyl)-1H-pyrazol-3-yl]indolizine-2-carboxylate



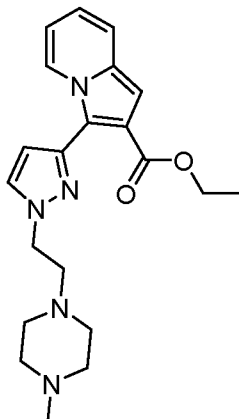
Ethyl 3-(1H-pyrazol-3-yl)indolizine-2-carboxylate H73 (1.165 g, 4.5 mmol) was dissolved in 11 ml of DMF, K₂CO₃ (1.897 g, 13.5 mmol) was added followed by 1-bromo-
15 2-chloroethane (1.12 ml, 13.5 mmol) and the mixture was stirred at 60 °C for 6 h. The mixture was diluted with ethyl acetate, the solid was filtered off and the filtrate was washed with brine. The organic phase was dried over sodium sulfate, the solvent was removed and the crude was purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : EtOAc = 90 : 10) to afford title compound as a pale yellow solid (0.995 g, 3.13
20 mmol, 69% yield). MS/ESI⁺ 317.9 [MH]⁺, Rt = 1.15 min (Method A).

Intermediate H75: ethyl 3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-}

120

ethyl 3-[1-(2-chloroethyl)-1H-pyrazol-3-yl]indolizine-2-carboxylate

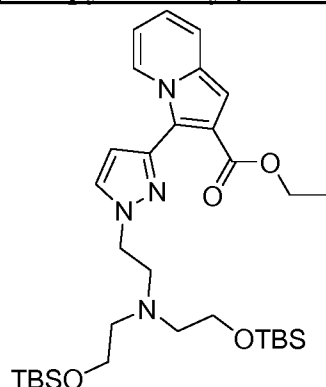
To a solution of ethyl 3-[1-(2-chloroethyl)-1H-pyrazol-3-yl]indolizine-2-carboxylate H74 (0.300 g, 0.94 mmol) acetonitrile (24 mL), KI (0.312 g, 1.88 mmol) and
5 K₂CO₃ (0.391 g, 2.83 mmol) were added followed by 2M dimethylamine in THF (1.41 ml, 2.83 mmol) and the mixture was stirred at 85 °C for 48 h. The mixture was diluted with ethyl acetate, the solid was filtered off and the filtrate was washed with brine. The organic phase was dried over sodium sulfate, the solvent was removed and the crude was purified by flash chromatography on Biotage silica gel cartridge (DCM : MeOH = 99 : 1 to 90 : 10)
10 to afford title compound as a pale yellow oil (0.212 g, 0.65 mmol, 70% yield). MS/ESI⁺ 327.3 [MH]⁺, Rt = 0.61 min (Method A).

Intermediate H76: ethyl 3-[1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl]indolizine-2-carboxylate

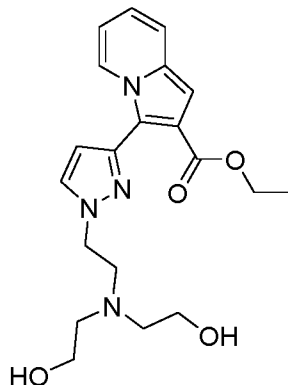
15 Prepared similarly to intermediate H75 starting from ethyl 3-[1-(2-chloroethyl)-1H-pyrazol-3-yl]indolizine-2-carboxylate H74 (0.300 g, 0.94 mmol + 0.025 mg, 0.078 mmol), KI (0.234 g, 1.41 mmol + 0.014 g, 0.086 mmol), K₂CO₃ (0.390 g, 2.82 mmol + 0.032 g, 0.234 mmol) and 1-methyl piperazine (0.208 ml, 1.88 mmol + 0.017 mL, 0.15 mmol) at 85

°C for 24 h, and purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow oil (0.316 g, 0.82 mmol, 81 % yield). MS/ESI⁺ 382.4 [MH]⁺, Rt = 0.61 min (Method A).

5 **Intermediate H77: ethyl 3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizine-2-carboxylate**



Step 1: ethyl 3-(1-{2-[bis(2-hydroxyethyl)amino]ethyl}-1H-pyrazol-3-yl)indolizine-2-carboxylate H77a

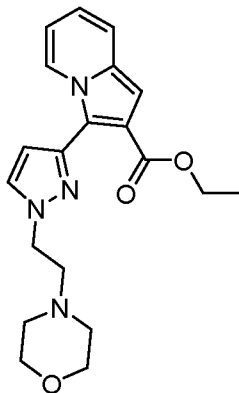


10 Prepared similarly to intermediate H75 starting from ethyl 3-[1-(2-chloroethyl)-1H-pyrazol-3-yl]indolizine-2-carboxylate H74 (0.200 g, 0.63 mmol), KI (0.314 g, 1.89 mmol), K₂CO₃ (0.348 g, 2.52 mmol) and 2-[(2-hydroxyethyl)amino]ethan-1-ol (0.181 ml, 1.89 mmol) at 85 °C for 24 h, and purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as a pale yellow oil
15 (0.076 g, 0.19 mmol, 31% yield). MS/ESI⁺ 387.4 [MH]⁺, Rt = 0.59 min (Method A).

Step 2: ethyl 3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-

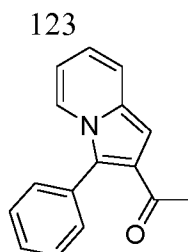
disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizine-2-carboxylate H77

Ethyl 3-(1-{2-[bis(2-hydroxyethyl)amino]ethyl}-1H-pyrazol-3-yl)indolizine-2-carboxylate H77a (0.121 g, 0.31 mmol) was dissolved in DCM (3 mL); imidazole (0.1055 g, 1.55 mmol) and tert-butyl(chloro)dimethylsilane (0.117 g, 0.77 mmol) were added and the mixture was stirred at room temperature for 2 h. The mixture was washed with water, then with brine, the organic phase was dried over sodium sulphate and the solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica gel Biotage column (DCM to DCM : MeOH = 95 : 5) affording title compound as a yellow oil (0.165 g, 0.27 mmol, 86% yield). MS/ESI⁺ 615.6 [MH]⁺, Rt = 1.25 min (Method A).

Intermediate H78: ethyl 3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizine-2-carboxylate

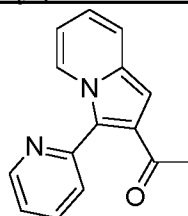
Ethyl 3-(1H-pyrazol-3-yl)indolizine-2-carboxylate H73 (567.4 mg, 1.54 mmol) was dissolved in 8 ml of THF, K₂CO₃ (0.866 g, 6.16 mmol) was added followed by 4-(2-chloroethyl)morpholine hydrochloride (0.573 g, 3.08 mmol) and the mixture was stirred at 60 °C for 2 h. The mixture was diluted with ethyl acetate, the solid was filtered off and the filtrate was washed with brine. The organic phase was then dried over sodium sulfate, the solvent was removed and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow solid (0.068 g, 0.18 mmol). MS/ESI⁺ 369.4 [MH]⁺, Rt = 0.65 min (Method A).

Intermediate I1: 1-(3-phenylindolizin-2-yl)ethan-1-one



A mixture of commercially available 1-(indolizin-2-yl)ethan-1-one (0.250 g, 1.57 mmol), Pd(OAc)₂ (0.018 g, 0.0785 mmol), tricyclopentylphosphine tetrafluoroborate (0.051 g, 0.157 mmol) and Cs₂CO₃ (1.530 g, 4.71 mmol) was flushed with nitrogen and toluene (3 mL) was added followed by chlorobenzene (0.320 mL, 3.52 mmol). The reaction was stirred at r.t. for 10 min, then heated at 130 °C for 16 h. The mixture was cooled to RT, diluted with DCM and filtered through a Celite® pad. The filtrate was evaporated to dryness and purified by flash chromatography on silica Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 93 : 7) to afford title compound as a yellow oil (0.095 g, 0.40 mmol, 26% yield). MS/ESI⁺ 236.1 [MH]⁺, Rt = 1.11 min (Method A).

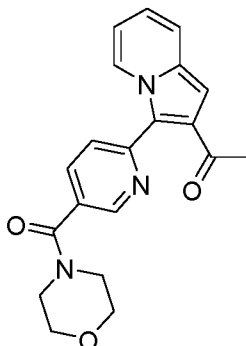
Intermediate I2: 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-one



A mixture of 1-(indolizin-2-yl)ethan-1-one (0.250 g, 1.57 mmol), Pd(OAc)₂ (0.018 g, 0.0785 mmol), tricyclopentylphosphine tetrafluoroborate (0.051 g, 0.157 mmol) and Cs₂CO₃ (1.535 g, 4.71 mmol) was flushed with nitrogen and toluene (3 mL) was added followed by 2-chloropyridine (0.223 mL, 2.36 mmol). The mixture was stirred at RT for 10 minutes, then heated at 130 °C overnight. Additional Pd(OAc)₂ (0.018 g, 0.0785 mmol) and tricyclopentylphosphine tetrafluoroborate (0.051 g, 0.157 mmol) were added at RT followed by 2-chloropyridine (0.148 mL, 1.57 mmol) and the mixture was heated at 130 °C for 24 h. Additional Pd(OAc)₂ (0.018 g, 0.0785 mmol) and tricyclopentylphosphine tetrafluoroborate (0.051 g, 0.157 mmol) were added at RT and the mixture was heated at 130 °C for further 8 h. The mixture was diluted with DCM and filtered through a Celite® pad. The filtrate was evaporated to dryness and the crude was purified by flash

chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as an orange oil (0.055 g, 0.233 mmol, 15% yield). MS/ESI⁺ 237.1 [MH]⁺, Rt = 0.66 min (Method A).

5 **Intermediate I3: 1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethan-1-one**

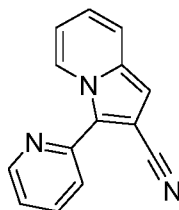


To a solution of N,N'-dimethylethylenediamine (0.250 mL, 2.32 mmol + 0.062 mL, 0.580 mmol) in toluene (6 mL+1.5 mL) cooled to 0°C under nitrogen atmosphere, a 2M solution of trimethylaluminum in toluene (3.27 mL, 6.54 mmol + 0.817 mL, 1.63 mmol) was added drop-wise and the resulting mixture was stirred at r.t. for 1 h. A solution of ethyl 3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizine-2-carboxylate H47 (0.800 g, 2.11 mmol + 0.200 g, 0.527 mmol) in toluene (6 mL + 1.5 mL) was added and the reaction was heated to reflux for 4 h. The mixture was cooled to room temperature, quenched with 1N aqueous HCl solution and extracted with EtOAc; the organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure.

Combined crude was purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow foam (0.140 g, 0.401 mmol, 15% yield). MS/ESI⁺ 350.2 [MH]⁺, Rt = 0.78 min (Method A).

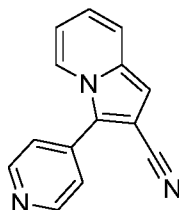
Intermediate J1: 3-(pyridin-2-yl)indolizine-2-carbonitrile

125



A mixture of indolizine-2-carbonitrile B5 (1.3 g, 9.14 mmol), Pd(OAc)₂ (0.102 g, 0.46 mmol), tricyclopentylphosphine tetrafluoroborate (0.298 g, 0.914 mmol) and Cs₂CO₃ (8.93 g, 27.42 mmol) was flushed with nitrogen and toluene (5 mL) was added followed by 2-chloropyridine (1.7 mL, 18.28 mmol). The reaction was heated at 130°C overnight. The mixture was diluted with DCM and filtered through a Celite® pad; the filtrate was evaporated to dryness and the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : DCM = 61 : 39) to afford title compound as a light yellow solid (1.226 g, 5.59 mmol, 61% yield). MS/ESI⁺ 220.1 [MH]⁺, Rt = 1.05 min (Method A).

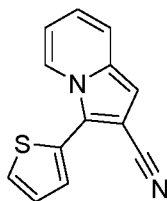
Intermediate J2: 3-(pyridin-4-yl)indolizine-2-carbonitrile



Prepared similarly to intermediate J1, starting from indolizine-2-carbonitrile B5 (0.150 g, 1.05 mmol), Pd(OAc)₂ (0.012 g, 0.053 mmol), tricyclopentylphosphine tetrafluoroborate (0.034 g, 0.105 mmol), Cs₂CO₃ (1.026 g, 3.15 mmol), toluene (1.8 mL) and 4-chloropyridine (0.240 g, 2.11 mmol), heating at 130°C overnight. The crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (DCM to DCM : EtOAc = 70 : 30) to afford title compound as a yellow solid (0.095 g, 0.433 mmol, 41% yield). MS/ESI⁺ 220.1 [MH]⁺, Rt = 0.53 min (Method A).

Intermediate J3: 3-(thiophen-2-yl)indolizine-2-carbonitrile

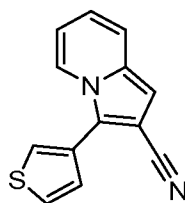
126



Prepared similarly to intermediate J1, starting from indolizine-2-carbonitrile B5 (0.150 g, 1.05 mmol), Pd(OAc)₂ (0.012 g, 0.053 mmol), tricyclopentylphosphine tetrafluoroborate (0.034 g, 0.105 mmol), Cs₂CO₃ (1.026 g, 3.15 mmol), toluene (2 mL) and 2-chlorothiophene (0.195 mL, 2.11 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.012 g, 0.053 mmol), tricyclopentylphosphine tetrafluoroborate (0.034 g, 0.105 mmol) and 2-chlorothiophene (0.195 mL, 2.11 mmol) were added heating at the same temperature for further 24 h. After work-up, the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 95 : 5); a further purification by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : DCM = 95 : 5 to 80 : 20) was required to afford title compound (0.072 g). MS/ESI⁺ 225.0 [MH]⁺, Rt = 1.13 min (Method A).

Intermediate J4: 3-(thiophen-3-yl)indolizine-2-carbonitrile

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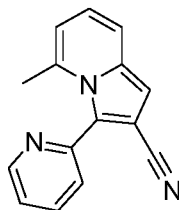


Prepared similarly to intermediate J1, starting from indolizine-2-carbonitrile B5 (0.150 g, 1.05 mmol), Pd(OAc)₂ (0.012 g, 0.053 mmol), tricyclopentylphosphine tetrafluoroborate (0.034 g, 0.105 mmol), Cs₂CO₃ (1.026 g, 3.15 mmol), toluene (2 mL) and 3-chlorothiophene (0.196 mL, 2.11 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.012 g, 0.053 mmol), tricyclopentylphosphine tetrafluoroborate (0.034 g, 0.105 mmol) and 3-chlorothiophene (0.195 mL, 2.11 mmol) were added heating at the same temperature for further 24 h. After work-up the crude was purified by flash chromatography on Biotage

silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound which was used in the next step without any additional purification (0.097 g). MS/ESI⁺ 225.0 [MH]⁺, Rt = 1.12 min (Method A).

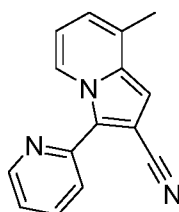
Intermediate J5: 5-methyl-3-(pyridin-2-yl)indolizine-2-carbonitrile

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Prepared similarly to intermediate J1, starting from 5-methylindolizine-2-carbonitrile B6 (0.567 g, 3.63 mmol), Pd(OAc)₂ (0.081 g, 0.363 mmol), tricyclopentylphosphine tetrafluoroborate (0.236 g, 0.726 mmol), Cs₂CO₃ (3.55 g, 10.89 mmol), toluene (7 mL) and 2-chloropyridine (0.687 mL, 7.26 mmol), at 130°C overnight. Additional Pd(OAc)₂ (0.0081 g, 0.363 mmol) and tricyclopentylphosphine tetrafluoroborate (0.236 g, 0.0726 mmol) were added and the mixture was heated at 130°C for further 48 h. After work-up the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 95 : 5 to 90:10) to yield title compound as a yellow solid (0.084 g, 0.036 mmol, 10% yield). MS/ESI⁺ 234.1 [MH]⁺, Rt = 0.95 min (Method A).

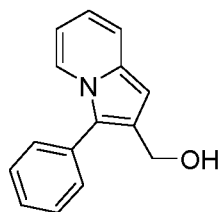
Intermediate J6: 8-methyl-3-(pyridin-2-yl)indolizine-2-carbonitrile



Prepared similarly to intermediate J1, starting from 8-methylindolizine-2-carbonitrile B7 (0.245 g, 1.57 mmol), Pd(OAc)₂ (0.035 g, 0.157 mmol), tricyclopentylphosphine tetrafluoroborate (0.102 g, 0.314 mmol), Cs₂CO₃ (1.530 g, 4.71 mmol) and 2-chloropyridine (0.296 mL, 3.13 mmol), at 130°C overnight. Additional

Pd(OAc)₂ (0.035 g, 0.157 mmol) and tricyclopentylphosphine tetrafluoroborate (0.102 g, 0.314 mmol) were added and the mixture was heated at 130°C for further 12 h. After work-up, the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5). A further purification by flash
5 chromatography on Biotage silica gel SNAP cartridge (cyclohexane : DCM = 50 : 50 to 100% DCM) was required to yield title compound as a white solid (0.164 g, 0.70 mmol, 45% yield). MS/ESI⁺ 234.1 [MH]⁺, Rt = 1.16 min (Method A).

Intermediate K1: (3-phenylindolizin-2-yl)methanol



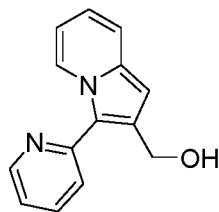
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To a solution of ethyl 3-phenylindolizine-2-carboxylate H1 (0.475 g, 1.79 mmol) in DCM (19 mL) cooled at -78°C under nitrogen, a solution of 1M DIBAL in toluene (5.37 mL, 5.37 mmol) was added drop-wise over 15 minutes and the reaction was stirred at -78°C for 1.5 h. The reaction mixture was quenched by drop-wise addition of a saturated
15 ammonium chloride solution and gradually warmed up to room temperature. The mixture was extracted several times with DCM and the combined organic layers were filtered through a Phase Separator tube washing with DCM, dried over sodium sulfate and concentrated *in vacuo*. The crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title
20 compound as a fluorescent yellow-green solid (0.360 g, 1.61 mmol, 90% yield). MS/ESI⁺ 224.1 [MH]⁺, Rt = 0.99 min (Method A).

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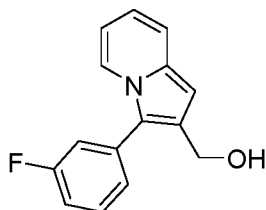
Intermediate K2: [3-(pyridin-2-yl)indolizin-2-yl]methanol

129



Prepared similarly to intermediate K1, starting from 3-(pyridin-2-yl)indolizine-2-carboxylate H2 (0.554 g, 2.08 mmol), stirring for 1 h, and purified by flash chromatography on silica-NH Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as a yellow oil (0.402 g, 1.79 mmol, 86% yield). MS/ESI⁺ 225.1 [MH]⁺, Rt = 0.54 min (Method A).

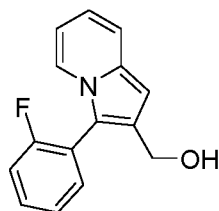
Intermediate K3: [3-(3-fluorophenyl)indolizin-2-yl]methanol



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Prepared similarly to intermediate K1, starting from ethyl 3-(3-fluorophenyl)indolizine-2-carboxylate H3 (0.674 g, 2.38 mmol), stirring for 1.5 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as a yellow oil (0.400 g, 1.66 mmol, 70% yield). MS/ESI⁺ 242.1 [MH]⁺, Rt = 1.01 min (Method A).

Intermediate K4: [3-(2-fluorophenyl)indolizin-2-yl]methanol

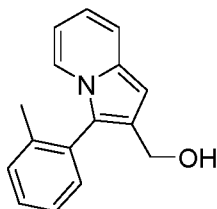


Prepared similarly to intermediate K1, starting from ethyl 3-(2-fluorophenyl)indolizine-2-carboxylate H4 (0.638 g, 2.25 mmol), stirring for 1 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to

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cyclohexane : EtOAc = 90 : 10) to afford title compound as a pale green oil (0.448 g, 1.857 mmol, 82% yield). MS/ESI⁺ 242.1 [MH]⁺, Rt = 0.96 min (Method B).

Intermediate K5: [3-(2-methylphenyl)indolizin-2-yl]methanol

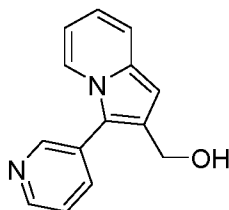


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Prepared similarly to intermediate K1, starting from ethyl 3-(2-methylphenyl)indolizine-2-carboxylate H5 (2.65 mmol), stirring for 1 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as a fluorescent pale green solid (0.443 g, 1.867 mmol, 71% yield). MS/ESI⁺ 238.2 [MH]⁺, Rt = 1.05 min (Method A).

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Intermediate K6: [3-(pyridin-3-yl)indolizin-2-yl]methanol



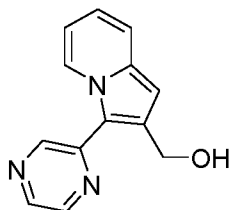
Prepared similarly to intermediate K1, starting from ethyl 3-(pyridin-3-yl)indolizine-2-carboxylate H6 (0.344 g, 1.29 mmol), stirring for 1 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 70 : 30 to 100% EtOAc) to afford title compound as a pale yellow oil (0.234 g, 1.04 mmol, 81% yield). MS/ESI⁺ 225.1 [MH]⁺, Rt = 0.48 min (Method A).

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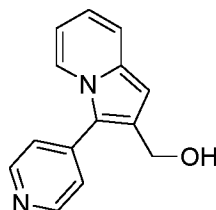
Intermediate K7: [3-(pyrazin-2-yl)indolizin-2-yl]methanol

131



Prepared similarly to intermediate K1, starting from ethyl 3-(pyrazin-2-yl)indolizine-2-carboxylate H7 (0.098 g, 0.367 mmol), stirring for 2 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (DCM to DCM : EtOAc = 40 : 60) to afford title compound as a yellow solid (0.042 g, 0.186 mmol, 51% yield). MS/ESI⁺ 226.1 [MH]⁺, Rt = 0.74 min (Method A).

Intermediate K8: [3-(pyridin-4-yl)indolizin-2-yl]methanol

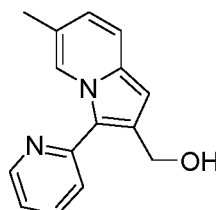


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Prepared similarly to intermediate K1, starting from ethyl 3-(pyridin-4-yl)indolizine-2-carboxylate H8 (0.250 g, 0.939 mmol), stirring for 2 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude title compound was used without any additional purification (0.200 g, 0.892 mmol, 95% yield). MS/ESI⁺ 225.1 [MH]⁺, Rt = 0.38 min (Method A).

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Intermediate K9: [6-methyl-3-(pyridin-2-yl)indolizin-2-yl]methanol

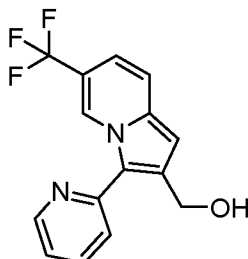


Prepared similarly to intermediate K1, starting from ethyl 6-methyl-3-(pyridin-2-yl)indolizine-2-carboxylate H9 (0.197 g, 0.70 mmol), stirring for 30 min, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium

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tartrate tetrahydrate; the crude title compound was used without any additional purification (0.136 g, 0.57 mmol, 81% yield). MS/ESI⁺ 239.2 [MH]⁺, Rt = 0.63 min (Method A).

Intermediate K10: [3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]methanol

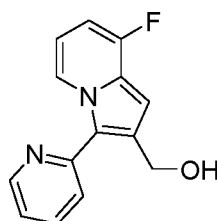


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Prepared similarly to intermediate K1, starting from ethyl 3-(pyridin-2-yl)-6-(trifluoromethyl)indolizine-2-carboxylate H10 (0.255 g, 0.763 mmol), stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude title compound, obtained as a pale yellow solid, was used without any additional purification (0.197 g, 0.674 mmol, 88% yield). MS/ESI⁺ 239.3 [MH]⁺, Rt = 1.02 min (Method A).

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Intermediate K11: [8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]methanol



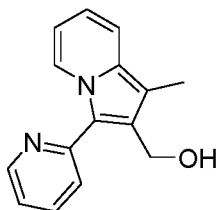
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Prepared similarly to intermediate K1, starting from ethyl 8-fluoro-3-(pyridin-2-yl)indolizine-2-carboxylate H11 (0.140 g, 0.49 mmol), stirring for 1 h, and the crude title compound (0.120 g, 0.49 mmol, quantitative yield) was used without any additional purification. MS/ESI⁺ 243.1 [MH]⁺, Rt = 0.71 min (Method A).

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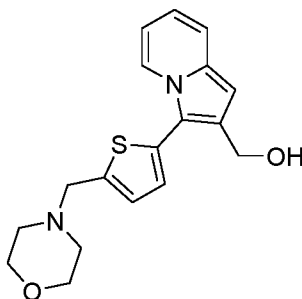
Intermediate K12: [1-methyl-3-(pyridin-2-yl)indolizin-2-yl]methanol

133



Prepared similarly to intermediate K1, starting from ethyl 1-methyl-3-(pyridin-4-yl)indolizine-2-carboxylate H12 (0.088 g, 0.314 mmol), stirring for 2 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude title compound was used without any additional purification (0.061 g, 0.256 mmol, 82% yield). MS/ESI⁺ 239.1 [MH]⁺, Rt = 0.60 min (Method A).

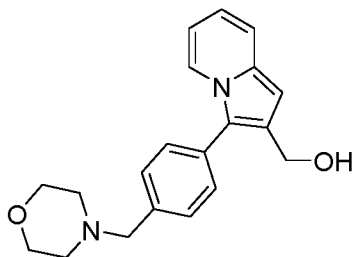
Intermediate K13: {3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl}methanol



Prepared similarly to intermediate K1, starting from ethyl 3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizine-2-carboxylate H13 (0.569 g, 1.53 mmol), stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.364 g, 1.11 mmol, 72% yield). MS/ESI⁺ 328.2 [MH]⁺, Rt = 0.50 min (Method A).

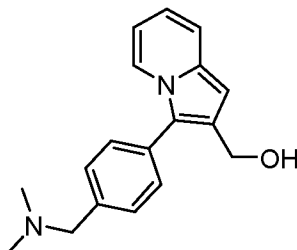
Intermediate K14: {3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-

134

yl}methanol

Prepared similarly to intermediate K1, starting from ethyl 3-[4-(morpholin-4-ylmethyl)phenyl]indolizine-2-carboxylate H14 (0.488 g, 1.34 mmol), stirring for 3 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 100 : 0 to 0 : 100) to afford title compound as a dark yellow oil (0.271 g, 0.84 mmol, 63% yield). MS/ESI⁺ 323.3 [MH]⁺, Rt = 0.50 min (Method A).

10 **Intermediate K15: (3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)methanol**

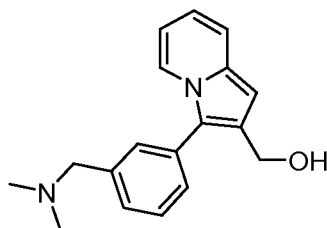


Prepared similarly to intermediate K1, starting from ethyl 3-{4-[(dimethylamino)methyl]phenyl}indolizine-2-carboxylate H15 (0.421 g, 1.30 mmol), stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a pale yellow oil (0.235 g, 0.83 mmol, 64% yield). MS/ESI⁺ 281.2 [MH]⁺, Rt = 0.49 min (Method A).

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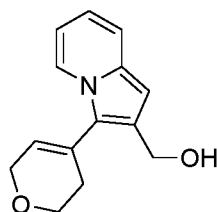
Intermediate K16: (3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-

135

yl)methanol

Prepared similarly to intermediate K1, starting from ethyl 3-{3-
 5 [(dimethylamino)methyl]phenyl}indolizine-2-carboxylate H16 (0.457 g, 1.42 mmol),
 stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution
 of potassium and sodium tartrate tetrahydrate; the crude was purified by flash
 chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane :
 EtOAc = 50 : 50) to afford title compound as a pale yellow oil (0.285 g, 1.02 mmol, 71%
 yield). MS/ESI⁺ 281.3 [MH]⁺, Rt = 0.52 min (Method A).

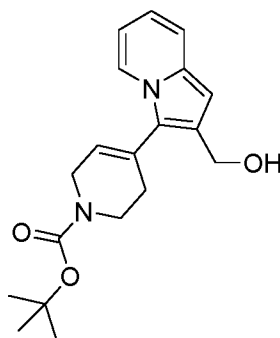
10 **Intermediate K17: [3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]methanol**



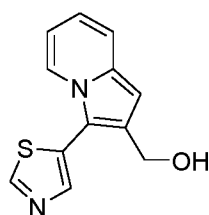
Prepared similarly to intermediate K1, starting from ethyl 3-(3,6-dihydro-2H-pyran-
 4-yl)indolizine-2-carboxylate H17 (0.134 g, 0.49 mmol), stirring for 1 h, and the reaction
 15 was quenched by drop-wise addition of a saturated solution of potassium and sodium
 tartrate tetrahydrate; the crude was purified by flash chromatography on silica gel Biotage
 SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound
 as a pale yellow oil (0.078 g, 0.34 mmol, 70% yield). MS/ESI⁺ 230.1 [MH]⁺, Rt = 0.79 min
 (Method A).

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Intermediate K18: tert-butyl 4-[2-(hydroxymethyl)indolizin-3-yl]-1,2,3,6-

tetrahydropyridine-1-carboxylate

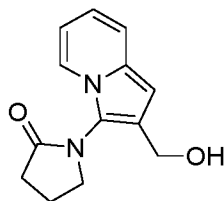
Prepared similarly to intermediate K1, starting from ethyl 3-{1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}indolizine-2-carboxylate H18 (0.370 g, 0.91 mmol), stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.194 g, 0.59 mmol, 65% yield).
MS/ESI⁺ 329.3 [MH]⁺, Rt = 1.08 min (Method A).

Intermediate K19: [3-(1,3-thiazol-5-yl)indolizin-2-yl]methanol

Prepared similarly to intermediate K1, starting from ethyl 3-(1,3-thiazol-5-yl)indolizine-2-carboxylate H19 (0.169 g, 0.62 mmol), stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude title compound was used without any additional purification (0.143 g, 0.62 mmol, quantitative yield). MS/ESI⁺ 231.1 [MH]⁺, Rt = 0.75 min (Method A).

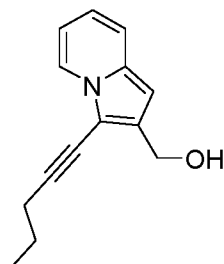
Intermediate K20: 1-[2-(hydroxymethyl)indolizin-3-yl]pyrrolidin-2-one

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Prepared similarly to intermediate K1, starting from ethyl 3-(2-oxopyrrolidin-1-yl)indolizine-2-carboxylate H20 (0.315 g, 1.16 mmol), stirring for 1h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 100 : 0 to 0 : 100) to afford title compound as a brown oil (0.057 g, 0.27 mmol, 21% yield). MS/ESI⁺ 231.2 [MH]⁺, Rt = 0.61 min (Method A).

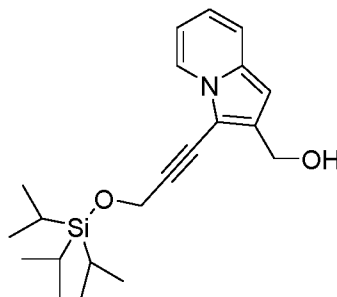
Intermediate K21: [3-(pent-1-yn-1-yl)indolizin-2-yl]methanol



Prepared similarly to intermediate K1, starting from 3-(pent-1-yn-1-yl)indolizine-2-carboxylate H21 (0.260 g, 1.02 mmol), stirring for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude title compound was used without any additional purification (0.217 g, 1.02 mmol, quantitative yield). MS/ESI⁺ 214.2 [MH]⁺, Rt = 1.09 min (Method A).

Intermediate K22: [3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-

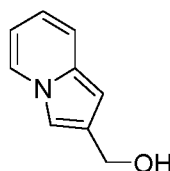
138

2-yl]methanol

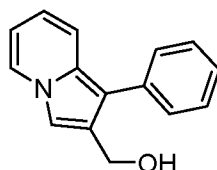
Prepared similarly to intermediate K1, starting from ethyl 3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizine-2-carboxylate H23 (0.501 g, 1.25 mmol), stirring
5 for 1 h, and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate; the crude title compound was used without any additional purification (0.393 g, 1.10 mmol, 88% yield). MS/ESI⁺ 358.1 [MH]⁺, Rt = 1.55 min (Method A).

Intermediate K23: indolizin-2-ylmethanol

10



Prepared similarly to intermediate K1, starting from ethyl indolizine-2-carboxylate B1 (0.500 g, 2.642 mmol), stirring for 1 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as
15 a white solid (0.334 g, 2.269 mmol, 86% yield). MS/ESI⁺ 148.0 [MH]⁺, Rt = 0.30 min. (Method A).

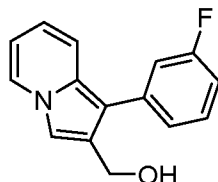
Intermediate K24: (1-phenylindolizin-2-yl)methanol

20 Prepared similarly to intermediate K1, starting from ethyl 1-phenylindolizine-2-carboxylate H24 (0.475 g, 1.79 mmol), stirring for 2 h, and purified by flash

chromatography on silica gel Biotage SNAP cartridge (DCM : cyclohexane = 90 : 10 to 100% DCM) to afford title compound as a yellow solid (0.230 g, 1.03 mmol, 57% yield). MS/ESI⁺ 224.1 [MH]⁺, Rt = 0.97 min (Method A).

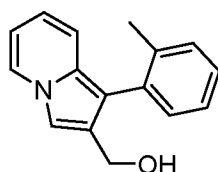
Intermediate K25: [1-(3-fluorophenyl)indolizin-2-yl]methanol

5



Prepared similarly to intermediate K1, starting from ethyl 1-(3-fluorophenyl)indolizine-2-carboxylate H25 (0.585 g, 2.06 mmol), stirring for 2 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (DCM : cyclohexane = 90 : 10 to 100% DCM) to afford title compound as a blue oil (0.330 g, 1.36 mmol, 66.3% yield). MS/ESI⁺ 242.1 [MH]⁺, Rt = 1.02 min (Method A).

Intermediate K26 [1-(2-methylphenyl)indolizin-2-yl]methanol

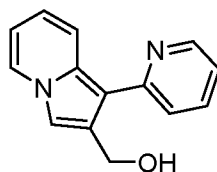


Prepared similarly to intermediate K1, starting from ethyl 1-(2-methylphenyl)indolizine-2-carboxylate H26 (0.547 g, 1.95 mmol), stirring for 2 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (DCM : cyclohexane = 90 : 10 to 100% DCM) to afford title compound as a yellow oil (0.230 g, 0.96 mmol, 50% yield). MS/ESI⁺ 238.1 [MH]⁺, Rt = 0.99 min (Method A).

20

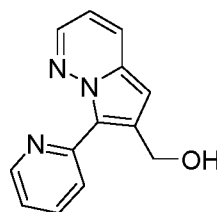
Intermediate K27: [1-(pyridin-2-yl)indolizin-2-yl]methanol

140



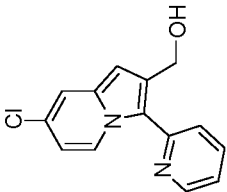
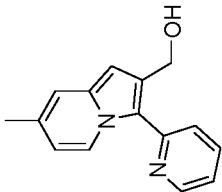
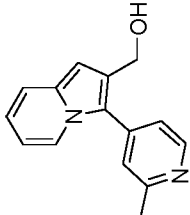
Prepared similarly to intermediate K1, starting from ethyl 1-(pyridin-2-yl)indolizine-2-carboxylate H27 (0.446 g, 1.67 mmol), stirring for 15 min, and the crude
5 title compound obtained after work-up was used without any additional purification (0.358 g, 1.59 mmol, 96% yield). MS/ESI⁺ 225.1 [MH]⁺, Rt = 0.38 min (Method A).

Intermediate K28: [7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methanol

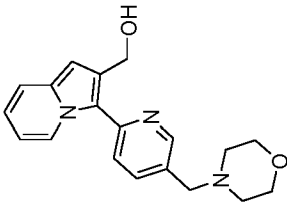
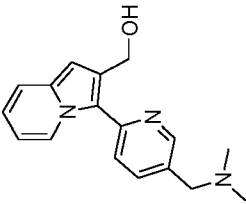
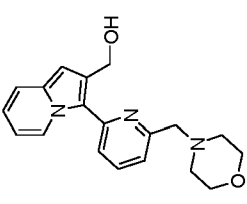
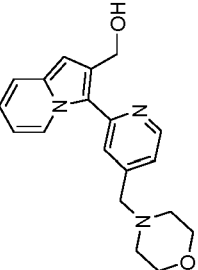


10 To a solution of methyl 7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazine-6-carboxylate H28 (0.120 g, 0.47 mmol) in DCM (3.7 mL) cooled at -78°C under nitrogen, a solution of 1 M DIBALH in toluene (0.95 mL, 0.95 mmol) was added drop-wise over 10 min and the reaction was stirred at -78°C for 1 h. Additional 1M DIBAL in toluene (0.23 mL, 0.23 mmol) was added drop-wise over 10 min. and the reaction was stirred at -78°C for further
15 1 h. The reaction mixture was quenched by drop-wise addition of saturated ammonium chloride solution and gradually warmed up to room temperature. The mixture was extracted with DCM and the combined organic layers were filtered through a phase separator tube, dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane : EtOAc = 80 : 20 to 50 : 50)
20 to afford title compound as a pale yellow solid (0.078 g, 0.35 mmol, 74% yield). MS/ESI⁺ 226.1 [MH]⁺, Rt = 0.39 min (Method A).

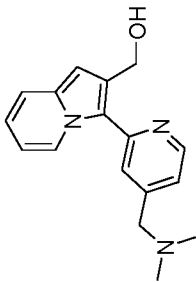
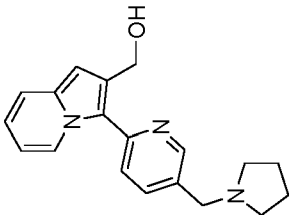
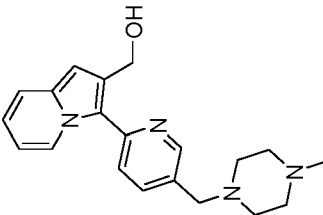
Intermediates K29-45, K47, K50-52, K54-66 and K-68-71 found in the table below may be prepared from suitable intermediates reported below following similar procedures as for compound K1.

Intermediate	Name and Molecular Structure		Reagent	Analytical data
K29	[7-chloro-3-(pyridin-2-yl)indolizin-2-yl]methanol		H29	MS/ESI ⁺ 259.1 [MH] ⁺ , Rt = 0.85 min (Method A)
K30	[7-methyl-3-(pyridin-2-yl)indolizin-2-yl]methanol		H30	MS/ESI ⁺ 239.2 [MH] ⁺ , Rt = 0.63 min (Method A)
K31	[3-(2-methylpyridin-4-yl)indolizin-2-yl]methanol		H31	MS/ESI ⁺ 239.2 [MH] ⁺ , Rt = 0.40 min (Method A)

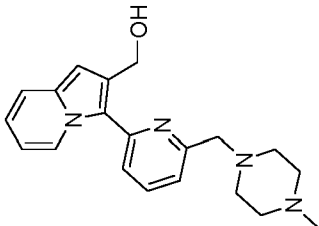
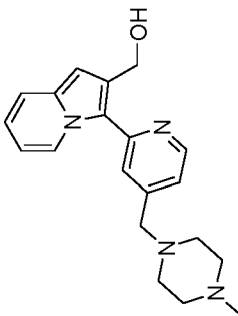
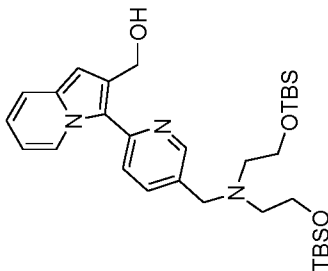
(continued)

K32	{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}methanol		H32	MS/ESI ⁺ 324.3 [MH] ⁺ , Rt = 0.42 min (Method A)
K33	(3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H33	MS/ESI ⁺ 282.2 [MH] ⁺ , Rt = 0.40 min (Method A)
K34	{3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}methanol		H34	MS/ESI ⁺ 324.3 [MH] ⁺ , Rt = 0.46 min (Method A)
K35	{3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}methanol		H35	MS/ESI ⁺ 324.2 [MH] ⁺ , Rt = 0.44 min (Method A)

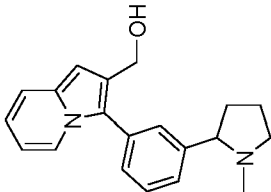
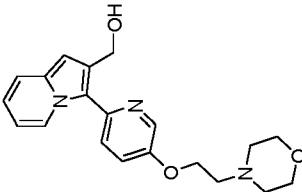
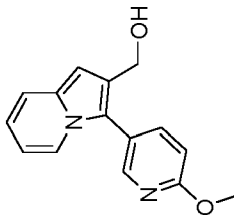
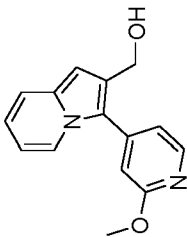
(continued)

K36	(3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H36	MS/ESI ⁺ 282.3 [MH] ⁺ , Rt = 0.43 min (Method A)
K37	{3-[5-(pyrrolidin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H37	MS/ESI ⁺ 308.2 [MH] ⁺ , Rt = 0.44 min (Method A)
K38	(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H38	MS/ESI ⁺ 337.4 [MH] ⁺ , Rt = 0.38 – 0.40 min (Method A)

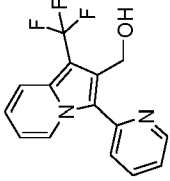
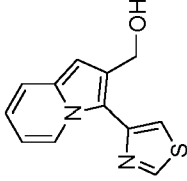
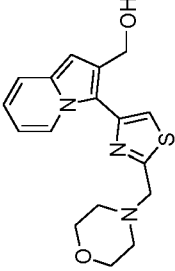
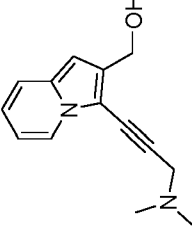
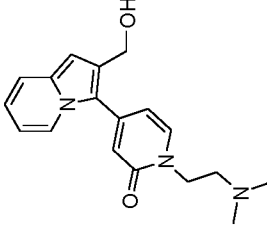
(continued)

K39	(3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H39	MS/ESI ⁺ 337.4 [MH] ⁺ , Rt = 0.44 min (Method A)
K40	(3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H40	MS/ESI ⁺ 337.5 [MH] ⁺ , Rt = 0.36 min (Method A)
K41	(3-{5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)methyl]pyridin-2-yl}indolizin-2-yl)methanol		H41	MS/ESI ⁺ 570.5 [MH] ⁺ , Rt = 1.16 min (Method A)

(continued)

K42	{3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizin-2-yl}methanol		H42	MS/ESI ⁺ 307.3 [MH] ⁺ , Rt = 0.53 min (Method A)
K43	(3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizin-2-yl)methanol		H43	MS/ESI ⁺ 354.1 [MH] ⁺ , Rt = 0.82 min (Method C)
K44	[3-(6-methoxypyridin-3-yl)indolizin-2-yl]methanol (		H44	MS/ESI ⁺ 255.0 [MH] ⁺ , Rt = 0.88 min (Method A)
K45	[3-(2-methoxypyridin-4-yl)indolizin-2-yl]methanol		H45	MS/ESI ⁺ 255.2 [MH] ⁺ , Rt = 0.80 min (Method A)

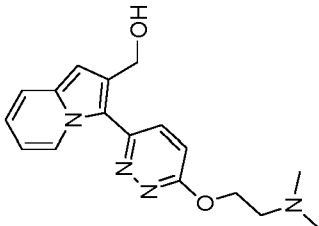
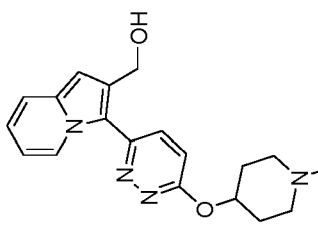
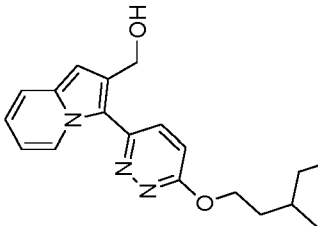
(continued)

K47	[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]methanol		H48	MS/ESI ⁺ 293.2 [MH] ⁺ , Rt = 1.00 min (Method A)
K50	[3-(1,3-thiazol-4-yl)indolizin-2-yl]methanol		H52	MS/ESI ⁺ 231.1 [MH] ⁺ , Rt = 0.82 min (Method A)
K51	{3-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]indolizin-2-yl}methanol		H53	MS/ESI ⁺ 330.2 [MH] ⁺ , Rt = 0.49 min (Method A)
K52	{3-[3-(dimethylamino)prop-1-yn-1-yl]indolizin-2-yl}methanol		H54	MS/ESI ⁺ 228.8 [MH] ⁺ , Rt = 0.39 min (Method A)
K54	1-[2-(dimethylamino)ethyl]-4-[2-(hydroxymethyl)indolizin-3-yl]-1,2-dihydropyridin-2-one		H56	MS/ESI ⁺ 312.4 [MH] ⁺ , Rt = 0.45 min (Method A)

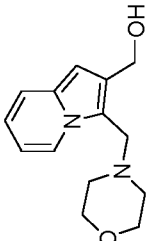
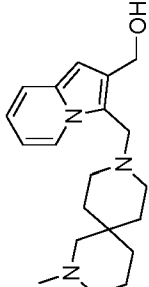
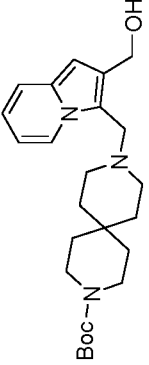
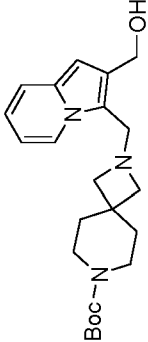
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K55	6-[2-(hydroxymethyl)indolizin-3-yl]-2-[2-(pyrrolidin-1-yl)ethyl]-2,3-dihydropyridazin-3-one		H60	MS/ESI ⁺ 339.3 [MH] ⁺ , Rt = 0.41 - 0.44 min (Method A)
K56	6-[2-(hydroxymethyl)indolizin-3-yl]-2-[2-(4-methylpiperazin-1-yl)ethyl]-2,3-dihydropyridazin-3-one		H61	MS/ESI ⁺ 368.4 [MH] ⁺ , Rt = 0.43 min (Method A)
K57	6-[2-(hydroxymethyl)indolizin-3-yl]-2-[2-(morpholin-4-yl)ethyl]-2,3-dihydropyridazin-3-one		H62	MS/ESI ⁺ 355.3 [MH] ⁺ , Rt = 0.42 min (Method A)
K58	(3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)methanol		H63	MS/ESI ⁺ 368.3 [MH] ⁺ , Rt = 0.41 - 0.43 min (Method A)

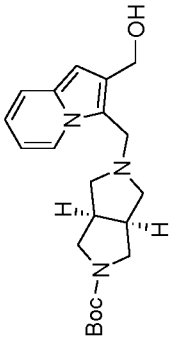
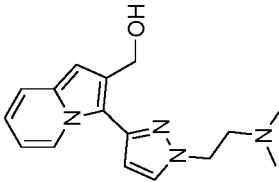
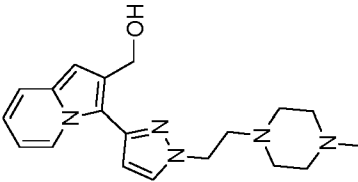
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K59	(3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizin-2-yl)methanol		H64	MS/ESI ⁺ 313.3 [MH] ⁺ , Rt = 0.46 min (Method A)
K60	(3-{6-[1-(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizin-2-yl)methanol		H65	MS/ESI ⁺ 339.3 [MH] ⁺ , Rt = 0.45 - 0.47 min (Method A)
K61	(3-{6-[2-(1-methylpiperidin-4-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)methanol		H66	MS/ESI ⁺ 367.4 [MH] ⁺ , Rt = 0.53 min (Method A)

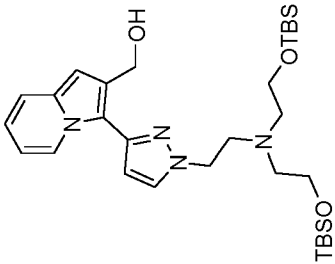
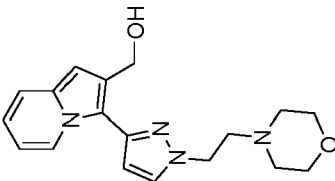
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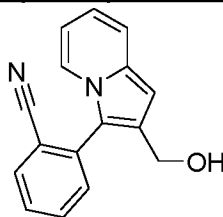
K62	[3-(morpholin-4-ylmethyl)indolizin-2-yl]methanol		H67	MS/ESI ⁺ 160.2 found, Rt = 0.75 min (Method C)
K63	[3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl)indolizin-2-yl]methanol		H68	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.09 – 8.13 (m, 1 H), 7.33 – 7.38 (m, 1 H), 6.63 – 6.69 (m, 1 H), 6.51 – 6.57 (m, 1 H), 6.35 (s, 1 H), 4.91 (t, 1 H), 4.55 (d, 2 H), 3.73 (s, 2 H), 2.25 – 2.37 (m, 4 H), 2.11 – 2.23 (m, 2 H), 2.08 (s, 3 H), 1.98 – 2.10 (m, 2 H), 1.16 – 1.51 (m, 8 H)
K64	tert-butyl (hydroxymethyl)indolizin-3-ylmethyl-3,9-diazaspiro[5.5]undecane-3-carboxylate		H69	MS/ESI ⁺ 414.5 [MH] ⁺ , Rt = 0.67 min (Method A)
K65	tert-butyl (hydroxymethyl)indolizin-3-ylmethyl-2,7-diazaspiro[3.5]nonane-7-carboxylate		H70	MS/ESI ⁺ 386.5 [MH] ⁺ , Rt = 0.60 min (Method A)

(continued)

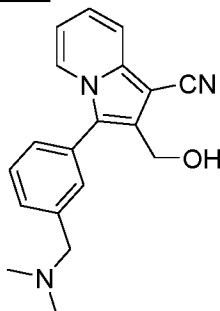
K66	tert-butyl (3aR,6aS)-5-{{[2-(hydroxymethyl)indolizin-3-yl]methyl}-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate		H71	MS/ESI ⁺ 372.3 [MH] ⁺ , Rt = 1.09 min (Method C)
K68	(3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)methanol		H75	MS/ESI ⁺ 285.3 [MH] ⁺ , Rt = 0.44 min (Method A)
K69	(3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)methanol		H76	MS/ESI ⁺ 340.3 [MH] ⁺ , Rt = 0.46 min (Method A)

(continued)

K70	(3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)methanol		H77	MS/ESI ⁺ 573.5 [MH] ⁺ , Rt = 1.11 min (Method A)
K71	(3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)methanol		H78	MS/ESI ⁺ 327.3 [MH] ⁺ , Rt = 0.50 min (Method A)

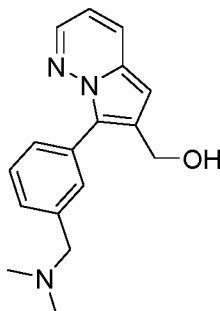
Intermediate K46: 2-[2-(hydroxymethyl)indolizin-3-yl]benzonitrile

To a stirred solution of ethyl 3-(2-cyanophenyl)indolizine-2-carboxylate H46 (0.240 g, 0.827 mmol) in THF (12 mL), 2M LiBH₄ solution in THF (0.83 mL, 1.654 mmol) and MeOH (0.4 mL) were added and the reaction was stirred at 50°C for 2 h. Additional 2M LiBH₄ solution in THF (0.83 mL, 1.654 mmol) was added and the solution was stirred at the same temperature overnight. The reaction mixture was diluted with EtOAc and washed with H₂O. The organic phase was concentrated under reduced pressure and the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane: EtOAc = 60: 40) to afford title compound (0.140 g, 0.56 mmol, 68% yield). MS/ESI⁺ 249.2 [MH]⁺, Rt = 0.89 min (Method A).

Intermediate K48: 3-{3-[(dimethylamino)methyl]phenyl}-2-(hydroxymethyl)indolizine-1-carbonitrile

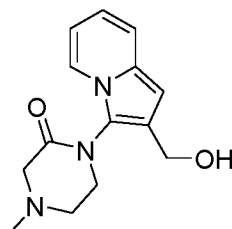
Prepared similarly to intermediate K28, starting from ethyl 1-cyano-3-{3-[(dimethylamino)methyl]phenyl}indolizine-2-carboxylate H50 (2.7 g, 7.77 mmol) and the reaction was quenched by drop-wise addition of a saturated solution of potassium and sodium tartrate tetrahydrate, to afford crude title compound which was used without any additional purification (theoretical 7.77 mmol, yield considered to be quantitative). MS/ESI⁺ 306.3 [MH]⁺, Rt = 0.97 min (Method J).

Intermediate K49: (7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazin-6-yl)methanol

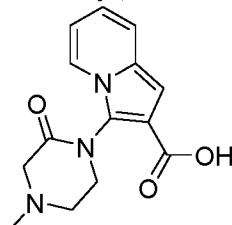


Prepared similarly to intermediate K28, starting from methyl 7-{3-
 5 [(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazine-6-carboxylate H51 (0.713 g, 2.3 mmol), and purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound (0.530 g, 1.88 mmol, 82 % yield). MS/ESI⁺ 282.3 [MH]⁺, Rt = 0.42 - 0.44 min (Method A).

Intermediate K53: 1-[2-(hydroxymethyl)indolizin-3-yl]-4-methylpiperazin-2-one



Step1: 3-(4-methyl-2-oxopiperazin-1-yl)indolizine-2-carboxylic acid K53a



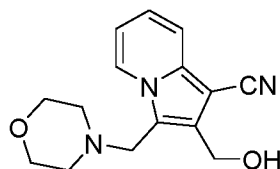
Ethyl 3-(4-methyl-2-oxopiperazin-1-yl)indolizine-2-carboxylate H55 (0.694 g, 2.3
 15 mmol) was dissolved in THF (11.4 mL) and water (5.5 mL), lithium hydroxide (0.110 g, 4.6 mmol) was added and the mixture was heated at 60°C for 24 h. The organic solvent was removed under reduced pressure and the aqueous residue was acidified with 1N HCl and extracted with DCM; the combined organic layers were dried over sodium sulfate and evaporated. The aqueous phase was evaporated and the residue was taken-up with DCM

and MeOH and filtered; the filtered solution was evaporated under reduce pressure. The two fractions were combined to afford title compound as a brown solid (0.598 g). MS/ESI⁺ 274.2 [MH]⁺, Rt = 0.35 min (Method A).

Step2: 1-[2-(hydroxymethyl)indolizin-3-yl]-4-methylpiperazin-2-one K53

5 NaBH₄ (0.166 g, 4.4 mmol) was added to dry THF (4 mL), and the mixture was cooled at 10°C before BF₃•Et₂O (0.70 mL, 5.72 mmol) was added drop-wise. Then a solution of 3-(4-methyl-2-oxopiperazin-1-yl)indolizine-2-carboxylic acid K53a (0.598 g) in THF (2.6 mL) was carefully added, and the mixture was allowed to stir at room temperature for 4 h. The reaction was quenched with methanol; 10% aqueous HCl was
10 added and the mixture was heated at 60°C for 1 h. The pH of reaction mixture was adjusted to neutral with 50% aqueous NaOH and the volatiles were evaporated under reduced pressure. The aqueous residue was extracted with DCM and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 99 : 1) to afford
15 title compound as an orange oil (0.122 g) which was used without any additional purification. MS/ESI⁺ 260.2 [MH]⁺, Rt = 0.31 min (Method A).

Intermediate K67: 2-(hydroxymethyl)-3-(morpholin-4-ylmethyl)indolizine-1-carbonitrile

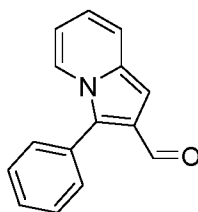


20 To a solution of ethyl 1-cyano-3-(morpholin-4-ylmethyl)indolizine-2-carboxylate H72 (0.382 g, 1.21 mmol) in THF (24 mL) cooled at 0°C under nitrogen, a solution of LiAlH₄ 1M in THF (0.30 mL, 0.3 mmol) was added drop-wise and the reaction was stirred at 0°C for 30 min. Additional LiAlH₄ 1M in THF (0.12 mL, 0.12 mmol) was added drop-wise and the reaction was stirred at 0°C for 30 min. A new portion of LiAlH₄ 1M in THF
25 (0.12 mL, 0.12 mmol) was added drop-wise and the reaction was stirred at 0°C for further 30 min. The reaction mixture was quenched by portion-wise addition of sodium sulfate

decahydrate, the mixture was filtered and the filtrate was concentrated in vacuo. The crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound as a pale yellow oil (0.145 g, 0.53 mmol, 44% yield).

5 ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 8.18 - 8.23 (m, 1 H), 7.62 - 7.67 (m, 1 H), 7.08 - 7.13 (m, 1 H), 6.80 - 6.86 (m, 1 H), 4.88 (s, 2 H), 3.85 (s, 2 H), 3.66 - 3.72 (m, 4 H), 2.47 - 2.53 (m, 4 H).

Intermediate L1: 3-phenylindolizine-2-carbaldehyde

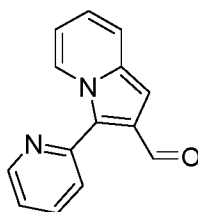


10

To a solution of (3-phenylindolizin-2-yl)methanol K1 (0.227 g, 1.016 mmol) in DCM (5 mL), MnO_2 (1.061 g, 12.20 mmol) was added and the mixture was heated at 50°C for 2 h. The mixture was diluted with DCM and filtered through a Celite® pad. The filtrate was evaporated to dryness to afford title compound as a yellow oil (0.189 g, 0.854 mmol, 85% yield). MS/ESI⁺ 222.1 [MH]⁺, R_t = 1.11 min (Method A).

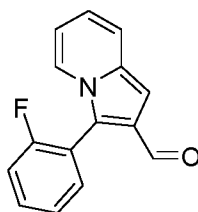
15

Intermediate L2 3-(pyridin-2-yl)indolizine-2-carbaldehyde

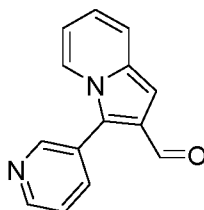


20

Prepared similarly to intermediate L1 starting from [3-(pyridin-2-yl)indolizin-2-yl]methanol K2 (0.185 g, 0.825 mmol) and MnO_2 (1.08 g, 12.37 mmol) was added and the mixture was heated at 50°C for 4 h. The mixture was diluted with DCM and filtered through a Celite® pad. The filtrate was evaporated to dryness to afford title compound as a yellow solid (0.170 g, 0.765 mmol, 93% yield). MS/ESI⁺ 223.1 [MH]⁺, R_t = 0.84 min (Method A).

Intermediate L3: 3-(2-fluorophenyl)indolizine-2-carbaldehyde

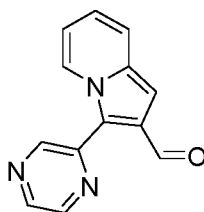
Prepared similarly to intermediate L1, starting from [3-(2-fluorophenyl)indolizin-
5 2-yl]methanol K4 (0.202 g, 0.837 mmol) and MnO₂ (1.114 g, 12.813 mmol), at 50°C for 4
h, to afford title compound as a brown oil (0.169 g, 0.706 mmol, 84% yield). MS/ESI⁺
240.1 [MH]⁺, Rt = 1.11 min (Method A).

Intermediate L4: 3-(pyridin-3-yl)indolizine-2-carbaldehyde

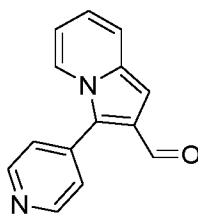
10

Prepared similarly to intermediate L1, starting from [3-(pyridin-3-yl)indolizin-2-
yl]methanol K6 (0.200 g, 0.892 mmol) and MnO₂ (0.930 g, 10.70 mmol), at 50°C for 2 h,
to afford title compound as a yellow solid (0.168 g, 0.756 mmol, 85% yield). MS/ESI⁺
223.1 [MH]⁺, Rt = 0.67 min (Method A).

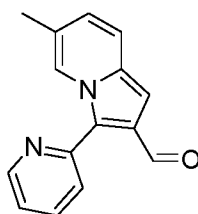
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Intermediate L5: 3-(pyrazin-2-yl)indolizine-2-carbaldehyde

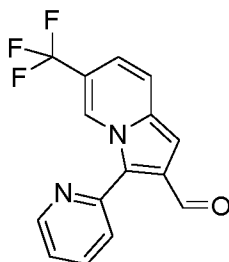
Prepared similarly to intermediate L1, starting from [3-(pyrazin-2-yl)indolizin-2-
yl]methanol K7 (0.042 g, 0.186 mmol) and MnO₂ (0.194 g, 2.232 mmol), at 50°C for 2 h,
20 to afford title compound as a yellow solid (0.037 g, 0.165 mmol, 89% yield). MS/ESI⁺
224.0 [MH]⁺, Rt = 0.79 min (Method A).

Intermediate L6: 3-(pyridin-4-yl)indolizine-2-carbaldehyde

Prepared similarly to intermediate L1, starting from [3-(pyridin-4-yl)indolizin-2-yl]methanol K8 (0.130 g, 0.580 mmol) and MnO₂ (0.762 g, 8.70 mmol), at 50°C for 4 h; after work-up the crude was purified by flash chromatography on 10 g Biotage silica gel SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound (0.100 g, 0.450 mmol, 78% yield). MS/ESI⁺ 223.1 [MH]⁺, Rt = 0.51 min (Method A).

Intermediate L7: 6-methyl-3-(pyridin-2-yl)indolizine-2-carbaldehyde

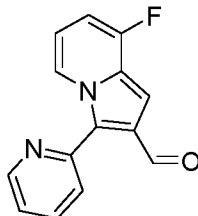
Prepared similarly to intermediate L1, starting from [6-methyl-3-(pyridin-2-yl)indolizin-2-yl]methanol K9 (0.136 g, 0.57 mmol) and MnO₂ (0.744 g, 8.56 mmol), at 50°C for 1 h to afford title compound as a yellow solid (0.127 g, 0.53 mmol, 94% yield). MS/ESI⁺ 237.1 [MH]⁺, Rt = 0.93 min (Method A).

Intermediate L8: 3-(pyridin-2-yl)-6-(trifluoromethyl)indolizine-2-carbaldehyde

Prepared similarly to intermediate L1, starting from [3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]methanol K10 (0.197 g, 0.674 mmol) and MnO₂ (0.879 g,

10.11 mmol), at 50°C for 2 h to afford title compound as a yellow solid (0.150 g, 0.517 mmol, 77% yield). MS/ESI⁺ 291.3 [MH]⁺, Rt = 1.12 min. (Method A).

Intermediate L9: 8-fluoro-3-(pyridin-2-yl)indolizine-2-carbaldehyde

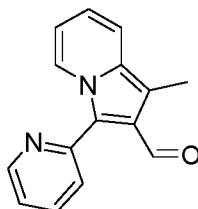


5

Prepared similarly to intermediate L1, starting from [8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]methanol K11 (0.120 g, 0.49 mmol) and MnO₂ (0.521 g, 6.00 mmol), at 50°C for 3 h, to afford title compound as a yellow solid (0.103 g, 0.43 mmol, 85% yield). MS/ESI⁺ 241.1 [MH]⁺, Rt = 0.93 min (Method A).

10

Intermediate L10: 1-methyl-3-(pyridin-2-yl)indolizine-2-carbaldehyde



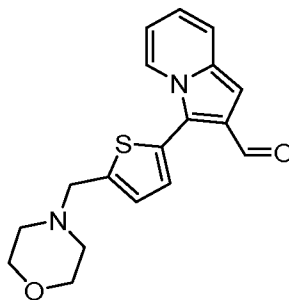
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To a stirred solution of oxalyl chloride (0.033 mL) in DCM (1.5 mL) at -78°C and under nitrogen atmosphere, DMSO (0.055 mL) was slowly added. The mixture was stirred for 10 min then a solution of [1-methyl-3-(pyridin-2-yl)indolizin-2-yl]methanol K12 (0.061 g, 0.256 mmol) in DCM (0.5 mL) was slowly added. The reaction mixture was stirred for 0.5 h then TEA (0.107 mL, 0.768 mmol) was added drop-wise and the mixture was stirred for further 2 h at -78°C. Aqueous saturated sodium bicarbonate was added and the mixture was extracted with DCM. The organic phase was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate and the solvent removed under reduced pressure to afford title compound which was used without any additional purification (0.046 g, 0.195 mmol, 76% yield). MS/ESI⁺ 237.1 [MH]⁺, Rt = 0.94 min (Method A).

20

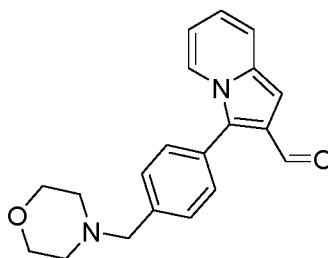
Intermediate L11: 3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizine-2-

159

carbaldehyde

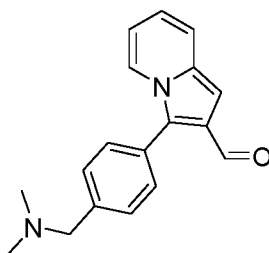
Prepared similarly to intermediate L1, starting from {3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl}methanol K13 (0.364 g, 1.11 mmol) and MnO₂ (1.447 g, 16.65 mmol), at 50°C for 4 h, to afford title compound as an orange oil (0.337 g, 1.03 mmol, 93% yield). MS/ESI⁺ 327.2 [MH]⁺, Rt = 0.54 min (Method A).

Intermediate L12: 3-[4-(morpholin-4-ylmethyl)phenyl]indolizine-2-carbaldehyde



Prepared similarly to intermediate L1, starting from {3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}methanol K14 (0.271 g, 0.84 mmol) and MnO₂ (1.095 g, 12.6 mmol), at 50°C for 4 h, to afford title compound as a dark yellow oil (0.240 g, 0.75 mmol, 89% yield). MS/ESI⁺ 321.2 [MH]⁺, Rt = 0.54 min (Method A).

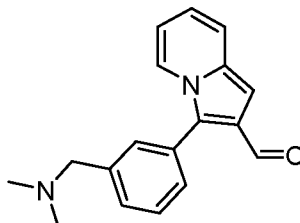
Intermediate L13: 3-[4-[(dimethylamino)methyl]phenyl]indolizine-2-carbaldehyde



Prepared similarly to intermediate L1, starting from (3-[4-[(dimethylamino)methyl]phenyl]indolizin-2-yl)methanol K15 (0.235 g, 0.83 mmol) and

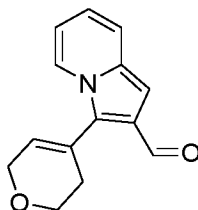
MnO₂ (1.082 g, 12.45 mmol), at 50°C for 4 h, to afford title compound as an orange oil (0.196 g, 0.70 mmol, 84% yield). MS/ESI⁺ 279.2 [MH]⁺, Rt = 0.53 min (Method A).

Intermediate L14: 3-{3-[(dimethylamino)methyl]phenyl}indolizine-2-carbaldehyde



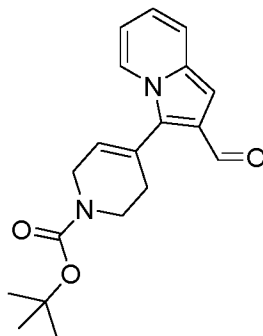
Prepared similarly to intermediate L1, starting from (3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)methanol K16 (0.285 g, 1.02 mmol) and MnO₂ (1.330 g, 15.3 mmol), at 50°C for 4 h, to afford title compound as an orange oil (0.199 g, 0.71 mmol, 70% yield). MS/ESI⁺ 279.2 [MH]⁺, Rt = 0.55 min (Method A).

Intermediate L15: 3-(3,6-dihydro-2H-pyran-4-yl)indolizine-2-carbaldehyde



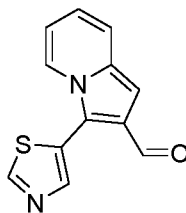
Prepared similarly to intermediate L1, starting from [3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]methanol K17 (0.078 g, 0.34 mmol) and MnO₂ (0.440 g, 5.06 mmol), at 50°C for 4 h, to afford title compound as a yellow solid (0.057 g, 0.25 mmol, 74% yield). MS/ESI⁺ 228.1 [MH]⁺, Rt = 0.89 min (Method A).

Intermediate L16: tert-butyl 4-(2-formylindolizin-3-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate



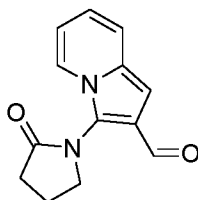
5 Prepared similarly to intermediate L1, starting from **tert-butyl 4-[2-(hydroxymethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate** K18 (0.193 g, 0.58 mmol) and MnO₂ (0.888 g, 10.21 mmol), at 50°C for 4 h, to afford title compound as a yellow solid (0.135 g, 0.41 mmol, 71% yield). MS/ESI⁺ 327.3 [MH]⁺, Rt = 1.17 min (Method A).

10 **Intermediate L17: 3-(1,3-thiazol-5-yl)indolizine-2-carbaldehyde**



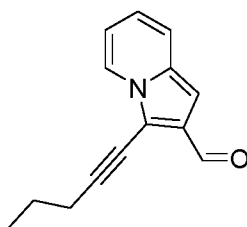
Prepared similarly to intermediate L1, starting from [3-(1,3-thiazol-5-yl)indolizin-2-yl]methanol K19 (0.143 g, 0.62 mmol) and MnO₂ (0.808 g, 9.3 mmol), at 50 °C for 4 h,
15 to afford title compound as an orange solid (0.097 g, 0.42 mmol, 68% yield). MS/ESI⁺ 229.1 [MH]⁺, Rt = 0.83 min (Method A).

Intermediate L18: 3-(2-oxopyrrolidin-1-yl)indolizine-2-carbaldehyde



Prepared similarly to intermediate L1, starting from 1-[2-(hydroxymethyl)indolizin-3-yl]pyrrolidin-2-one K20 (0.057 g, 0.25 mmol) and MnO₂ (0.326 g, 3.75 mmol), at 50°C for 4 h, to afford title compound as a brown oil (0.036 g, 0.16 mmol, 63% yield). MS/ESI⁺ 229.1 [MH]⁺, Rt = 0.70 min (Method A).

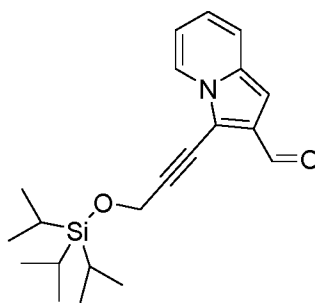
5 **Intermediate L19: 3-(pent-1-yn-1-yl)indolizine-2-carbaldehyde**



Prepared similarly to intermediate L1, starting from {[3-(pent-1-yn-1-yl)indolizin-2-yl]methanol K21 (theoric 1.02 mmol) and MnO₂ (1.330 g, 15.3 mmol), at 50°C for 4 h.

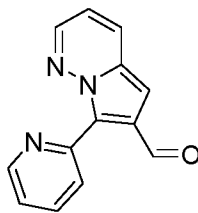
10 The crude was purified by flash chromatography on Biotage silica SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 :10) to afford title compound as a yellow solid (0.158 g, 0.74 mmol, 73%). MS/ESI⁺ 212.1 [MH]⁺, Rt = 1.22 min (Method A).

Intermediate L20: 3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizine-2-carbaldehyde



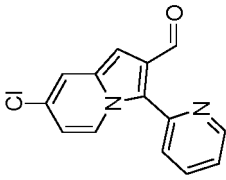
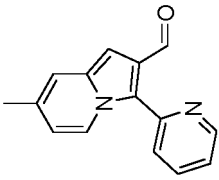
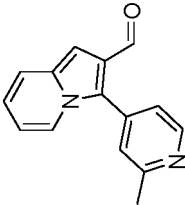
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Prepared similarly to intermediate L1, starting from [3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]methanol K22 (0.392 g, 1.09 mmol) and MnO₂ (1.09 g, 16.35 mmol), at 50 °C for 4 h, to afford title compound as a yellow dark oil (0.332 g, 0.93 mmol, 86% yield). MS/ESI⁺ 356.1 [MH]⁺, Rt = 1.66 min (Method A).

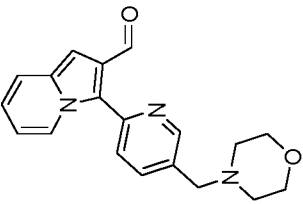
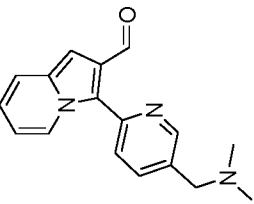
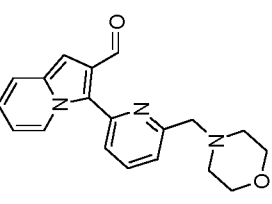
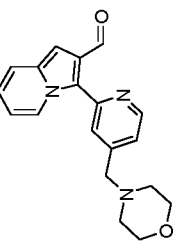
Intermediate L21: 7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazine-6-carbaldehyde

Prepared similarly to intermediate L1, starting from [7-(pyridin-2-yl)pyrrolo[1,2-
5 b]pyridazin-6-yl]methanol K28 (0.078 g, 0.35 mmol) and MnO₂ (0.456 g, 5.25 mmol), at
50 °C for 1 h to afford title compound as a yellow solid (0.072 g, 0.32 mmol, 92% yield).
MS/ESI⁺ 224.2 [MH]⁺, Rt = 0.63 min (Method A).

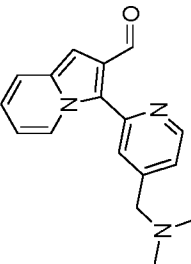
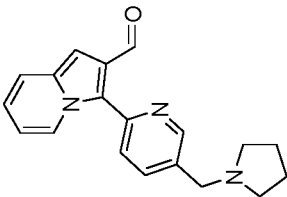
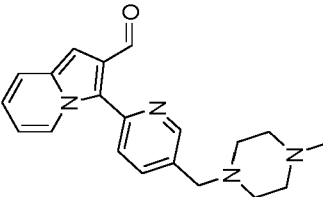
Intermediates L22-40 and L42-65 found in the table below may be prepared from suitable intermediates reported below following similar procedures as for compound L1.

Intermediate	Name and Molecular Structure		Reagent	Analytical data
L22	7-chloro-3-(pyridin-2-yl)indolizine-2-carbaldehyde		K29	MS/ESI ⁺ 257.1 [MH] ⁺ , Rt = 1.04 min (Method A)
L23	7-methyl-3-(pyridin-2-yl)indolizine-2-carbaldehyde		K30	MS/ESI ⁺ 237.2 [MH] ⁺ , Rt = 0.96 min (Method A)
L24	3-(2-methylpyridin-4-yl)indolizine-2-carbaldehyde		K31	MS/ESI ⁺ 237.1 [MH] ⁺ , Rt = 0.47 min (Method A)

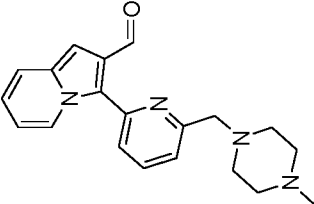
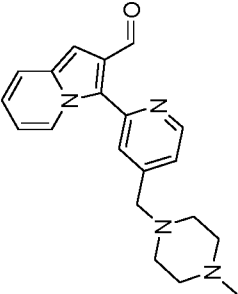
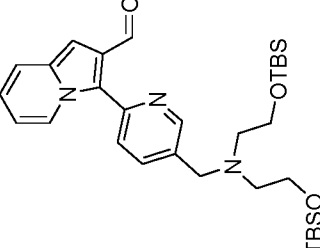
(continued)

L25	3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizine-2-carbaldehyde		K32	MS/ESI ⁺ 322.2 [MH] ⁺ , Rt = 0.45 min (Method A)
L26	3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizine-2-carbaldehyde		K33	MS/ESI ⁺ 280.2 [MH] ⁺ , Rt = 0.43 min (Method A)
L27	3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizine-2-carbaldehyde		K34	MS/ESI ⁺ 322.3 [MH] ⁺ , Rt = 0.48 min (Method A)
L28	3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizine-2-carbaldehyde		K35	MS/ESI ⁺ 322.3 [MH] ⁺ , Rt = 0.48 min (Method A)

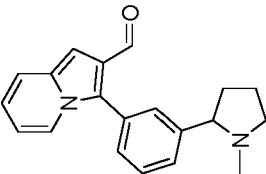
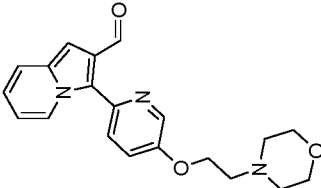
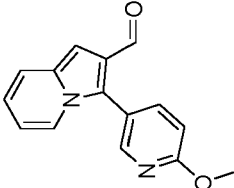
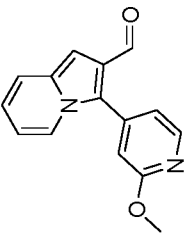
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L29	3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizine-2-carbaldehyde		K36	MS/ESI ⁺ 280.4 [MH] ⁺ , Rt = 0.45 min (Method A)
L30	3-[5-(pyrrolidin-1-yl)methyl]pyridin-2-yl]indolizine-2-carbaldehyde		K37	MS/ESI ⁺ 306.2 [MH] ⁺ , Rt = 0.47 min (Method A)
L31	3-{5-[4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizine-2-carbaldehyde		K38	MS/ESI ⁺ 335.4 [MH] ⁺ , Rt = 0.48 min (Method A)

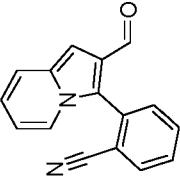
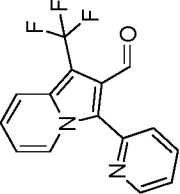
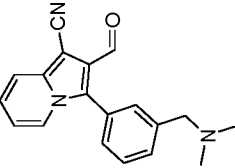
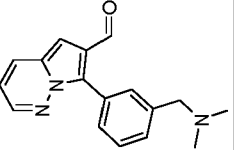
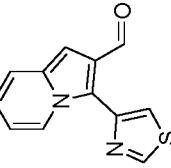
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L32	3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizine-2-carbaldehyde		K39	MS/ESI ⁺ 335.4 [MH] ⁺ , Rt = 0.49 min (Method A)
L33	3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizine-2-carbaldehyde		K40	MS/ESI ⁺ 335.4 [MH] ⁺ , Rt = 0.47 min (Method A)
L34	3-{5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)methyl]pyridin-2-yl}indolizine-2-carbaldehyde		K41	MS/ESI ⁺ 568.5 [MH] ⁺ , Rt = 1.21 min (Method A)

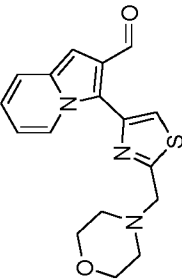
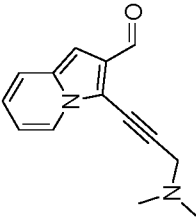
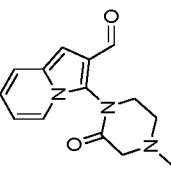
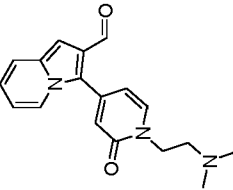
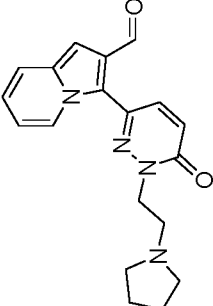
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L35	3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizine-2-carbaldehyde		K42	MS/ESI ⁺ 305.3 [MH] ⁺ , Rt = 0.55 min (Method A)
L36	3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizine-2-carbaldehyde		K43	MS/ESI ⁺ 352.2 [MH] ⁺ , Rt = 0.88 min (Method C)
L37	3-(6-methoxypyridin-3-yl)indolizine-2-carbaldehyde		K44	MS/ESI ⁺ 253.2 [MH] ⁺ , Rt = 1.00 min (Method A)
L38	3-(2-methoxypyridin-4-yl)indolizine-2-carbaldehyde		K45	MS/ESI ⁺ 253.2 [MH] ⁺ , Rt = 0.99 min (Method A)

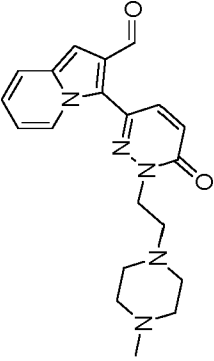
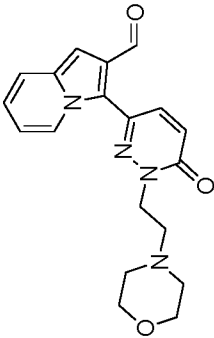
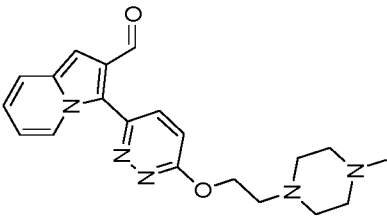
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L39	2-(2-formylindolizin-3-yl)benzonitrile		K46	MS/ESI ⁺ 247.1 [MH] ⁺ , Rt = 0.97 min (Method A).
L40	3-(pyridin-2-yl)-1-(trifluoromethyl)indolizine-2-carbaldehyde		K47	MS/ESI ⁺ 291.2 [MH] ⁺ , Rt = 1.07 min (Method A)
L42	3-{3-[(dimethylamino)methyl]phenyl}-2-formylindolizine-1-carbonitrile		K48	MS/ESI ⁺ 304.3 [MH] ⁺ , Rt = 1.02 min (Method J)
L43	7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazine-6-carbaldehyde		K49	MS/ESI ⁺ 280.3 [MH] ⁺ , Rt = 0.43 - 0.47 min (Method A)
L44	3-(1,3-thiazol-4-yl)indolizine-2-carbaldehyde		K50	MS/ESI ⁺ 229.1 [MH] ⁺ , Rt = 0.89 min (Method A)

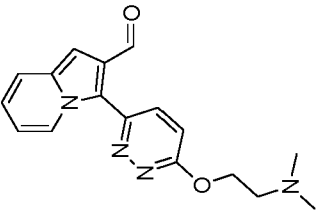
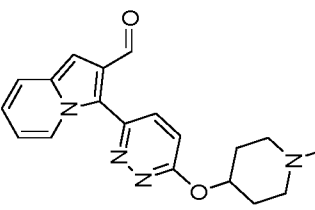
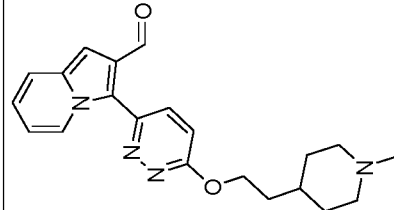
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L45	3-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]indolizine-2-carbaldehyde		K51	MS/ESI ⁺ 328.3 [MH] ⁺ , Rt = 0.63 min (Method A)
L46	3-[3-(dimethylamino)prop-1-yn-1-yl]indolizine-2-carbaldehyde		K52	MS/ESI ⁺ 226.9 [MH] ⁺ , Rt = 0.43 min (Method A)
L47	3-(4-methyl-2-oxopiperazin-1-yl)indolizine-2-carbaldehyde		K53	MS/ESI ⁺ 258.2 [MH] ⁺ , Rt = 0.35 min (Method A)
L48	3-{1-[2-(dimethylamino)ethyl]-2-oxo-1,2-dihydropyridin-4-yl}indolizine-2-carbaldehyde		K54	MS/ESI ⁺ 310.3 [MH] ⁺ , Rt = 0.48 min (Method A)
L49	3-{6-oxo-1-[2-(pyrrolidin-1-yl)ethyl]-1,6-dihydropyridazin-3-yl}indolizine-2-carbaldehyde		K55	MS/ESI ⁺ 337.3 [MH] ⁺ , Rt = 0.46 min (Method A)

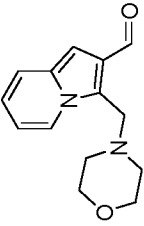
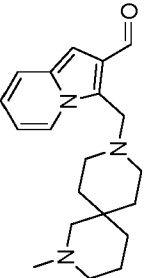
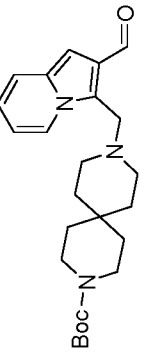
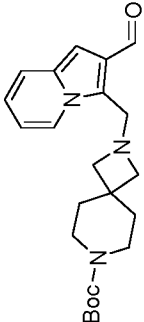
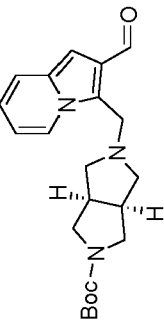
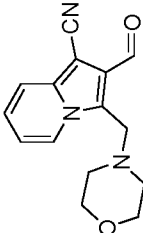
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L50	3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-6-oxo-1,6-dihydropyridazin-3-yl}indolizine-2-carbaldehyde		K56	MS/ESI ⁺ 366.3 [MH] ⁺ , Rt = 0.43 - 0.46 min (Method A)
L51	3-{1-[2-(morpholin-4-yl)ethyl]-6-oxo-1,6-dihydropyridazin-3-yl}indolizine-2-carbaldehyde		K57	MS/ESI ⁺ 353.3 [MH] ⁺ , Rt = 0.41 - 0.44 min (Method A)
L52	3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizine-2-carbaldehyde		K58	MS/ESI ⁺ 366.4 [MH] ⁺ , Rt = 0.74 min (Method J)

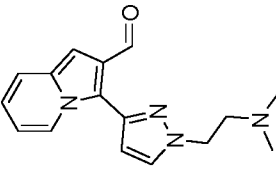
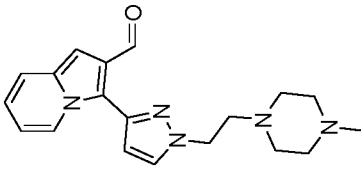
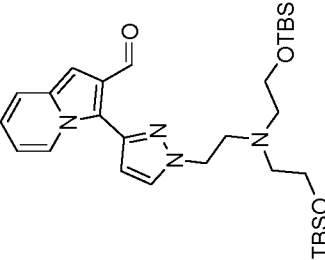
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L53	3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizine-2-carbaldehyde		K59	MS/ESI ⁺ 311.4 [MH] ⁺ , Rt = 0.48 min (Method A)
L54	3-{6-[(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizine-2-carbaldehyde		K60	MS/ESI ⁺ 337.3 [MH] ⁺ , Rt = 0.51 min (Method A)
L55	3-{6-[2-(1-methylpiperidin-4-yl)ethoxy]pyridazin-3-yl}indolizine-2-carbaldehyde		K61	MS/ESI ⁺ 365.3 [MH] ⁺ , Rt = 0.57 min (Method A)

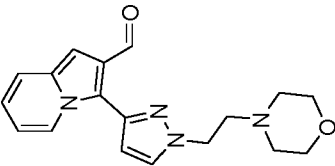
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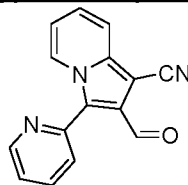
L56	3-(morpholin-4-ylmethyl)indolizine-2-carbaldehyde		K62	MS/ESI ⁺ 245.3 [MH] ⁺ , Rt = 0.86 min (Method C)
L57	3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl)indolizine-2-carbaldehyde		K63	MS/ESI ⁺ 326.0 [MH] ⁺ , Rt = 1.30 min (Method J)
L58	tert-butyl 9-[(2-formylindolizin-3-yl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate		K64	MS/ESI ⁺ 412.5 [MH] ⁺ , Rt = 0.70 min (Method A)
L59	tert-butyl 2-[(2-formylindolizin-3-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate		K65	MS/ESI ⁺ 384.4 [MH] ⁺ , Rt = 0.64 min (Method A)
L60	tert-butyl (3aR,6aS)-5-[(2-formylindolizin-3-yl)methyl]-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate		K66	MS/ESI ⁺ 370.4 [MH] ⁺ , Rt = 1.18 min (Method C)
L61	2-formyl-3-(morpholin-4-ylmethyl)indolizine-1-carbonitrile		K67	MS/ESI ⁺ 270.2 [MH] ⁺ , Rt = 0.41 - 0.42 min (Method A)

(continued)

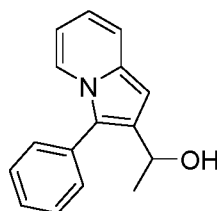
L62	3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl}indolizine-2-carbaldehyde		K68	MS/ESI ⁺ 283.3 [MH] ⁺ , Rt = 0.47 min (Method A)
L63	3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizine-2-carbaldehyde		K69	MS/ESI ⁺ 338.3 [MH] ⁺ , Rt = 0.49 min (Method A)
L64	3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizine-2-carbaldehyde		K70	MS/ESI ⁺ 571.5 [MH] ⁺ , Rt = 1.15 min (Method A)

(continued)

L65	3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizine-2-carbaldehyde		K71	MS/ESI ⁺ 325.3 [MH] ⁺ , Rt = 0.52 min (Method A)
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Intermediate L41: 2-formyl-3-(pyridin-2-yl)indolizine-1-carbonitrile

To a solution of ethyl 1-cyano-3-(pyridin-2-yl)indolizine-2-carboxylate H49 (0.100 g, 0.34 mmol) in DCM (3.5 mL) cooled at -78°C under nitrogen, a solution of DIBALH 1M in toluene (1.02 mL, 1.02 mmol) was added drop-wise over 10 min and the reaction was stirred at -78°C for 10 min. The reaction mixture was quenched by portion-wise addition of sodium sulphate decahydrate, the mixture was filtered through a celite pad and the organic phase was concentrated in vacuo. The crude mixture was dissolved in DCM (3 ml), MnO_2 (0.295 g, 3.4 mmol) was added and the reaction was heated at 50°C for 3 h. The mixture was diluted with DCM and filtered through a celite pad. The filtrate was evaporated to dryness and the crude was purified by flash chromatography on Biotage silica gel cartridge (DCM : EtOAc = 98 : 2 to 95 : 5) to afford title compound as a yellow solid (0.033 g, 0.13 mmol, 40% yield). MS/ESI⁺ 248.2 [MH]⁺, Rt = 0.83 min (Method A).

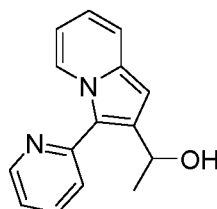
Intermediate M1: 1-(3-phenylindolizin-2-yl)ethan-1-ol

to a solution of 3-phenylindolizine-2-carbaldehyde L1 (0.188 g, 0.850 mmol) in THF (8 mL) cooled to 0°C , 3M MeMgBr solution in Et₂O (0.420 mL, 1.27 mmol) was added drop-wise and the reaction was stirred at that temperature for 30 min. The mixture was quenched with 1 mL of MeOH, then diluted with EtOAc and washed with a mixture of aqueous saturated NH_4Cl and water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography on silica gel

Biotage SNAP cartridge (cyclohexane : EtOAc = 95 : 5 to 60 : 40) to afford title compound as a green-brown oil (0.190 g, 0.80 mmol, 94% yield). MS/ESI⁺ 238.1 [MH]⁺, Rt = 1.07 min (Method A).

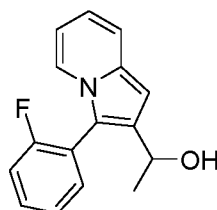
Intermediate M2: 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol

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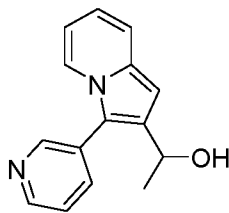
Prepared similarly intermediate M1, , starting from 3-(pyridin-2-yl)indolizine-2-carbaldehyde L2 (0.990 g, 4.45 mmol), stirring at 0°C for 30 min, and purified by flash chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane : EtOAc = 65 : 35) to afford title compound as a yellow oil (1.02 g, 4.28 mmol, 96% yield). MS/ESI⁺ 239.2 [MH]⁺, Rt = 0.64 min (Method A).

Intermediate M3: 1-[3-(2-fluorophenyl)indolizin-2-yl]ethan-1-ol

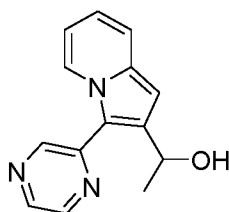


15 Prepared similarly to intermediate M1 , starting from 3-(2-fluorophenyl)indolizine-2-carbaldehyde L3 (0.169 g, 0.706 mmol), stirring at 0°C for 30 min, and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 95 : 5 to 60 : 40) to afford title compound as a yellow oil (0.171 g, 0.669 mmol, 95% yield). MS/ESI⁺ 256.2 [MH]⁺, Rt = 1.09 min (Method A).

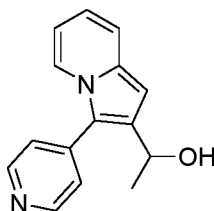
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Intermediate M4: 1-[3-(pyridin-3-yl)indolizin-2-yl]ethan-1-ol

Prepared similarly to intermediate M1, starting from 3-(pyridin-3-yl)indolizine-2-carbaldehyde L4 (0.167 g, 0.751 mmol) and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 50 : 50 to 100% EtOAc) to afford title compound as a pale yellow oil (0.179 g, 0.751 mmol, quantitative yield). MS/ESI⁺ 239.1 [MH]⁺, Rt = 0.50 min (Method A).

Intermediate M5: 1-[3-(pyrazin-2-yl)indolizin-2-yl]ethan-1-ol

Prepared similarly to intermediate M1 starting from 3-(pyrazin-2-yl)indolizine-2-carbaldehyde L5 (0.037 g, 0.166 mmol) and purified by flash chromatography on Biotage silica gel SNAP cartridge (DCM to DCM : EtOAc = 30 : 70) to afford title compound as a yellow oil (0.033 g, 0.138 mmol, 83% yield). MS/ESI⁺ 240.1 [MH]⁺, Rt = 0.78 min (Method A).

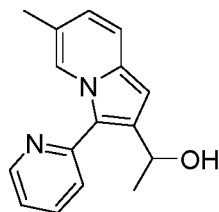
Intermediate M6 : 1-[3-(pyridin-4-yl)indolizin-2-yl]ethan-1-ol

Prepared similarly to intermediate M1, starting from 3-(pyridin-4-yl)indolizine-2-carbaldehyde L6 (0.100 g, 0.450 mmol), stirring at 0°C for 1 h, and purified by flash

chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.100 g, 0.420 mmol, 93% yield). MS/ESI⁺ 239.2 [MH]⁺, Rt = 0.43 min (Method A).

Intermediate M7: 1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol

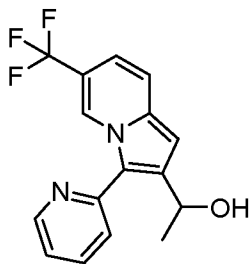
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Prepared similarly to intermediate M1, starting from 6-methyl-3-(pyridin-2-yl)indolizine-2-carbaldehyde L7 (0.127 g, 0.53 mmol), stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 70 : 30) to afford title compound as a yellow solid (0.092 g, 0.36 mmol, 70% yield). MS/ESI⁺ 253.1 [MH]⁺, Rt = 0.72 min (Method A).

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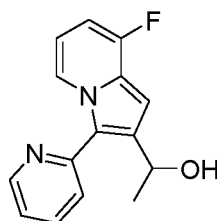
Intermediate M8: 1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethan-1-ol



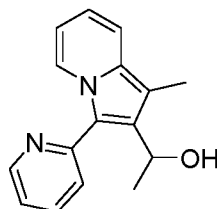
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Prepared similarly to intermediate M1, starting from 3-(pyridin-2-yl)-6-(trifluoromethyl)indolizine-2-carbaldehyde L8 (0.150 g, 0.517 mmol), stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane: EtOAc = 70 : 30) to afford title compound as a yellow oil (0.145 g, 0.473 mmol, 92% yield). MS/ESI⁺ 307.3 [MH]⁺, Rt = 1.06 min (Method A).

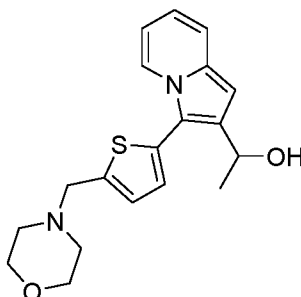
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Intermediate M9: 1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol

Prepared similarly to intermediate M1, starting from 8-fluoro-3-(pyridin-2-yl)indolizine-2-carbaldehyde L9 (0.103 g, 0.43 mmol), stirring at 0°C for 10 min, and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane : EtOAc = 70 : 30 to 50 : 50) to afford title compound as a pale yellow oil (0.094 g, 0.37 mmol, 85% yield). MS/ESI⁺ 257.1 [MH]⁺, Rt = 0.78 min (Method A).

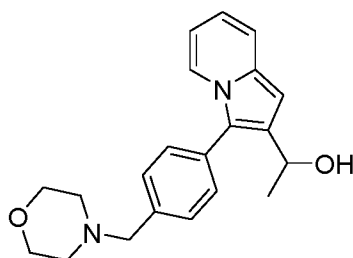
Intermediate M10: 1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol

Prepared similarly to intermediate M1, starting from 1-methyl-3-(pyridin-2-yl)indolizine-2-carbaldehyde L10 (0.071 g, 0.30 mmol), stirring at 0°C for 30 min, and purified by flash chromatography on Biotage silica gel cartridge (cyclohexane : EtOAc = 70 : 30 to 50 : 50) to afford title compound as a yellow oil (0.052 g, 0.21 mmol, 68% yield). MS/ESI⁺ 253.1 [MH]⁺, Rt = 0.63 min (Method A).

Intermediate M11: 1-[3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl]ethan-1-ol

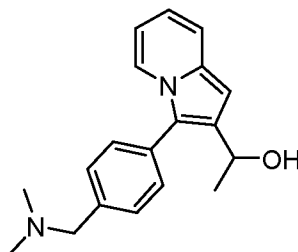
Prepared similarly to intermediate M1, starting from 3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizine-2-carbaldehyde L11 (0.337 g, 1.03 mmol), stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil
5 (0.324 g, 0.94 mmol, 92% yield). MS/ESI⁺ 343.3 [MH]⁺, Rt = 0.55 min (Method A).

Intermediate M12: 1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethan-1-ol



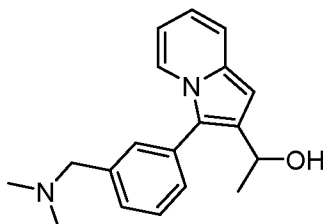
10 Prepared similarly to intermediate M1, starting from 3-[4-(morpholin-4-ylmethyl)phenyl]indolizine-2-carbaldehyde L12 (0.240 g, 0.75 mmol), stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.203 g, 0.60 mmol, 80% yield). MS/ESI⁺ 337.3 [MH]⁺, Rt = 0.54 min (Method A).

15 **Intermediate M13: 1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethan-1-ol**



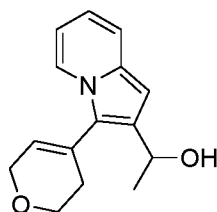
Prepared similarly to intermediate M1, starting from 3-{4-[(dimethylamino)methyl]phenyl}indolizine-2-carbaldehyde L13 (0.196 g, 0.70 mmol),
20 stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.186 g, 0.63 mmol, 90% yield). MS/ESI⁺ 295.2 [MH]⁺, Rt = 0.53 min (Method A).

Intermediate M14: 1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethan-1-ol



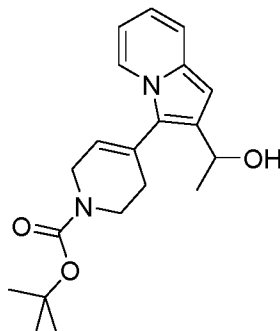
5 Prepared similarly to intermediate M1, starting from 3-{3-[(dimethylamino)methyl]phenyl}indolizine-2-carbaldehyde L14 (0.199 g, 0.71 mmol), stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.197 g, 0.67 mmol, 94% yield). MS/ESI⁺ 295.3 [MH]⁺, Rt = 0.56 min (Method A).

10 **Intermediate M15: 1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethan-1-ol**



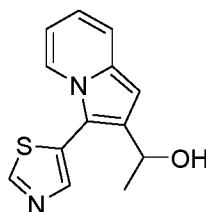
Prepared similarly to intermediate M1, starting from 3-(3,6-dihydro-2H-pyran-4-yl)indolizine-2-carbaldehyde L15 (0.057 g, 0.25 mmol), and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as a yellow oil (0.043 g, 0.177 mmol, 71% yield). MS/ESI⁺ 244.2 [MH]⁺, Rt = 0.85 min (Method A).

Intermediate M16: tert-butyl 4-[2-(1-hydroxyethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate

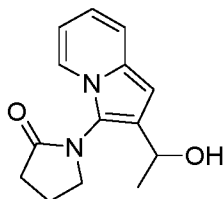


5 Prepared similarly to intermediate M1 , starting from tert-butyl 4-(2-formylindolizin-3-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate L16 (0.134 g, 0.41 mmol), and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as a yellow oil (0.100 g, 0.29 mmol, 71%). MS/ESI⁺ 343.3 [MH]⁺, Rt = 1.13 min (Method A).

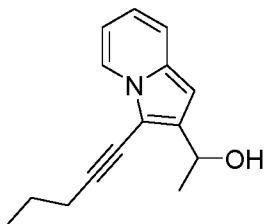
10 **Intermediate M17: 1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethan-1-ol**



15 Prepared similarly to intermediate M1 , starting from 3-(1,3-thiazol-5-yl)indolizine-2-carbaldehyde L17 (0.097 g, 0.42 mmol), stirring at 0°C for 1 h, and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a yellow oil (0.104 g, 0.42 mmol, quantitative yield). MS/ESI⁺ 245.1 [MH]⁺, Rt = 0.81 min (Method A).

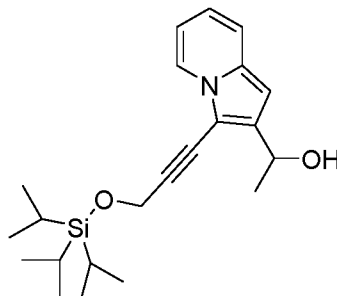
Intermediate M18: 1-[2-(1-hydroxyethyl)indolizin-3-yl]pyrrolidin-2-one

Prepared similarly to intermediate M1 , starting from 3-(2-oxopyrrolidin-1-yl)indolizine-2-carbaldehyde L18 (0.036 g, 0.15 mmol), stirring at 0°C for 1 h; additional
5 3M MeMgBr solution in Et₂O (0.08 mL, 0.24 mmol) was added and the reaction mixture was stirred at 0°C for further 5 h. After work-up the residue was purified by flash chromatography on silica gel cartridge (cyclohexane : EtOAc = 100 : 0 to 0 : 100) to afford title compound as a dark oil (0.028 g, 0.11 mmol, 76% yield). MS/ESI⁺ 244.9 [MH]⁺, Rt =
10 0.65 min (Method A).

Intermediate M19: 1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethan-1-ol

Prepared similarly to intermediate M1 , starting from 3-(pent-1-yn-1-yl)indolizine-
15 2-carbaldehyde L19 (0.156 g, 0.74 mmol), and the crude title compound was used without any additional purification (0.168 g, 0.74 mmol, quantitative yield). MS/ESI⁺ 228.2 [MH]⁺, Rt = 1.15 min (Method A).

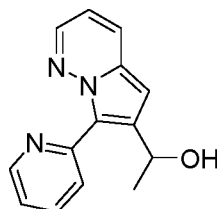
Intermediate M20: 1-[3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]ethan-1-ol



5 Prepared similarly to intermediate M1, starting from 3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizine-2-carbaldehyde L20 (0.330 g, 0.93 mmol), stirring at 0°C for 4 h, and the title compound was used without any additional purification (0.328 g, 0.88 mmol, 95% yield). MS/ESI⁺ 372.1 [MH]⁺, Rt = 1.60 min (Method A).

Intermediate M21: 1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethan-1-ol

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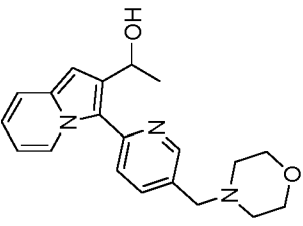
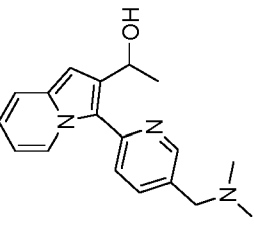
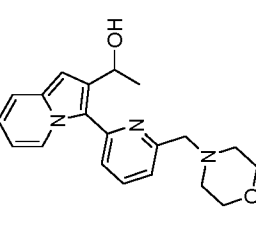
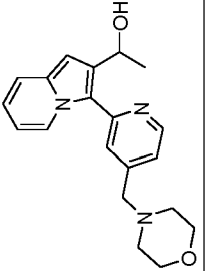


Prepared similarly to intermediate M1, starting from 7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazine-6-carbaldehyde L21 (0.072 g, 0.32 mmol), stirring at 0°C for 15 min, and purified by flash chromatography on Biotage silica gel cartridge (cyclohexane : EtOAc =
 15 90 : 10 to 70 : 30) to afford title compound as a pale yellow oil (0.060 g, 0.25 mmol, 78% yield). MS/ESI⁺ 240.0 [MH]⁺, Rt = 0.47 min (Method A).

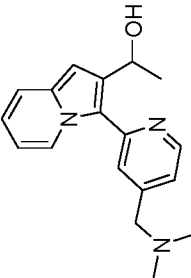
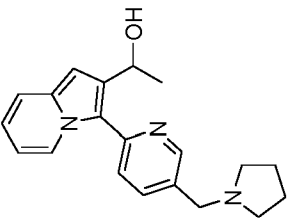
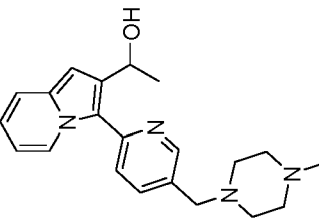
Intermediates M22-39 and M41-66 found in the table below may be prepared from suitable intermediates reported below following similar procedures as for compound M1.

Intermediate	Name and Molecular Structure		Reagent	Analytical data
M22	1-[7-chloro-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol		L22	MS/ESI ⁺ 273.1 [MH] ⁺ , Rt = 0.88 min (Method A)
M23	1-[7-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol		L23	MS/ESI ⁺ 253.3 [MH] ⁺ , Rt = 0.69 min (Method A)
M24	1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethan-1-ol		L24	MS/ESI ⁺ 253.2 [MH] ⁺ , Rt = 0.44 min (Method A)

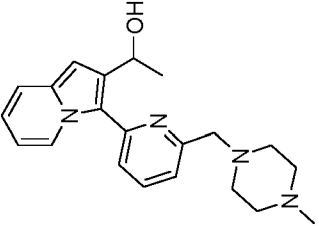
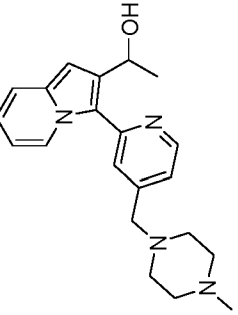
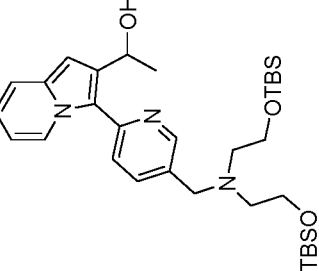
(continued)

M25	1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethan-1-ol		L25	MS/ESI ⁺ 338.3 [MH] ⁺ , Rt = 0.46 min (Method A)
M26	1-(3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L26	MS/ESI ⁺ 296.2 [MH] ⁺ , Rt = 0.45 min (Method A)
M27	1-{3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethan-1-ol		L27	MS/ESI ⁺ 338.3 [MH] ⁺ , Rt = 0.50 min (Method A)
M28	1-{3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethan-1-ol		L28	MS/ESI ⁺ 338.3 [MH] ⁺ , Rt = 0.48 min (Method A)

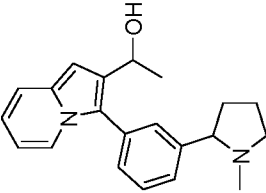
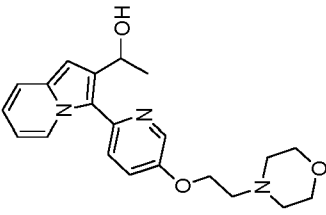
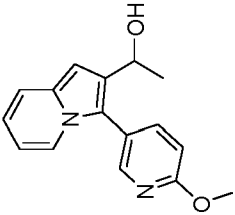
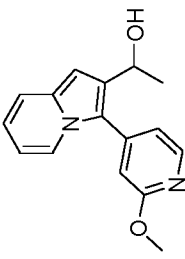
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M29	1-(3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L29	MS/ESI ⁺ 296.3 [MH] ⁺ , Rt = 0.46 min (Method A)
M30	1-{3-[5-(pyrrolidin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl}ethan-1-ol		L30	MS/ESI ⁺ 304.1 [MH-H ₂ O] ⁺ , Rt = 0.48 min (Method A)
M31	1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L31	MS/ESI ⁺ 351.4 [MH] ⁺ , Rt = 0.45 min (Method A)

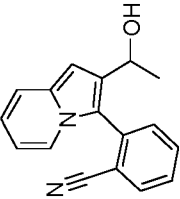
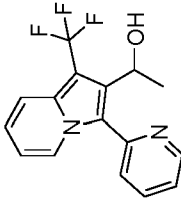
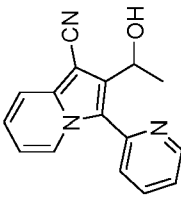
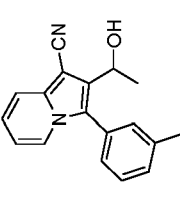
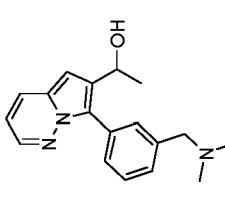
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M32	1-(3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L32	MS/ESI ⁺ 351.4 [MH] ⁺ , Rt = 0.48 min (Method A)
M33	1-(3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L33	MS/ESI ⁺ 351.4 [MH] ⁺ , Rt = 0.43 min (Method A)
M34	1-(3-{5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L34	MS/ESI ⁺ 584.6 [MH] ⁺ , Rt = 1.15 min (Method A)

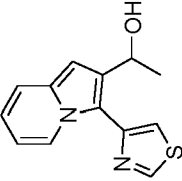
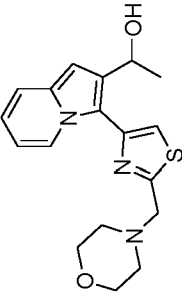
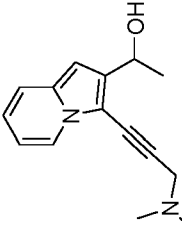
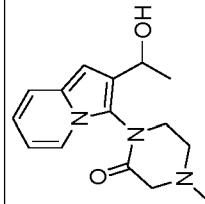
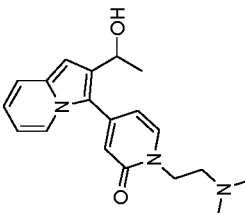
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M35	1-{3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizin-2-yl}ethan-1-ol		L35	MS/ESI ⁺ 321.3 [MH] ⁺ , Rt = 0.56 min (Method A)
M36	1-(3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizin-2-yl)ethan-1-ol		L36	MS/ESI ⁺ 368.1 [MH] ⁺ , Rt = 0.87 min (Method C)
M37	1-[3-(6-methoxypyridin-3-yl)indolizin-2-yl]ethan-1-ol		L37	MS/ESI ⁺ 269.3 [MH] ⁺ , Rt = 0.96 min (Method A)
M38	1-[3-(2-methoxypyridin-4-yl)indolizin-2-yl]ethan-1-ol		L38	MS/ESI ⁺ 269.3 [MH] ⁺ , Rt = 0.90 min (Method A)

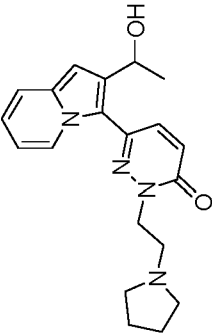
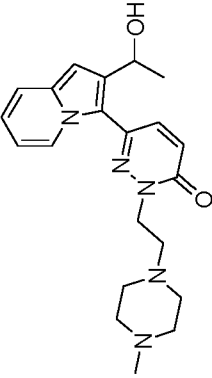
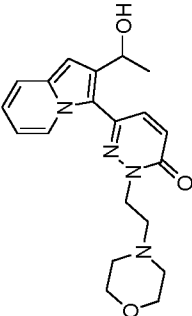
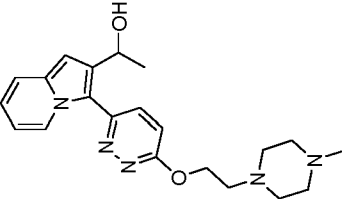
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M39	2-[2-(1-hydroxyethyl)indolizin-3-yl]benzonitrile		L39	MS/ESI ⁺ 263.1 [MH] ⁺ , Rt = 0.92 and 0.97 min (mixture of isomers) (Method A)
M41	1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethan-1-ol		L40	MS/ESI ⁺ 307.4 [MH] ⁺ , Rt = 1.01 min (Method A)
M42	2-(1-hydroxyethyl)-3-(pyridin-2-yl)indolizine-1-carbonitrile		L41	MS/ESI ⁺ 264.2 [MH] ⁺ , Rt = 0.79 min (Method A)
M43	3-{3-[(dimethylamino)methyl]phenyl}-2-(1-hydroxyethyl)indolizine-1-carbonitrile		L42	MS/ESI ⁺ 320.4 [MH] ⁺ , Rt = 1.02 min (Method J)
M44	1-(7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazin-6-yl)ethan-1-ol		L43	MS/ESI ⁺ 296.3 [MH] ⁺ , Rt = 0.46 - 0.48 min (Method A)

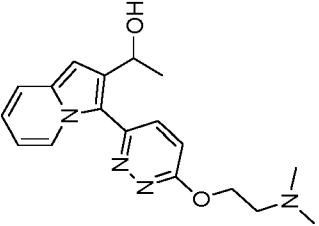
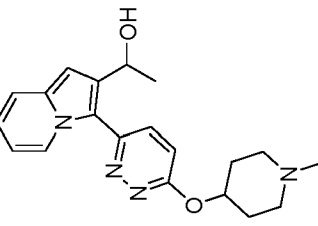
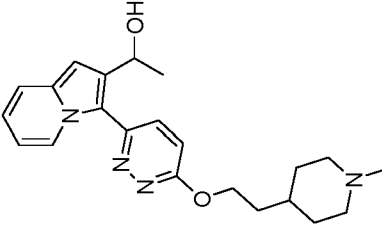
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M45	1-[3-(1,3-thiazol-4-yl)indolizin-2-yl]ethan-1-ol		L44	MS/ESI ⁺ 245.1 [MH] ⁺ , Rt = 0.88 min (Method A)
M46	1-{3-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]indolizin-2-yl}ethan-1-ol		L45	MS/ESI ⁺ 344.2 [MH] ⁺ , Rt = 0.54 min (Method A)
M47	1-{3-[3-(dimethylamino)prop-1-yn-1-yl]indolizin-2-yl}ethan-1-ol		L46	MS/ESI ⁺ 243.8 [MH] ⁺ , Rt = 0.44 min (Method A)
M48	1-[2-(1-hydroxyethyl)indolizin-3-yl]-4-methylpiperazin-2-one		L47	MS/ESI ⁺ 274.3 [MH] ⁺ , Rt = 0.34 - 0.37 min (Method A)
M49	1-[2-(dimethylamino)ethyl]-4-[2-(1-hydroxyethyl)indolizin-3-yl]-1,2-dihydropyridin-2-one		L48	MS/ESI ⁺ 326.3 [MH] ⁺ , Rt = 0.46 min (Method A)

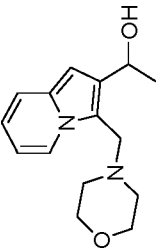
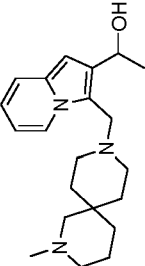
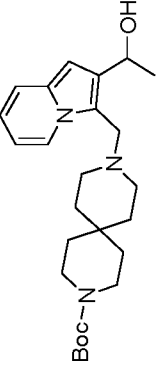
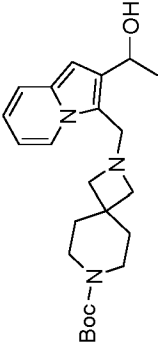
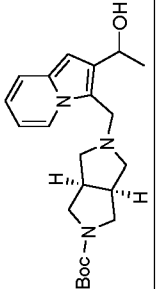
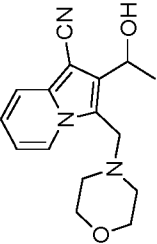
(continued)

M50	6-[2-(1-hydroxyethyl)indolizin-3-yl]- 2-[2-(pyrrolidin-1-yl)ethyl]-2,3- dihydropyridazin-3-one		L49	MS/ESI ⁺ 353.3 [MH] ⁺ , Rt = 0.47 min (Method A)
M51	6-[2-(1-hydroxyethyl)indolizin-3-yl]- 2-[2-(4-methylpiperazin-1-yl)ethyl]- 2,3-dihydropyridazin-3-one		L50	MS/ESI ⁺ 382.4 [MH] ⁺ , Rt = 0.44 - 0.47 min (Method A)
M52	6-[2-(1-hydroxyethyl)indolizin-3-yl]- 2-[2-(morpholin-4-yl)ethyl]-2,3- dihydropyridazin-3-one		L51	MS/ESI ⁺ 369.3 [MH] ⁺ , Rt = 0.42 - 0.46 min (Method A)
M53	1-(3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethan-1-ol		L52	MS/ESI ⁺ 382.4 [MH] ⁺ , Rt = 0.47 min (Method A)

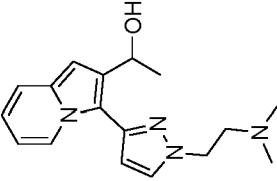
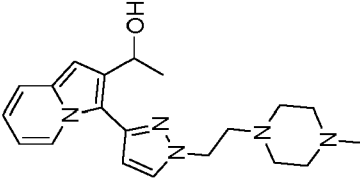
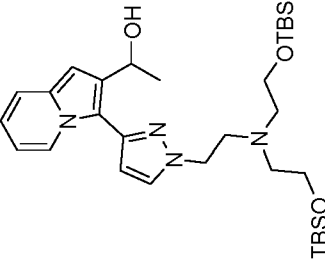
(continued)

M54	1-(3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethan-1-ol		L53	MS/ESI ⁺ 327.3 [MH] ⁺ , Rt = 0.44 - 0.47 min (Method A)
M55	1-(3-{6-[(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizin-2-yl)ethan-1-ol		L54	MS/ESI ⁺ 353.4 [MH] ⁺ , Rt = 0.51 (Method A)
M56	1-(3-{6-[2-(1-methylpiperidin-4-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethan-1-ol		L55	MS/ESI ⁺ 381.4 [MH] ⁺ , Rt = 0.57 (Method A)

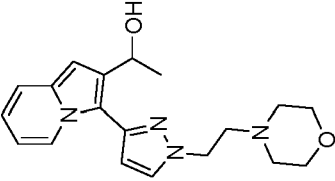
(continued)

M57	1-[3-(morpholin-4-ylmethyl)indolizin-2-yl]ethan-1-ol		L56	MS/ESI ⁺ 174.2 found, R _t = 0.83 min (Method C)
M58	1-[3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl)indolizin-2-yl]ethan-1-ol		L57	MS/ESI ⁺ 342.5 [MH] ⁺ , R _t = 1.25 min (Method J)
M59	tert-butyl 9-{[2-(1-hydroxyethyl)indolizin-3-yl]methyl}-3,9-diazaspiro[5.5]undecane-3-carboxylate		L58	MS/ESI ⁺ 428.5 [MH] ⁺ , R _t = 0.72 min (Method A)
M60	tert-butyl 2-{[2-(1-hydroxyethyl)indolizin-3-yl]methyl}-2,7-diazaspiro[3.5]nonane-7-carboxylate		L59	MS/ESI ⁺ 400.4 [MH] ⁺ , R _t = 0.69 min (Method A)
M61	tert-butyl (3aR,6aS)-5-{[2-(1-hydroxyethyl)indolizin-3-yl]methyl}-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate		L60	MS/ESI ⁺ 386.4 [MH] ⁺ , R _t = 1.15 min (Method C)
M62	2-(1-hydroxyethyl)-3-(morpholin-4-ylmethyl)indolizine-1-carbonitrile (A/1734/55/1)		L61	MS/ESI ⁺ 286.3 [MH] ⁺ , R _t = 0.39 min (Method A)

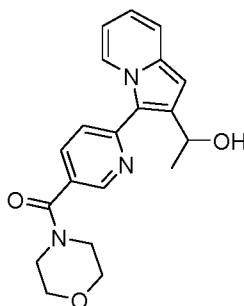
(continued)

M63	1-(3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethan-1-ol		L62	MS/ESI ⁺ 299.3 [MH] ⁺ , Rt = 0.48 min (Method A)
M64	1-(3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethan-1-ol		L63	MS/ESI ⁺ 354.4 [MH] ⁺ , Rt = 0.50 min (Method A)
M65	1-(3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethan-1-ol		L64	MS/ESI ⁺ 587.6 [MH] ⁺ , Rt = 1.15 min (Method A)

(continued)

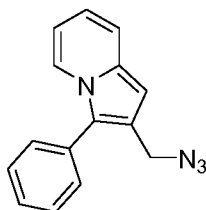
M66	1-(3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethan-1-ol		L65	MS/ESI ⁺ 341.3 [MH] ⁺ , Rt = 0.51 - 0.52 min (Method A)
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Intermediate M40: 1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethan-1-ol



To a solution of 1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethan-1-one I3 (0.140 g, 0.401 mmol) in MeOH (4.5 mL), cooled to 0°C, NaBH₄ (0.030 g, 0.802 mmol) was added in two portions. After the addition was complete, the solution was stirred at 0°C for 30 min and then concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and the solvent was removed to afford title compound which was used without purification
5 (0.140 g, 0.398 mmol, 99 % yield). MS/ESI⁺ 352.3 [MH]⁺, Rt = 0.76 min (Method A).
10

Intermediate N1: 2-(azidomethyl)-3-phenylindolizine



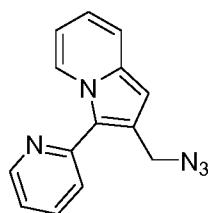
To a solution of (3-phenylindolizin-2-yl)methanol K1 (0.150 g, 0.672 mmol, in THF
15 (10 mL) under nitrogen, DPPA (0.289 mL, 1.344 mmol) was added followed by DBU (0.201 mL, 1.344 mmol) and the mixture was stirred at r.t. overnight. The solvent was removed under vacuum and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate, filtered and evaporated.

20 In a different flask, to a solution of (3-phenylindolizin-2-yl)methanol K1 (0.050 g, 0.224 mmol, in THF (4 mL) under nitrogen, DPPA (0.096 mL, 0.448 mmol) was added followed by DBU (0.067 mL, 0.448 mmol) and the reaction was stirred at r.t. overnight.

The mixture was diluted with EtOAc, washed with water and brine, dried over sodium sulfate, filtered and evaporated.

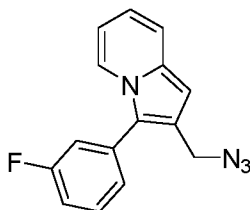
The two batches were combined and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow oil (0.166 g, 0.668 mmol, 75% yield). MS/ESI⁺ 249.1 [MH]⁺, Rt = 1.33 min (Method A).

Intermediate N2: 2-(azidomethyl)-3-(pyridin-2-yl)indolizine



To a solution of [3-(pyridin-2-yl)indolizin-2-yl]methanol K2 (0.245 g, 1.09 mmol) in THF (10 mL) under nitrogen, DPPA (0.471 mL, 2.18 mmol) was added followed by DBU (0.326 mL, 2.18 mmol) at 0°C and the mixture was stirred at RT overnight. The solvent was removed under vacuum and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed and the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound as a pale yellow oil (0.272 g, 1.09 mmol, quantitative yield). MS/ESI⁺ 250.2 [MH]⁺, Rt = 1.07 min (Method A).

Intermediate N3: 2-(azidomethyl)-3-(3-fluorophenyl)indolizine

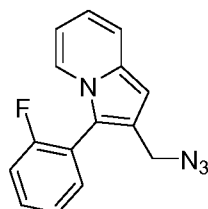


Prepared similarly to intermediate N2, starting from [3-(3-fluorophenyl)indolizin-2-yl]methanol K3 (0.250 g, 1.04 mmol) and purified by flash chromatography on silica gel

Biotage cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow oil (0.250 g, 0.939 mmol, 90% yield). MS/ESI⁺ 267.2 [MH]⁺, Rt = 1.32 min (Method A).

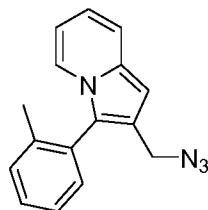
Intermediate N4: 2-(azidomethyl)-3-(2-fluorophenyl)indolizine

5



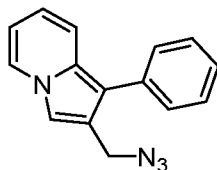
Prepared similarly to intermediate N2, starting from [3-(2-fluorophenyl)indolizin-2-yl]methanol K4 (0.293 g, 1.21 mmol) and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a pale yellow oil (0.279 g, 1.05 mmol, 86% yield). MS/ESI⁺ 267.1 [MH]⁺, Rt = 1.28 min (Method A).

Intermediate N5: 2-(azidomethyl)-3-(2-methylphenyl)indolizine

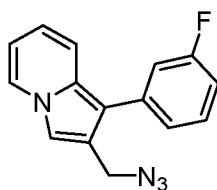


Prepared similarly to intermediate N2, starting from [3-(2-methylphenyl)indolizin-2-yl]methanol K5 (0.278 g, 1.17 mmol) and purified by flash chromatography on silica gel Biotage cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a pale yellow oil (0.262 g, 1.00 mmol, 85% yield). MS/ESI⁺ 263.2 [MH]⁺, Rt = 1.37 min (Method A).

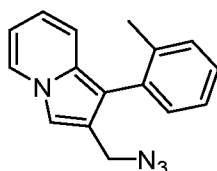
20

Intermediate N6: 2-(azidomethyl)-1-phenylindolizine

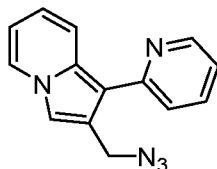
Prepared similarly to intermediate N2, starting from (1-phenylindolizin-2-yl)methanol K24 (0.180 g, 0.80 mmol), stirring for 1.5 h, and the crude was used without purification. MS/ESI⁺ 249.1 [MH]⁺, Rt = 1.29 min (Method A).

Intermediate N7: 2-(azidomethyl)-1-(3-fluorophenyl)indolizine

Prepared similarly to intermediate N2, starting from [1-(3-fluorophenyl)indolizin-2-yl]methanol K25 (0.165 g, 0.68 mmol), stirring for 1.5 h, and the crude was used without purification. MS/ESI⁺ 267.1 [MH]⁺, Rt = 1.30 min (Method A).

Intermediate N8: 2-(azidomethyl)-1-(2-methylphenyl)indolizine

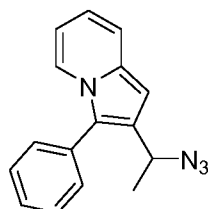
Prepared similarly to intermediate N2, starting from [1-(2-methylphenyl)indolizin-2-yl]methanol K26 (0.100 g, 0.42 mmol), stirring for 1.5 h, and the crude was used without purification. MS/ESI⁺ 263.1 [MH]⁺, Rt = 1.34 min (Method A).

Intermediate N9: 2-(azidomethyl)-1-(pyridin-2-yl)indolizine

Prepared similarly to intermediate N2, starting from [1-(pyridin-2-yl)indolizin-2-yl]methanol K27 (0.200 g, 0.90 mmol), stirring for 1.5 h, and the crude was used without purification. MS/ESI⁺ 250.1 [MH]⁺, Rt = 0.55 min (Method A).

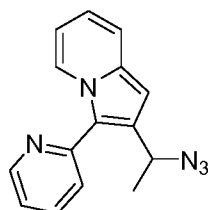
Intermediate O1: 2-(1-azidoethyl)-3-phenylindolizine

5

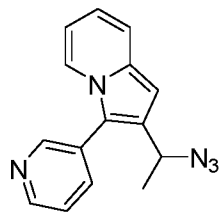


To a solution of 1-(3-phenylindolizin-2-yl)ethan-1-ol M1 (0.078 g, 0.329 mmol) in THF (3 mL) under nitrogen, DPPA (0.142 mL, 0.657 mmol) was added followed by DBU (0.098 mL, 0.657 mmol) and the mixture was stirred at RT overnight. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed and the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 98 : 2) to afford title compound as a pale green oil (0.050 g, 0.191 mmol, 56% yield). MS/ESI⁺ 263.1 [MH]⁺, Rt = 1.38 min (Method A).

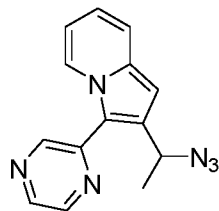
Intermediate O2: 2-(1-azidoethyl)-3-(pyridin-2-yl)indolizine



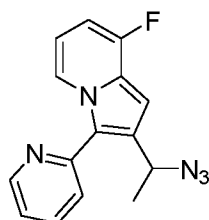
Prepared similarly to intermediate O1, starting from 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol M2 (0.085 g, 0.357 mmol), and the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford title compound as a pale yellow oil (0.085 g, 0.323 mmol, 90% yield). MS/ESI⁺ 264.1 [MH]⁺, Rt = 1.16 min (Method A).

Intermediate O3: 2-(1-azidoethyl)-3-(pyridin-3-yl)indolizine

Prepared similarly to intermediate O1, starting from 1-[3-(pyridin-3-yl)indolizin-2-yl]ethan-1-ol M4 (0.175 g, 0.734 mmol), and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 60 : 40) to afford title compound as a pale green oil (0.141 g, 0.535 mmol, 73% yield). MS/ESI⁺ 264.1 [MH]⁺, Rt = 0.97 min (Method A).

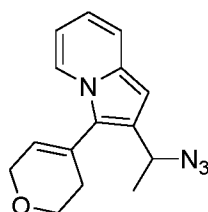
Intermediate O4: 2-(1-azidoethyl)-3-(pyrazin-2-yl)indolizine

Prepared similarly to intermediate O1, starting from 1-[3-(pyrazin-2-yl)indolizin-2-yl]ethan-1-ol M5 (0.033 g, 0.138 mmol); after stirring at r.t. overnight, the addition of a further equivalent of both DPPA and DBU was required, and the stirring was continued for additional 24 h. After work-up the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 80 : 20) to afford title compound as a yellow oil (0.030 g, 0.114 mmol, 82% yield). MS/ESI⁺ 265.1 [MH]⁺, Rt = 1.11 min (Method A).

Intermediate O5: 2-(1-azidoethyl)-8-fluoro-3-(pyridin-2-yl)indolizine

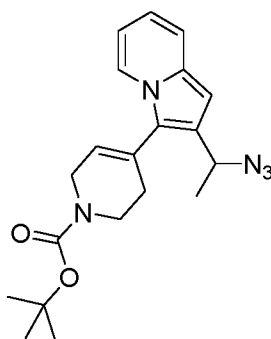
Prepared similarly to intermediate O1, starting from 1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol M9 (0.094 g, 0.37 mmol), stirring at RT for 6 h, and the crude title compound was used without any additional purification. MS/ESI⁺ 282.1 [MH]⁺, Rt = 1.23 min (Method A).

5 **Intermediate O6: 2-(1-azidoethyl)-3-(3,6-dihydro-2H-pyran-4-yl)indolizine**



Prepared similarly to intermediate O1, starting from 1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethan-1-ol M15 (0.043 g, 0.177 mmol), and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as a yellow oil (0.047 g, 0.177 mmol, quantitative yield). MS/ESI⁺ 269.2 [MH]⁺, Rt = 1.22 min (Method A).

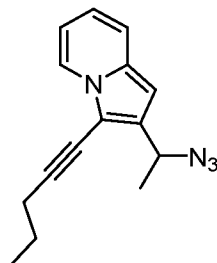
15 **Intermediate O7: tert-butyl 4-[2-(1-azidoethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate**



Prepared similarly to intermediate O1, starting from tert-butyl 4-[2-(1-hydroxyethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate M16 (0.099 g, 0.29 mmol); after stirring at r.t. overnight additional 0.6 eq of DPPA and 0.6 eq of DBU were added and the stirring was continued for further 24 h. After work-up, the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane to

cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow oil (0.106 g, 0.29 mmol, quantitative yield). MS/ESI⁺ 368.3 [MH]⁺, Rt = 1.43 min (Method A).

Intermediate O8: 2-(1-azidoethyl)-3-(pent-1-yn-1-yl)indolizine

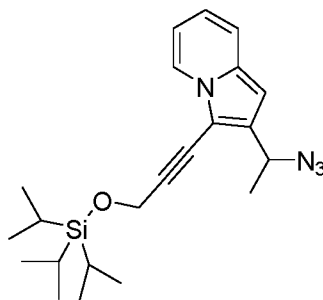


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Prepared similarly to intermediate O1, starting from 1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethan-1-ol M19 (0.168 g, 0.74 mmol, and purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 95 : 5) to afford title compound as a yellow oil (0.130 g, 0.51 mmol, 70% yield). MS/ESI⁺ 253.0 [MH]⁺, Rt = 1.46 min (Method A).

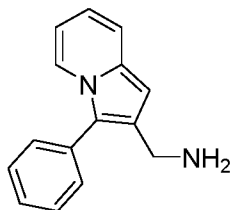
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Intermediate O9: 2-(1-azidoethyl)-3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizine

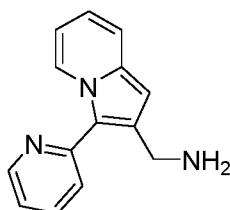


Prepared similarly to intermediate O1, starting from 1-[3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]ethan-1-ol M20 (0.328 g, 0.88 mmol), and used without purification (0.349 g, 0.88 mmol, quantitative yield). MS/ESI⁺ 397.2 [MH]⁺, Rt = 1.78 min (Method A).

15

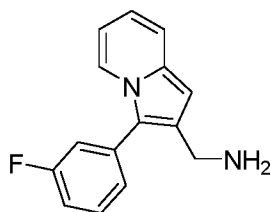
Intermediate P1: (3-phenylindolizin-2-yl)methanamine

To a solution of 2-(azidomethyl)-3-phenylindolizine N1 (0.166 g, 0.668 mmol) in
5 THF (10 mL) under nitrogen, PPh₃ (0.350 g, 1.336 mmol) was added and the mixture was
stirred at RT for 2 h. Additional PPh₃ (0.088 g, 0.334 mmol) was added and the reaction
was stirred at r.t. overnight. Water was added and the reaction was stirred at RT for 3 h.
The solvent was removed under reduced pressure and the residue was dissolved in MeOH
and purified on SCX cartridge (2 g), washing with MeOH. The product was eluted with 1M
10 ammonia in MeOH and the volatiles were removed under reduced pressure to afford title
compound as brown oil (0.148 g, 0.665 mmol, quantitative yield). MS/ESI⁺ 223.2 [MH]⁺,
Rt = 0.55 min (Method A).

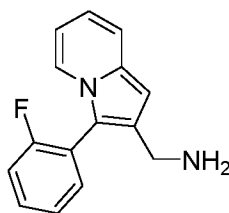
Intermediate P2: [3-(pyridin-2-yl)indolizin-2-yl]methanamine

15

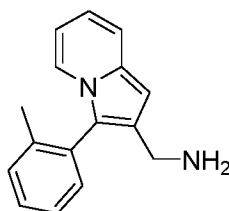
To a solution of 2-(azidomethyl)-3-(pyridin-2-yl)indolizine N2 (0.272 g, 1.09
mmol) in THF (10 mL) under nitrogen, PPh₃ (0.572 g, 2.18 mmol) was added and the
mixture was stirred at RT overnight. Water was added and the reaction was stirred at RT
for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in
20 MeOH and purified on scx cartridge (5 g), washing with MeOH. The product was eluted
with 1M ammonia in MeOH and the volatiles were removed under reduced pressure to
afford title compound as yellow oil (0.204 g, 0.914 mmol, 84% yield). MS/ESI⁺ 224.2
[MH]⁺, Rt = 0.42 min (Method A).

Intermediate P3: [3-(3-fluorophenyl)indolizin-2-yl]methanamine

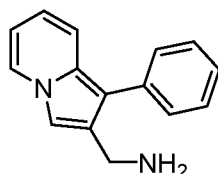
Prepared similarly to intermediate P2, starting from 2-(azidomethyl)-3-(3-fluorophenyl)indolizine N3 (0.248 g, 0.931 mmol), to give title compound as a yellow oil (0.217 g, 0.903 mmol, 97% yield). MS/ESI⁺ 241.1 [MH]⁺, Rt = 0.58 min (Method A).

Intermediate P4: [3-(2-fluorophenyl)indolizin-2-yl]methanamine

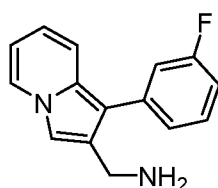
Prepared similarly to intermediate P2, starting from 2-(azidomethyl)-3-(2-fluorophenyl)indolizine N4 (0.277 g, 1.04 mmol,) to give title compound as yellow oil (0.250 g, 1.04 mmol, quantitative yield). MS/ESI⁺ 241.1 [MH]⁺, Rt = 0.55 min (Method A).

Intermediate P5: [3-(2-methylphenyl)indolizin-2-yl]methanamine

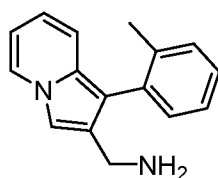
Prepared similarly to intermediate P2, starting from 2-(azidomethyl)-3-(2-methylphenyl)indolizine N5 (0.260 g, 0.991 mmol), to give title compound as yellow oil (0.226 g, 0.956 mmol, 96% yield). MS/ESI⁺ 237.0 [MH]⁺, Rt = 0.70 min (Method B).

Intermediate P6: (1-phenylindolizin-2-yl)methanamine

Prepared similarly to intermediate P2, starting from crude 2-(azidomethyl)-1-phenylindolizine N6 (0.80 mmol), to give title compound as blue oil (0.170 g, 0.76 mmol, 96% yield). MS/ESI⁺ 223.1 [MH]⁺, Rt = 0.56 min (Method A).

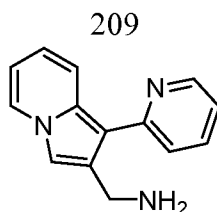
Intermediate P7: [1-(3-fluorophenyl)indolizin-2-yl]methanamine

Prepared similarly to intermediate P2, starting from crude 2-(azidomethyl)-1-(3-fluorophenyl)indolizine N7 (0.68 mmol) to give title compound as a green oil (0.124 g, 0.51 mmol, 75% yield). MS/ESI⁺ 241.1 [MH]⁺, Rt = 0.59 min (Method A).

Intermediate P8: [1-(2-methylphenyl)indolizin-2-yl]methanamine

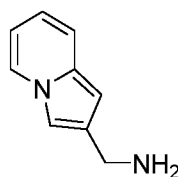
Prepared similarly to intermediate P2, starting from crude 2-(azidomethyl)-1-(2-methylphenyl)indolizine N8 (0.42 mmol) to give title compound as an orange oil (0.093 g, 0.39 mmol, 93% yield). MS/ESI⁺ 237.1 [MH]⁺, Rt = 0.62 min (Method A).

Intermediate P9: [1-(pyridin-2-yl)indolizin-2-yl]methanamine



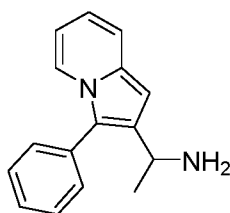
Prepared similarly to intermediate P2, starting from 2-(azidomethyl)-1-(pyridin-2-yl)indolizine N9 (0.90 mmol) to afford title compound (0.088 g, 0.39 mmol, 44% yield). MS/ESI⁺ 224.1 [MH]⁺, Rt = 0.40 min (Method A).

5 **Intermediate P10: indolizin-2-ylmethanamine**



to a solution of indolizine-2-carbonitrile B5 (0.241 g, 1.7 mmol) in anhydrous THF (17 mL), 1M LiAlH₄ in THF (2.55 mL, 2.55 mmol) was added at -25°C and the resulting solution was stirred at the same temperature for 2 h. The reaction was quenched by drop-
 10 wise addition of water (97 µl), followed by aqueous 15% NaOH (97 µl) and water (291 µl), and gradually warmed up to room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure; the residue was combined with the crude batch described above and purified by flash chromatography on Biotage silica-NH SNAP
 15 cartridge (DCM to DCM : MeOH = 99 : 1.0) affording title compound as a light pink solid (0.139 g, 0.95 mmol, 46% yield). MS/ESI⁺ 147.0 [MH]⁺, Rt = 0.27 min (Method A).

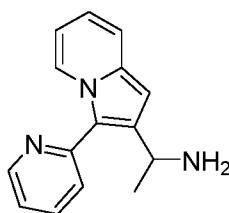
Intermediate Q1: 1-(3-phenylindolizin-2-yl)ethan-1-amine



20 To a solution of 2-(1-azidoethyl)-3-phenylindolizine O1 (0.050 g, 1.191 mmol) in THF (3 mL) under nitrogen, PPh₃ (0.100 g, 0.382 mmol) was added and the mixture was stirred at RT overnight. Water was added and the reaction was stirred at RT for 1 h.

Additional PPh₃ (0.050 g, 0.191 mmol) was added and the mixture was stirred at RT for 5 h and then heated at 50°C for 1 h. The solvent was removed under vacuum and the residue was dissolved in MeOH and purified on a SCX cartridge (2 g), washing with MeOH. The product was eluted with 1M ammonia in MeOH and the volatiles were removed under reduced pressure to afford title compound as a pale yellow oil (0.041 g, 0.174 mmol, 91% yield). MS/ESI⁺ 237.1 [MH]⁺, Rt = 0.60 min (Method A).

Intermediate Q2: 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine



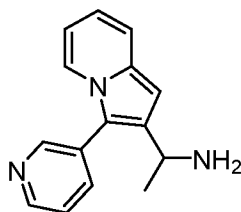
To a solution of 3-(pyridin-2-yl)indolizine-2-carbonitrile J1 (0.800 g, 3.6 mmol) in THF (10.8 mL) cooled at 0°C, a solution of 3M MeMgBr in Et₂O (4.25 mL, 12.7 mmol) was added and the resulting mixture was heated under microwave irradiation at 100°C for 45 min. After cooling to RT the mixture was carefully added to a freshly prepared solution of NaBH₄ (0.272 g, 7.2 mmol) in MeOH (18 mL) and the reaction was stirred at RT for 30 min. The mixture was evaporated to dryness.

In a different flask to a solution of 3-(pyridin-2-yl)indolizine-2-carbonitrile J1 (0.100 g, 0.45 mmol) in THF (1.35 mL) cooled at 0°C, a solution of 3M MeMgBr in Et₂O (0.525 mL, 1.575 mmol) was added and the resulting mixture was heated under microwave irradiation at 100°C for 45 min. After cooling to RT the mixture was carefully added to a freshly prepared solution of NaBH₄ (0.034 g, 0.9 mmol) in MeOH (2.25 mL) and the reaction was stirred at RT for 30 min. The mixture was evaporated to dryness.

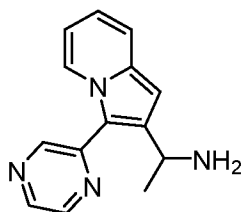
The two crudes were combined and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98.5 : 1.5) to afford title compound as a yellow oil (0.779 g, 3.3 mmol, 81% yield). MS/ESI⁺ 238.1 [MH]⁺, Rt = 0.47 min (Method A).

Intermediate Q3: 1-[3-(pyridin-3-yl)indolizin-2-yl]ethan-1-amine

5



To a solution of 2-(1-azidoethyl)-3-(pyridin-3-yl)indolizine O3 (0.140 g, 0.532 mmol) in THF (5 mL) under nitrogen, PPh₃ (0.279 g, 1.06 mmol) was added and the mixture was stirred at RT overnight. Additional PPh₃ (0.140 g, 0.532 mmol) was added and the mixture was stirred at RT for 1 h. Water was added and the reaction was heated at 50°C for 1 h. The solvent was removed under vacuum and the residue was dissolved in DCM/MeOH and purified on a SXC cartridge (5 g), washing with MeOH. The product was eluted with 1M ammonia in MeOH and the volatiles were removed under reduced pressure to afford title compound as a brown oil which was used for the next step without any further purifications (0.130 g). MS/ESI⁺ 238.1 [MH]⁺, Rt = 0.37 min (Method A).

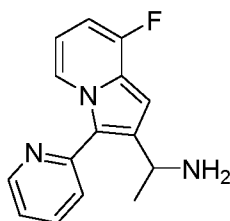
Intermediate Q4: 1-[3-(pyrazin-2-yl)indolizin-2-yl]ethan-1-amine

To a solution of 2-(1-azidoethyl)-3-(pyrazin-2-yl)indolizine O4 (0.030 g, 0.114 mmol) in THF (2.5 mL) under nitrogen, PPh₃ (0.060 g, 0.227 mmol) was added and the mixture was stirred at RT overnight. Water was added and the reaction was heated at 50°C for 2 h. The solvent was removed under vacuum and the residue was dissolved in DCM/MeOH and purified on a SCX cartridge (1 g), washing with MeOH. The product was

eluted with 1M NH₃ in MeOH and the volatiles were removed under reduced pressure to afford title compound as a brown oil which was used without any additional purification (0.030 g). MS/ESI⁺ 239.1 [MH]⁺, Rt = 0.43 min (Method A).

Intermediate Q5 1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine

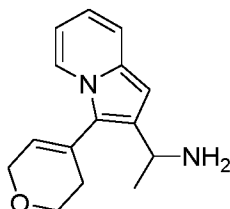
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To a solution of 2-(1-azidoethyl)-8-fluoro-3-(pyridin-2-yl)indolizine O5 (0.104 g, 0.37 mmol) in THF (4.8 mL) under nitrogen, PPh₃ (0.194 g, 0.74 mmol) was added and the mixture was stirred at RT overnight. Water was added and the reaction was stirred at RT for 2 h. The solvent was removed under vacuum and the residue was dissolved in MeOH and charged on a SCX cartridge (5 g), washing with MeOH. The product was eluted with 1M ammonia in MeOH and the volatiles were removed under reduced pressure to afford title compound (0.084 g, 0.32 mmol, 88% yield), which was used without further purifications. MS/ESI⁺ 256.1 [MH]⁺, Rt = 0.51 min (Method A).

15

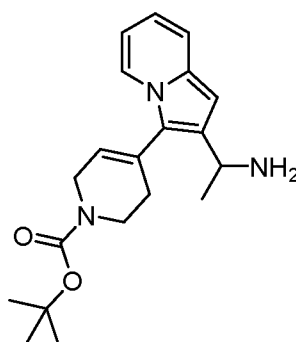
Intermediate Q6: 1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethan-1-amine



Prepared similarly to compound Q4, starting from 2-(1-azidoethyl)-3-(3,6-dihydro-2H-pyran-4-yl)indolizine O6 (0.047 g, 0.177 mmol), and heating at 50°C for 1 h after the addition of water, to afford title compound as a yellow oil (0.033 g, 0.137 mmol, yield 78%). MS/ESI⁺ 256.1 [MH - NH₃]⁺, Rt = 0.49 min (Method A).

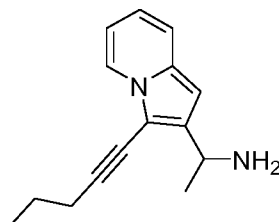
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Intermediate Q7: tert-butyl 4-[2-(1-aminoethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate



Prepared similarly to compound Q4, starting from tert-butyl 4-[2-(1-azidoethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate P7 (0.106 g, 0.29 mmol), and heating at 50°C for 1 h after the addition of water, to afford title compound as a yellow oil (0.041 g, 0.12 mmol, 41% yield). MS/ESI⁺ 325.1 [MH – NH₃]⁺, Rt = 0.70 min (Method A).

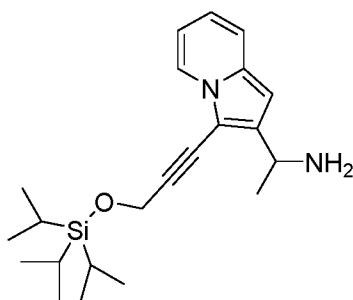
Intermediate Q8: 1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethan-1-amine



To a solution of 2-(1-azidoethyl)-3-(pent-1-yn-1-yl)indolizine O8 (0.129 g, 0.51 mmol), in THF (4.8 mL) under nitrogen, PPh₃ (0.267 g, 1.02 mmol) was added and the mixture was stirred at RT overnight. Water was added and the reaction was heated at 50°C for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : AcOEt = 95 : 5) to afford crude title compound which was used without any additional purification.

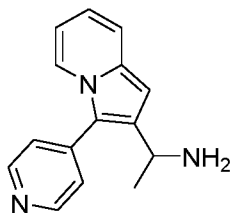
MS/ESI⁺ 210.2 [MH – NH₃]⁺, Rt = 0.65 min (Method A).

Intermediate Q9: 1-[3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]ethan-1-amine



Prepared similarly to compound Q8, starting from 2-(1-azidoethyl)-3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizine O9 (0.349 g, 0.88 mmol), heating at 50°C for 5 h after the addition of water. The crude residue was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM) followed by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc= 95 : 5 to 50 : 50) to afford title compound as a brown oil (0.089 g, 0.24 mmol, 27% yield). MS/ESI⁺ 371.4 [MH]⁺, Rt = 1.02 min (Method A).

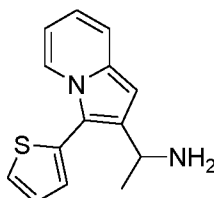
Intermediate Q10: 1-[3-(pyridin-4-yl)indolizin-2-yl]ethan-1-amine



To a suspension of 3-(pyridin-4-yl)indolizine-2-carbonitrile J2 (0.094 mg, 0.424 mmol) in THF (2 mL) cooled at 0°C, 3M MeMgBr solution in Et₂O (0.495 mL, 1.485 mmol) was added drop-wise and the resulting mixture was heated under MW irradiation at 100°C for 1 h. After cooling to RT the mixture was added to a freshly prepared suspension of NaBH₄ (0.032 g, 0.848 mmol) in MeOH (2 mL) cooled at 0°C and the reaction was

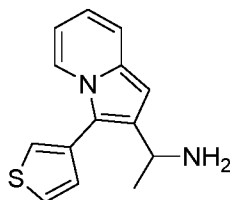
stirred at the same temperature for 30 min. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to yield title compound as a yellow oil (0.064 g, 0.270 mmol, 64% yield). MS/ESI⁺ 238.1 [[MH]⁺, Rt = 0.28 min (Method A).

5 **Intermediate Q11: 1-[3-(thiophen-2-yl)indolizin-2-yl]ethan-1-amine**



To a solution of 3-(thiophen-2-yl)indolizine-2-carbonitrile J3 (0.072) in THF (0.96 mL) cooled at 0°C, a solution of 3M MeMgBr in Et₂O (0.37 mL, 1.12 mmol) was added and the resulting mixture was heated under microwave irradiation at 100°C for 1 h. After cooling to RT the resulting mixture was carefully added to a freshly prepared solution of NaBH₄ (0.0242 g, 0.64 mmol) in MeOH (1.6 ml) and the mixture was stirred for 30 minutes at RT. The solvent was evaporated and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 70 : 30 to 50 : 50) to afford title compound that was used in the next step without further purification (0.058 g). MS/ESI⁺ 243.0 [MH]⁺, Rt = 0.58 min (Method A).

15 **Intermediate Q12: 1-[3-(thiophen-3-yl)indolizin-2-yl]ethan-1-amine**

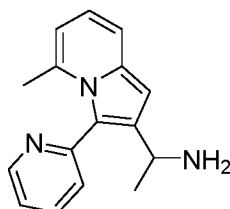


20 Prepared similarly to intermediate Q11, starting from 3-(thiophen-3-yl)indolizine-2-carbonitrile J4 (0.095 g), stirring at r.t. for 15 min after the addition to NaBH₄ solution. The crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound which was used in the next step without

further purifications (0.067 g). MS/ESI⁺ 243. [MH]⁺, Rt = 0.58 min (Method A).

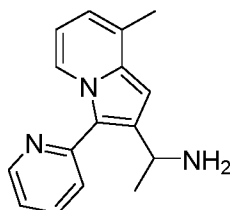
Intermediate Q13: 1-[5-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine

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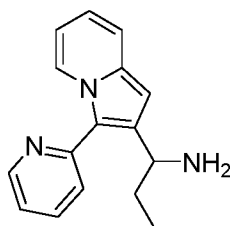
Prepared similarly to intermediate Q11, starting from 5-methyl-3-(pyridin-2-yl)indolizine-2-carbonitrile J5 (0.083 g, 0.35 mmol). The crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford
10 title compound as a yellow oil (0.045 g, 0.18 mmol, 51% yield). MS/ESI⁺ 252.1 [MH]⁺, Rt = 0.43 min (Method A).

Intermediate Q14: 1-[8-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine

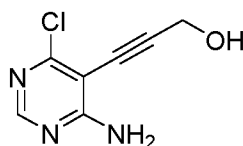


15 Prepared similarly to intermediate Q11, starting from 8-methyl-3-(pyridin-2-yl)indolizine-2-carbonitrile J6 (0.083 g, 0.35 mmol). The crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford
title compound as a yellow oil (0.051 g, 0.20 mmol, 58% yield). MS/ESI⁺ 252.1 [MH]⁺, Rt = 0.55 min (Method A).

20

Intermediate Q15: 1-[3-(pyridin-2-yl)indolizin-2-yl]propan-1-amine

To a solution of 3-(pyridin-2-yl)indolizine-2-carbonitrile J1 (0.150 g, 0.68 mmol) in THF (2.04 mL) cooled at 0°C, a solution of 1M EtMgBr in THF (2.39 mL, 2.39 mmol) was added and the resulting mixture was heated under MW irradiation at 100°C for 1 h. Additional 1M EtMgBr in THF (1.5 mL, 1.5 mmol) was added and the resulting mixture was heated under microwave irradiation at 100°C for 45 min. The resulting mixture was carefully added to a freshly prepared solution of NaBH₄ (0.051 g, 1.36 mmol) in MeOH (3.4 mL) at RT. After stirring for 1 h the mixture was evaporated to dryness and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 99 : 1) to afford title compound as an orange oil (0.102 g, 0.40 mmol, 60% yield). MS/ESI⁺ 252.1 [MH]⁺, Rt = 0.53 min (Method A).

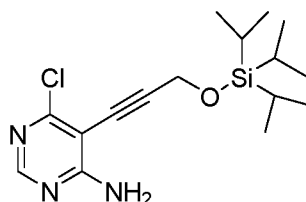
Intermediate AA1: 3-(4-amino-6-chloropyrimidin-5-yl)prop-2-yn-1-ol

A mixture of 6-chloro-5-iodopyrimidin-4-amine (prepared accordingly to the procedure reported in *Tetrahedron Letters*, 2010, 51, 27, 3597 - 3598, 0.200 g, 0.78 mmol), 3-trimethylsiloxy-1-propyne (0.500 g, 3.94 mmol), CuI (0.052 g, 0.273 mmol) and diethylamine (0.95 mL, 8.57 mmol) in DMF (3.3 mL) was degassed and then Pd(PPh₃)₂Cl₂ (0.097 g, 0.14 mmol) was added. The reaction was stirred at room temperature for 2 h, then diluted with EtOAc and filtered through a Celite® pad. The filtrate was washed with water and brine, then dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc =

100 : 0 to 0 : 100) to afford title compound as a yellow solid (0.078 g, 0.42 mmol, 54% yield). MS/ESI⁺ 184.0 [MH]⁺, Rt = 0.46 min (Method A).

Intermediate AA2: 6-chloro-5-(3-([tris(propan-2-yl)silyl]oxy)prop-1-yn-1-yl)pyrimidin-4-amine

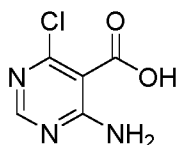
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To a stirred mixture of 3-(4-amino-6-chloropyrimidin-5-yl)prop-2-yn-1-ol AA1 (0.078 g, 0.42 mmol) and imidazole (0.071 g, 1.05 mmol) in DMF (0.5 mL) triisopropylsilyl chloride (0.083 g, 0.43 mmol) was added at RT and the reaction was stirred
10 overnight. The mixture was diluted with EtOAc and washed with a saturated solution of NH₄Cl; the organic phase was dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as a white solid (0.075 g, 0.22 mmol, 53% yield). MS/ESI⁺ 340.2 [MH]⁺, Rt = 1.45 min (Method A).

15

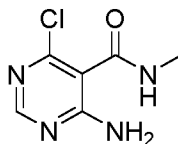
Intermediate AA3: 4-amino-6-chloropyrimidine-5-carboxylic acid



To a solution of commercially available 4-amino-6-chloropyrimidine-5-carbaldehyde (0.500 g, 3.17 mmol) in THF (10 mL), sulfamic acid (0.493 g, 5.07 mmol)
20 was added at RT and the mixture was cooled to 0°C. A solution of sodium chlorite (0.860 g, 9.51 mmol) in water (5 mL) was added and the reaction mixture was allowed to warm to RT and stirred for 30 min. The mixture was then concentrated in vacuo and the crude was purified on a Biotage C18 cartridge (H₂O : MeOH = 99 : 1 to 1 : 99) to afford title compound as a white solid (0.400 g, 2.3 mmol, 73% yield). MS/ESI⁺ 173.9 [MH]⁺, Rt = 0.39 min

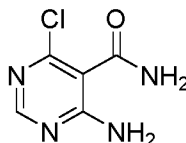
(Method A).

Intermediate AA4: 4-amino-6-chloro-N-methylpyrimidine-5-carboxamid



To a solution of 4-amino-6-chloropyrimidine-5-carboxylic acid AA3 J3 (0.030 g, 0.173 mmol) in DCM (2 mL), SOCl₂ (0.251 mL, 3.457 mmol) was added and the mixture was heated to reflux for 1 h. Additional SOCl₂ (0.251 mL, 3.457 mmol) was added and the mixture was heated to reflux for further 30 min. The volatiles were removed under vacuum and the residue was suspended in DCM (3 mL). 2M MeNH₂ in THF (0.260 mL, 0.519 mmol) was added and the mixture was stirred at RT for 15 min. The solvent was removed under reduced pressure and the crude was used for the next step without any additional purification. MS/ESI⁺ 187.0 [MH]⁺, Rt = 0.29 min (Method A).

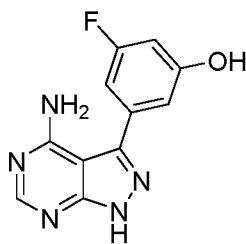
Intermediate AA5: 4-amino-6-chloropyrimidine-5-carboxamid



To a suspension of 4-amino-6-chloropyrimidine-5-carboxylic acid AA3 R3 (0.025 g, 0.144 mmol) in DCM (2 mL), SOCl₂ (0.104 mL, 1.44 mmol) was added and the mixture was stirred at RT for 30 minutes. Additional SOCl₂ (0.104 mL, 1.44 mmol) was added and the mixture was heated to reflux for 1 h. The volatiles were removed under vacuum and the residue was suspended in DCM (3 mL); aqueous concentrated 30% ammonium hydroxide (0.200 mL, 1.54 mmol) was added and the mixture was stirred at RT for 1 h. The volatiles were removed under vacuum and the crude solid was used without any additional work-up and purification as a mixture with some starting material. MS/ESI⁺ 173.0 [MH]⁺, Rt = 0.24 min (Method A).

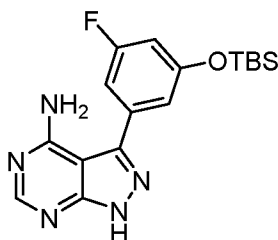
]⁺, Rt = 0.24 min (Method A).

Intermediate AA6: 3-{4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol



3-Iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.00 g, 3.83 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.896 g, 5.7 mmol), PdCl₂(dppf) (0.700 g, 0.95 mmol) and K₃PO₄ (1.625 g, 7.66 mmol) were dissolved in a mixture of DMF (10 ml) and water (6 mL) and the reaction was heated at 120°C for 20 h. The mixture was diluted with EtOAc and 2M HCl and the resulting suspension was filtered. The phases were separated and the organic layer was extracted twice with 2M HCl. The combined aqueous layers were basified with a saturated aqueous solution of Na₂CO₃ to pH 10 and extracted with EtOAc. The organic phase was dried over sodium sulfate and the solvent was evaporated to afford title compound as a crude (yield considered to be quantitative) which was used in the next step without any additional purification. MS/ESI⁺ 246.2 [MH]⁺, Rt = 0.40 min (Method A).

Intermediate AA7: 3-{3-[(tert-butyldimethylsilyl)oxy]-5-fluorophenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine

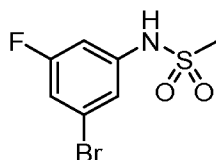


To a solution of crude 3-{4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol AA6 (theoretical 3.83 mmol) in DMF (13 ml), imidazole (1.30 g, 19.15 mmol) and tert-butyl(chloro)dimethylsilane (2.88 g, 19.15 mmol) were added and the mixture was stirred at RT for 1 h. The mixture was diluted with EtOAc and washed with a saturated solution of NH₄Cl, then with brine. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure; the residue was purified by flash

chromatography on silica gel Biotage column (cyclohexane : EtOAc = 50 : 50 to 20 : 80) affording title compound as a white solid (0.220 g, 0.61 mmol). MS/ESI⁺ 360.3 [MH]⁺, Rt = 1.07 min (Method A).

Intermediate S1: N-(3-bromo-5-fluorophenyl)methanesulfonamide

5

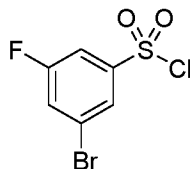


A solution of commercially available 3-bromo-5-fluoroaniline (0.500 g, 2.64 mmol) in pyridine (9.4 mL) was cooled to 0°C and methanesulfonyl chloride (0.265 mL, 3.43 mmol) was added drop-wise; the resulting solution was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure and the crude was partitioned between EtOAc and aqueous 1N HCl. The organic phase was dried over sodium sulfate and the solvent was removed; the crude was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a white solid (0.543 g, 2.03 mmol, 77% yield). MS/ESI⁺ not detectable [MH]⁺, Rt = 0.91 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.29 (s, 1 H), 7.23 - 7.30 (m, 1 H), 7.19 (s, 1 H), 6.99 - 7.06 (m, 1 H), 3.12 (s, 3 H).

Intermediate S2: 3-bromo-5-fluorobenzene-1-sulfonyl chloride

20



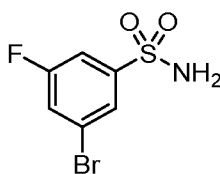
To a solution of 3-bromo-5-fluoroaniline (0.500 g, 2.63 mmol) in glacial acetic acid (0.70 mL) cooled in an ice bath, concentrated hydrochloric acid (2.15 mL) was added. Then, a solution of sodium nitrite (0.199 g, 2.89 mmol) in water (0.45 mL) was slowly added maintaining the temperature around 0°C. After completion of the addition, the reaction

mixture was further stirred for 20 min. The resulting solution was slowly added to a freshly prepared mixture of aqueous ~40% sodium bisulfite solution (1.915 mL, 7.36 mmol), copper chloride (0.052 g, 0.526 mmol), glacial acetic acid (5.0 mL) and concentrated hydrochloric acid (1 mL) at room temperature and the reaction was stirred at RT for 2.5 h.

5 The mixture was then cooled to 0°C, additional sodium nitrite (0.5 eq) was added and the stirring was continued at r.t. for 1 h. The mixture was extracted with EtOAc and the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure to afford title compound which was used without any additional purification (0.450 g, 1.65 mmol, 63% yield).

10 ^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.54 - 7.58 (m, 1 H), 7.50 - 7.54 (m, 1 H), 7.30 - 7.36 (m, 1 H).

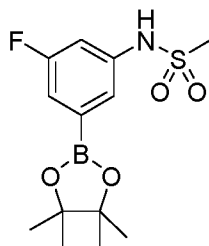
Intermediate S3: 3-bromo-5-fluorobenzene-1-sulfonamide



15 Aqueous 30% NH_4OH (17 mL) was added to a solution of 3-bromo-5-fluorobenzene-1-sulfonyl chloride S2 (0.450 g, 1.65 mmol) in dioxane (14 mL) and the reaction was allowed to proceed overnight at RT. Water was added and the mixture was extracted twice with EtOAc and twice with DCM. The combined organic layers were dried over sodium sulfate and the solvent was evaporated to afford title compound as orange solid

20 (0.320 g, 1.26, 76% yield), which was used without any further purification. MS/ESI 252.0 – 254.0 $[\text{M-H}]^-$, R_t = 0.76 min. (254.1 - 256.1) (Method A).

Intermediate T1: N-[3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide



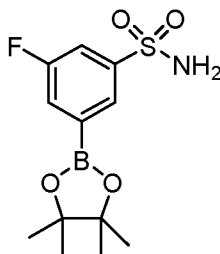
5

A mixture of N-(3-bromo-5-fluorophenyl)methanesulfonamide S1 (0.100 g, 0.37 mmol), bis(pinacolato) diboron (0.190 g, 0.74 mmol), KOAc (0.145 g, 1.48 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.027 g, 0.037 mmol) in dioxane (3.7 mL) was stirred at 90°C for 2 h. The solvent was removed and the residue was purified by flash chromatography on Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford an unclean product.

In a different flask a mixture of N-(3-bromo-5-fluorophenyl)methanesulfonamide S1 (0.315 g, 1.18 mmol), bis(pinacolato) diboron (0.599 g, 2.36 mmol), potassium acetate (0.463 g, 4.72 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.086 g, 0.118 mmol) in anhydrous dioxane (11.8 mL) was stirred at 90°C for 1 h. The solvent was removed under reduced pressure and the residue was combined with the unclean product obtained in the batch described above. This crude was purified by flash chromatography on Biotage silica gel cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound (0.438 g, 1.39 mmol, 89% yield).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.01 (s, 1 H), 7.33 (d, J=1.5 Hz, 1 H), 7.11 - 7.18 (m, 1 H), 7.04 - 7.10 (m, 1 H), 3.02 (s, 3 H), 1.29 (s, 12 H).

Intermediate T2: 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1-sulfonamide

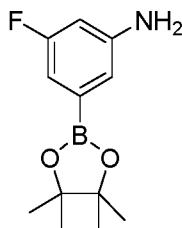


5

A mixture of 3-bromo-5-fluorobenzene-1-sulfonamide S3 (0.050 g, 0.197 mmol), bis(pinacolato) diboron (0.100 g, 0.394 mmol), KOAc (0.077 g, 0.788 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (14.4 mg, 0.0197 mmol) in dioxane (2 mL) was stirred at 90°C for 3 h. Then the solvent was removed under reduced pressure and the residue was purified by flash chromatography on 10 g Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford an impure product.

In a different flask, a mixture of 3-bromo-5-fluorobenzene-1-sulfonamide S3 (0.170 g, 0.669 mmol), bis(pinacolato) diboron (0.340 g, 1.338 mmol), KOAc (0.263 g, 2.676 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.049 g, 0.0669 mmol) in anhydrous dioxane (7 mL) was stirred at 90°C for 1.5 h. Then the solvent was removed and the crude was purified by flash chromatography on 25 g Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 90 : 10) to afford an impure product. The two batches were combined and purified by flash chromatography on 50 g Biotage silica gel SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 75 : 25) to afford title compound (0.070 g, 0.232 mmol, 27% yield).

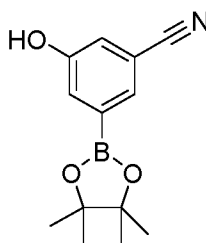
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.98 (s, 1 H), 7.69 - 7.75 (m, 1 H), 7.56 - 7.62 (m, 1 H), 7.52 (s, 2 H), 1.34 (s, 12 H).

Intermediate T3: 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

5 A mixture of 3-bromo-5-fluoroaniline (0.200 g, 1.05 mmol), bis(pinacolato) diboron 0.535 g, 2.11 mmol), KOAc (0.361 g, 3.68 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.077 g, 0.105 mmol) in dioxane (10 mL) was purged with N₂ and heated in a sealed tube at 90°C overnight. The solvent was removed and the crude was purified by flash chromatography on Biotage silica gel SNAP
10 cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound (0.270 g) which was used without any additional purification. MS/ESI⁺ 238.2 [MH]⁺, Rt = 1.02 min (Method A).

Intermediate T4: 3-hydroxy-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

15

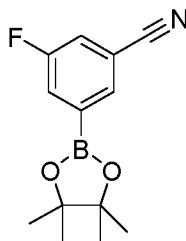


A microwave vial was charged with 3-chloro-5-hydroxybenzonitrile (0.300 g, 1.95 mmol), Pd₂(dba)₃ (0.055 g, 0.06 mmol), tricyclohexylphosphine (0.066 g, 0.234 mmol), KOAc (0.288 g, 2.93 mmol) and bis(pinacolato) diboron (0.546 g, 2.15 mmol), DME (3
20 mL) was added and the mixture was purged with N₂ and heated under microwave irradiation at 150°C for 1 h. After cooling to room temperature the mixture was diluted with water and extracted with Et₂O. The combined organic layers were concentrated *in vacuo*

and purified by flash chromatography on 50 g silica gel Biotage cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20) to afford title compound as white solid (0.340 g, 1.39 mmol, 71% yield). This compound was used without any additional purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.23 (s, 1 H), 7.36 - 7.40 (m, 2 H), 7.24 - 7.28 (m, 1 H), 1.31 (s, 12 H).

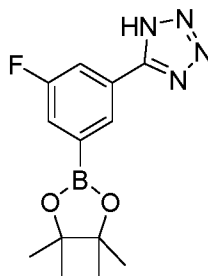
Intermediate T5: 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile



A mixture of 3-bromo-5-fluorobenzonitrile (0.300 g, 1.5 mmol), bis(pinacolato) diboron (0.762 g, 3 mmol), KOAc (0.589 g, 6.0 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.110 g, 0.15 mmol) in dioxane (15 mL) was stirred at 90°C for 2 h. The solvent was removed and the residue was purified by flash chromatography on Biotage silica 50 g cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound (0.360 g, 1.46 mmol, 97% yield).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.98 - 8.03 (m, 1 H), 7.81 - 7.85 (m, 1 H), 7.68 - 7.73 (M, 1 H), 1.33 (s, 12 H).

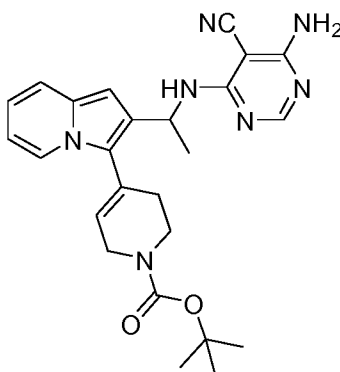
Intermediate T6: 5-[3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-1,2,3,4-tetrazole



To a solution of 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile T5 (0.200 g, 0.809 mmol) in DME (1.5 mL), azidotrimethylsilane (0.186 g, 1.618 mmol) and

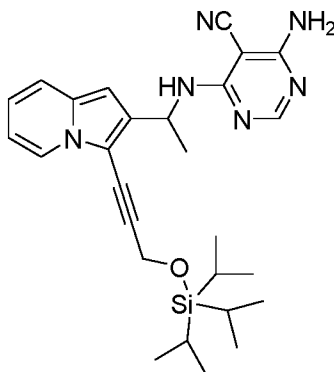
dibutyltin oxide (0.020 g, 0.0809 mmol) were added and reaction was heated under MW irradiation for 10 min at 150°C. After cooling to room temperature the mixture was concentrated under reduced and the residue was partitioned between Et₂O and aqueous 2N NaOH; the organic phase was extracted with aqueous 2N NaOH and the combined aqueous layers were washed with Et₂O, acidified to pH 3-4 with aqueous 6N HCl and extracted with DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford title compound as white solid (0.150 g, 0.517 mmol, 64% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.21 (s, 1 H), 7.94 - 8.00 (m, 1 H), 7.53 - 7.60 (m, 1 H), 1.35 (s, 12 H).

10 **Intermediate U1: tert-butyl 4-(2-{1-[(6-amino-5-cyanopyrimidin-4-yl)amino]ethyl}indolizin-3-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate**



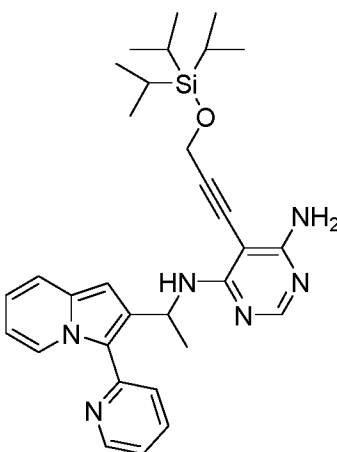
To a solution of tert-butyl 4-[2-(1-aminoethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate Q7 (0.039 g, 0.11 mmol) in *t*-BuOH (1.5 mL), 4-amino-6-chloropyrimidine-5-carbonitrile (0.017 g, 0.11 mmol) was added followed by DIPEA (0.038 mL, 0.22 mmol) and the resulting mixture was heated to reflux for 3 h. The solvent was removed and the crude was partitioned between DCM/MeOH $\approx$ 4/1 and water; the organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : AcOEt = 50 : 50) to afford title compound as a yellow oil (0.045 g, 0.098 mmol, 89% yield). MS/ESI⁺ 460.4 [MH]⁺, Rt = 1.14 min (Method A).

Intermediate U2: 4-amino-6-({1-[3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile



5 Prepared similarly to intermediate U1 using 1-[3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]ethan-1-amine Q9 (0.089 g, 0.24 mmol) and 4-amino-6-chloropyrimidine-5-carbonitrile (0.037 g, 0.24 mmol), and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc= 85 : 25) to afford title compound as a yellow solid (0.062 g, 0.13 mmol, 53%
10 yield). MS/ESI⁺ 489.4 [MH]⁺, Rt = 1.61 min (Method A).

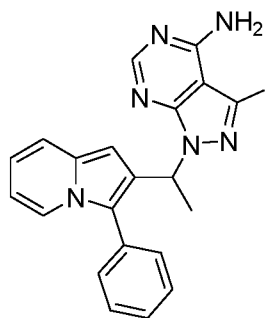
Intermediate V: 4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-5-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)pyrimidine-4,6-diamine



15 To a solution of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.052 g, 0.22 mmol) in n-BuOH (3 mL), 6-chloro-5-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)pyrimidin-4-amine AA2 J2 (0.075 g, 0.22 mmol) was added followed by DIPEA (0.077

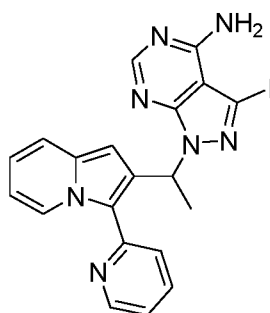
mL, 0.44 mmol) and the resulting mixture was heated to reflux for 48 h. The solvent was removed and the crude was partitioned between DCM and water, the organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 70 : 30) to afford title compound as yellow oil (0.057 g, 0.106 mmol, 48% yield). MS/ESI⁺ 541.4 [MH]⁺, Rt = 1.16 min (Method A).

Intermediate W1: 3-iodo-1-[1-(3-phenylindolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine



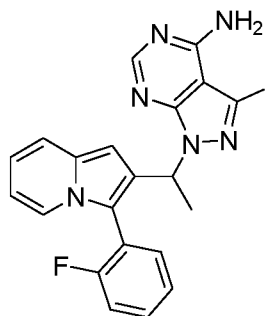
To a mixture of 1-(3-phenylindolizin-2-yl)ethan-1-ol M1 (0.190 g, 0.80 mmol), 3-iodo-1H-pyrazolo [3,4-d]pyrimidin-4-amine (0.252 g, 0.96 mmol) and PPh₃ (0.273 g, 1.04 mmol) in dry THF (9 mL), a solution of DIAD (0.19 mL, 0.96 mmol) in THF (5 mL) was added drop-wise at RT and the reaction was stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 95:5 to 100% EtOAc) to afford title compound as a light- brown solid (0.110 g, 0.23 mmol, 29% yield). MS/ESI⁺ 481.2 [MH]⁺, Rt 1.17 min (Method A).

Intermediate W2: 3-iodo-1-[1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine



To a mixture of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol M2 (1.02 g, 4.28 mmol), 3-iodo-1H-pyrazolo [3,4-d]pyrimidin-4-amine (1.34 g, 5.14 mmol) and PPh₃ (1.46 g, 5.56 mmol) in dry THF (70 mL), a solution of DIAD (1.01 mL, 5.14 mmol) in THF (10 mL) was added drop-wise at r.t. and the reaction was stirred for 2 h. The solvent was removed and the residue was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : EtOAc = 95 : 5) to afford title compound (0.950 g, 1.97 mmol, 46% yield). MS/ESI⁺ 482.1 [MH]⁺, Rt 0.81 min (Method A).

Intermediate W3: 1-{1-[3-(2-fluorophenyl)indolizin-2-yl]ethyl}-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

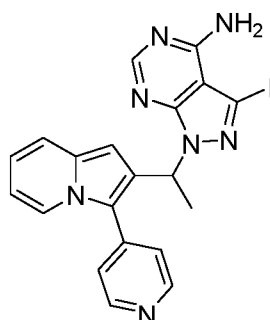


10

Prepared similarly to intermediate W1, starting from 1-[3-(2-fluorophenyl)indolizin-2-yl]ethan-1-ol M3 (0.171 g, 0.669 mmol), stirring at RT for 2 h, and purified by flash chromatography on silica gel Biotage SNAP cartridge (cyclohexane : EtOAc = 95:5 to 100% EtOAc) to afford title compound as a light- brown solid (0.114 g.). MS/ESI⁺ 499.2 [MH]⁺, Rt 1.11 min (Method A).

15

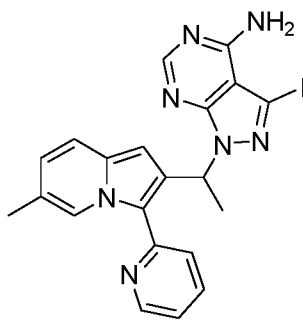
Intermediate W4: 3-iodo-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



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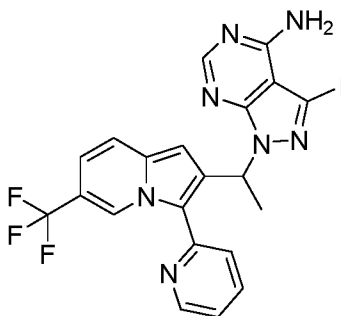
Prepared similarly to intermediate W1, starting from 1-[3-(pyridin-4-yl)indolizin-2-yl]ethan-1-ol M6 (0.300 g, 1.26 mmol), stirring at RT for 2 h, and purified by flash chromatography on Biotage silica-NH gel SNAP cartridge (DCM to DCM : MeOH 98 : 2) to afford title compound (0.216 g, 0.45 mmol, 36% yield). MS/ESI⁺ 482.2 [MH]⁺, Rt 0.64 min (Method A).

Intermediate W5: 3-iodo-1-{1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared similarly to intermediate W1 starting from 1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol M7 (0.092 g, 0.36 mmol), stirring at RT for 2 h, and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 95 : 5) to afford a crude title compound which was used without any additional purification (0.130 g). MS/ESI⁺ 496.2 [MH]⁺, Rt 0.89 min (Method A).

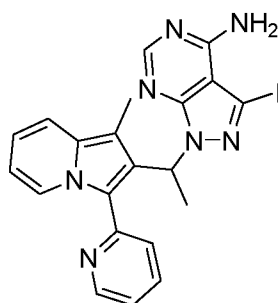
Intermediate W6: 3-iodo-1-{1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared similarly to intermediate W1 starting from 1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethan-1-ol M8 (0.145 g, 0.473 mmol), stirring at RT for 1

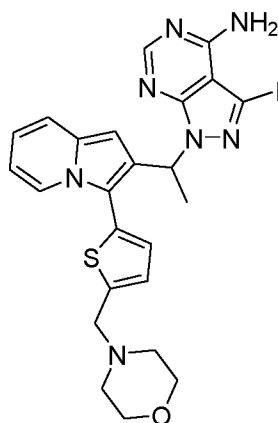
h and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2). The residue was purified on SCX cartridge (1 g) washing with MeOH and the product was eluted with 1M ammonia in MeOH to afford title compound (0.085 g, 0.155 mmol, 33% yield). MS/ESI⁺ 550.1 [MH]⁺, Rt 1.13 min (Method A).

5 **Intermediate W7: 3-iodo-1-{1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine**



Prepared similarly to intermediate W1, starting from [1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-ol M10 (0.052 g, 0.21 mmol), stirring at RT overnight, and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane : EtOAc = 80 : 20 to 60 : 40) to afford crude title compound which was used in the next step without any additional purification (0.106 g). MS/ESI⁺ 496.2 [MH]⁺, Rt 0.81 min (Method A).

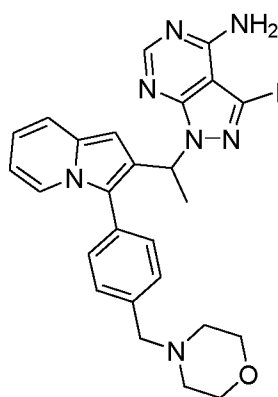
15 **Intermediate W8: 3-iodo-1-(1-{3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine**



Prepared similarly to intermediate W1, starting from 1-{3-[5-(morpholin-4-

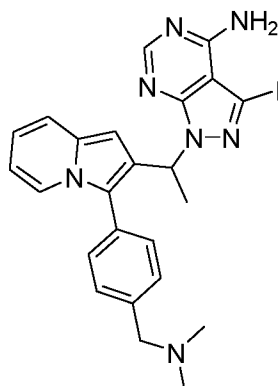
ylmethyl)thiophen-2-yl]indolizin-2-yl}ethan-1-ol M11 (0.324 g, 0.94 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.319 g, 1.22 mmol), PPh₃ (0.370 g, 1.41 mmol) and DIAD (0.252 mL, 1.22 mmol), stirring at RT for 4 h, and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : EtOAc = 90 : 10) to afford crude title
5 compound as a yellow oil (0.325 g). MS/ESI⁺ 586.2 [MH]⁺, Rt 1.24 min (Method C).

Intermediate W9: 3-iodo-1-(1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



10 Prepared similarly to intermediate W1, starting from 1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethan-1-ol M12 (0.203 g, 0.60 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.203 g, 0.78 mmol), PPh₃ (0.236 g, 0.90 mmol) and DIAD (0.153 mL, 0.78 mmol), stirring at RT for 4 h, and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : EtOAc = 90 : 10) to afford crude title
15 compound as a yellow oil (0.320 g). MS/ESI⁺ 580.3 [MH]⁺, Rt 0.66 min (Method A).

Intermediate W10: 1-[1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

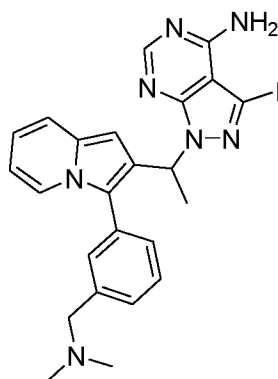


5

Prepared similarly to intermediate W1, starting from 1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethan-1-ol M13 (0.186 g, 0.63 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.214 g, 0.82 mmol), PPh₃ (0.248 g, 0.94 mmol) and DIAD (0.161 mL, 0.82 mmol), stirring at r.t. for 1 h, and purified by flash chromatography on 5 g silica-NH cartridge (DCM to DCM : EtOAc = 90 : 10) to afford title compound as a yellow oil (0.188 g). MS/ESI⁺ 538.3 [MH]⁺, Rt 0.66 min (Method A).

10

Intermediate W11: 1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

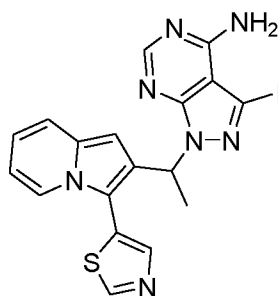


15

Prepared similarly to intermediate W1, starting from 1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethan-1-ol M14 (0.197 g, 0.67 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.227 g, 0.87 mmol), PPh₃ (0.264 g, 1.0

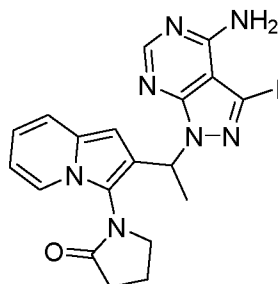
mmol) and DIAD (0.171 mL, 0.87 mmol), stirring at RT for 2 h, and purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM to DCM : EtOAc = 90 : 10); the compound was further purified on SCX cartridge (1 g), eluting with 1M ammonia in MeOH to afford title compound as a brown solid (0.091 g). MS/ESI⁺ 538.3 [MH]⁺, Rt 1.07 min (Method C).

Intermediate W12: 3-iodo-1-{1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared similarly to intermediate W1, starting from 1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethan-1-ol M17 (0.104 g, 0.42 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.142 g, 0.546 mmol), PPh₃ (0.165 g, 0.63 mmol) and DIAD (0.107 mL, 0.546 mmol), stirring at RT for 4 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : EtOAc = 90 : 10); a further purification on SCX cartridge, eluting with 1M ammonia in MeOH was required to afford title compound as a brown solid (0.042 g, 0.086 mmol, 20% yield). MS/ESI⁺ 488.1 [MH]⁺, Rt 0.93 min (Method A).

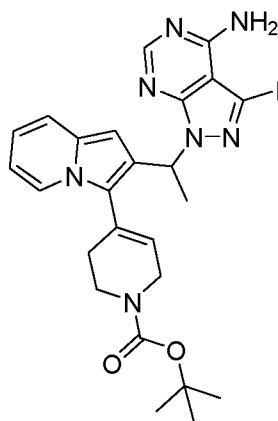
Intermediate W13: 1-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]pyrrolidin-2-one



Prepared similarly to intermediate W1, starting from 1-[2-(1-

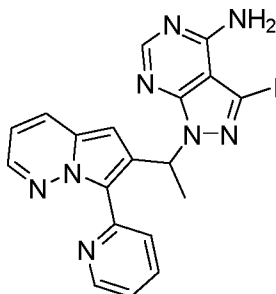
hydroxyethyl)indolizin-3-yl]pyrrolidin-2-one M18 (0.028 g, 0.11 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.037 g, 0.143 mmol), PPh₃ (0.043 g, 0.165 mmol) and DIAD (0.028 mL, 0.143 mmol), stirring at RT for 4 h, and purified by flash chromatography on 5 g silica-NH cartridge (DCM to DCM : EtOAc = 90 : 10) to afford title compound as a
5 brown oil (0.034 g). MS/ESI⁺ 488.2 [MH]⁺, Rt 0.80 min (Method A).

Intermediate W14: tert-butyl 4-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate



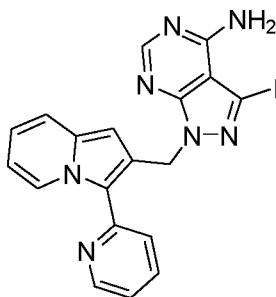
10 Prepared similarly to intermediate W1, starting from tert-butyl 4-[2-(1-hydroxyethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate M16 (0.066 g, 0.19 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.065 g, 0.247 mmol), PPh₃ (0.075 g, 0.285 mmol) and DIAD (0.049 mL, 0.247 mmol), stirring at r.t. for 3 h, and purified by
15 flash chromatography on silica-NH Biotage SNAP cartridge (DCM to DCM : EtOAc = 90 : 10) to afford crude title compound as a yellow oil which was used without any additional purification. MS/ESI⁺ 586.3 [MH]⁺, Rt 1.23 min (Method A).

Intermediate W15: 3-iodo-1-{1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



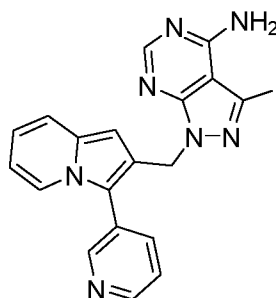
5 Prepared similarly to intermediate W1, starting from 1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethan-1-ol M21 (0.060 g, 0.25 mmol), stirring at RT for 16 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 50 : 50) to afford crude title compound which was used without any additional purification (0.060 g). MS/ESI⁺ 483.2 [MH]⁺, Rt 0.65 min (Method
10 A).

Intermediate W16: 3-iodo-1-{3-(pyridin-2-yl)indolizin-2-yl}methyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



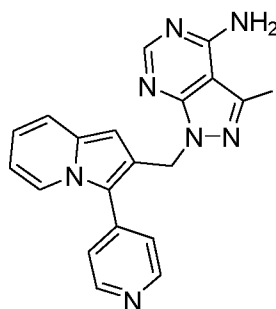
15 Prepared similarly to intermediate W1, starting from [3-(pyridin-2-yl)indolizin-2-yl]methanol K2 (0.060 g, 0.268 mmol), stirring at RT for 2 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (0.020 g, 0.043 mmol, 16% yield). MS/ESI⁺ 468.0 [MH]⁺, Rt 0.79 min (Method A).

20 **Intermediate W17: 3-iodo-1-{3-(pyridin-3-yl)indolizin-2-yl}methyl}-1H-**

pyrazolo[3,4-d]pyrimidin-4-amine

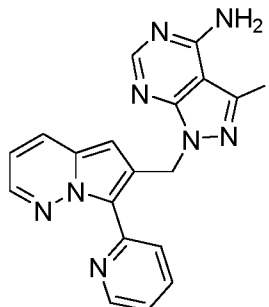
Prepared similarly to intermediate W1, starting from [3-(pyridin-3-yl)indolizin-2-yl]methanol K6 (0.120 g, 0.53 mmol), stirring at RT overnight, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 50 : 50 to 100% EtOAc) to afford title compound as a pale yellow oil (0.035 g, 0.075 mmol, 14% yield). MS/ESI⁺ 468.2 [MH]⁺, Rt 0.71 min (Method A).

Intermediate W18: 3-iodo-1-([3-(pyridin-4-yl)indolizin-2-yl]methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared similarly to intermediate W1, starting from [3-(pyridin-4-yl)indolizin-2-yl]methanol K8 (0.070 g, 0.312 mmol), stirring at RT for 2 h, and purified by flash chromatography on Biotage silica gel SNAP cartridge (EtOAc to EtOAc : MeOH 70 : 30) to afford title compound (0.055 g, 0.118 mmol, 38% yield). MS/ESI⁺ 468.2 [MH]⁺, Rt 0.57 min (Method A).

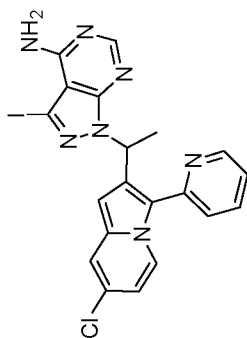
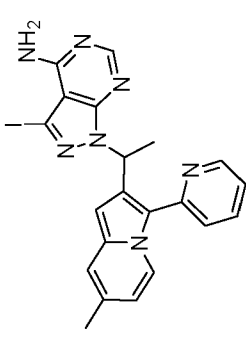
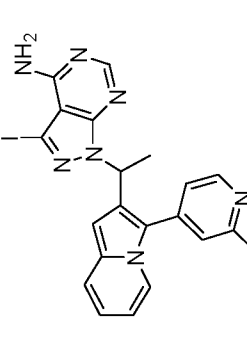
Intermediate and compound W19: 3-iodo-1-{[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



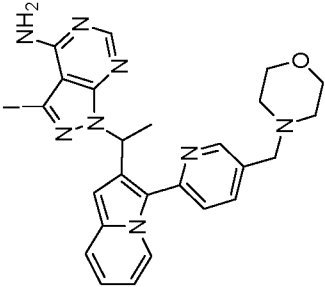
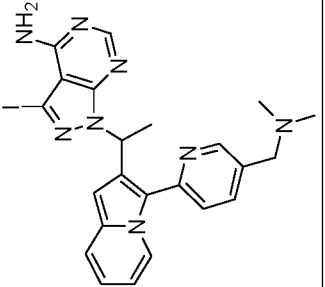
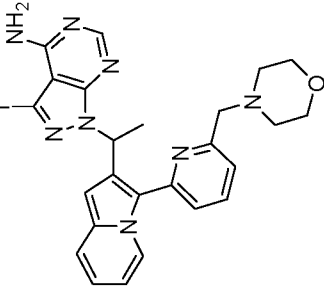
5 Prepared similarly to intermediate W1, starting from [7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methanol K28 (0.050 g, 0.22 mmol), stirring at RT overnight, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 50 : 50) to afford title compound as a pale yellow solid (0.026 g, 0.055 mmol, 25% yield). MS/ESI⁺ 469.1 [MH]⁺, Rt 0.61 min (Method A).

10 ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.71 - 8.78 (m, 1 H), 8.49 (d, *J*=8.0 Hz, 1 H), 8.36 (s, 1 H), 8.12 - 8.17 (m, 1 H), 7.80 - 7.89 (m, 1 H), 7.66 - 8.71 (m, 1 H), 7.20 - 7.26 (m, 1 H), 6.61 (dd, *J*=9.2, 4.4 Hz, 1 H), 6.18 - 6.24 (m, 3 H), 6.01 (br. s., 2 H).

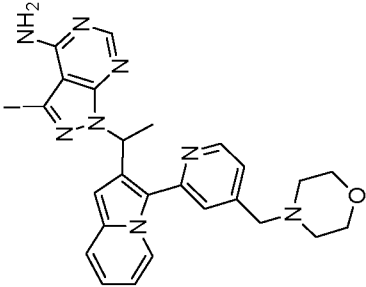
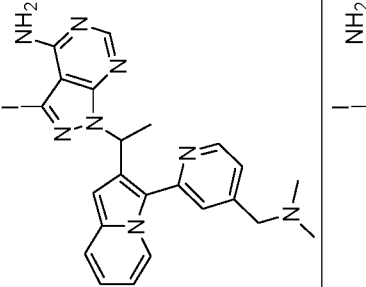
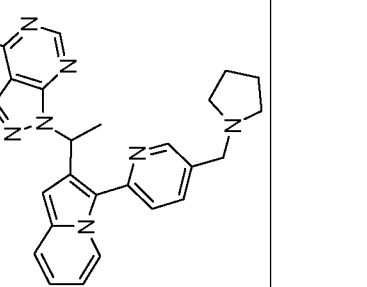
Intermediates W20-34, W35a, W36a, W37-47 and W49-63 found in the table below may be prepared from suitable intermediates reported below following similar procedures as for compound W1.

Intermediate	Name and Molecular Structure		Reagent	Analytical data
W20	1-{1-[7-chloro-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M22	MS/ESI ⁺ 516.2 [MH] ⁺ , Rt 1.02 min (Method A)
W21	3-iodo-1-{1-[7-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M23	MS/ESI ⁺ 496.2 [MH] ⁺ , Rt 0.88 min (Method A)
W22	3-iodo-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M24	MS/ESI ⁺ 496.2 [MH] ⁺ , Rt 0.63 min (Method A)

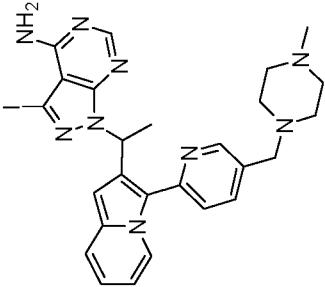
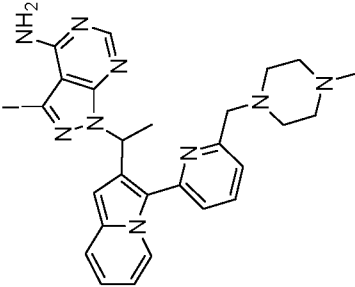
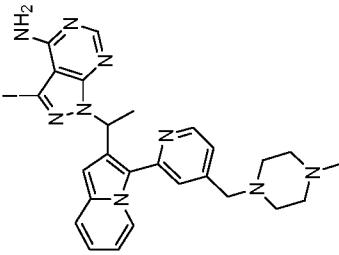
(continued)

W23	3-iodo-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M25	MS/ESI ⁺ 581.2 [MH] ⁺ , Rt 0.61 min (Method A)
W24	1-[1-(3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M26	MS/ESI ⁺ 539.1 [MH] ⁺ , Rt 0.60 min (Method A)
W25	3-iodo-1-(1-{3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M27	MS/ESI ⁺ 581.4 [MH] ⁺ , Rt 0.64 min (Method A)

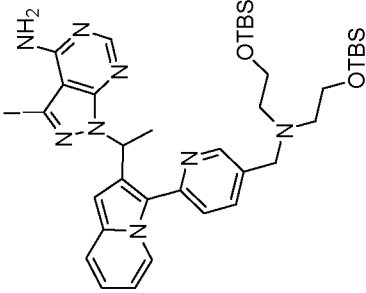
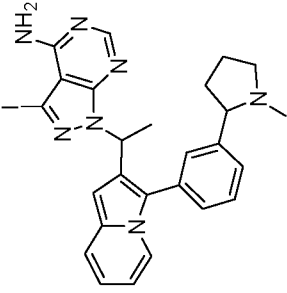
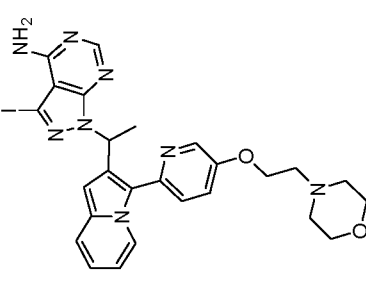
(continued)

W26	3-iodo-1-(1-{3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M28	MS/ESI ⁺ 581.5 [MH] ⁺ , Rt 0.62 min (Method A)
W27	1-[1-(3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M29	MS/ESI ⁺ 539.3 [MH] ⁺ , Rt 0.59 min (Method A)
W28	3-iodo-1-(1-{3-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M30	MS/ESI ⁺ 565.2 [MH] ⁺ , Rt 0.61 min (Method A)

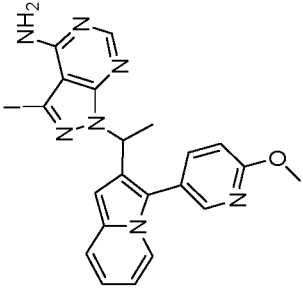
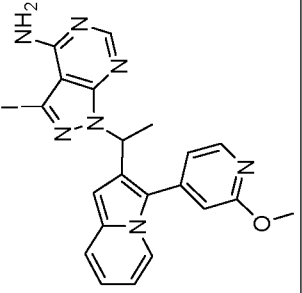
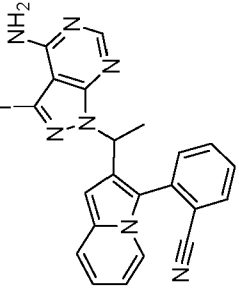
(continued)

W29	3-iodo-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M31	MS/ESI ⁺ 594.4 [MH] ⁺ , Rt 0.58 min (Method A)
W30	3-iodo-1-[1-(3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M32	MS/ESI ⁺ 594.4 [MH] ⁺ , Rt 0.61 min (Method A)
W31	3-iodo-1-[1-(3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M33	MS/ESI ⁺ 594.3 [MH] ⁺ , Rt 0.55 min (Method A)

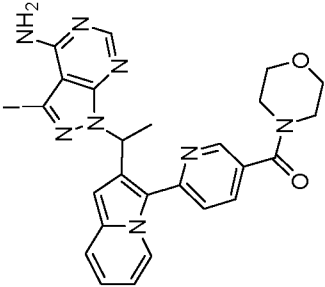
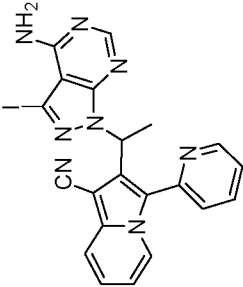
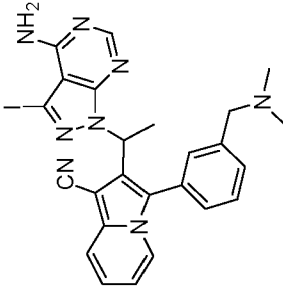
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W32	3-iodo-1-[1-(3-{5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M34	MS/ESI ⁺ 827.6 [MH] ⁺ , Rt 1.23 min (Method A)
W33	3-iodo-1-(1-{3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M35	MS/ESI ⁺ 564.4 [MH] ⁺ , Rt 0.70 min (Method A)
W34	3-iodo-1-[1-(3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M36	MS/ESI ⁺ 611.1 [MH] ⁺ , Rt 0.97 min (Method C)

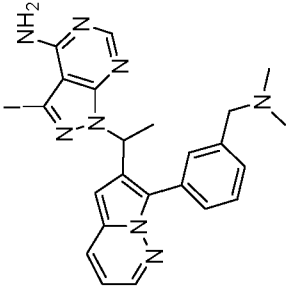
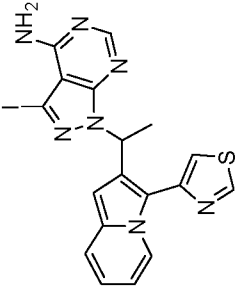
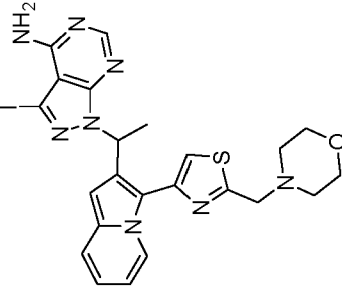
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W35a	3-iodo-1-{1-[3-(6-methoxypyridin-3-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M37	MS/ESI ⁺ 512.0 [MH] ⁺ , Rt 1.02 min (Method A)
W36a	3-iodo-1-{1-[3-(2-methoxypyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M38	MS/ESI ⁺ 512.3 [MH] ⁺ , Rt 1.03 min (Method A)
W37	2-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]benzonitrile		M39	MS/ESI ⁺ 506.2 [MH] ⁺ , Rt 1.06 and 1.09 min (mixture of isomers) (Method A)

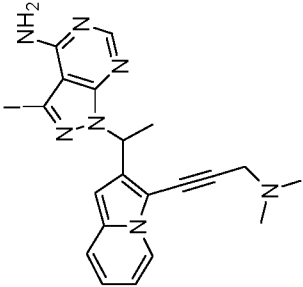
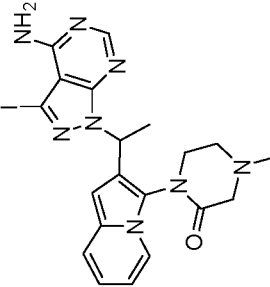
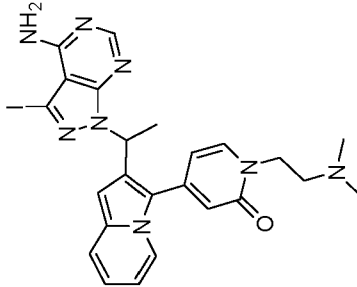
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W38	3-iodo-1-(1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M40	MS/ESI ⁺ 595.2 [MH] ⁺ , Rt 0.87 min (Method A)
W39	2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)-3-(pyridin-2-yl)indolizine-1-carbonitrile		M42	MS/ESI ⁺ 507.1 [MH] ⁺ , Rt 0.85 min (Method A)
W40	2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)-3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile		M43	MS/ESI ⁺ 563.2 [MH] ⁺ , Rt 0.60 min (Method A)

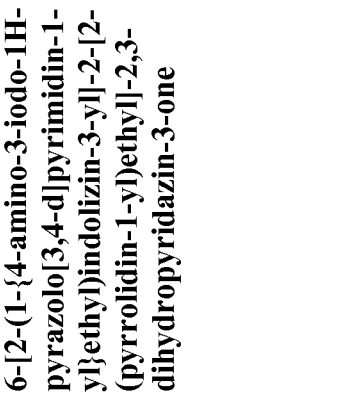
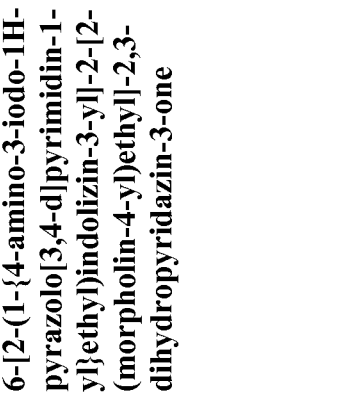
(continued)

W41	1-[1-(7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazin-6-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M44	MS/ESI ⁺ 539.3 [MH] ⁺ , Rt 0.59 min (Method A)
W42	3-iodo-1-{1-[3-(1,3-thiazol-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M45	MS/ESI ⁺ 488.1 [MH] ⁺ , Rt 0.98 min (Method A)
W43	3-iodo-1-(1-{3-[2-(morpholin-4-yl)methyl]-1,3-thiazol-4-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M46	MS/ESI ⁺ 587.2 [MH] ⁺ , Rt 0.70 min (Method A)

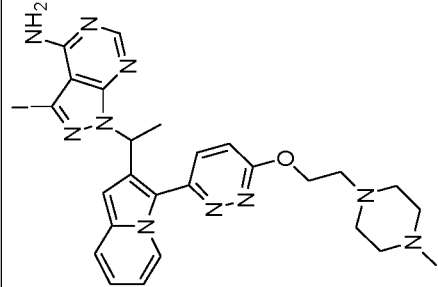
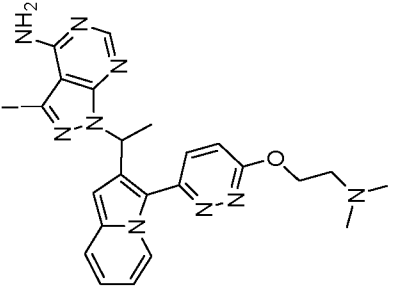
(continued)

W44	1-(1-{3-[3-(dimethylamino)prop-1-yn-1-yl]indolizin-2-yl}ethyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M47	MS/ESI ⁺ 486.1 [MH] ⁺ , Rt 1.00 min (Method C)
W45	1-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-4-methylpiperazin-2-one		M48	MS/ESI ⁺ 517.2 [MH] ⁺ , Rt 0.78 min (Method C)
W46	4-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one		M49	MS/ESI ⁺ 569.3 [MH] ⁺ , Rt 0.88 min (Method J)

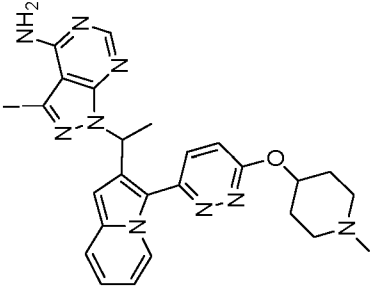
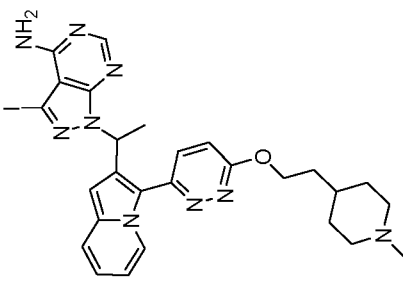
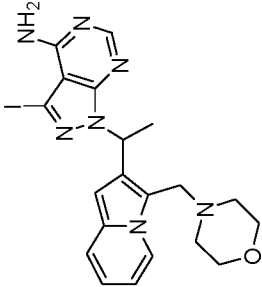
(continued)

W47	6-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-2-[2-(pyrrolidin-1-yl)ethyl]-2,3-dihydropyridazin-3-one		M50	MS/ESI ⁺ 596.5 [MH] ⁺ , Rt 0.61 min (Method A)
W49	6-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-2-[2-(morpholin-4-yl)ethyl]-2,3-dihydropyridazin-3-one		M52	MS/ESI ⁺ 612.3 [MH] ⁺ , Rt 0.61 min (Method A)

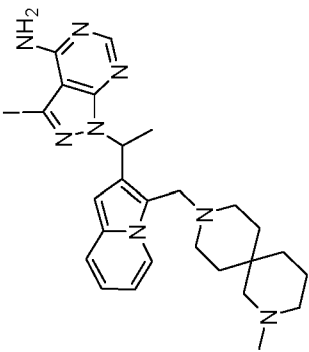
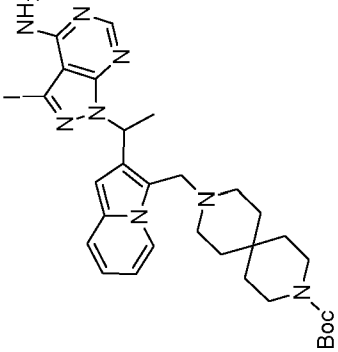
(continued)

W50	3-iodo-1-[1-(3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M53	MS/ESI ⁺ 625.3 [MH] ⁺ , Rt 0.61 min (Method A)
W51	1-[1-(3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M54	MS/ESI ⁺ 570.4 [MH] ⁺ , Rt 0.61 min (Method A)

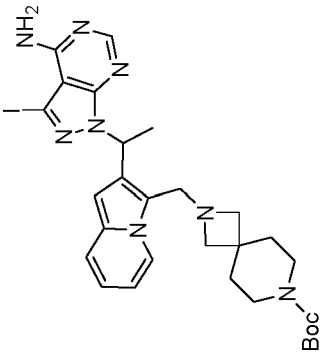
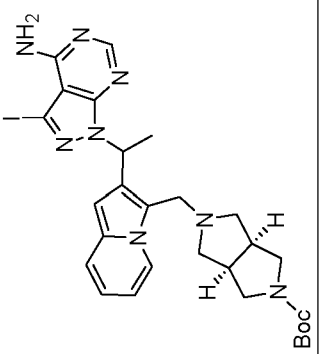
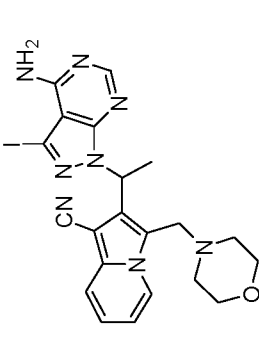
(continued)

W52	3-iodo-1-[1-(3-{6-[(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine)		M55	MS/ESI ⁺ 596.3 [MH] ⁺ , Rt 0.63 min (Method A)
W53	3-iodo-1-[1-(3-{6-[2-(1-methoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M56	MS/ESI ⁺ 624.4 [MH] ⁺ , Rt 0.65 min (Method A)
W54	3-iodo-1-{1-[3-(morpholin-4-yl)methyl]indolizin-2-yl}ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M57	MS/ESI ⁺ 504.3 [MH] ⁺ , Rt 1.05 min (Method C)

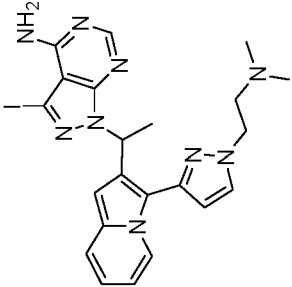
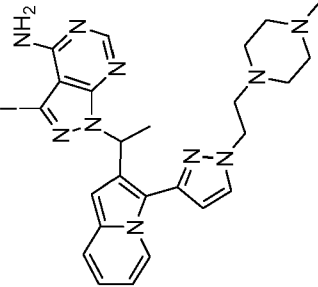
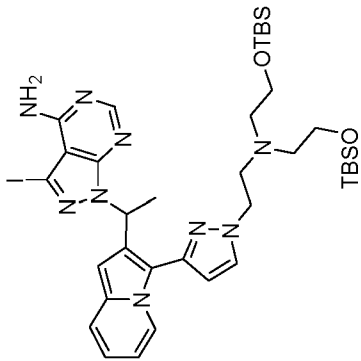
(continued)

W55	3-iodo-1-{1-[3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl)methyl}indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M58	MS/ESI ⁺ 585.3 [MH] ⁺ , Rt 1.41 min (Method J)
W56	tert-butyl 9-{[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]methyl}-3,9-diazaspiro[5.5]undecane-3-carboxylate		M59	MS/ESI ⁺ 671.5 [MH] ⁺ , Rt 1.51 min (Method J)

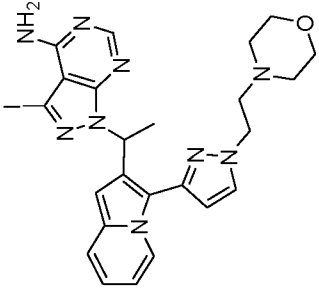
(continued)

W57	tert-butyl 2-([2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate		M60	MS/ESI ⁺ 643.4 [MH] ⁺ , Rt 1.36 min (Method J)
W58	tert-butyl (3aR,6aS)-5-{[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl)methyl]-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate		M61	MS/ESI ⁺ 629.4 [MH] ⁺ , Rt 1.30 min (Method C)
W59	2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)-3-(morpholin-4-yl)methyl)indolizine-1-carbonitrile		M62	MS/ESI ⁺ 529.3 [MH] ⁺ , Rt 0.58 min (Method A)

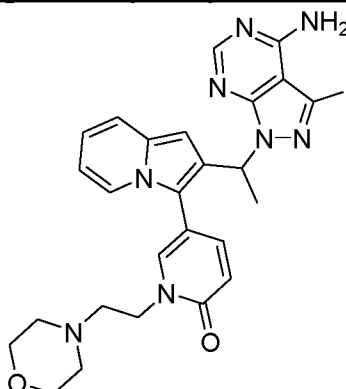
(continued)

W60	1-[1-(3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M63	MS/ESI ⁺ 542.3 [MH] ⁺ , Rt 0.62 min (Method A)
W61	3-iodo-1-[1-(3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M64	MS/ESI ⁺ 597.4 [MH] ⁺ , Rt 0.63 min (Method A)
W62	3-iodo-1-[1-(3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M65	MS/ESI ⁺ 830.6 [MH] ⁺ , Rt 1.21 min (Method A)

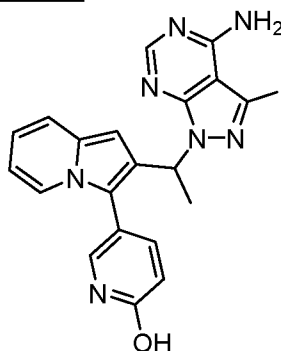
(continued)

W63	3-iodo-1-[1-(3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine		M66	MS/ESI ⁺ 584.5 [MH] ⁺ , Rt 0.66 min (Method A)
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Intermediate W35: 5-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one



Step 1: 5-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]pyridin-2-ol W35b

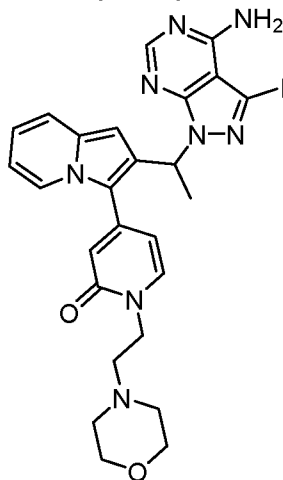


Iodotrimethylsilane (0.583 mL, 4.1 mmol) was added to a solution of 3-iodo-1-{1-[3-(6-methoxypyridin-3-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W35a (0.210 g, 0.41 mmol) in dry acetonitrile (8.3 mL) and the resulting mixture was heated at 50°C for 3 h. Then, at that temperature, MeOH (8.3 mL) was added and stirring was carried out for further 15 minutes. After cooling to RT, the mixture was diluted with DCM and washed with an aqueous solution of Na₂S₂O₅ and then with brine. The organic phase was concentrated under reduce pressure and the residue was purified by flash chromatography on SNAP C18 cartridge (H₂O : MeCN = 95 : 5 + 0.1% HCOOH to H₂O : MeCN = 50 : 50 + 0.1% HCOOH) to afford title compound as a yellow solid (0.144 g, 0.28 mmol, 68% yield). MS/ESI⁺ 498.3 [MH]⁺, Rt 0.79 min (Method A).

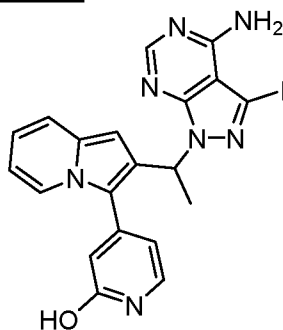
Step 2: 5-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one W35

To a solution of 5-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]pyridin-2-ol W35b (0.144 g, 0.28 mmol) in acetone (2.5 mL) 5 K₂CO₃ (0.178 g, 1.28 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (0.155 g, 0.83 mmol) were added and the resulting mixture was heated to 60°C overnight. Water was added and the mixture was extracted with DCM/MeOH 4/1; the combined organic layers were concentrated and the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a clear semi- 10 solid (0.069 g). MS/ESI⁺ 611.4 [MH]⁺, Rt 0.62 min (Method A).

Intermediate W36: 4-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one



Step 1: 4-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]pyridin-2-ol W36b



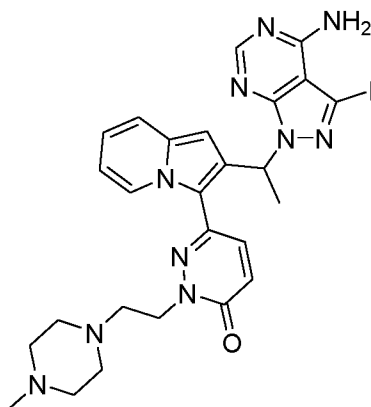
Prepared similarly to intermediate W35b starting from 3-iodo-1-{1-[3-(2-

methoxypyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W36a (1.27 g) and at 60°C for 3 h, to afford crude title compound as a brown solid (1.09 g, 2.19 mmol) which was used without any additional purification. MS/ESI⁺ 498.3 [MH]⁺, Rt 0.77 min (Method A).

5 **Step 2: 4-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one W36**

Prepared similarly to intermediate W35 Step 2 starting from 4-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]pyridin-2-ol W36b (1.09 g, 2.19 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (1.21 g, 6.52 mmol) and
10 purified by flash chromatography on SNAP C18 cartridge (from H₂O : MeCN = 95 : 5 with 0.1% HCOOH to H₂O : MeCN = 50 : 50 with 0.1% HCOOH). Acetonitrile was evaporated, the aqueous residue was neutralized with sodium bicarbonate and extracted with a mixture of DCM and MeOH 4 : 1. The organic layer was evaporated to afford title compound as a clear semi-solid (0.380 g, 0.62 mmol, 28% yield). MS/ESI⁺ 611.3 [MH]⁺, Rt 0.61 min
15 (Method A).

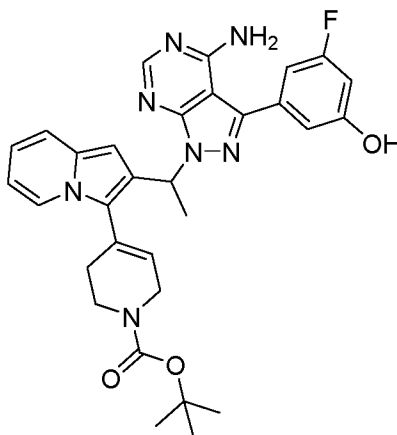
Intermediate W48: 6-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]-2-[2-(4-methylpiperazin-1-yl)ethyl]-2,3-dihydropyridazin-3-one



20 To a mixture of 6-[2-(1-hydroxyethyl)indolizin-3-yl]-2-[2-(4-methylpiperazin-1-yl)ethyl]-2,3-dihydropyridazin-3-one M51 (24 mg), 3-iodo-1H-pyrazolo [3,4-d]pyrimidin-4-amine (16.4 mg, 0.094 mmol) and PPh₃ (28.1 mg, 0.10 mmol) in dry THF (1 mL), DIAD

(0.01 mL, 0.05 mmol) was added drop-wise at RT and the reaction was stirred for 30 min. Additional DIAD (0.01 mL, 0.05 mmol) was added drop-wise at RT and the reaction was stirred at rt for 30 min. After that time, PPh₃ (10 mg, 0.038 mmol) was added followed by DIAD (0.01 mL, 0.05 mmol) and the mixture was stirred at RT for further 30 min. The solvent was removed and the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound (24.5 mg) which was used in the next step without any further purification. MS/ESI⁺ 625.4 [MH]⁺, Rt 0.60 min (Method A).

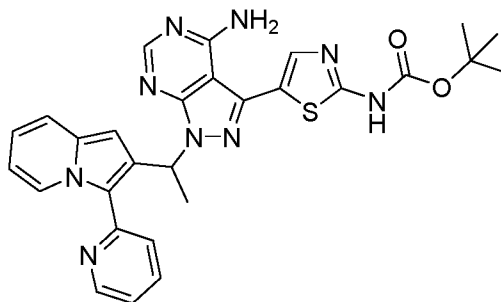
Intermediate X: tert-butyl 4-(2-(1-(4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)indolizin-3-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate



A mixture of crude tert-butyl 4-[2-(1-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)indolizin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate (0.19 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.032 g, 0.209 mmol) and Pd(PPh₃)₄ (0.010 g, 0.0095 mmol) DME (7.7 mL), ethanol (1.37 mL) and saturated aqueous sodium carbonate (2.60 mL) was heated at 80°C for 4 h. The mixture was partitioned between water and DCM, the aqueous phase was extracted with DCM and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on 5 g silica-NH cartridge (DCM to DCM : MeOH = 94 : 6) to afford title compound as light-

yellow oil (0.021 g, 0.037 mmol). MS/ESI⁺ 570.5 [MH]⁺, Rt 1.17 min (Method A).

Intermediate Y: tert-butyl N-[5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3-thiazol-2-yl]carbamate



5

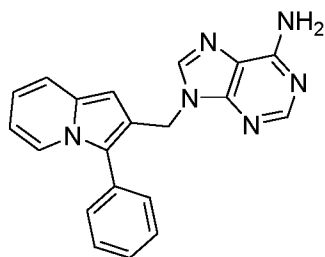
A mixture of 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.070 g, 0.145 mmol), tert-butyl 4-(tributylstannyl)thiazol-2-ylcarbamate (0.142 g, 0.291 mmol), Pd(PPh₃)₄ (0.017 g, 0.0145 mmol) and lithium chloride (6.15 mg, 0.145 mmol) in dioxane (1.5 mL) was purged with N₂ and heated at 100°C for 3 h. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 95 : 5) affording title compound as a yellow solid (0.060 g, 0.108 mmol, 75% yield). MS/ESI⁺ 554.4 [MH]⁺, Rt = 0.97 min (Method A).

10

PREPARATION OF COMPOUNDS:

15

Example 1: 9-[(3-phenylindolizin-2-yl)methyl]-9H-purin-6-amine



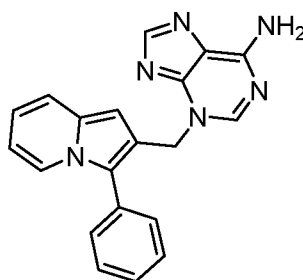
To a mixture of (3-phenylindolizin-2-yl)methanol K1 (0.100 g, 0.449 mmol), adenine (0.073 g, 0.537 mmol) and PPh₃ (0.153 g, 0.584 mmol) in dry THF (8 mL), a solution of DIAD (0.106 mL, 0.537 mmol) in THF (1 mL) was added drop-wise at room temperature and the reaction was stirred for 1 h. Additional PPh₃ (0.059 g, 0.225 mmol)

20

and DIAD (0.026 mL, 0.135 mmol) were added and the stirring was continued for 40 min. The solvent was removed under reduced pressure, the residue was dissolved in DCM and filtered. The filtrate was evaporated to dryness and purified by flash chromatography on Biotage silica-NH 28 g SNAP cartridge (DCM to DCM : MeOH = 98 : 2). Two fractions
 5 containing different isomers were collected. The first eluted fraction was evaporated to afford a residue which was triturated with Et₂O. The obtained solid (0.040 g) was further purified by flash chromatography on silica-NH Biotage SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 10 : 90) to yield title compound as a beige solid (0.032 g). MS/ESI⁺ 341.2 [MH]⁺, Rt = 0.76 min (LC/MS Method A).

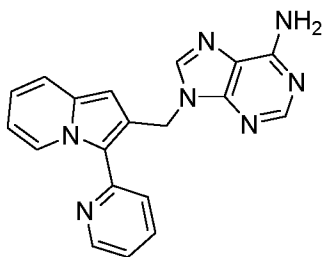
10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.11 (s, 1 H), 8.01 (d, 1 H), 7.99 (s, 1 H), 7.53 - 7.63 (m, 4 H), 7.44 - 7.51 (m, 1 H), 7.40 (d, 1 H), 7.17 (br. s, 2 H), 6.69 - 6.76 (m, 1 H), 6.51 - 6.59 (m, 1H), 6.30 (s, 1 H), 5.39 (s, 2 H).

Example 2: 3-[(3-phenylindolizin-2-yl)methyl]-3H-purin-6-amine



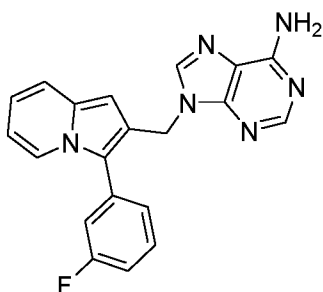
15 The second eluted fraction obtained from the reaction described in Example 1 was concentrated and further purified by reverse phase semi-preparative MDAP under acidic conditions (Method E), followed by evaporation, and extraction with DCM washing with aqueous sat. NaHCO₃, to afford title compound as an off-white solid. MS/ESI⁺ 341.1
 20 [MH]⁺, Rt = 0.63 min (LC/MS Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.16 (s, 1 H), 7.99 (d, 1 H), 7.76 - 7.95 (m, 2 H), 7.72 (s, 1 H), 7.63 - 7.70 (m, 2 H), 7.55 - 7.63 (m, 2 H), 7.45 - 7.52 (m, 1 H), 7.39 (d, 1 H), 6.69 - 6.76 (m, 1 H), 6.51 - 6.58 (m, 1 H), 6.31 (s, 1 H), 5.57 (s, 2 H)

Example 3: 9-{{3-(pyridin-2-yl)indolizin-2-yl}methyl}-9H-purin-6-amine

To a mixture of ethyl [3-(pyridin-2-yl)indolizin-2-yl]methanol K2 (0.150, 0.669
5 mmol), adenine (0.117 g, 0.869 mmol) and PPh₃ (0.263 g, 1.00 mmol) in dry THF (12 mL),
a solution of DIAD (0.171 mL, 0.869 mmol) in THF (1 mL) was added drop-wise at r.t.
and the reaction was stirred for 2 h. The reaction mixture was filtered and the filtrate was
evaporated under reduced pressure. The residue was purified by flash chromatography on
silica-NH Biotage SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 100% EtOAc) to
10 afford title compound as a white solid (0.065 g). MS/ESI⁺ 342.1 [MH]⁺, Rt = 0.51 min
(Method A).

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.90 (d, 1 H), 8.77 (d, 1 H), 8.16 (s, 1 H),
8.11 (s, 1 H), 7.96 (td, 1 H), 7.78 (d, *J*=7.8 Hz, 1 H), 7.44 (d, 1 H), 7.37 (dd, 1 H), 7.21 (s,
2 H), 6.83 (dd, 1 H), 6.65 (t, 1 H), 6.16 (s, 1 H), 5.61 (s, 2 H).

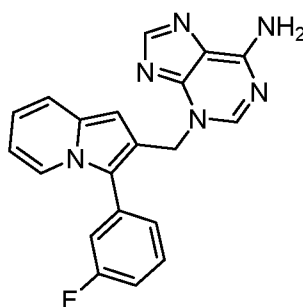
Example 4: 9-{{3-(3-fluorophenyl)indolizin-2-yl}methyl}-9H-purin-6-amine

Prepared similarly to Example 3, starting from [3-(3-fluorophenyl)indolizin-2-
yl]methanol K3 (0.165 g, 0.684 mmol) and purified by flash chromatography on silica-NH
20 Biotage SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 100% EtOAc); the first eluted
isomer was obtained as an off-white solid (0.047 g). MS/ESI⁺ 359.1 [MH]⁺, Rt = 0.79 min

(Method A).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.12 (s, 1 H), 8.07 (d, 1 H), 8.05 (s, 1 H), 7.58 - 7.66 (m, 1 H), 7.48 - 7.54 (m, 1 H), 7.40 - 7.47 (m, 2 H), 7.27 - 7.35 (m, 1 H), 7.20 (s, 2 H), 6.74 - 6.81 (m, 1 H), 6.55 - 6.63 (m, 1 H), 6.33 (s, 1 H), 5.43 (s, 2 H).

5 **Example 5: 3-([3-(3-fluorophenyl)indolizin-2-yl]methyl)-3H-purin-6-amine**

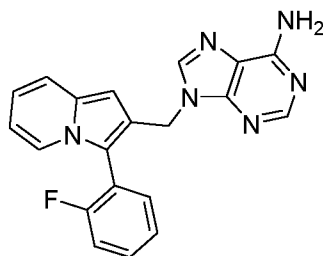


Obtained as the minor isomer from the reaction described in Example 4 and purified by reverse phase semi-preparative MDAP under basic conditions (Method F) to afford an off-white solid. MS/ESI⁺ 359.2 [MH]⁺, Rt = 0.89 min (Method C).

^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.23 (s, 1 H), 8.04 (d, 1 H), 7.78 - 7.96 (m, 2 H), 7.71 (s, 1 H), 7.58 - 7.68 (m, 2 H), 7.50 (d, 1 H), 7.39 (d, 1 H), 7.30 (td, 1 H), 6.71 - 6.77 (m, 1 H), 6.57 (t, 1 H), 6.31 (s, 1 H), 5.58 (s, 2 H).

Example 6: 9-([3-(2-fluorophenyl)indolizin-2-yl]methyl)-9H-purin-6-amine

15

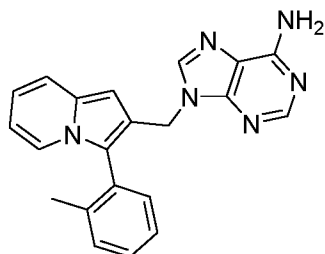


Prepared similarly to compound Example 3, starting from [3-(2-fluorophenyl)indolizin-2-yl]methanol K4 (0.150 g, 0.622 mmol) and purified by flash chromatography on silica-NH (cyclohexane : EtOAc = 90 : 10 to 100% EtOAc) followed by trituration with Et₂O to yield title compound as an off white solid (0.050 g) MS/ESI⁺ 359.2 [MH]⁺, Rt = 0.80 min (Method B).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.10 (s, 1 H), 8.00 (s, 1 H), 7.64 - 7.75 (m, 2 H), 7.55 - 7.63 (m, 1 H), 7.36 - 7.50 (m, 3 H), 7.18 (s, 2 H), 6.77 - 6.82 (m, 1 H), 6.58 - 6.64 (m, 1 H), 6.39 (s, 1 H), 5.36 (s, 2 H).

Example 7: 9-([3-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine

5



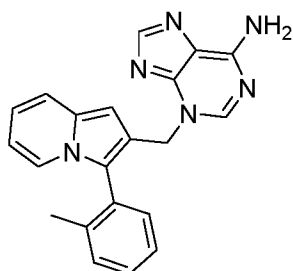
Prepared similarly to Example 3, starting from [3-(2-methylphenyl)indolizin-2-yl]methanol K5 (0.150 g, 0.632 mmol). The crude mixture was purified by reverse phase semi-preparative MDAP under acidic conditions (Method E). The collected fractions containing the main product (slower compound under reverse phase UPLC conditions) were concentrated under reduced pressure, basified with aqueous sat. NaHCO_3 and extracted with DCM. The organic phase was dried over sodium sulfate and the solvent was evaporated. The residue was further purified by flash chromatography on silica-NH Biotage 11g SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 10 : 90) to afford title compound as a white solid (0.044 g). MS/ESI $^+$ 355.2 $[\text{MH}]^+$, R_t = 0.82 min (Method A).

15

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.07 (s, 1 H), 7.85 (s, 1 H), 7.40 - 7.45 (m, 3 H), 7.32 - 7.37 (m, 3 H), 7.14 (s, 2 H), 6.69 - 6.75 (m, 1 H), 6.50 - 6.55 (m, 1 H), 6.41 (s, 1 H), 5.18 - 5.29 (m, 2 H), 1.88 (s, 3 H)

Example 8: 3-([3-(2-methylphenyl)indolizin-2-yl]methyl}-3H-purin-6-amine

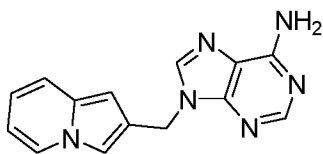
20



Obtained as the minor isomer (faster compound under reverse phase UPLC conditions) from the purification described in Example 7. The collected fractions were concentrated under reduced pressure, basified with sat. NaHCO_3 and extracted with DCM. The organic phase was dried over sodium sulfate and evaporated. The residue was further
5 purified by flash chromatography on silica-NH Biotage cartridge (DCM to DCM : MeOH = 95 : 5) to yield title compound as a white solid (0.021 g). MS/ESI⁺ 355.2 [MH]⁺, Rt = 0.65 min (Method A).

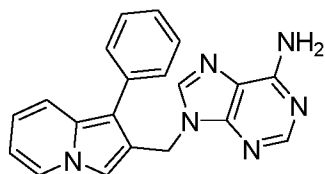
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.99 (s, 1 H), 7.83 (br. s., 2 H), 7.71 (s, 1 H), 7.32 - 7.50 (m, 6 H), 6.70 - 6.77 (m, 1 H), 6.51 - 6.57 (m, 1 H), 6.47 (s, 1 H), 5.44 (s, 2
10 H), 1.89 (s, 3 H).

Example 9: 9-(indolizin-2-ylmethyl)-9H-purin-6-amine



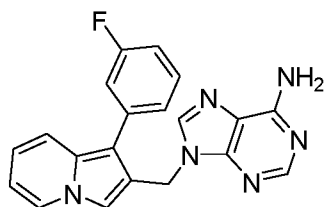
Prepared similarly to Example 3, starting from indolizin-2-ylmethanol K23 (0.150
15 g, 1.02 mmol) and purified by flash chromatography on silica-NH 28 g Biotage SNAP cartridge (DCM to DCM : MeOH = 95 : 5) followed by flash chromatography on silica-NH Biotage SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 100% EtOAc). A further purification by reverse phase semi-preparative MDAP under basic conditions (Method G) was required to obtain title compound as a white solid (0.011 g). MS/ESI⁺ 265.1 [MH]⁺, Rt = 0.68 min (Method C).

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.16 (s, 1 H), 8.14 (dd, 1 H), 8.11 (s, 1 H), 7.44 (s, 1 H), 7.27 (d, 1 H), 7.14 (br. s, 2 H), 6.59 - 6.62 (m, 1 H), 6.44 (t, 1 H), 6.28 (s, 1 H), 5.36 (s, 2 H).

Example 10: 9-[(1-phenylindolizin-2-yl)methyl]-9H-purin-6-amine

To a mixture of (1-phenylindolizin-2-yl)methanol K24 (0.050 g, 0.22 mmol),
5 adenine (0.0356 g, 0.29 mmol) and PPh₃ (0.075 g, 0.286 mmol) in dry THF (4.5 mL), a
solution of DIAD (0.052 mL, 0.26 mmol) in THF (1 mL) was added drop-wise at RT and
the reaction was stirred at 50°C for 48 h. The solvent was removed and the residue was
purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to
cyclohexane : EtOAc = 96 : 4). A further purification by reverse phase semi-preparative
10 MDAP under acidic conditions (Method A), followed by extraction with DCM washing
with aqueous sat. NaHCO₃, was required to afford title compound as pale yellow solid
(0.003 g). MS/ESI⁺ 341.1 [MH]⁺, Rt = 0.75 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.22 (d, *J*=7.0 Hz, 1 H), 8.12 (s, 1 H), 7.95
(s, 1 H) 7.39 - 7.51 (m, 5 H), 7.27 - 7.36 (m, 2 H), 7.21 (s, 2 H), 6.72 - 6.78 (m, 1 H), 6.54
15 - 6.59 (m, 1 H), 5.52 (s, 2 H).

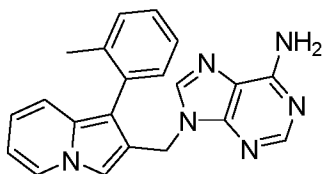
Example 11: 9-[[1-(3-fluorophenyl)indolizin-2-yl]methyl]-9H-purin-6-amine

Prepared similarly to Example 10, starting from [1-(3-fluorophenyl)indolizin-2-
20 yl]methanol K25 (0.165 g, 0.68 mmol), and purified by flash chromatography on silica-NH
25 g Biotage cartridge (DCM to DCM : MeOH = 98 : 2). A further purification by flash
chromatography on silica NH Biotage SNAP cartridge (cyclohexane : EtOAc = 30:70 to
100% EtOAc) was required to afford title compound (0.015 g). MS/ESI⁺ 359.1 [MH]⁺, Rt
= 0.79 min (Method A).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 8.23 (d, 1 H), 8.11 (s, 1 H), 7.98 (s, 1 H), 7.45 - 7.50 (m, 1 H), 7.44 (d, 1 H), 7.34 (s, 1 H), 7.30 (d, 1 H), 7.25 - 7.28 (m, 1 H), 7.19 (br. s, 2 H), 7.11 (td, 1 H), 6.75 - 6.81 (m, 1 H), 6.56 - 6.61 (m, 1 H), 5.52 (s, 2 H).

Example 12: 9-([1-(2-methylphenyl)indolizin-2-yl]methyl)-9H-purin-6-amine

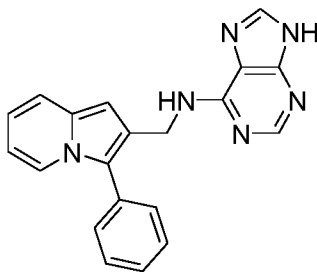
5



Prepared similarly to Example 10, starting from [1-(2-methylphenyl)indolizin-2-yl]methanol K26 (0.085 g, 0.36 mmol), and purified by flash chromatography on Biotage silica-NH 10 g SNAP cartridge (DCM to DCM : MeOH = 97 : 3). A further purification by
 10 flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 30 : 70 to 100% EtOAc) was required to afford title compound (0.007 g). MS/ESI⁺ 355.2 [MH]⁺, Rt = 0.77 min (Method A).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.24 (d, 1 H), 8.08 (s, 1 H), 7.66 (s, 1 H), 7.49 (s, 1 H), 7.15 - 7.35 (m, 6 H), 6.88 (d, 1 H), 6.64 - 6.70 (m, 1 H), 6.52 - 6.57 (m, 1 H),
 15 5.19 - 5.34 (m, 2 H), 1.99 (s, 3 H).

Example 13: N-[(3-phenylindolizin-2-yl)methyl]-9H-purin-6-amine

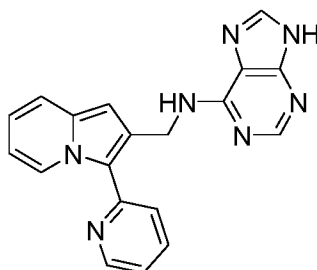


To a solution of (3-phenylindolizin-2-yl)methanamine P1 (0.070 g, 0.315 mmol) in
 20 *t*-BuOH (4 mL), 6-bromopurine (0.063 g, 0.315 mmol) was added followed by DIPEA (0.110 mL, 0.630 mmol) and the resulting mixture was heated to reflux for 1 h. The solvent was removed under reduced pressure and the crude was partitioned between DCM/MeOH $\approx$ 3/1 and water; the organic phase was dried over sodium sulfate, the solvent was removed

under vacuum and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow solid (0.067 g). MS/ESI⁺ 341.1 [MH]⁺, Rt = 0.76 min (Method A).

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.06 - 13.46 (m, 1 H), 8.15 - 8.18 (m, 1 H),
5 8.08 - 8.10 (m, 1 H), 8.04 (d, 1 H), 7.77 - 7.98 (m, 1 H), 7.59 - 7.64 (m, 2 H), 7.53 - 7.59
(m, 2 H), 7.37 - 7.46 (m, 2 H), 6.67 - 6.71 (m, 1 H), 6.48 - 6.54 (m, 2 H), 4.63 - 4.88 (m, 2
H).

Example 14: N-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine

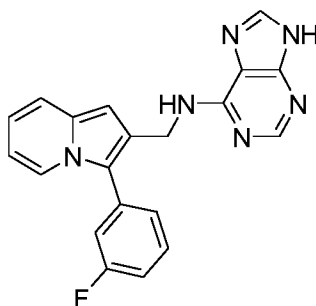


10

Prepared similarly to Example 13, starting from [3-(pyridin-2-yl)indolizin-2-yl]methanamine P2 (0.103 g, 0.461 mmol), heating to reflux for 5 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as a pale yellow solid (0.110 g). MS/ESI⁺ 342.2 [MH]⁺, Rt = 0.56
15 min (Method B).

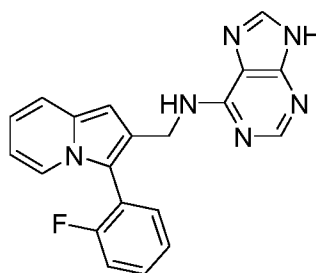
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.81 (br. s., 1 H), 9.04 (d, 1 H), 8.73 - 8.78
(m, 1 H), 8.18 (s, 1 H), 8.12 (s, 1 H), 8.06 (br. s., 1 H), 7.95 (td, 1 H), 7.78 (d, 1 H), 7.46
(d, 1 H), 7.30 - 7.38 (m, 1 H), 6.79 - 6.86 (m, 1 H), 6.60 - 6.67 (m, 1 H), 6.54 (s, 1 H), 4.97
(br. s., 2 H).

20

Example 15: N-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine (

Prepared similarly to Example 13, starting from [3-(3-fluorophenyl)indolizin-2-yl]methanamine P3 (0.100 g, 0.416 mmol), heating to reflux for 4 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow solid (0.087 g). MS/ESI⁺ 359.2 [MH]⁺, Rt = 0.85 min (Method B).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.80 (br. s., 1 H), 8.18 (s, 1 H), 8.06 - 8.15 (m, 2 H), 7.96 (br. s., 1 H), 7.50 - 7.66 (m, 2 H), 7.38 - 7.50 (m, 2 H), 7.23 - 7.32 (m, 1 H), 6.69 - 6.77 (m, 1 H), 6.50 - 6.60 (m, 2 H), 4.79 (br. s., 2 H).

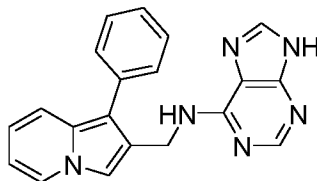
Example 16: N-{[3-(2-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine

Prepared similarly to Example 13, starting from [3-(2-fluorophenyl)indolizin-2-yl]methanamine P4 (0.115 g, 0.476 mmol), heating to reflux for 2 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as an off-white solid (0.115 g) MS/ESI⁺ 359.1 [MH]⁺, Rt = 0.77 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.79 (br. s., 1 H), 8.16 (s, 1 H), 8.10 (s, 1 H), 7.89 (br. s., 1 H), 7.65 - 7.77 (m, 2 H), 7.51 - 7.61 (m, 1 H), 7.35 - 7.50 (m, 3 H), 6.72

- 7.79 (m, 1 H), 6.52 - 6.61 (m, 2 H), 4.73 (br. s., 2 H).

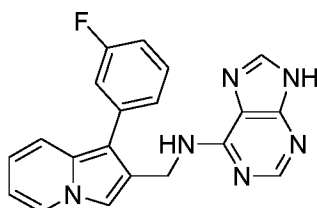
Example 17: N-[(1-phenylindolizin-2-yl)methyl]-9H-purin-6-amine



5 Prepared similarly to Example 13, starting from (1-phenylindolizin-2-yl)methanamine P6 (0.050 g, 0.224 mmol), heating to reflux for 6 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 94 : 6) to afford title compound as a pale yellow solid (0.030 g). MS/ESI⁺ 341.1 [MH]⁺, Rt = 0.77 min (Method A).

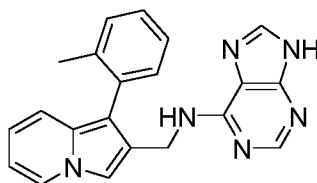
10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.85 (br. s., 1 H), 8.24 (d, 1 H), 8.19 (s, 1 H), 8.12 (s, 1 H), 7.97 (br. s., 1 H), 7.50 - 7.55 (m, 3 H), 7.41 - 7.49 (m, 3 H), 7.25 - 7.33 (m, 1 H), 6.68 - 6.75 (m, 1 H), 6.50 - 6.55 (m, 1 H), 4.86 (br. s., 2 H).

Example 18: N-[1-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine



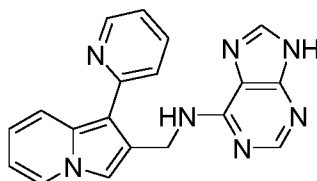
15 Prepared similarly to Example 13, starting from [1-(3-fluorophenyl)indolizin-2-yl]methanamine P7 (0.074 g, 0.31 mmol), heating to reflux for 3 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 97 : 3) to afford title compound as an off-white solid (0.044 g). MS/ESI⁺ 359.1 [MH]⁺, Rt = 0.82 min (Method A).

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.92 (br. s., 1 H), 7.93 - 8.37 (m, 4 H), 7.41 - 7.57 (m, 3 H), 7.26 - 7.40 (m, 2 H), 7.05 - 7.14 (m, 1 H), 6.70 - 6.81 (m, 1 H), 6.50 - 6.61 (m, 1 H), 4.74 - 4.97 (m, 2 H).

Example 19: N-{[1-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine

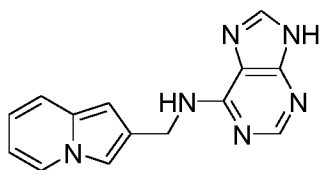
Prepared similarly Example 13, starting from [1-(2-methylphenyl)indolizin-2-yl]methanamine P8 (0.047 g, 0.20 mmol), heating to reflux for 5 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as an off-white solid as a mixture of isomers (0.040 g). MS/ESI⁺ 355.2 [MH]⁺, Rt = 0.96 min (Method C).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.91 - 12.94 (m, 1 H), 8.02 - 8.30 (m, 3 H), 7.74 - 7.89 (m, 1 H), 7.46 - 7.71 (m, 1 H), 7.15 - 7.40 (m, 4 H), 6.83 - 6.94 (m, 1 H), 6.58 - 6.70 (m, 1 H), 6.44 - 6.57 (m, 1 H), 4.45 - 4.72 (m, 2 H), 2.08 - 2.14 (m, 3 H).

Example 20: N-{[1-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine

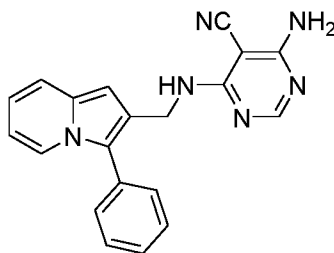
Prepared similarly to Example 13, starting from [1-(pyridin-2-yl)indolizin-2-yl]methanamine P9 (0.044 g, 0.20 mmol), heating to reflux for 6 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale brown solid (0.025 g). MS/ESI⁺ 342.1 [MH]⁺, Rt = 0.43 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.97 (br. s., 1 H), 8.70 (d, 1 H), 8.03 - 8.41 (m, 4 H), 7.93 (d, 1 H), 7.86 (t, 1 H), 7.69 (d, 1 H), 7.56 (br. s., 1 H), 7.20 - 7.26 (m, 1 H), 6.84 - 6.93 (m, 1 H), 6.59 - 6.67 (m, 1 H), 5.00 (br. s., 2 H).

Example 21: N-(indolizin-2-ylmethyl)-9H-purin-6-amine

Prepared similarly to Example 13, starting from indolizin-2-ylmethanamine P10
5 (0.065 g, 0.44 mmol), heating to reflux for 2 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound as an off-white solid (0.057 g). MS/ESI⁺ 264.9 [MH]⁺, Rt = 0.66 min (Method C).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.79 (br. s., 1 H), 8.14 - 8.28 (m, 2 H), 8.11
10 (s, 1H), 7.94 (br. s., 1 H), 7.46 (s, 1 H), 7.31 (d, 1 H), 6.58 - 6.66 (m, 1 H), 6.41 - 6.49 (m, 1 H), 6.35 (s, 1 H), 4.77 (br. s., 2 H).

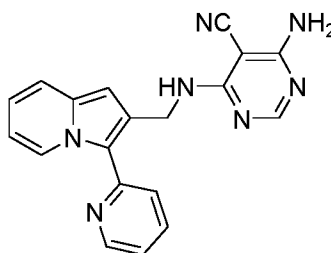
Example 22: 4-amino-6-[(3-phenylindolizin-2-yl)methyl]amino}pyrimidine-5-carbonitrile

15 To a solution of (3-phenylindolizin-2-yl)methanamine P1 (0.076 g, 0.342 mmol) in *t*-BuOH (4 mL), 4-amino-6-chloropyrimidine-5-carbonitrile (0.053 g, 0.342 mmol) was added followed by DIPEA (0.119 mL, 0.742 mmol) and the resulting mixture was heated to reflux for 1 h. The solvent was removed and the crude was partitioned between DCM
20 and water; the organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure and the crude was purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 60 : 40) to afford title compound as a pale yellow solid (0.065 g). MS/ESI⁺ 341.1 [MH]⁺, Rt = 0.99 min (Method

A).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.01 - 8.05 (m, 1 H), 8.00 (s, 1 H), 7.76 (t, 1 H), 7.53 - 7.61 (m, 4 H), 7.40 - 7.48 (m, 2 H), 7.21 (br. s., 2 H), 6.67 - 6.75 (m, 1 H), 6.49 - 6.55 (m, 1 H), 6.47 (s, 1 H), 4.63 (d, 2 H).

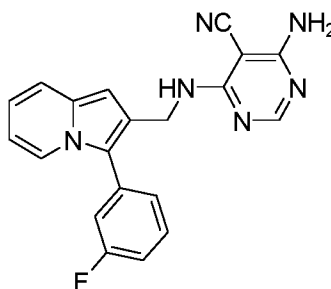
5 **Example 23:** **4-amino-6-({[3-(pyridin-2-yl)indolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile**



Prepared similarly to Example 22, starting from [3-(pyridin-2-yl)indolizin-2-yl]methanamine P2 (0.097 g, 0.434 mmol), heating to reflux for 2 h, and purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow solid (0.120 g). MS/ESI⁺ 342.2 [MH]⁺, Rt = 0.58 min (Method A).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.96 (d, 1 H), 8.71 - 8.78 (m, 1 H), 7.98 - 8.06 (m, 2 H), 7.95 (td, 1 H), 7.72 (d, 1 H), 7.50 (d, 1 H), 7.32 - 7.37 (m, 1 H), 7.25 (br. s., 2 H), 6.81 - 6.87 (m, 1 H), 6.61 - 6.67 (m, 1 H), 6.48 (s, 1 H), 4.79 (d, 2 H).

Example 24: **4-amino-6-({[3-(3-fluorophenyl)indolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile**



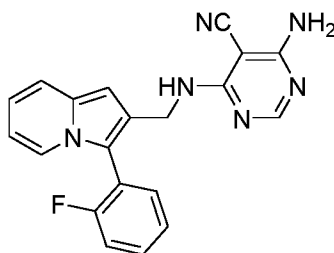
Prepared similarly to Example 22, starting from [3-(3-fluorophenyl)indolizin-2-

yl]methanamine P3 (0.101 g, 0.421 mmol), heating to reflux for 1 h, and purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 60 : 40) to afford title compound as a pale yellow solid (0.100 g). MS/ESI⁺ 359.2 [MH]⁺, Rt = 1.01 min (Method B).

5 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.07 (d, 1 H), 7.99 (s, 1 H), 7.80 (t, 1 H), 7.55 - 7.64 (m, 1 H), 7.39 - 7.51 (m, 3 H), 7.24 - 7.31 (m, 1H), 7.22 (br. s., 2 H), 6.71 - 6.78 (m, 1 H), 6.52 - 6.57 (m, 1 H), 6.49 (s, 1 H), 4.64 (d, 2 H).

Example 25: 4-amino-6-([3-(2-fluorophenyl)indolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile

10



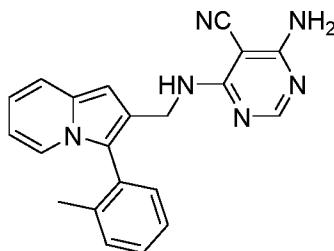
15 Prepared similarly to Example 22, starting from [3-(2-fluorophenyl)indolizin-2-yl]methanamine P4 (0.130 g, 0.541 mmol), heating to reflux for 2 h, and purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 98 : 2) to afford title compound as an off-white solid (0.140 g). MS/ESI⁺ 359.1 [MH]⁺, Rt = 0.98 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.96 (s, 1 H), 7.74 (t, 1 H), 7.61 - 7.71 (m, 2 H), 7.51 - 7.60 (m, 1 H), 7.36 - 7.50 (m, 3 H), 7.20 (br. s., 2 H), 6.73 - 6.79 (m, 1 H), 6.53 - 6.60 (m, 1 H), 6.51 (s, 1 H), 4.51 - 4.65 (m, 2 H).

20

25

Example 26: 4-amino-6-({[3-(2-methylphenyl)indolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile

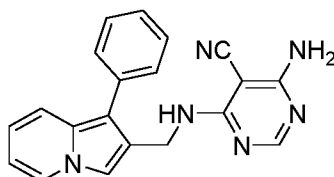


5 Prepared similarly to Example 22, starting from [3-(2-methylphenyl)indolizin-2-yl]methanamine P5 (0.129 g, 0.546 mmol), heating to reflux for 2 h, and purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as an off-white solid (0.132 g). MS/ESI⁺ 355.2 [MH]⁺, Rt = 1.05 min (Method A).

10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.94 (s, 1 H), 7.63 (t, 1 H), 7.29 - 7.47 (m, 6 H), 7.17 (br. s., 2 H), 6.67 - 6.73 (m, 1 H), 6.45 - 6.52 (m, 2 H), 4.42 - 4.55 (m, 2 H), 1.97 (s, 3 H).

Example 27: 4-amino-6-({[1-phenylindolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile

15

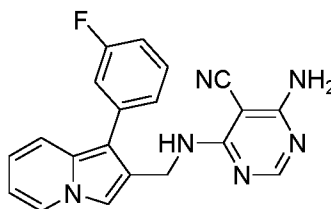


Prepared similarly to Example 22, starting from (1-phenylindolizin-2-yl)methanamine P6 (0.050 g, 0.224 mmol), heating to reflux for 1 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 70 : 30 to 20 50 : 50) to afford title compound as an off-white solid (0.037 g). MS/ESI⁺ 341.2 [MH]⁺, Rt = 0.99 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.27 (d, 1 H), 8.00 (s, 1 H), 7.79 (t, 1 H), 7.44 - 7.49 (m, 5 H), 7.39 - 7.43 (m, 1 H), 7.19 - 7.33 (m, 3 H), 6.68 - 6.74 (m, 1 H), 6.51 -

6.56 (m, 1 H), 4.72 (d, 2 H).

Example 28: 4-amino-6-({[1-(3-fluorophenyl)indolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile



5

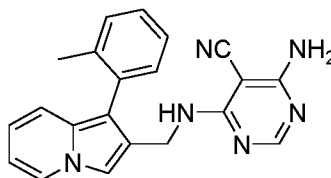
Prepared similarly to Example 22, starting from [1-(3-fluorophenyl)indolizin-2-yl]methanamine P7 (0.055 g, 0.23 mmol), heating to reflux for 2 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 99.5 : 0.5) to afford title compound as an off-white solid (0.033 g). MS/ESI⁺ 359.1 [MH]⁺, Rt 1.02 min (Method A).

10

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.30 (d, 1 H), 8.01 (s, 1 H), 7.81 (t, 1 H), 7.43 - 7.53 (m, 3 H), 7.26 - 7.34 (m, 2 H), 7.24 (br. s, 2 H), 7.07 - 7.15 (m, 1 H), 6.74 - 6.80 (m, 1 H), 6.55 - 6.61 (m, 1 H), 4.73 (d, 2 H).

Example 29: 4-amino-6-({[1-(2-methylphenyl)indolizin-2-yl]methyl}amino)pyrimidine-5-carbonitrile

15



Prepared similarly to Example 22, starting from [1-(2-methylphenyl)indolizin-2-yl]methanamine P8 (0.046 g, 0.19 mmol), heating to reflux for 2 h, and purified by flash chromatography on 11 g Biotage silica-NH cartridge (cyclohexane : EtOAc = 80 : 20 to 50 : 50) to afford title compound as an off-white solid (0.024 g). MS/ESI⁺ 355.2 [MH]⁺, Rt 0.96 min (Method C).

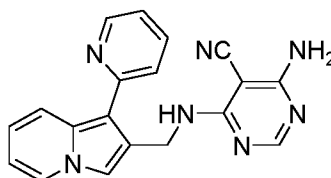
20

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.23 - 8.29 (m, 1 H), 7.96 (s, 1 H), 7.59 (t,

1 H), 7.49 (s, 1 H), 7.33 (d, 1 H), 7.22 - 7.30 (m, 3 H), 7.19 (br. s., 2 H), 6.87 (d, 1 H), 6.60 - 6.67 (m, 1 H), 6.48 - 6.54 (m, 1 H), 4.48 (d, 2 H), 2.10 (s, 3 H).

Example 30: 4-amino-6-([1-(pyridin-2-yl)indolizin-2-yl]methyl)amino)pyrimidine-5-carbonitrile

5

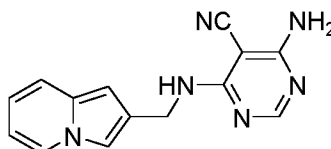


Prepared similarly to Example 22, starting from [1-(pyridin-2-yl)indolizin-2-yl]methanamine P9 (0.044 g, 0.20 mmol), heating to reflux for 1 h, and purified by flash chromatography on 11 g Biotage silica-NH cartridge (cyclohexane : EtOAc = 70 : 30 to 40 : 60) to afford title compound as a pale brown solid (0.0416 g). MS/ESI⁺ 342.1 [MH]⁺, Rt 0.49 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.61 - 8.71 (m, 2 H), 8.34 (d, 1 H), 8.05 (s, 1 H), 7.81 - 7.92 (m, 2 H), 7.69 (d, 1 H), 7.59 (s, 1 H), 7.19 - 7.32 (m, 3 H), 6.88 - 6.95 (m, 1 H), 6.63 - 6.70 (m, 1 H), 4.80 (d, 2 H).

15

Example 31: 4-amino-6-[(indolizin-2-ylmethyl)amino]pyrimidine-5-carbonitrile

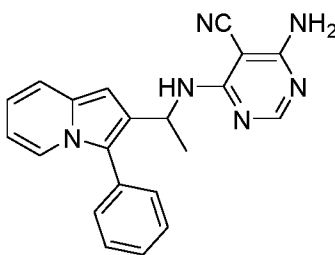


Prepared similarly to Example 22, starting from indolizin-2-ylmethanamine P10 (0.065 g, 0.44 mmol), heating to reflux for 2 h, and purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 99.9 : 0.1) to afford title compound as an off-white solid (0.040 g). MS/ESI⁺ 265.1 [MH]⁺, Rt 0.78 min (Method C).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.17 - 8.21 (m, 1 H), 8.04 (s, 1 H), 7.79 (t, 1 H), 7.41 (s, 1 H), 7.32 (d, 1 H), 7.22 (br. s., 2 H), 6.60 - 6.66 (m, 1 H), 6.43 - 6.49 (m, 1 H), 6.30 (s, 1 H), 4.62 (d, 2 H).

20

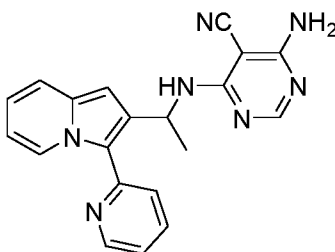
Example 32: 4-amino-6-([1-(3-phenylindolizin-2-yl)ethyl]amino)pyrimidine-5-carbonitrile



Prepared similarly to Example 22, starting from 1-(3-phenylindolizin-2-yl)ethan-1-amine Q1 (0.041 g, 0.174 mmol), heating to reflux for 2 h, and purified by flash chromatography on Biotage silica-NH cartridge (cyclohexane : EtOAc = 90 : 10 to 60 : 40). A further purification by trituration with Et₂O was required to afford title compound as a white solid (0.035 g). MS/ESI⁺ 355.2 [MH]⁺, Rt 1.05 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.88 - 7.94 (m, 2 H), 7.39 - 7.58 (m, 6 H), 7.27 (d, 1 H), 7.17 (br. s., 2 H), 6.68 - 6.76 (m, 2 H), 6.47 - 6.55 (m, 1 H), 5.44 - 5.54 (m, 1 H), 1.45 (d, 3 H).

Example 33: 4-amino-6-([1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile



15

Prepared similarly to Example 22, starting from 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.050 g, 0.211 mmol), heating to reflux for 2 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 30 : 70) to afford title compound as a yellow solid (0.049 g). MS/ESI⁺ 365.1 [MH]⁺, Rt 0.64 min (Method A).

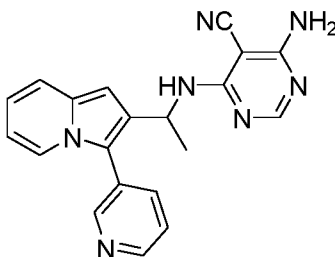
20

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.74 - 8.79 (m, 1 H), 8.67 (d, 1 H), 8.10 (d, 1 H), 7.90 - 8.00 (m, 2 H), 7.77 (d, 1 H), 7.52 (d, 1 H), 7.34 - 7.40 (m, 1 H), 7.21 (br. s., 2

H), 6.80 - 6.88 (m, 1 H), 6.71 (s, 1 H), 6.59 - 6.67 (m, 1 H), 5.68 - 5.79 (m, 1 H), 1.39 (d, 3 H).

Example 34: 4-amino-6-({1-[3-(pyridin-3-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile

5

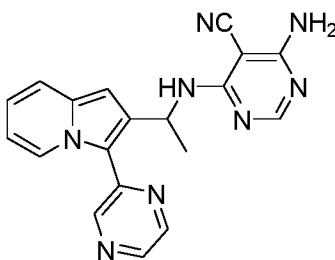


Prepared similarly to Example 22, starting from 1-[3-(pyridin-3-yl)indolizin-2-yl]ethan-1-amine Q3 (0.062 g.), heating to reflux for 3 h, and purified by flash chromatography on Biotage silica-NH cartridge (DCM : EtOAc = 80 : 20 to 30 : 70) to afford title compound as a pale yellow solid (0.045 g). MS/ESI⁺ 356.1 [MH]⁺, Rt 0.66 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.68 (d, 1 H), 8.62 (dd, 1 H), 7.93 - 7.98 (m, 1 H), 7.91 (d, 1 H), 7.87 (s, 1 H), 7.52 - 7.58 (m, 1 H), 7.49 (d, 1 H), 7.36 (d, 1 H), 7.15 (br. s., 2 H), 6.72 - 6.80 (m, 2 H), 6.50 - 6.57 (m, 1 H), 5.39 - 5.49 (m, 1 H), 1.49 (d, 3 H).

Example 35: 4-amino-6-({1-[3-(pyrazin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile

15



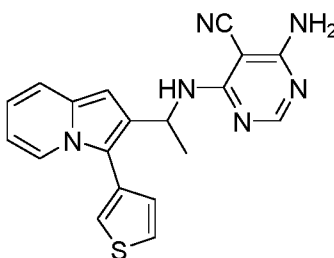
Prepared similarly to Example 22, starting from crude 1-[3-(pyrazin-2-yl)indolizin-2-yl]ethan-1-amine Q4 (0.114 mmol), heating to reflux for 4 h, and purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : EtOAc = 30 : 70) to afford title compound as a pale yellow solid (0.024 g). MS/ESI⁺ 357.1 [MH]⁺, Rt 0.81 min

20

chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 80 : 20). A further purification by reverse phase semi-preparative MDAP under acidic conditions (Method A) followed by dissolution in DCM and washing with sat. NaHCO₃ was required to afford title compound as a pale yellow solid (0.020 g). MS/ESI⁺ 361.1 [MH]⁺, Rt 1.04 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.97 - 8.03 (m, 1 H), 7.92 (s, 1 H), 7.75 (dd, 1 H), 7.44 - 7.49 (m, 1 H), 7.26 - 7.30 (m, 2 H), 7.23 - 7.26 (m, 1 H), 7.15 (br. s., 2 H), 6.73 - 6.79 (m, 1 H), 6.68 (s, 1 H), 6.55 - 6.61 (m, 1 H), 5.49 - 5.59 (m, 1 H), 1.46 (d, 3 H).

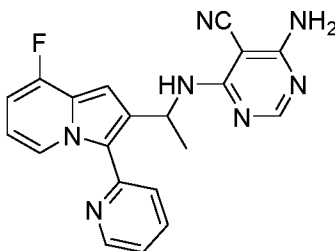
Example 38: 4-amino-6-({1-[3-(thiophen-3-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile



Prepared similarly to Example 22, starting from 1-[3-(thiophen-3-yl)indolizin-2-yl]ethan-1-amine Q12 (0.061 g), heating to reflux for 2 h, and purified by flash chromatography on 11g Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 80 : 20). A further purification by reverse phase semi-preparative MDAP under acidic conditions (Method E) followed by dissolution in DCM and washing with sat. NaHCO₃ was required to afford title compound as a pale green solid (0.030 g). MS/ESI⁺ 361.1 [MH]⁺, Rt 1.04 min. (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.96 (s, 1 H), 7.91 - 7.95 (m, 1 H), 7.74 - 7.77 (m, 2 H), 7.45 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.27 (d, 1 H), 7.17 (br. s., 2 H), 6.67 - 6.74 (m, 2 H), 6.51 - 6.56 (m, 1 H), 5.48 - 5.58 (m, 1 H), 1.45 (d, 3 H).

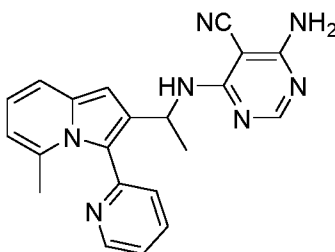
Example 39: 4-amino-6-({1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile



- 5 Prepared similarly to Example 22, starting from 1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q5 (0.084 g, 0.33 mmol), heating to reflux for 1 h, and purified by flash chromatography on 11 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 98 : 2); a further flash chromatography on 10 g Biotage silica SNAP cartridge (cyclohexane : EtOAc = 60 : 40 to 40 : 60) to afford title compound (0.052 g).
- 10 MS/ESI⁺ 374.2 [MH]⁺, Rt 0.76 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.74 - 8.80 (m, 1 H), 8.48 (d, 1 H), 7.92 - 8.03 (m, 3 H), 7.81 (d, 1 H), 7.38 - 7.44 (m, 1 H), 7.23 (br. s., 2 H), 6.91 (s, 1 H), 6.68 - 6.75 (m, 1 H), 6.57 - 6.64 (m, 1 H), 5.69 - 5.76 (m, 1 H), 1.42 (d, 3 H).

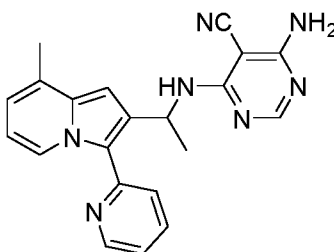
Example 40: 4-amino-6-({1-[5-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile



- 15 Prepared similarly to Example 22, starting from 1-[5-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q13 (0.045 g, 0.18 mmol), heating to reflux for 2 h, and purified by flash chromatography on 11 g Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 80 : 20 to 50 : 50) to afford title compound as a pale white solid (0.036 g).
- MS/ESI⁺ 370.1 [MH]⁺, Rt 0.91 min (Method C)

^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.55 - 8.74 (m, 1 H), 7.50 - 8.02 (m, 4 H), 7.02 - 7.48 (m, 4 H), 6.64 - 6.77 (m, 2 H), 6.40 (d, 1 H), 5.31 - 5.43 (m, 1 H), 1.95 (s, 3 H), 1.10 - 1.40 (m, 3 H).

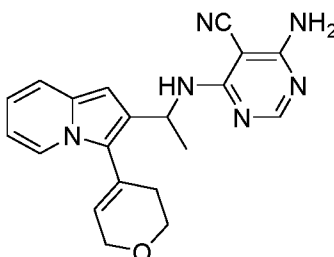
Example 41: 4-amino-6-({1-[8-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile



Prepared similarly to Example 22, starting from 1-[8-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q14 (0.050 g, 0.20 mmol), heating to reflux for 1 h, and purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 98 : 2); a further purification by flash chromatography on 11g Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 50 : 50) was required to afford title compound as a pale yellow solid (0.019 g). MS/ESI⁺ 370.2 [MH]⁺, Rt 0.70 min (Method A).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.74 - 8.79 (m, 1 H), 8.51 (d, 1 H), 8.16 (d, 1 H), 7.90 - 8.00 (m, 2 H), 7.76 (d, 1 H), 7.35 - 7.40 (m, 1 H), 7.22 (br. s., 2 H), 6.72 (s, 1 H), 6.68 (d, 1 H), 6.55 - 6.60 (m, 1 H), 5.68 - 5.78 (m, 1 H), 2.40 (s, 3 H), 1.38 (d, 3 H).

Example 42: 4-amino-6-({1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile

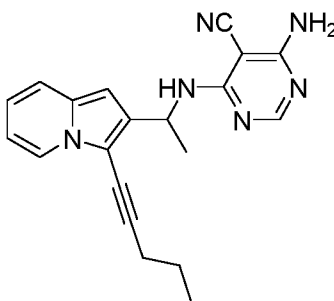


Prepared similarly to Example 22, starting from 1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethan-1-amine Q6 (0.033 g, 0.13 mmol), heating to reflux for 3 h, and

purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 50 : 50) followed by reverse phase semi-preparative MDAP under basic conditions (Method F) to afford title compound as a white solid (0.0055 g). MS/ESI⁺ 361.2 [MH]⁺, Rt 0.92 min (Method C).

5 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.98 (s, 1 H), 7.88 (d, 1 H), 7.38 (d, 1 H), 7.25 (d, 1 H), 7.14 (br. s., 2 H), 6.60 - 6.69 (m, 1 H), 6.46 - 6.56 (m, 2 H), 5.91 (br. s., 1 H), 5.53 - 5.63 (m, 1 H), 4.18 - 4.23 (m, 2 H), 3.76 - 3.88 (m, 2 H), 2.24 - 2.31 (m, 2 H), 1.50 (d, 3 H).

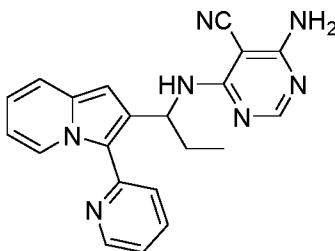
10 **Example 43: 4-amino-6-({1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile**



Prepared similarly to Example 22, starting from crude 1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethan-1-amine Q8 (0.20 mmol) and 4-amino-6-chloropyrimidine-5-carbonitrile (0.031 g, 0.20 mmol), heating to reflux for 3 h, and purified by reverse phase semi-preparative MDAP under basic conditions (Method F) to afford title compound as a white solid (0.030 g). MS/ESI⁺ 345.3 [MH]⁺, Rt 1.18 min (Method C).

20 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.13 (d, 1 H), 8.00 (s, 1 H), 7.45 (d, 1 H), 7.35 (d, 1 H), 7.21 (br. s., 2 H), 6.77 - 6.85 (m, 1 H), 6.68 - 6.76 (m, 1 H), 6.44 (s, 1 H), 5.63 - 5.72 (m, 1 H), 2.48 - 2.57 (m, 2 H), 1.51 - 1.64 (m, 5 H), 1.02 (t, 3 H).

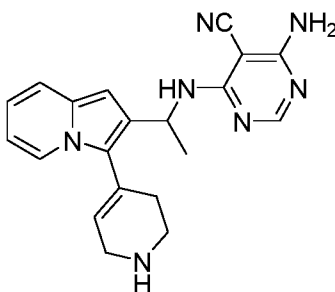
Example 44: 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]propyl}amino)pyrimidine-5-carbonitrile



5 Prepared similarly to Example 22, starting from 1-[3-(pyridin-2-yl)indolizin-2-yl]propan-1-amine Q15 (0.102 g, 0.40 mmol), heating to reflux for 3 h, and purified by flash chromatography on Biotage silica-NH cartridge (Cy:AcOEt = 8:2 to Cy:AcOEt = 1 : 1) to afford the compound as a yellow solid (0.0463 g). MS/ESI⁺ 370.2 [MH]⁺, Rt 0.73 min (Method A).

10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.76 - 8.80 (m, 1 H), 8.62 (d, 1 H), 8.29 (d, 1 H), 7.92 - 8.02 (m, 2 H), 7.86 (d, 1 H), 7.51 (d, 1 H), 7.36 - 7.42 (m, 1 H), 7.20 (br. s., 2 H), 6.80 - 6.87 (m, 1 H), 6.69 (s, 1 H), 6.59 - 6.66 (m, 1 H), 5.48 - 5.57 (m, 1 H), 1.73 - 1.86 (m, 1 H), 1.53 - 1.67 (m, 1 H), 0.71 (t, 3 H).

Example 45: 4-amino-6-({1-[3-(1,2,3,6-tetrahydropyridin-4-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile

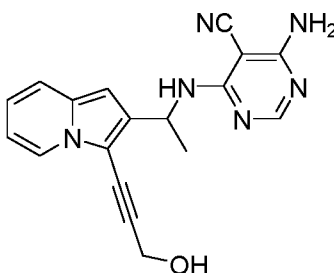


To a solution of tert-butyl 4-(2-{{1-[(6-amino-5-cyanopyrimidin-4-yl)amino]ethyl}indolizin-3-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate U1 (0.045 g, 0.098 mmol) in DCM (0.5 mL), trifluoroacetic acid (0.045 mL, 0.59 mmol) was slowly added at 0°C and the reaction was stirred at r.t. for 1 h. The mixture was partitioned between

DCM and aqueous sat. NaHCO_3 and the aqueous phase was extracted with DCM; the combined organic layers were washed with brine, dried over anhydrous MgSO_4 and concentrated. The crude was purified by flash chromatography on silica-NH cartridge (cyclohexane to cyclohexane AcOEt = 50 : 50) followed by reverse phase flash chromatography on C18 cartridge (H_2O : CH_3CN = 95 : 5 to 70 : 30, with 0.1% HCOOH) to afford title compound as a brown solid (0.0067 g). MS/ESI⁺ 360.3 $[\text{MH}]^+$, Rt 0.53 min (Method A).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.99 (s, 1 H), 7.85 (d, 1 H), 7.36 (d, 1 H), 7.08 - 7.27 (m, 3 H), 6.59 - 6.67 (m, 1 H), 6.47 - 6.53 (m, 2 H), 5.85 (br. s., 1 H), 5.51 - 5.62 (m, 1 H), 3.26 - 3.41 (m, 2 H), 2.84 - 2.98 (m, 2 H), 2.16 (br. s., 2 H), 1.49 (d, 3 H).

Example 46: 4-amino-6-({1-[3-(3-hydroxyprop-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile



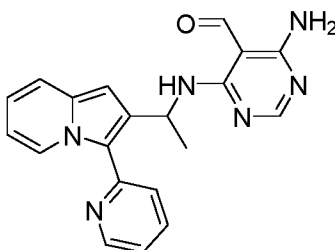
To a solution of 4-amino-6-({1-[3-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile U2 (0.062 g, 0.13 mmol) in THF (0.65 mL), tetrabutylammonium fluoride 1M in THF (0.14 mL, 0.14 mmol) was added the resulting mixture was stirred at room temperature for 30 min and then quenched with saturated aqueous NH_4Cl . The mixture was extracted with DCM and the combined organic layers were dried, filtered and concentrated. The residue was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 100 : 0 to 0 : 100) to afford title compound as yellow solid (0.017 g). MS/ESI⁺ 333.2 $[\text{MH}]^+$, Rt 0.83 min (Method C).

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.20 (d, 1 H), 7.99 (s, 1 H), 7.47 (d, 1 H),

7.40 (d, 1 H), 7.20 (br. s., 2 H), 6.81 - 6.89 (m, 1 H), 6.71 - 6.78 (m, 1 H), 6.45 (s, 1 H), 5.60 - 5.72 (m, 1 H), 5.33 (t, 1 H), 4.38 - 4.50 (m, 2 H), 1.54 (d, 3 H).

Example 47: 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbaldehyde

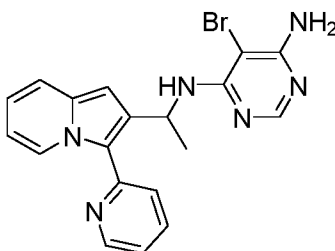
5



To a solution of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.150 g, 0.63 mmol) in *t*-BuOH (6.7 mL), 4-amino-6-chloro-5-pyrimidinecarbaldehyde (0.100 g, 0.63 mmol) was added followed by DIPEA (0.219 mL, 1.26 mmol) and the resulting mixture was heated to reflux for 2 h. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 99 : 1) to afford title compound as a yellow solid (0.106 g). MS/ESI⁺ 359.1 [MH]⁺, Rt 0.61 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.01 (s, 1 H), 9.38 (d, 1 H), 8.69 - 8.79 (m, 2 H), 7.96 (s, 1 H), 7.90 (td, 1 H), 7.46 - 7.75 (m, 4 H), 7.30 - 7.36 (m, 1 H), 6.82 - 6.90 (m, 1 H), 6.60 - 6.70 (m, 2 H), 5.68 - 5.77 (m, 1 H), 1.52 (d, 3 H).

Example 48: 5-bromo-4-N-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-4,6-diamine



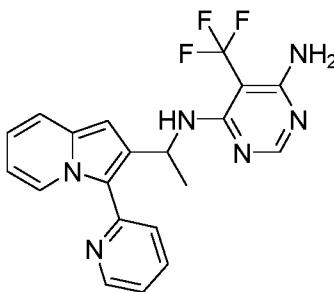
20

Prepared similarly to Example 47, starting from 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.171 g, 0.72 mmol) and 5-bromo-6-chloropyrimidin-4-amine (0.150

g, 0.72 mmol), heating to reflux for 6 days, and purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 99.5 : 0.5) followed by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane : EtOAc = 90 : 10 to 80 : 20) to afford title compound as a white solid (0.144 g). MS/ESI⁺ 408.9 – 410.9 [MH]⁺,
5 Rt 0.63 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.73 - 7.77 (m, 1 H), 8.67 (d, 1 H), 7.92 (td, 1 H), 7.82 (s, 1 H), 7.74 (d, 1 H), 7.49 (d, 1 H), 7.32 - 7.37 (m, 1 H), 6.77 - 6.86 (m, 2 H), 6.68 (s, 1 H), 6.57 - 6.64 (m, 1 H), 6.43 (br. s., 2 H), 5.58 - 5.68 (m, 1 H), 1.40 (d, 3 H).

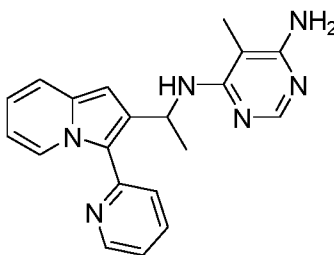
Example 49: 4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-5-(trifluoromethyl)pyrimidine-4,6-diamine
10



Prepared similarly to Example 47, starting from 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.036 g, 0.15 mmol) and 6-chloro-5-(trifluoromethyl)pyrimidin-4-amine (prepared accordingly to the procedure reported in the patent WO2011/146882) (0.030 g, 0.15 mmol), heating to reflux for 10 h, and purified by flash chromatography on 11g Biotage silica-NH SNAP cartridge (cyclohexane: EtOAc = 70 : 30). A further purification by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 99 : 1), was required to afford title compound (0.007 g). MS/ESI⁺ 399.2 [MH]⁺,
20 Rt 0.74 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.64 - 8.73 (m, 2 H), 7.90 - 7.96 (m, 2 H), 7.74 (d, 1 H), 7.50 (d, 1 H), 7.33 - 7.39 (m, 1 H), 7.01 - 7.07 (m, 1 H), 6.80 - 6.86 (m, 1 H), 6.69 (br. s., 2 H), 6.59 - 6.66 (m, 2 H), 5.76 - 5.85 (m, 1 H), 1.37 (d, 3 H).

Example 50: 5-methyl-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-5-(trifluoromethyl)pyrimidine-4,6-diamine

yllethyl}pyrimidine-4,6-diamine

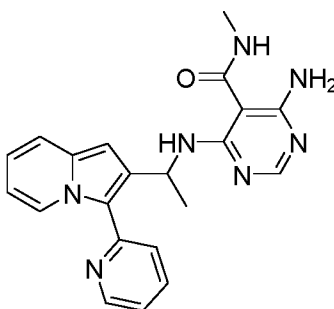
To a solution of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.100 g, 0.42
5 mmol) in *t*-BuOH (4.5 mL), 6-chloro-5-methylpyrimidin-4-amine (0.060 g, 0.42 mmol)
was added followed by DIPEA (0.146 mL, 0.84 mmol) and the resulting mixture was
heated to reflux for 24 h. Additional 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2
(0.100 g, 0.42 mmol) was added over 48 h heating to reflux. The solvent was removed and
the crude was dissolved in *n*-BuOH (4.5 mL); DIPEA (0.146 mL, 0.84 mmol) was added
10 and the reaction was heated to 130°C for 10 days.

An additional experiment was performed: to a solution of 1-[3-(pyridin-2-
yl)indolizin-2-yl]ethan-1-amine Q2 (0.059 g, 0.25 mmol) in *n*-BuOH (2.7 mL), 6-chloro-
5-methylpyrimidin-4-amine (0.036 g, 0.25 mmol) was added followed by DIPEA (0.087
mL, 0.50 mmol) and the resulting mixture was heated under MW irradiation for 2 h at
15 120°C and for 2 h at 150°C. Then the mixture was heated under thermal conditions at 130°C
for 24 h. Additional 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.059 g, 0.25
mmol) was added over 10 days continuing the heating at 130°C.

The two reaction mixtures were combined, the solvent was removed and the crude
was partitioned between DCM/MeOH $\approx$ 4/1 and water. The organic phase was dried over
20 sodium sulfate, the solvent was removed under reduced pressure and the crude was purified
by flash chromatography on Biotage silica-NH cartridge (cyclohexane : EtOAc = 50 : 50
to 40 : 60); two further purifications by flash chromatography on Biotage silica cartridge
(DCM to DCM : MeOH = 98 : 2) were required to afford title compound as a dark yellow
solid (0.0207 g). MS/ESI⁺ 345.2 [MH]⁺, Rt 0.56 min (Method A).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.78 (d, 1 H), 8.69 - 8.74 (m, 1 H), 7.80 - 7.92 (m, 2H), 7.77 (s, 1 H), 7.46 (d, 1 H), 7.27 - 7.35 (m, 1 H), 6.76 - 6.83 (m, 1 H), 6.67 (s, 1 H), 6.54 - 6.61 (m, 1 H), 6.24 - 6.33 (m, 1 H), 5.85 (br. s., 2 H), 5.60 - 5.70 (m, 1 H), 1.80 (s, 3 H), 1.41 (d, 3 H).

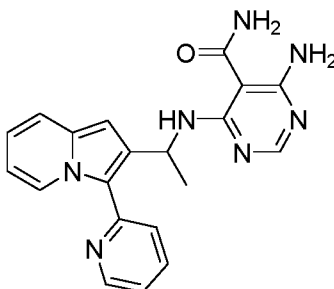
5 **Example 51: 4-amino-N-methyl-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxamide**



To a suspension of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.040 g,
10 0.172 mmol) and crude 4-amino-6-chloro-N-methylpyrimidine-5-carboxamide AA4
(0.173 mmol) in *t*-BuOH (3 mL), DIPEA (0.090 mL, 0.516 mmol) was added and the
resulting mixture was heated at 100°C overnight. Additional DIPEA (0.090 mL, 0.516
mmol) was added and the mixture was stirred at the same temperature for 100 h. The solvent
was removed and the crude was partitioned between DCM and water. The organic phase
15 was dried over sodium sulfate, the solvent was removed under reduced pressure and the
crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM : EtOAc
= 80 : 20 to 100% EtOAc) to afford title compound as a brown amorphous solid (0.010 g).
MS/ESI⁺ 388.3 [MH]⁺, Rt 0.55 min (Method A).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.79 (d, 1 H), 8.74 (d, 1 H), 7.80 - 7.97 (m,
20 3 H), 7.74 (d, 1 H), 7.64 (d, 1 H), 7.53 (d, 1 H), 7.32 - 7.37 (m, 1 H), 6.81 - 6.89 (m, 1 H),
6.57 - 6.68 (m, 2 H), 6.43 (s, 2 H), 5.52 - 5.62 (m, 1 H), 2.70 (d, 3 H), 1.45 (d, 3 H).

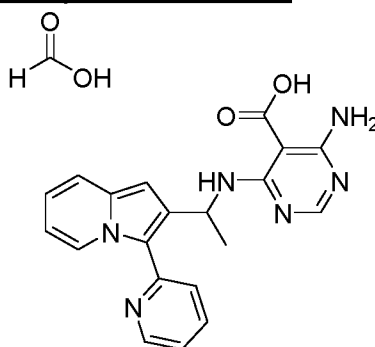
Example 52: 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxamide



To a solution of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.034 g, 0.144 mmol) in *t*-BuOH (1.6 mL), crude 4-amino-6-chloropyrimidine-5-carboxamide AA5 (containing some 4-amino-6-chloropyrimidine-5-carboxylic acid (0.144 mmol) was added followed by DIPEA (0.050 mL, 0.29 mmol) and the resulting mixture was heated to reflux for 4 h. The solvent was removed and the crude was partitioned between DCM/MeOH $\approx$ 4/1 and water. The organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure and the crude was purified by semi-preparative MDAP under acidic conditions (Method E) to afford two fractions. The first eluted fraction afforded title compound as a yellow solid (0.0055 g). MS/ESI⁺ 374.1 [MH]⁺, Rt 0.50 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.79 (d, 1 H), 8.73 (d, 1 H), 7.86 - 7.97 (m, 3 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 7.40 (s, 2 H), 7.31 - 7.36 (m, 1 H), 6.81 - 6.87 (m, 1 H), 6.59 - 6.67 (m, 2 H), 6.49 (s, 2 H), 5.51 - 6.60 (m, 1 H), 1.46 (d, 3 H).

Example 53: 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxylic acid formate



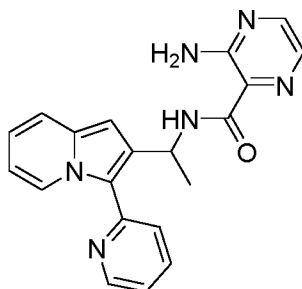
The second fraction eluted from the purification by semi-preparative MDAP under

acidic conditions (Method E) of the reaction mixture described in Example 52 was evaporated to dryness to afford title compound as a brown solid (0.0035 g) MS/ESI⁺ 375.1 [MH]⁺, Rt 0.63 min (Method A).

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 13.27 (br. s, 1 H), 9.98 (br. s, 1 H), 8.80 (d, 1 H), 8.72 (d, 1 H), 7.84 - 7.92 (m, 2 H), 7.62 (d, 1 H), 7.51 (d, 1 H), 7.29 - 7.35 (m, 1 H), 6.80 - 6.87 (m, 1 H), 6.58 - 6.66 (m, 2 H), 7.36 (br. s, 2 H), 5.52 - 5.68 (m, 1 H), 1.47 (d, 3 H).

Presence of ~ 31% mol of formic acid

Example 54: 3-amino-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrazine-2-carboxamide

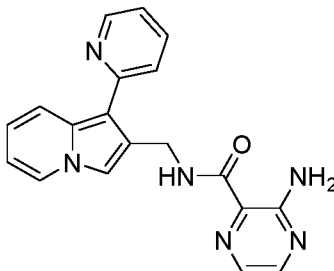


A mixture of 3-amino-2-pyrazinecarboxylic acid (0.032 g, 0.232 mmol), HOBt (0.037 g) and EDC HCl (0.053 g, 0.274 mmol) in DMF (2 mL) was stirred at r.t. for 20 min. DIPEA (0.055 mL, 0.316 mmol) was added followed by a solution of 1-[3-(pyridin-2-yl)indolizin-2-yl]ethan-1-amine Q2 (0.050 g, 0.211 mmol) in DMF (0.5 mL) and the reaction was stirred at RT for 1 h. The mixture was partitioned between DCM and water and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine and dried over sodium sulfate. The crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 80 : 20). The obtained material was treated with pentane, evaporated and triturated with Et₂O to afford title compound as a light yellow solid (0.037 g). MS/ESI⁺ 359.1 [MH]⁺, Rt 0.81 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.01 (d, 1 H), 8.70 - 8.78 (m, 2 H), 8.21 (d, 1 H), 7.97 (td, 1 H), 7.83 (d, 1 H), 7.73 (d, 1 H), 7.39 - 7.62 (m, 3 H), 7.34 - 7.39 (m, 1 H),

6.81 - 6.87 (m, 1 H), 6.77 (s, 1 H), 6.58 - 6.66 (m, 1 H), 5.42 - 5.53 (m, 1 H), 1.52 (d, 3 H).

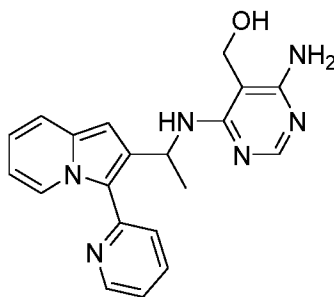
Example 55: 3-amino-N-{[1-(pyridin-2-yl)indolizin-2-yl]methyl}pyrazine-2-carboxamide



5 Prepared similarly to Example 54, starting from [1-(pyridin-2-yl)indolizin-2-yl]methanamine P9 (0.086 g, 0.385 mmol) and purified by flash chromatography on Biotage silica-NH SNAP cartridge (cyclohexane to cyclohexane : EtOAc = 50 : 50) to afford title compound as a light yellow solid (0.079 g). MS/ESI⁺ 345.1 [MH]⁺, Rt 0.54 min (Method A).

10 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.60 (t, 1 H), 8.65 - 8.71 (m, 1 H), 8.34 (d, 1 H), 8.21 (d, 1 H), 7.79 - 7.93 (m, 3 H), 7.33 - 7.74 (m, 4 H), 7.19 - 7.25 (m, 1 H), 6.86 - 6.93 (m, 1 H), 6.62 - 6.69 (m, 1 H), 4.73 (d, 2 H).

Example 56: [4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidin-5-yl]methanol



15

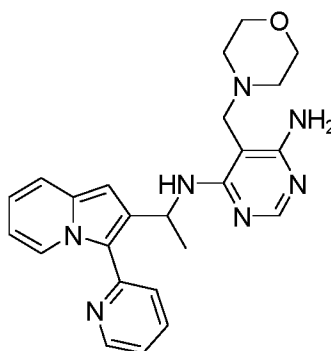
To a solution of 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbaldehyde of Example 47 (0.031 g) in MeOH (0.44 mL), NaBH₄ (0.005 g, 0.13 mmol) was added at 0°C and the mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 97 : 3)

20

to afford title compound as a white foamy solid (0.021 g). MS/ESI⁺ 359.1 [MH]⁺, Rt 0.81 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.82 (d, 1 H), 8.71 - 8.75 (m, 1 H), 7.90 (td, 1 H), 7.83 (s, 1 H), 7.75 (d, 1 H), 7.49 (d, 1 H), 7.30 - 7.36 (m, 1 H), 6.79 - 6.86 (m, 1 H),
5 6.67 (s, 1 H), 6.57 - 6.64 (m, 1 H), 6.54 (d, 1 H), 5.94 (s, 2 H), 5.55 - 5.65 (m, 1 H), 4.94 (t, 1 H), 4.30 - 4.44 (m, 2 H), 1.45 (d, 3 H).

Example 57: 5-(morpholin-4-ylmethyl)-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrimidine-4,6-diamine



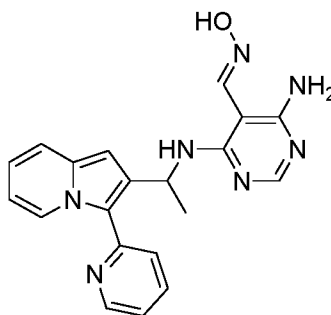
10 To a suspension of 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbaldehyde of Example 47 (0.065 g) in DCM (4 mL), morpholine (0.024 mL, 0.272 mL) was added followed by a catalytic amount of acetic acid (pH ≈ 6), and the resulting solution was stirred at r.t. for 20 minutes. Na(OAc)₃BH (0.077 g, 0.363 mmol) was added and the reaction was stirred at r.t overnight. The mixture was
15 diluted with DCM and washed with aqueous sat. Na₂CO₃; the organic phase was dried over sodium sulfate and the solvent was removed. The crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM : EtOAc = 70 : 30 to 100% EtOAc) followed by flash chromatography on silica-NH cartridge (DCM : MeOH = 99 : 1). A further purification by preparative TLC on silica NH (DCM : MeOH = 97 : 3) was
20 required to afford title compound as a pale yellow solid (0.007 g). MS/ESI⁺ 430.1 [MH]⁺, Rt 0.95 min (Method C).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.84 (d, 1 H), 8.70 - 8.74 (m, 1 H), 7.84 - 7.90 (m, 2 H), 7.65 (d, 1 H), 7.50 (d, 1 H), 7.47 - 7.59 (m, 1 H), 7.28 - 7.34 (m, 1 H), 6.80

- 6.87 (m, 1 H), 6.68 (s, 1 H), 6.58 - 6.64 (m, 1 H), 6.16 (br. s., 2 H), 5.43 - 5.60 (m, 1 H), 3.41 - 3.52 (m, 4 H), 3.31 (s, 2 H), 2.22 - 2.42 (m, 4 H), 1.47 (d, 3 H).

Example 58: 5-[(1E)-(hydroxyimino)methyl]-4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}pyrimidine-4,6-diamine

5



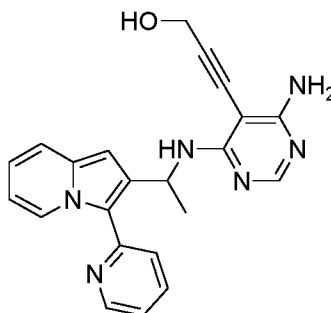
To a solution of 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbaldehyde of Example 47 (0.050 g) in EtOH (2 mL), pyridine (0.013 mL, 0.156 mmol) was added followed by hydroxylamine hydrochloride (0.011 g, 0.156 mmol) and the resulting mixture was stirred at r.t. overnight. The volatiles were removed under reduced pressure and the crude was partitioned between DCM and water. The organic layer was washed with brine and dried over sodium sulfate, the solvent removed under reduced pressure, the residue was dissolved in CH₃CN and dried under vacuum to afford title compound as a yellow solid (0.024 g). MS/ESI⁺ 374.2 [MH]⁺, Rt 0.57 min (Method A).

15

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.96 (s, 1 H), 8.80 (d, 1 H), 8.69 - 8.73 (m, 1 H), 8.51 (s, 1 H), 8.41 (d, 1 H), 7.83 - 7.90 (m, 2 H), 7.63 (d, 1 H), 7.50 (d, 1 H), 7.32 (dd, 1 H), 6.80 - 6.90 (m, 3 H), 6.57 - 6.66 (m, 2 H), 5.69 (t, 1H), 1.50 (d, 3 H).

20

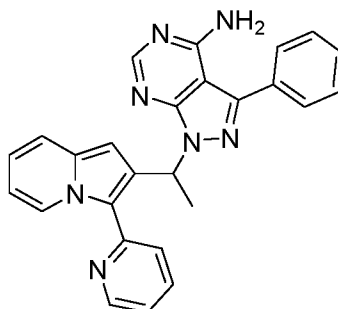
Example 59: 3-[4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidin-5-yl]prop-2-yn-1-ol



5 To a solution of 4-N-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-5-(3-{[tris(propan-2-yl)silyl]oxy}prop-1-yn-1-yl)pyrimidine-4,6-diamine V (0.057 g, 0.10 mmol) in THF (0.5 mL), tetrabutylammonium fluoride 1M in THF (0.110 mL, 0.110 mmol) was added and the resulting mixture was stirred at room temperature for 30 minutes. The reaction was quenched with saturated aqueous NH₄Cl and extracted with DCM; the combined organic
10 layers were dried over sodium sulfate, filtered and concentrated. The residue was dissolved in MeOH and charged on SCX cartridge (2 g), washing with MeOH. The product was eluted with 1M NH₃ in MeOH and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography on 11 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95:5) to afford title compound as a yellow solid (0.022 g). MS/ESI⁺ 385.3
15 [MH]⁺, Rt 0.56 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.73 - 8.77 (m, 1 H), 8.70 (d, 1 H), 7.84 - 7.95 (m, 2 H), 7.72 (d, 1 H), 7.50 (d, 1 H), 7.31 - 7.37 (m, 1 H), 6.79 - 6.86 (m, 1 H), 6.58 - 6.72 (m, 3 H), 6.42 (br. s., 2 H), 5.59 - 5.71 (m, 1 H), 5.19 (t, 1 H), 4.36 (d, 2 H), 1.39 (d, 3 H).

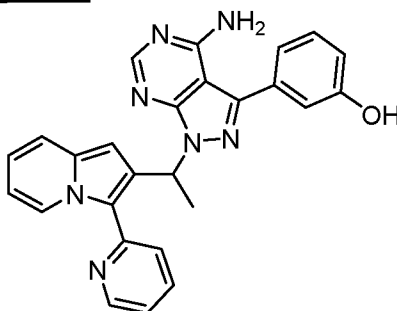
Example 60: 3-phenyl-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



5 A mixture of 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.030 g, 0.062 mmol), phenylboronic acid (8.4 mg, 0.062 mmol) and Pd(PPh₃)₄ (3.6 mg, 0.0031 mmol) in DME (4.5 mL), ethanol (0.65 mL) and saturated aqueous Na₂CO₃ (1.2 mL) was stirred at 80°C overnight. The mixture was quenched with water and extracted with DCM; the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : EtOAc = 90 : 10) to afford title compound (8.0 mg). MS/ESI⁺ 432.3 [MH]⁺, Rt 0.86 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.70 - 8.74 (m, 1 H), 8.62 (dd, 1 H), 8.18 (s, 1 H), 7.91 (td, 1 H), 7.73 - 7.77 (m, 1 H), 7.65 - 7.69 (m, 2 H), 7.53 - 7.58 (m, 2 H), 7.46 - 7.52 (m, 2 H), 7.33 - 7.38 (m, 1 H), 6.73 - 6.82 (m, 1 H), 6.70 (s, 1 H), 6.56 - 6.61 (m, 1 H), 6.50 (q, 1 H), 6.09 - 7.13 (m, 2H), 1.92 (d, 3 H).

Example 61: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol

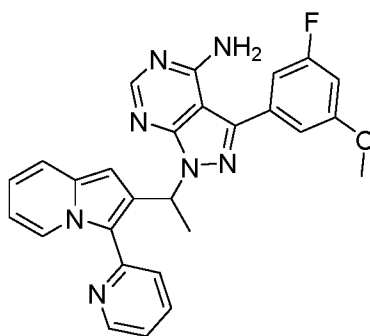


20 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-

yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.030, 0.063 mmol), 3-hydroxyphenylboronic acid (9.5 mg, 0.068 mmol) and Pd(PPh₃)₄ (3.6 mg, 0.0031 mmol), in DME (6.2 mL), EtOH (0.93 mL) and saturated aqueous Na₂CO₃ (1.76 mL), heating at 80°C for 2 h. After work-up, the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM MeOH = 99:1 to 95 : 5) to afford title compound (0.010 g). MS/ESI⁺ 432.3 [MH]⁺, Rt 0.86 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.73 (s, 1 H), 8.71 - 8.75 (m, 1 H), 8.64 (d, 1 H), 8.18 (s, 1 H), 7.93 (td, 1 H), 7.76 (d, 1 H), 7.50 (d, 1 H), 7.31 - 7.40 (m, 2 H), 7.06 - 7.11 (m, 2 H), 6.86 - 6.90 (m, 1 H), 6.78 - 6.84 (m, 1 H), 6.69 (s, 1 H), 6.57 - 6.62 (m, 1 H), 6.49 (q, 1 H), 5.70- 7.45 (m, 2H), 1.92 (d, 3 H).

Example 62: 3-(3-fluoro-5-methoxyphenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine

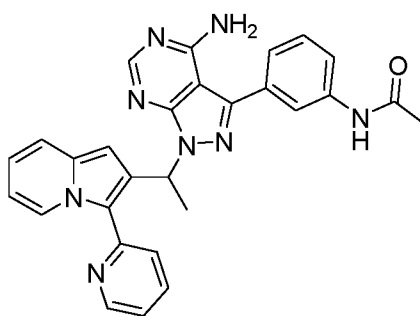


Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.030 g, 0.063 mmol), (3-fluoro-5-methoxyphenyl)boronic acid (0.012 g, 0.069 mmol) and Pd(PPh₃)₄ (4.0 mg, 0.0031 mmol), in DME (6.3 mL), EtOH (1 mL) and saturated aqueous Na₂CO₃ (1.7 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on silica Biotage cartridge (DCM to DCM : EtOAc = 10 : 90). A further purification by reverse phase semi-preparative MDAP under acidic conditions (Method E) was required, followed by evaporation and filtration through a silica-NH cartridge eluting with DCM : MeOH = 95 : 5 to afford title compound as a pale yellow solid (0.007 g). MS/ESI⁺ 480.3

[MH]⁺, Rt 0.96 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.70 - 8.74 (m, 1 H), 8.61 (d, 1 H), 8.17 (s, 1 H), 7.91 (td, 1 H), 7.74 (d, 1 H), 7.49 (d, 1 H), 7.30 - 7.39 (m, 1 H), 6.98 - 7.05 (m, 2 H), 6.90 - 6.99 (m, 1 H), 6.77 - 6.82 (m, 1 H), 6.69 (s, 1 H), 6.54 - 6.63 (m, 1 H), 6.53 - 7.30 (m, 2H), 6.49 (q, 1 H), 3.85 (s, 3 H), 1.91 (d, 3 H)

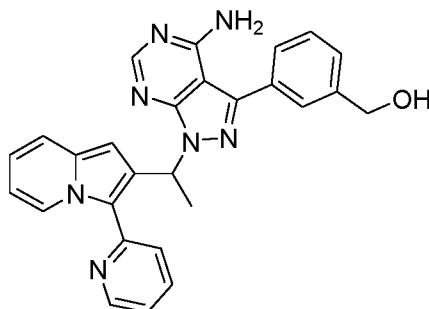
Example 63: N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]acetamide



Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.030 g, 0.063 mmol), 3-acetamidophenylboronic acid (0.012 g, 0.068 mmol) and Pd(PPh₃)₄ (3.6 mg, 0.0031 mmol), in DME (4.5 mL), EtOH (0.65 mL) and saturated aqueous Na₂CO₃ (1.2 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (5.0 mg). MS/ESI⁺ 489.3 [MH]⁺, Rt 0.74 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.18 (s, 1 H), 8.71 - 8.75 (m, 1 H), 8.64 (d, 1 H), 8.19 (s, 1 H), 7.89 - 7.97 (m, 2 H), 7.77 (d, 1 H), 7.61 - 7.66 (m, 1 H), 7.45 - 7.53 (m, 2 H), 7.33 - 7.40 (m, 2 H), 6.77 - 6.85 (m, 1 H), 6.69 (s, 1 H), 6.57 - 6.63 (m, 1 H), 6.51 (q, 1 H), 6.00 - 8.00 (m, 2H), 2.10 (s, 3 H), 1.94 (d, 3 H).

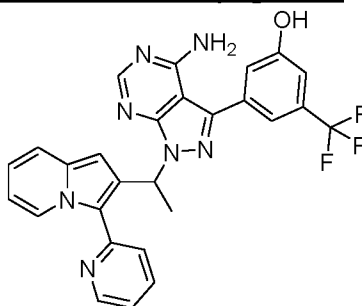
Example 64: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol



5 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), 3-(hydroxymethyl)phenylboronic acid (0.023 g, 0.150 mmol) and Pd(PPh₃)₄ (7.2 mg, 0.0062 mmol), in DME (9 mL), EtOH (1.3 mL) and saturated aqueous Na₂CO₃ (2.4 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography
10 on Biotage silica-NH cartridge (DCM to DCM : MeOH = 90 : 10). A further purification by filtration on SCX cartridge, eluting with 1M ammonia in MeOH, was required to afford title compound (9.0 mg). MS/ESI⁺ 462.3 [MH]⁺, Rt 0.71 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.72 - 9.76 (m, 1 H), 8.64 (d, 1 H), 8.19 (s, 1 H), 7.89 - 7.98 (m, 1 H), 7.77 (d, 1 H), 7.64 (s, 1 H), 7.48 - 7.55 (m, 3 H), 7.42 - 7.47 (m,
15 1 H), 7.33 - 7.40 (m, 1 H), 6.78 - 6.85 (m, 1 H), 6.70 (s, 1 H), 6.57 - 6.63 (m, 1 H), 6.52 (q, 1 H), 6.00 - 7.18 (m, 2H), 5.30 (t, 1 H), 4.62 (d, 2 H), 1.94 (d, 3 H).

Example 65: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-(trifluoromethyl)phenol

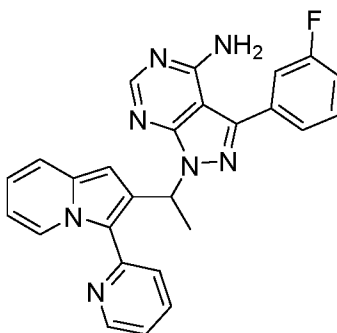


20 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-

yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), [3-hydroxy-5-(trifluoromethyl)phenyl]boronic acid (0.031 g, 0.150 mmol) and Pd(PPh₃)₄ (7.2 mg, 0.0062 mmol), in DME (9 mL), EtOH (1.3 mL) and saturated aqueous Na₂CO₃ (2.4 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 70 : 30). A further purification by filtration on SCX cartridge, eluting with 1M ammonia in MeOH, was required to afford title compound (0.023 g). MS/ESI⁺ 516.0 [MH]⁺, Rt 0.94 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.39 (br. s., 1 H), 8.70 - 8.74 (m, 1 H), 8.60 - 8.64 (m, 1 H), 8.20 (s, 1 H), 7.91 (td, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.30 - 7.40 (m, 3 H), 7.14 (s, 1 H), 6.77 - 6.85 (m, 1 H), 6.68 (s, 1 H), 6.56 - 7.30 (m, 2H), 6.57 - 6.63 (m, 1 H), 6.52 (q, 1 H), 1.94 (d, 3 H).

Example 66: 3-(3-fluorophenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine

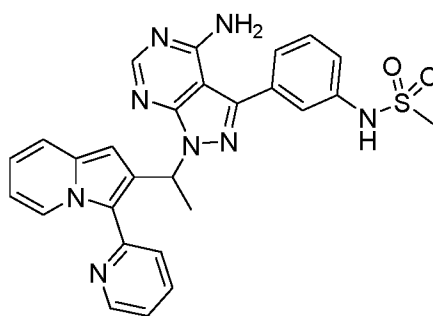


Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), 3-fluorophenylboronic acid (0.021 g, 0.150 mmol) and Pd(PPh₃)₄ (7.2 mg, 0.0062 mmol), in DME (9 mL), EtOH (1.3 mL) and saturated aqueous Na₂CO₃ (2.4 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica-NH cartridge (DCM to DCM : MeOH = 98 : 2). A further purification by flash chromatography on silica-NH cartridge (DCM : EtOAc = 90 : 10) was required to afford

title compound (0.015 g). MS/ESI⁺ 450.3 [MH]⁺, Rt 0.92 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.71 - 8.76 (m, 1 H), 8.63 (d, 1 H), 8.20 (s, 1 H), 7.93 (td, 1 H), 7.76 (d, 1 H), 7.57 - 7.64 (m, 1 H), 7.48 - 7.55 (m, 2 H), 7.43 - 7.48 (m, 1 H), 7.30 - 7.39 (m, 2 H), 6.78 - 6.84 (m, 1 H), 6.72 (s, 1 H), 6.57 - 6.64 (m, 1 H), 6.52 (q, 1 H), 6.25 - 7.30 (m, 2H), 1.94 (d, 3 H).

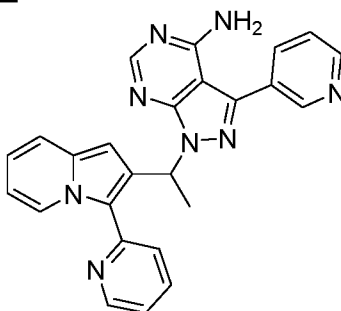
Example 67: N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]methanesulfonamide



Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), (3-methanesulfonamidophenyl)boronic acid (0.032 g, 0.150 mmol) and Pd(PPh₃)₄ (7.2 mg, 0.0062 mmol), in DME (9 mL), EtOH (1.3 mL) and saturated aqueous Na₂CO₃ (2.4 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5). The obtained product was diluted with MeOH and the precipitate was collected by filtration; the filtrate solution was charged on SCX (1g) cartridge washing with MeOH and the product was eluted with 1M ammonia in MeOH. This material was combined with the collected solid and evaporated, treated with CH₃CN and water and evaporated to afford title compound as a white solid (9 mg). MS/ESI⁺ 535.3 [MH]⁺, Rt 0.77 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.93 (br. s., 1 H), 8.71 - 8.76 (m, 1 H), 8.63 (d, 1 H), 8.19 (s, 1 H), 7.90 - 7.96 (m, 1 H), 7.77 (d, 1 H), 7.46 - 7.57 (m, 3 H), 7.42 (d, 1 H), 7.31 - 7.40 (m, 2 H), 6.78 - 6.85 (m, 1 H), 6.71 (s, 1 H), 6.58 - 6.63 (m, 1 H), 6.51 (q, 1 H), 5.80 - 8.00 (m, 2H), 3.08 (s, 3 H), 1.94 (d, 3 H).

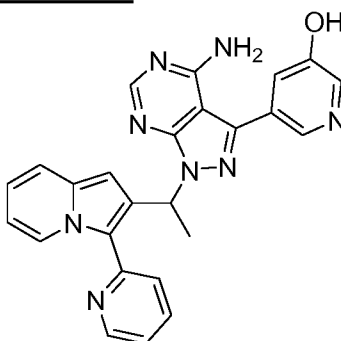
Example 68: 1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), 3-pyridinylboronic acid (0.018 g, 0.150 mmol) and Pd(PPh₃)₄ (7.2 mg, 0.0062 mmol), in DME (9 mL), EtOH (1.3 mL) and saturated aqueous Na₂CO₃ (2.4 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound (0.033 g). MS/ESI⁺ 433.3 [MH]⁺, Rt 0.65 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.83 - 8.85 (m, 1 H), 8.70 - 8.74 (m, 1 H), 8.65 - 8.69 (m, 1 H), 8.60 - 8.64 (m, 1 H), 8.19 (s, 1 H), 8.01 - 8.06 (m, 1 H), 7.89 - 7.95 (m, 1 H), 7.75 (d, 1 H), 7.53 - 7.59 (m, 1 H), 7.49 (d, 1 H), 7.33 - 7.38 (m, 1 H), 6.77 - 6.83 (m, 1 H), 6.72 (s, 1 H), 6.64 - 7.25 (m, 2H), 6.56 - 6.62 (m, 1 H), 6.51 (q, 1 H), 1.93 (d, 3 H).

Example 69: 5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-3-ol

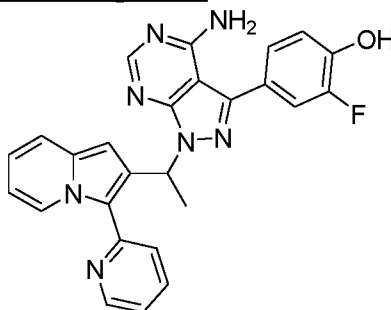


Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-

yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol),
5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ol (0.028 g, 0.125 mmol) and Pd(PPh₃)₄
(6.0 mg, 0.0052 mmol), in DME (5 mL), EtOH (0.8 mL) and saturated aqueous Na₂CO₃
(1.2 mL), heating at 80°C for 3 h. After work-up, the crude was purified by flash
5 chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 70 : 30)
to afford title compound (0.0135 g). MS/ESI⁺ 449.3 [MH]⁺, Rt 0.63 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.23 (br. s., 1 H), 8.71 - 8.76 (m, 1 H), 8.63
(d, 1 H), 8.31 (d, 1 H), 8.16 - 8.27 (m, 2 H), 7.93 (td, 1 H), 7.76 (d, 1 H), 7.50 (d, 1 H), 7.34
- 7.42 (m, 2 H), 6.94 (br. s., 2 H), 6.79 - 6.85 (m, 1 H), 6.71 (s, 1 H), 6.57 - 6.64 (m, 1 H),
10 6.52 (q, 1 H), 1.93 (d, 3 H).

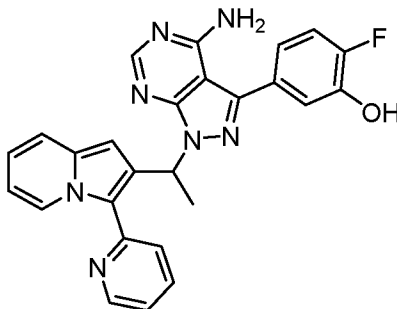
Example 70: 4-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol



Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-
15 yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol),
(3-fluoro-4-hydroxyphenyl)boronic acid (0.019 g, 0.125 mmol) and Pd(PPh₃)₄ (6.0 mg,
0.0052 mmol), in DME (8 mL), EtOH (1.2 mL) and saturated aqueous Na₂CO₃ (2.2 mL),
heating at 80°C overnight. After work-up, the crude was purified by flash chromatography
Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 70 : 30) to afford title
20 compound (0.015 g). MS/ESI⁺ 466.0 [MH]⁺, Rt 0.75 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.20 (br. s., 1 H), 8.71 - 8.77 (m, 1 H), 8.64
(d, 1 H), 8.17 (s, 1 H), 7.89 - 7.97 (m, 1 H), 7.76 (d, 1 H), 7.50 (d, 1 H), 7.24 - 7.44 (m, 3
H), 7.07 - 7.16 (m, 1 H), 6.77 - 6.86 (m, 1 H), 6.71 (s, 1 H), 6.56 - 6.64 (m, 1 H), 6.44 -
6.53 (m, 1 H), 6.25 - 7.22 (m, 2H), 1.92 (d, 3 H).

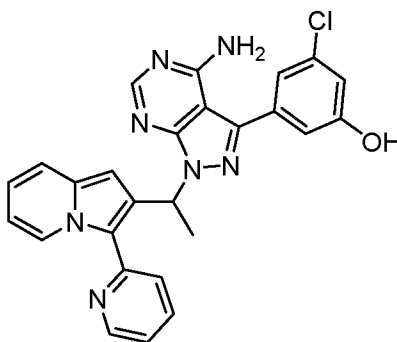
Example 71: 5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol



5 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol), (4-fluoro-3-hydroxyphenyl)boronic acid (0.019 g, 0.125 mmol) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol), in DME (8 mL), EtOH (1.2 mL) and saturated aqueous Na₂CO₃ (2.2 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography
10 on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 85 : 25) to afford title compound (0.012 g). MS/ESI⁺ 466.4 [MH]⁺, Rt 0.78 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.15 (br. s., 1 H), 8.72 - 8.75 (m, 1 H), 8.64 (d, 1 H), 8.18 (s, 1 H), 7.92 (td, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.22 - 7.40 (m, 3 H), 7.04 - 7.09 (m, 1 H), 6.78 - 6.86 (m, 1 H), 6.69 (s, 1 H), 6.57 - 6.64 (m, 1 H), 6.49 (q, 1 H), 6.00
15 - 7.60 (m, 2H), 1.92 (d, 3 H).

Example 72: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-chlorophenol

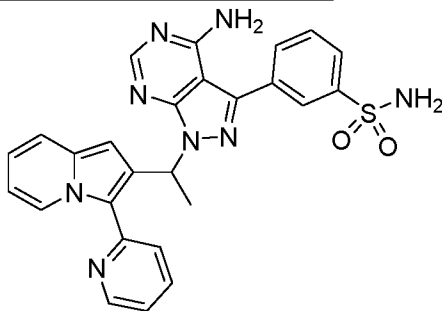


Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol), (3-chloro-5-hydroxyphenyl)boronic acid (0.021 g, 0.125 mmol) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol), in DME (8 mL), EtOH (1.2 mL) and saturated aqueous Na₂CO₃ (2.2 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound (0.019 g). MS/ESI⁺ 482.0 [MH]⁺, Rt 0.87 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.20 (br. s., 1 H), 8.71 - 8.75 (m, 1 H), 8.61 - 8.65 (m, 1 H), 8.19 (s, 1 H), 7.92 (td, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.34 - 7.39 (m, 1 H), 7.08 - 7.11 (m, 1 H), 7.00 - 7.04 (m, 1 H), 6.89 - 6.93 (m, 1 H), 6.78 - 6.85 (m, 1 H), 6.68 (s, 1 H), 6.57 - 6.64 (m, 1 H), 6.51 (q, 1 H), 6.41 - 7.45 (m, 2H), 1.92 (d, 3 H).

NH₂ not clearly visible: broad signal in aromatic region (2 H).

Example 73: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzene-1-sulfonamide



15

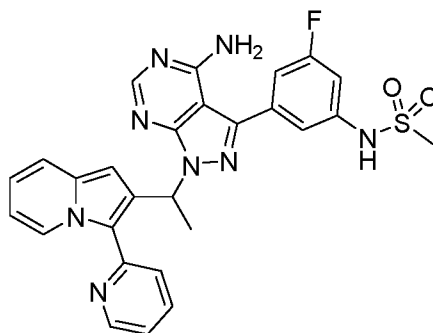
Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), (3-sulfamoylphenyl)boronic acid (0.029 g, 0.144 mmol) and Pd(PPh₃)₄ (6.9 mg, 0.0060 mmol), in DME (12 mL), EtOH (1.8 mL) and saturated aqueous Na₂CO₃ (3.75 mL), heating at 80°C overnight. After work-up, the crude was purified by flash chromatography on silica gel Biotage SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (0.015 g). MS/ESI⁺ 511.2 [MH]⁺, Rt 0.72 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.71 - 8.74 (m, 1 H), 8.62 (d, 1 H), 8.20 (s, 1 H), 8.12 - 8.16 (m, 1 H), 7.89 - 7.97 (m, 2 H), 7.87 (d, 1 H), 7.71 - 7.80 (m, 2 H), 7.45 -

7.53 (m, 3 H), 7.33 - 7.40 (m, 1 H), 6.78 - 6.84 (m, 1 H), 6.68 (s, 1 H), 6.56 - 6.64 (m, 1 H), 6.53 (q, 1 H), 6.40- 7.33 (m, 2H), 1.94 (d, 3 H).

Example 74: N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl]methanesulfonamide

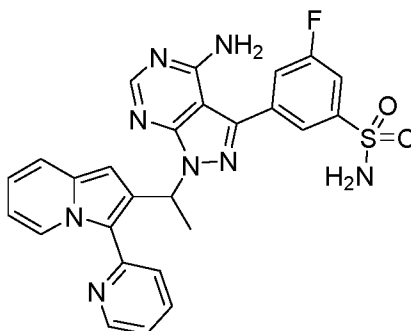
5



Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol), N-[3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide T1 (0.052 g, 0.166 mmol) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol), in DME (5 mL), EtOH (0.8 mL) and saturated aqueous Na₂CO₃ (1.2 mL), heating at 80°C for 2 h. After work-up, the crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as a white solid (0.034 g). MS/ESI⁺ 543.2 [MH]⁺, Rt 0.84 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.20 (br. s., 1 H), 8.70 - 8.73 (m, 1 H), 8.61 (d, 1 H), 8.18 (s, 1 H), 7.91 (td, 1 H), 7.74 (d, 1 H), 7.48 (d, 1 H), 7.32 - 7.38 (m, 1 H), 7.28 - 7.31 (m, 1 H), 7.06 - 7.17 (m, 2 H), 6.77 - 6.83 (m, 1 H), 6.69 (s, 1 H), 6.55 - 6.62 (m, 1 H), 6.49 (q, 1 H), 6.40- 7.53 (m, 2H), 3.11 (s, 3 H), 1.92 (d, 3 H).

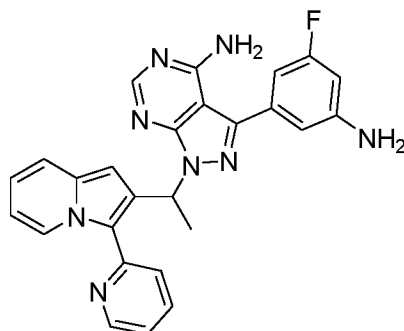
Example 75: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorobenzene-1-sulfonamide



5 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol), 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1-sulfonamide T2 (0.050 g, 0.145 mmol) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol), in DME (5 mL), EtOH (0.8 mL) and saturated aqueous Na₂CO₃ (1.2 mL), heating at 80°C overnight. After work-up, the crude
10 was purified by flash chromatography on 11 g silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound (0.014 g). MS/ESI⁺ 529.2 [MH]⁺, Rt 0.79 min. (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.70 - 8.74 (m, 1 H), 8.59 - 8.63 (m, 1 H), 8.20 (s, 1 H), 7.96 - 7.99 (m, 1 H), 7.92 (td, 1 H), 7.75 (d, 1 H), 7.63 - 7.70 (m, 2 H), 7.61
15 (s, 2 H), 7.48 (d, 1 H), 7.33 - 7.39 (m, 1 H), 7.07 (br. s, 2 H), 6.78 - 6.84 (m, 1 H), 6.67 (s, 1 H), 6.56 - 6.62 (m, 1 H), 6.53 (q, 1 H), 1.94 (d, 3 H).

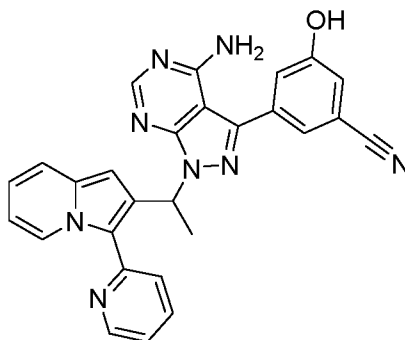
Example 76: 3-(3-amino-5-fluorophenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine



5 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.050 g, 0.104 mmol), 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline T3 (0.030 g, 0.125 mmol) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol), in DME (5 mL), EtOH (0.8 mL) and saturated aqueous Na₂CO₃ (1.2 mL), heating at 80°C for 3 h. Additional 3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline T3 (10 mg) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol) were added
10 and the heating was continued for 1 h. After work-up, the crude was purified by flash chromatography on 11 g silica-NH Biotage SNAP cartridge (DCM to DCM : EtOAc = 95 : 5) to afford title compound (0.011 g). MS/ESI⁺ 465.3 [MH]⁺, Rt 0.79 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.72 - 8.76 (m, 1 H), 8.64 (d, 1 H), 8.18 (s, 1 H), 7.90 - 7.96 (m, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.34 - 7.39 (m, 1 H), 6.79 - 6.84 (m, 1 H), 6.67 - 6.72 (m, 2 H), 6.57 - 6.63 (m, 1 H), 6.41 - 6.54 (m, 3 H), 6.25 - 7.32 (m, 2H), 5.71 (s, 2 H), 1.92 (d, 3 H).

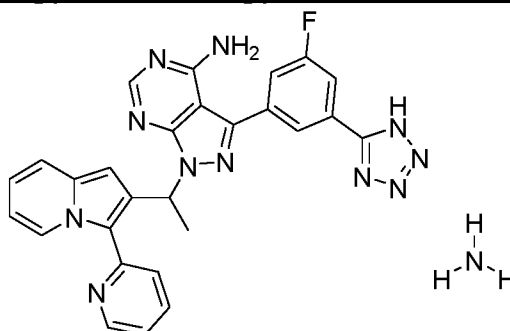
Example 77: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-hydroxybenzonitrile



5 Prepared similarly to Example 60, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), 3-hydroxy-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile T4 (0.037 g, 0.150 mmol) and Pd(PPh₃)₄ (7.2 mg, 0.0063 mmol), in DME (9.5 mL), EtOH (2.9 mL) and saturated aqueous Na₂CO₃ (1.4 mL), heating at 80°C overnight. After work-up, the crude was purified
10 by flash chromatography on silica- NH Biotage SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound (0.017 g). MS/ESI⁺ 473.3 [MH]⁺, Rt 0.81 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.47 (s, 1 H), 8.71 - 8.75 (m, 1 H), 8.63 (d, 1 H), 8.19 (s, 1 H), 7.92 (td, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.44 - 7.47 (m, 1 H), 7.33 -
15 7.40 (m, 2 H), 7.22 - 7.26 (m, 1 H), 7.01 (br. s., 2 H), 6.79- 6.85 (m, 1 H), 6.70 (s, 1 H), 6.57 - 6.64 (m, 1 H), 6.52 (q, 1 H), 1.93 (d, 3 H)

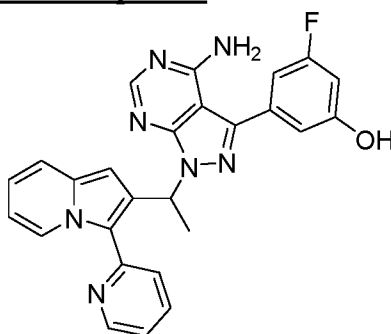
Example 78: 3-[3-fluoro-5-(1H-1,2,3,4-tetrazol-5-yl)phenyl]-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine : ammonia 2 : 1



3-Iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.100 g, 0.208 mmol) was split in two batches (0.050 g, 0.104 mmol each one). Both the batches were reacted with 5-[3-fluoro-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-1,2,3,4-tetrazole T6 (0.036 g, 0.125 mmol each one) and Pd(PPh₃)₄ (6.0 mg, 0.0052 mmol each one) in DME (5.0 mL each one), ethanol (0.8 mL each one) and saturated aqueous sodium carbonate (1.2 mL each one), at 80°C overnight. Water was added and the mixtures were acidified to pH 5-6 with aqueous 1N HCl and extracted with DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated. One batch was purified by flash chromatography on 10 g silica gel Biotage SNAP cartridge (DCM to DCM : MeOH 90 : 10 with 0.01% formic acid). The obtained compound was mixed with the second crude and purified by flash chromatography on 10 g Biotage silica gel SNAP cartridge (DCM to DCM : MeOH = 70 : 30). A further purification by reverse phase semi-preparative MDAP under basic conditions (Method F) was performed to obtain title compound (7.0 mg). MS/ESI⁺ 518.4 [MH]⁺, Rt 0.85 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.73 (d, 1 H), 8.62 (d, 1 H), 8.20 (s, 1 H), 8.16 (t, 1 H), 7.93 (td, 1 H), 7.83 - 7.89 (m, 1 H), 7.76 (d, 1 H), 7.45 - 7.53 (m, 2 H), 7.33 - 7.38 (m, 1 H), 6.76 - 6.83 (m, 1 H), 6.70 (s, 1 H), 6.56 - 6.62 (m, 1 H), 6.53 (q, 1 H), 6.41-7.54 (m, 2H), 1.94 (d, 3 H).

Example 79: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



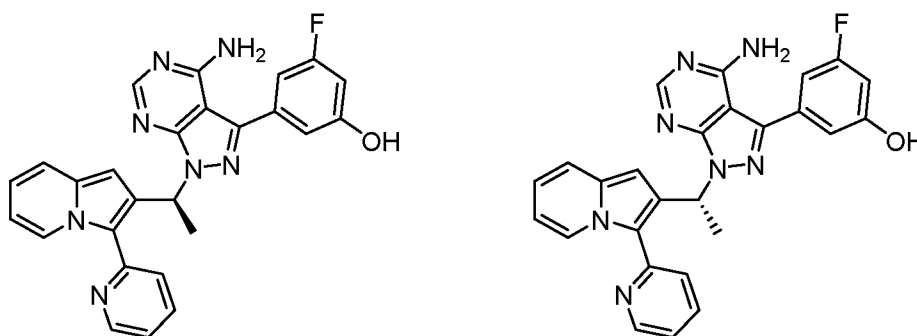
3-Iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.465 g, 0.96 mmol) was equally divided in five vials. Each one was reacted

with (3-fluoro-5-hydroxyphenyl)boronic acid (0.0374 g, 0.24 mmol), Pd(PPh₃)₄ (0.011 g, 0.0094 mmol), DME (18.7 ml), ethanol (2.8 ml) and saturated aqueous sodium carbonate (5.3 ml) at 80°C overnight. Then they were collected and quenched in water and finally extracted with DCM. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM : MeOH = 98 : 2 to 94 : 6) to afford title compound (0.265 g). MS/ESI⁺ 466.3 [MH]⁺, Rt 0.81 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (br. s., 1 H), 8.69 - 8.75 (m, 1 H), 8.59 - 8.65 (m, 1 H), 8.17 (s, 1 H), 7.91 (td, 1 H), 7.74 (d, 1 H), 7.49 (d, 1 H), 7.32 - 7.38 (m, 1 H), 6.89 - 6.93 (m, 1 H), 6.77 - 6.89 (m, 2 H), 6.63 - 6.70 (m, 2 H), 6.56 - 6.62 (m, 1 H), 6.49 (q, 1 H), 6.40 - 7.46 (m, 2H), 1.91 (d, 3 H).

Example 80 (enantiomer 1) and

Example 81 (enantiomer 2): 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol single enantiomers



Racemate

3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-

pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol described in Example 79 (0.260 g) was dissolved in EtOH/MeOH 1/1 (38 mL) and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak AD-H (25 x 2.0 cm); Mobile phase: n-Hexane/(Ethanol+0.1% isopropylamine) 80/20 v/v; UV detection: 220 nM; Flow Rate: 13 mL/min; Injection: 20.4 mg.

Compound 80 was obtained as the first eluted enantiomer as a yellow solid (0.095

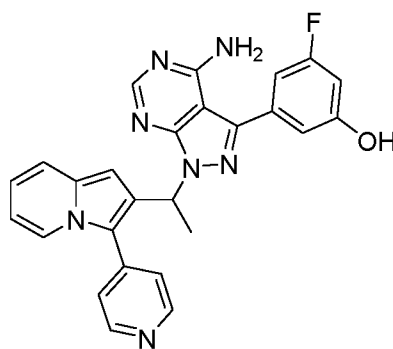
g). MS/ESI⁺ 466.3 [MH]⁺, Rt 0.82 min (Method A). Chiral HPLC Method H: Rt. = 8.2 min, ee > 99%

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.21 (br. s., 1 H), 8.69 - 8.75 (m, 1 H), 8.60 - 8.66 (m, 1 H), 8.18 (s, 1 H), 7.92 (td, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.32 - 7.39 (m, 1 H), 6.90 - 6.94 (m, 1 H), 6.78 - 6.90 (m, 2 H), 6.64 - 6.71 (m, 2 H), 6.56 - 6.62 (m, 1 H), 6.49 (q, 1 H), 6.40 - 7.46 (m, 2H), 1.91 (d, 3 H).

Compound 81 was obtained as the second eluted enantiomer as a yellow solid (0.095 g). MS/ESI⁺ 466.4 [MH]⁺, Rt 0.82 min (Method A). Chiral HPLC Method H: Rt. = 13.2 min, ee > 99%

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.21 (br. s., 1 H), 8.70 - 8.75 (m, 1 H), 8.60 - 8.66 (m, 1 H), 8.18 (s, 1 H), 7.92 (td, 1 H), 7.75 (d, 1 H), 7.50 (d, 1 H), 7.32 - 7.39 (m, 1 H), 6.90 - 6.94 (m, 1 H), 6.77 - 6.89 (m, 2 H), 6.64 - 6.71 (m, 2 H), 6.56 - 6.63 (m, 1 H), 6.49 (q, 1 H), 6.40 - 7.46 (m, 2H), 1.91 (d, 3 H).

Example 82: 3-(4-amino-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



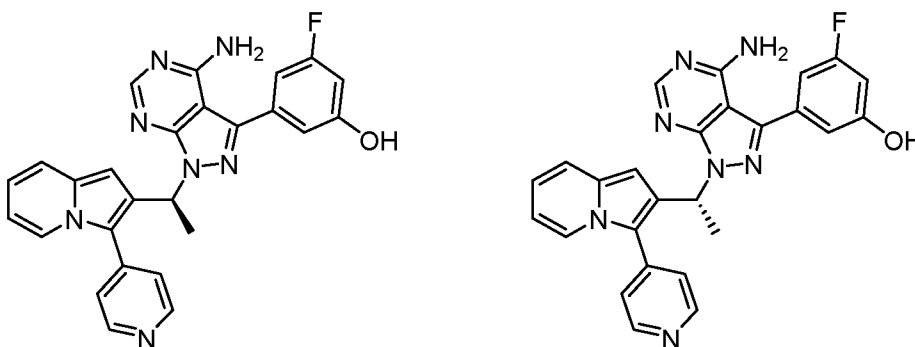
3-Iodo-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W4 (0.216 g, 0.45 mmol) was split in two vials (0.108 g each one); each one was reacted with (3-fluoro-5-hydroxyphenyl)boronic acid (0.0455 g, 0.29 mmol each one), Pd(PPh₃)₄ (0.013 g, 0.011 mmol each one), DME (15.4 mL each one), ethanol (2.3 mL each one) and saturated aqueous sodium carbonate (4.2 mL each one) at 80°C overnight. Then, they were collected and quenched with water and extracted with DCM. The combined

organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound (0.100 g). MS/ESI⁺ 466.3 [MH]⁺, Rt 0.68 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.18 (br. s., 1 H), 8.62 - 8.68 (m, 2 H), 8.19 (s, 1 H), 8.07 (d, 1 H), 7.48 - 7.55 (m, 3 H), 6.89 - 6.93 (m, 1 H), 6.77 - 6.88 (m, 2 H), 6.76 (s, 1 H), 6.64 - 6.70 (m, 1 H), 6.55 - 6.62 (m, 1 H), 6.30 (q, 1 H), 6.20 - 7.46 (m, 2H), 1.90 (d, 3 H)

Example 83 (enantiomer 1) and

Example 84 (enantiomer 2): 3-(4-amino-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol single enantiomers



Racemate

3-(4-amino-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-

pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol described in Example 82 (0.100 g) was dissolved in EtOH (60 mL) and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak IC (25 x 2.0 cm), 5 μ; Mobile phase: n-Hexane/(2-Propanol+0.1% isopropylamine) 60/40% v/v; UV detection: 220 nM; Flow Rate: 16 mL/min; Injection: 8.3 mg.

Compound 83 was obtained as the first eluted enantiomer as a pale yellow powder (0.030 g). MS/ESI⁺ 466.4 [MH]⁺, Rt 0.68 min (Method A). Chiral HPLC Method I: Rt = 6.8 min, 95.2% ee.

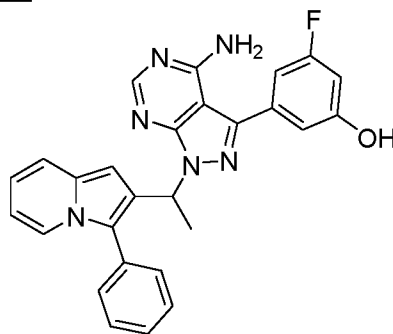
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.19 (br. s., 2 H), 8.62 - 8.69 (m, 2 H), 8.19

(s, 1 H), 8.07 (d, 1 H), 7.48 - 7.55 (m, 3 H), 6.89 - 6.93 (m, 1 H), 6.77 - 6.88 (m, 2 H), 6.76 (s, 1 H), 6.64 - 6.71 (m, 1 H), 6.55 - 6.62 (m, 1 H), 6.30 (q, 1 H), 6.20 - 7.47 (m, 2H), 1.89 (d, 3 H).

Compound 84 was obtained as the second eluted enantiomer as a pale yellow powder (0.032 g). MS/ESI⁺ 466.3 [MH]⁺, Rt 0.69 min (Method A). Chiral HPLC Method I: Rt = 8.7 min, 97.8% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (br. s., 1 H), 8.62 - 8.68 (m, 2 H), 8.19 (s, 1 H), 8.06 (d, 1 H), 7.48 - 7.55 (m, 3 H), 6.88 - 6.93 (m, 1 H), 6.77 - 6.88 (m, 2 H), 6.76 (s, 1 H), 6.64 - 6.71 (m, 1 H), 6.55 - 6.62 (m, 1 H), 6.30 (q, 1 H), 6.20 - 7.47 (m, 2H), 1.89 (d, 3 H).

Example 85: 3-{4-amino-1-[1-(3-phenylindolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol



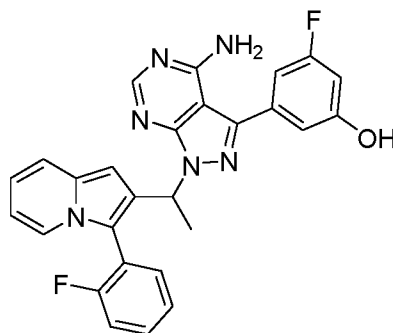
A mixture of 3-iodo-1-[1-(3-phenylindolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine W1 (0.110 g, 0.23 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.040 g, 0.25 mmol) and Pd(PPh₃)₄ (14.4 mg, 0.012 mmol), in DME (9.5 mL), EtOH (1.66 mL) and saturated aqueous Na₂CO₃ (3.2 mL) was heated at 80°C for 2 h. The mixture was partitioned between water and DCM, the aqueous phase was extracted with DCM and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on 28 g silica-NH Biotage SNAP cartridge (DCM : MeOH = 99 : 1 to 80 : 20) to afford title compound as a white solid (0.077 g). MS/ESI⁺ 465.3 [MH]⁺, Rt 1.09 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (br. s., 1 H), 8.16 (s, 1 H), 7.83 (d, 1

H), 7.38 - 7.54 (m, 6 H), 6.91 (br. s., 1 H), 6.81 - 6.89 (m, 1 H), 6.62 - 6.74 (m, 3 H), 6.46 - 6.53 (m, 1 H), 6.26 - 7.37 (m, 2H), 6.21 (q, 1 H), 1.84 (d, 3 H).

Example 86: 3-(4-amino-1-{1-[3-(2-fluorophenyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluoro-phenol

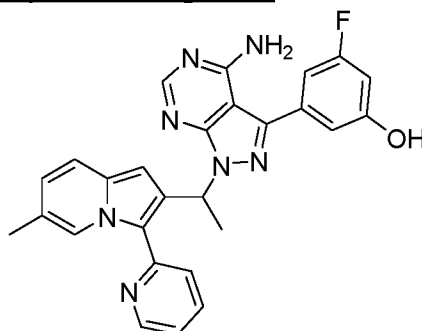
5



Prepared similarly to Example 85, starting from 1-{1-[3-(2-fluorophenyl)indolizin-2-yl]ethyl}-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine W3 (0.114 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.039 g, 0.251 mmol) and Pd(PPh₃)₄ (0.013 g, 0.0114 mmol),
 10 in DME (9.4 mL), EtOH (1.6 mL) and saturated aqueous Na₂CO₃ (3.2 mL), heating at 80°C for 3 h. After work-up the crude was purified by flash chromatography on silica N-H Biotage SNAP cartridge (DCM : MeOH = 98 : 2 to 80 : 20) to afford title compound as a white solid (0.020 g). MS/ESI⁺ 483.0 [MH]⁺, Rt 1.03 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.12 - 10.18 (m, 1 H), 8.02 - 8.18 (m, 1 H),
 15 7.16 - 7.62 (m, 6 H), 6.49 - 6.95 (m, 6 H), 6.09 - 6.25 (m, 1 H), 6.00 - 7.5 (m, 2H), 1.76 - 1.95 (M, 3 H)

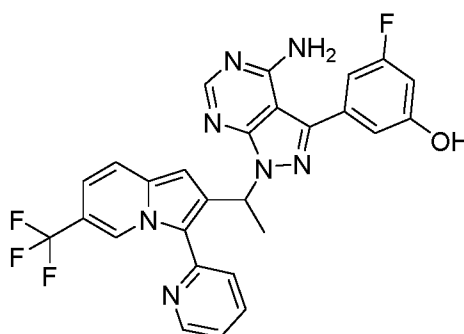
Example 87: 3-(4-amino-1-{1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



Prepared similarly to Example 85, starting from crude 3-iodo-1-{1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W5 (0.130 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.041 g, 0.26 mmol) and Pd(PPh₃)₄ (0.015 g, 0.013 mmol), in DME (15 mL), EtOH (2.6 mL) and saturated aqueous Na₂CO₃ (4 mL), heating at 80°C overnight. After work-up the crude was purified by flash chromatography on 11 g silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as an off-white solid (0.012 g). MS/ESI⁺ 480.3 [MH]⁺, Rt 0.88 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (s, 1 H), 8.70 - 8.74 (m, 1 H), 8.39 (s, 1 H), 8.16 (s, 1 H), 7.89 (td, 1 H), 7.70 (d, 1 H), 7.41 (d, 1 H), 7.31 - 7.37 (m, 1 H), 6.89 - 6.92 (m, 1 H), 6.82 - 6.88 (m, 1 H), 6.60 - 6.71 (m, 3 H), 6.45 (q, 1 H), 6.22 - 7.30 (m, 2H), 2.15 (s, 3 H), 1.88 (d, 3 H).

Example 88: 3-(4-amino-1-{1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

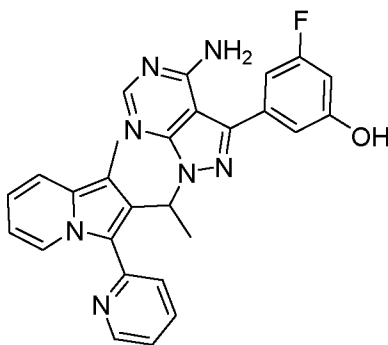


Prepared similarly to Example 85, starting from 3-iodo-1-{1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W6 (0.085 g, 0.155 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.029 g, 0.186 mmol) and Pd(PPh₃)₄ (9 mg, 0.008 mmol), in DME (7.0 mL), EtOH (1.1 mL) and saturated aqueous Na₂CO₃ (1.7 mL), heating at 80°C for 3 h. Additional (3-fluoro-5-hydroxyphenyl)boronic acid (0.029 g, 0.186 mmol) and Pd(PPh₃)₄ (9 mg, 0.008 mmol) were added and the heating was continued overnight. After work-up the crude was purified by flash chromatography

on 11 g silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as an off-white solid (20.5 mg). MS/ESI⁺ 534.3 [MH]⁺, Rt 1.09 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.22 (br. s., 1 H), 9.09 (br. s., 1 H), 8.75 - 8.81 (m, 1 H), 8.20 (s, 1 H), 7.97 (td, 1 H), 7.85 (d, 1 H), 7.75 (d, 1 H), 7.40 - 7.46 (m, 1 H), 6.98 - 7.04 (m, 1 H), 6.90 - 6.95 (m, 2 H), 6.84 - 6.90 (m, 1 H), 6.65 - 6.71 (m, 1 H), 6.51 (q, 1 H), 6.40 - 7.40 (m, 2H), 1.94 (d, 3 H).

Example 89: 3-(4-amino-1-{1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

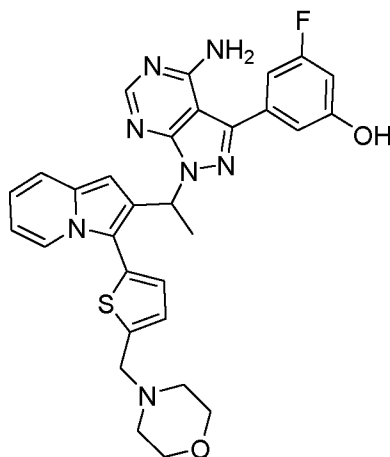


Prepared similarly to Example 85, starting from crude 3-iodo-1-{1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W7 (0.106 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.0233 g, 0.15 mmol) and Pd(PPh₃)₄ (6.6 mg, 0.005 mmol), in DME (7.0 mL), EtOH (1.3 mL) and saturated aqueous Na₂CO₃ (2 mL), heating at 80°C overnight. After work-up the crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM : MeOH = 99 : 1 to 95 : 5) to afford title compound (4.0 mg). MS/ESI⁺ 480.0 [MH]⁺, Rt 81 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.20 (br. s., 1 H), 8.74 - 8.78 (m, 1 H), 8.32 (d, 1 H), 8.11 (s, 1 H), 7.95 (td, 1 H), 7.81 (d, 1 H), 7.46 (d, 1 H), 7.37 - 7.43 (m, 1 H), 6.92 - 6.96 (m, 1 H), 6.83 - 6.89 (m, 1 H), 6.71 - 6.77 (m, 1 H), 6.63 - 6.71 (m, 1 H), 6.48 - 6.56 (m, 1 H), 6.38 - 6.46 (m, 1 H), 6.36 - 7.36 (m, 2H), 2.39 (s, 3 H), 1.94 (d, 3 H).

Example 90: 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)thiophen-2-

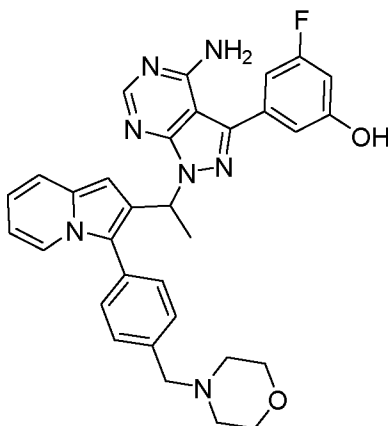
yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol



Prepared similarly to Example 85, starting from crude 3-iodo-1-(1-{3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine W8 (0.325 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.095 g, 0.61 mmol) and Pd(PPh₃)₄ (0.032 g, 0.027 mmol), in DME (20 mL), EtOH (3.8 mL) and saturated aqueous Na₂CO₃ (7.6 mL), heating at 80°C for 4 h. After work-up the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 94 : 6) to afford title compound as a white solid (0.074 g). MS/ESI⁺ 570.2 [MH]⁺, Rt 1.02 min (Method C).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.15 (s, 1 H), 8.13 (s, 1 H), 7.94 (d, 1 H), 7.46 (d, 1 H), 7.03 (d, 1 H), 6.99 (d, 1 H), 6.87 - 6.91 (m, 1 H), 6.80 - 6.86 (m, 1 H), 6.71 - 6.78 (m, 1 H), 6.61 - 6.68 (m, 2 H), 6.56 - 6.61 (m, 1 H), 6.50 - 7.43 (m, 2H), 6.30 (q, 1 H), 3.63 - 3.73 (m, 2 H), 3.52 - 3.61 (m, 4 H), 2.35 - 3.45 (m, 4 H), 1.85 (d, 3 H).

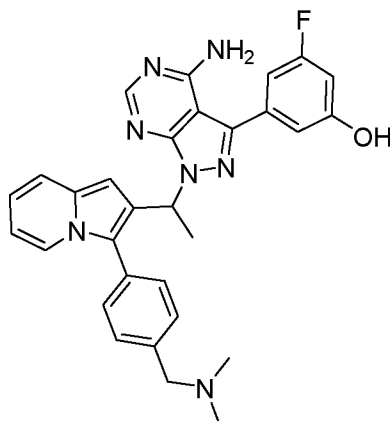
Example 91: 3-[4-amino-1-(1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol



5 Prepared similarly to Example 85, starting from 3-iodo-1-(1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine W9 (0.320 g, (3-fluoro-5-hydroxyphenyl)boronic acid (0.094 g, 0.60 mmol) and Pd(PPh₃)₄ (0.032 g, 0.027 mmol), in DME (21 mL), EtOH (3.9 mL) and saturated aqueous Na₂CO₃ (7.5 mL), heating at 80°C for 4 h. After work-up the crude was purified by flash chromatography on
10 11 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound as a pale yellow solid (0.057 g). MS/ESI⁺ 564.0 [MH]⁺, Rt 3.89 min (Method D).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.18 (br. s., 1 H), 8.14 (s, 1 H), 7.81 (d, 1 H), 7.45 (d, 1 H), 7.30 - 7.40 (m, 4 H), 6.86 - 6.89 (m, 1 H), 6.79 - 6.85 (m, 1 H), 6.63 -
15 6.73 (m, 3 H), 6.46 - 6.51 (m, 1 H), 6.32 - 7.30 (m, 2H), 6.25 (q, 1 H), 3.57- 3.66 (m, 4 H), 3.50 (s, 2 H), 2.33 - 2.42 (m, 4 H), 1.84 (d, 3 H).

Example 92: 3-{4-amino-1-[1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol



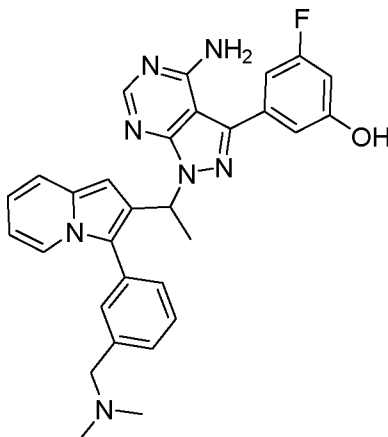
5 Prepared similarly to Example 85, starting from 1-[1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine W10 (0.188 g, (3-fluoro-5-hydroxyphenyl)boronic acid (0.060 g, 0.38 mmol) and Pd(PPh₃)₄ (0.020 g, 0.017 mmol), in DME (13 mL), EtOH (2.4 mL) and saturated aqueous Na₂CO₃ (4.8 mL), heating at 80°C for 4 h. After work-up the crude was

10 purified by flash chromatography on 11 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5). A further purification by reverse phase semi-preparative MDAP under basic conditions (Method F) was required to afford title compound as a yellow solid (0.022 g). MS/ESI⁺ 522.3 [MH]⁺, Rt 1.04 min (Method C).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.38 (br. s., 1 H), 8.14 (s, 1 H), 7.83 (d, 1 H), 7.44 (d, 1 H), 7.34 - 7.39 (m, 4 H), 6.87 (br. s., 1 H), 6.76 - 6.82 (m, 1 H), 6.59 - 6.73 (m, 3 H), 6.46 - 6.52 (m, 1 H), 6.23 (q, 1 H), 6.17 - 7.30 (m, 2H), 3.43 (s, 2 H), 2.18 (s, 6 H), 1.83 (d, 3 H).

15

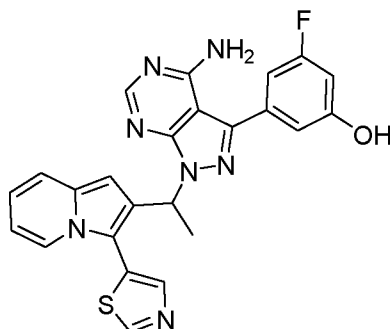
Example 93: 3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol



5 Prepared similarly to Example 85, starting from 1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine W11 (0.091 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.029 g, 0.187 mmol) and Pd(PPh₃)₄ (0.010 g, 0.009 mmol), in DME (6.3 mL), EtOH (1.2 mL) and saturated aqueous Na₂CO₃ (2.3 mL), heating at 80°C for 4 h. After work-up the crude was
10 purified by flash chromatography on 11 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5). A further purification by reverse phase semi-preparative MDAP under basic conditions (Method F) was required to afford title compound as a white solid (0.032 g). MS/ESI⁺ 522.3 [MH]⁺, Rt 1.07 min (Method C).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.19 (s, 1 H), 8.15 (s, 1 H), 7.82 (d, 1 H),
15 7.40 - 7.49 (m, 2 H), 7.28 - 7.36 (m, 2 H), 7.23 (br. s., 1 H), 6.88 - 6.92 (m, 1 H), 6.82 - 6.87 (m, 1 H), 6.64 - 6.74 (m, 3 H), 6.48 - 6.54 (m, 1 H), 6.20 (q, 1 H), 5.16 - 7.49 (m, 2H), 3.39 (br. s., 2 H), 2.14 (s, 6 H), 1.84 (d, 3 H).

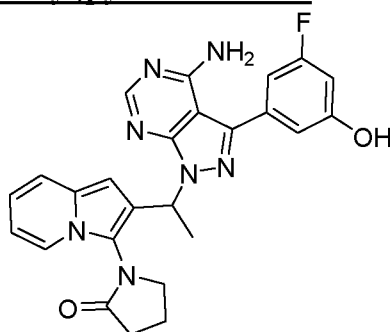
Example 94: 3-(4-amino-1-{1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



5 Prepared similarly to Example 85, starting from 3-iodo-1-{1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W12 (0.042 g, 0.086 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.015 g, 0.095 mmol) and Pd(PPh₃)₄ (5.0 mg, 0.0043 mmol), in DME (3.5 mL), EtOH (0.62 mL) and saturated aqueous Na₂CO₃ (1.2 mL), heating at 80°C for 4 h. After work-up the crude was purified by flash chromatography
10 on 28 g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 94 : 6) to afford title compound as a white solid (0.016 g). MS/ESI⁺ 472.3 [MH]⁺, Rt 0.90 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.20 (br. s., 1 H), 9.29 (s, 1 H), 8.15 (s, 1 H), 8.02 (s, 1 H), 7.89 (d, 1 H), 7.51 (d, 1 H), 6.89 - 6.92 (m, 1 H), 6.78 - 6.88 (m, 2 H), 6.72 (s, 1 H), 6.59 - 6.69 (m, 2 H), 6.22 (q, 1 H), 6.12 - 7.72 (m, 2H), 1.88 (d, 3 H).

15 **Example 95: 1-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)pyrrolidin-2-one**

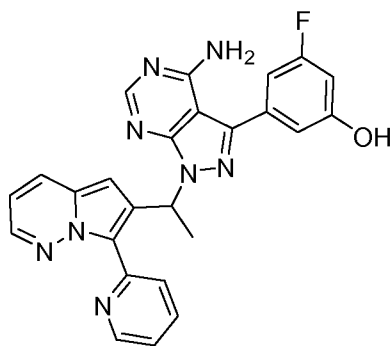


Prepared similarly to Example 85, starting from 1-[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl]pyrrolidin-2-one W13 (0.034 mmol),

(3-fluoro-5-hydroxyphenyl)boronic acid (0.012 g, 0.076 mmol) and Pd(PPh₃)₄ (4.0 mg, 0.003 mmol), in DME (2.8 mL), EtOH (0.50 mL) and saturated aqueous Na₂CO₃ (0.95 mL), heating at 80°C for 4 h; additional (3-fluoro-5-hydroxyphenyl)boronic acid (0.012 g, 0.076 mmol) and Pd(PPh₃)₄ (0.004 g, 0.003 mmol) were added and the mixture was heated at the same temperature overnight. After work-up the crude was purified by flash chromatography on 2 g silica-NH cartridge (DCM to DCM : MeOH = 94 : 6). A further purification by reverse phase semi-preparative MDAP under basic conditions (Method F) was required to afford title compound as a pink solid (mixture of diastereoisomers, ratio ~ 65/35 by ¹H NMR). (0.004 g). MS/ESI⁺ 472.3 [MH]⁺, Rt 0.78 min (Method C).

¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.38 (br. s., 1 H), 8.27 (s, 1 H), 7.86 (d, 1 H), 7.41 - 7.45 (m, 1 H), 6.82 - 6.88 (m, 1 H), 6.70 - 6.81 (m, 2H), 6.53 - 6.64 (m, 3 H), 6.39 - 7.50 (m, 2 H), 6.11 (q, 1 H), 3.57 - 3.63 (m, 1 H), 2.90 - 2.97 (m, 1 H), 2.38 - 2.56 (m, 2 H), 2.12 - 2.20 (m, 1 H), 1.84 - 1.94 (m, 4 H). Spectrum referred to the most abundant isomer.

Example 96: 3-(4-amino-1-{1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

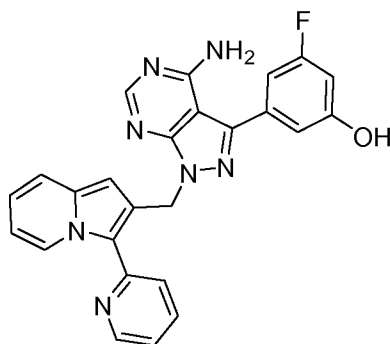


Prepared similarly to Example 85, starting from crude 3-iodo-1-{1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W15 (0.060 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.027 g, 0.17 mmol) and Pd(PPh₃)₄ (7.0 mg, 0.006 mmol), in DME (12 mL), EtOH (1.8 mL) and saturated aqueous Na₂CO₃ (3.42 mL), heating at 80°C for 2 h. After work-up the crude was purified by flash chromatography on

silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 97 : 3); a further purification by flash chromatography on 10 g silica gel Biotage SNAP cartridge (DCM to DCM : MeOH = 97 : 3) was required to afford title compound (0.010 g). MS/ESI⁺ 467.2 [MH]⁺, Rt 0.73 min (Method A).

5 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.21 (s, 1 H), 8.71 - 8.75 (m, 1 H), 8.25 - 8.32 (m, 2 H), 8.13 (s, 1 H), 8.00 - 8.04 (m, 1 H), 7.92 (td, 1 H), 7.31 - 7.36 (m, 1 H), 7.04 (q, 1 H), 6.88 - 6.98 (m, 2 H), 6.79 (dd, 1 H), 6.65 - 6.71 (m, 1 H), 6.59 (s, 1 H), 6.40- 7.50 (m, 2H), 1.95 (d, 3 H).

Example 97: 3-(4-amino-1-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



Prepared similarly to Example 85, starting from 3-iodo-1-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W16 (0.020 g, 0.043 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (7.3 mg, 0.047 mmol) and Pd(PPh₃)₄ (2.5 mg, 0.0022 mmol), in DME (4.5 mL), EtOH (0.65 mL) and saturated aqueous Na₂CO₃ (1.2 mL), heating at 80°C overnight. Additional (3-fluoro-5-hydroxyphenyl)boronic acid (7.3 mg, 0.047 mmol) and Pd(PPh₃)₄ (2.5 mg, 0.0022 mmol) were added and the heating was continued for further 2 h. After work-up, the crude was purified by flash chromatography on silica-NH Biotage SNAP cartridge (DCM to DCM : MeOH = 85 : 15) to afford title compound (0.012 g). MS/ESI⁺ 452.2 [MH]⁺, Rt 0.78 min (Method A).

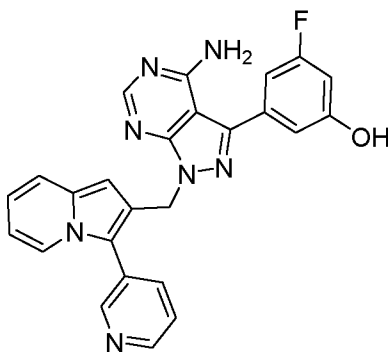
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.17 (br. s., 1 H), 8.91 - 8.95 (m, 1 H), 8.75 - 8.80 (m, 1 H), 8.28 (s, 1 H), 7.93 - 8.03 (m, 2 H), 7.44 (d, 1 H), 7.36 - 7.42 (m, 1 H), 6.90

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- 6.93 (m, 1 H), 6.79 - 6.89 (m, 2 H), 6.61 - 6.70 (m, 2 H), 6.35 - 7.46 (m, 2H), 6.26 (s, 1 H), 5.79 (s, 2 H).

Example 98: 3-(4-amino-1-{[3-(pyridin-3-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

5

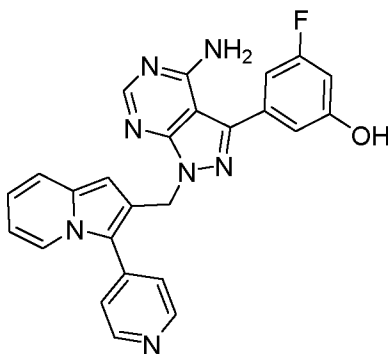


Prepared similarly to Example 85, starting from 3-iodo-1-{[3-(pyridin-3-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W17 (0.035 g, 0.075 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.015 g, 0.097 mmol) and Pd(PPh₃)₄ (4.3 mg, 0.0037 mmol), in DME (7.5 mL), EtOH (1.2 mL) and saturated aqueous Na₂CO₃ (2.1 mL), heating at 80°C overnight. After work-up the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 80 : 20) to afford title compound (0.011 g). MS/ESI⁺ 452.3 [MH]⁺, Rt 0.74 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.18 (br. s., 1 H), 8.84 (d, 1 H), 8.63 - 8.66 (m, 1 H), 8.26 (s, 1 H), 8.04 - 8.09 (m, 1 H), 8.01 (d, 1 H), 7.54 - 7.59 (m, 1 H), 7.44 (d, 1 H), 6.88 - 6.91 (m, 1 H), 6.81 - 6.87 (m, 1 H), 6.74 - 6.80 (m, 1 H), 6.63 - 6.70 (m, 1 H), 6.54 - 6.60 (m, 1 H), 6.45 (s, 1 H), 6.20 - 7.53 (m, 2H), 5.59 (s, 2 H).

20

Example 99: 3-(4-amino-1-{{3-(pyridin-4-yl)indolizin-2-yl}methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

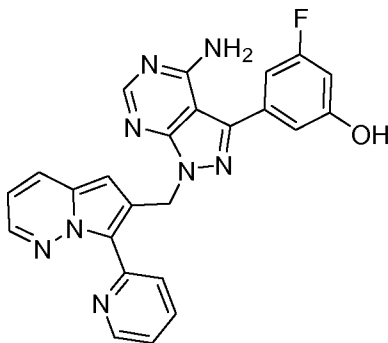


5 Prepared similarly to Example 85, starting from 3-iodo-1-{{3-(pyridin-4-yl)indolizin-2-yl}methyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W18 (0.055 g, 0.118 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.020 g, 0.130 mmol) and Pd(PPh₃)₄ (6.8 mg, 0.006 mmol), in DME (8 mL), EtOH (1.2 mL) and saturated aqueous Na₂CO₃ (2.2 mL), heating at 80°C overnight. Additional (3-fluoro-5-hydroxyphenyl)boronic acid (1 eq) and

10 Pd(PPh₃)₄ (6.8 mg, 0.006 mmol) were added and the heating was continued for further 2 h. After work-up the crude was purified by flash chromatography on g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 90 : 10); a further purification on SCX cartridge (1 g), eluting with 1M ammonia in MeOH was required to afford title compound (0.009 g). MS/ESI⁺ 452.3 [MH]⁺, Rt 0.61 min (Method A).

15 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.19 (br. s., 1 H), 8.70 - 8.76 (m, 2 H), 8.21 - 8.31 (m, 2 H), 7.71 - 7.77 (m, 2 H), 7.43 - 7.49 (m 1 H), 6.89 - 6.93 (m, 1 H), 6.77 - 6.88 (m, 2 H), 6.59 - 6.70 (m, 2 H), 6.40 (s, 1 H), 6.00 - 7.70 (m, 2H), 5.66 (s, 2 H).

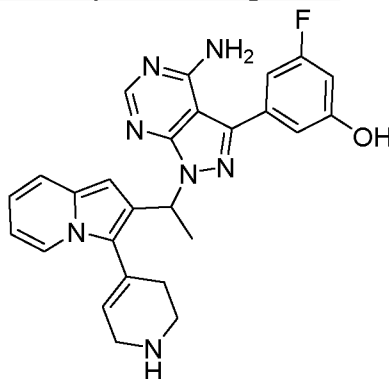
Example 100: 3-(4-amino-1-{[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



5 Prepared similarly to Example 85, 3-iodo-1-{[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W19 (0.026 g, 0.05 mmol), (3-fluoro-5-hydroxyphenyl)boronic acid (0.0113 g, 0.072 mmol) and Pd(PPh₃)₄ (2.9 mg, 0.0025 mmol), in DME (5 mL), EtOH (0.75 mL) and saturated aqueous Na₂CO₃ (1.42 mL), heating at 80°C for 3 h. After work-up the crude was purified by flash
10 chromatography on 10 g Biotage silica gel SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (0.012 g). MS/ESI⁺ 453.3 [MH]⁺, Rt 0.66 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.20 (s, 1 H), 8.74 - 8.77 (m, 1 H), 8.50 (d, 1 H), 8.30 - 8.34 (m, 1 H), 8.23 (s, 1 H), 7.93 - 8.00 (m, 2 H), 7.32 - 7.38 (m, 1 H), 6.90 - 6.95 (m, 1 H), 6.85 - 6.91 (m, 1 H), 6.81 (dd, 1 H), 6.63 - 6.69 (m, 1 H), 6.20 - 7.77 (m, 2
15 H), 6.12 (s, 1 H), 6.06 (s, 2 H).

Example 101: 3-(4-amino-1-{1-[3-(1,2,3,6-tetrahydropyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

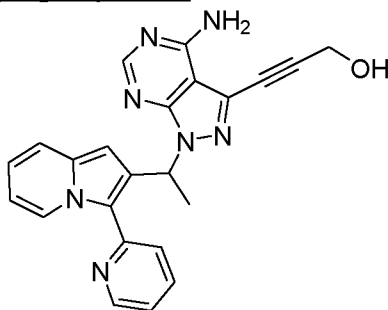


To a solution of tert-butyl 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate X (0.021 g, 0.037 mmol) in DCM (0.5 mL), trifluoroacetic acid (0.017 mL, 0.22 mmol) was slowly added at 0°C and the solution was stirred at room temperature for 3 days. The mixture was partitioned between saturated aqueous NaHCO₃ solution and DCM, the aqueous phase was further extracted with a mixture of DCM : MeOH (5 : 1), and the combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated. The crude was purified by reverse phase flash chromatography on 1 g C-18 cartridge (H₂O + 0.1% formic acid : CH₃CN + 0.1% formic acid = 95 : 5 to 50 : 50). A further purification by reverse phase semi-preparative MDAP under basic condition (Method F) was required to afford title compound as an orange solid (2 mg). MS/ESI⁺ 570.2 [MH]⁺, Rt 1.17 min (Method C).

¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.27 (s, 1 H), 7.83 (d, 1 H), 7.33 (d, 1 H), 6.87 - 6.90 (m, 1 H), 6.80 - 6.85 (m, 1 H), 6.59 - 6.66 (m, 3 H), 6.46 (t, 1 H), 6.37 (q, 1 H), 5.73 - 5.78 (m, 1 H), 3.35 - 3.38 (m, 2 H), 2.90 - 2.98 (m, 1 H), 2.80 - 2.90 (m, 1 H), 2.25 - 2.35 (m, 1 H), 1.94 - 2.05 (m, 4 H).

OH, NH and NH₂ not visible because of the chemical exchange with MeOH.

Example 102: 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)prop-2-yn-1-ol

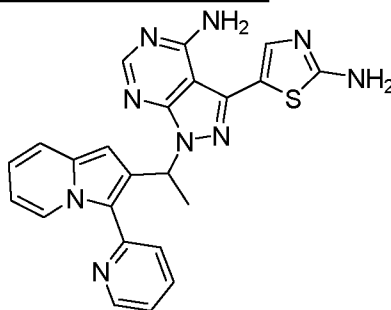


A mixture of 3-iodo-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine W2 (0.060 g, 0.125 mmol), propargyl alcohol (0.036 mL, 0.625 mmol), CuI (8.3 mg, 0.044 mmol) and diethylamine (0.13 mL, 1.25 mmol) in DMF (0.5 mL) was degassed, then Pd(PPh₃)₂Cl₂ (0.015 g, 0.021 mmol) was added and the reaction

was stirred at room temperature for 2 h. The mixture was diluted with EtOAc and filtered through a celite pad; the filtrate was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on 11g Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH 90 : 10). A further
5 purification on SCX (1g) cartridge eluting with 1M ammonia in MeOH was required to afford title compound (9.7 mg). MS/ESI⁺ 410.3 [MH]⁺, Rt 0.67 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.71 - 8.75 (m, 1 H), 8.64 (d, 1 H), 8.15 (s, 1 H), 7.93 (td, 1 H), 7.72 (d, 1 H), 7.51 (d, 1 H), 7.34 - 7.39 (m, 1 H), 6.79 - 6.86 (m, 1 H), 6.57 - 6.66 (m, 2 H), 6.44 (q, 1 H), 6.00 - 8.00 (m, 2H), 5.45 (t1 H), 4.40 (d, 2 H), 1.87 (d, 3 H).

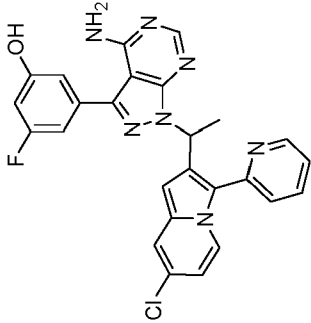
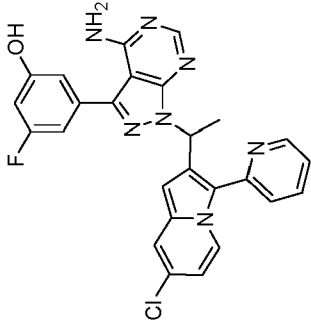
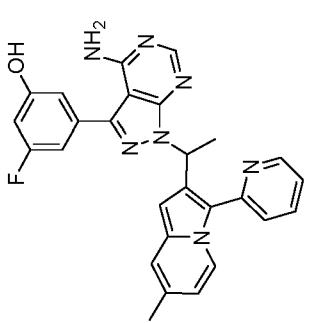
10 **Example 103: 5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3-thiazol-2-amine**



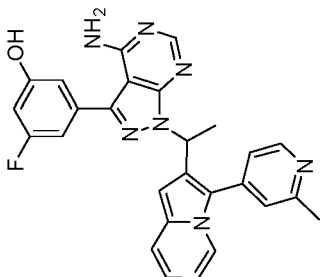
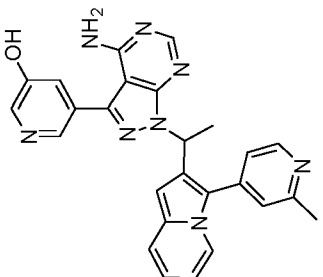
To a solution of tert-butyl N-[5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3-thiazol-2-yl]carbamate Y (0.060 g, 0.108
15 mmol) in DCM (2 mL), TFA (0.050 mL, 0.650 mmol) was slowly added at 0°C and the reaction was then stirred at RT for 3 h. Additional TFA (0.648 mmol) was added and the reaction mixture was stirred at RT overnight. The volatiles were removed under reduced pressure and the crude was purified by reverse phase flash chromatography on 12 g Biotage C18 SNAP cartridge (H₂O + 0.1% formic acid : acetonitrile + 0.1% formic = 95 : 5 to 70 :
20 30) to afford title compound (0.014 g). MS/ESI⁺ 454.3 [MH]⁺, Rt 0.59 min (Method A).

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.72 - 8.76 (m, 1 H), 8.64 (d, 1 H), 8.15 (s, 1 H), 7.94 (td, 1 H), 7.75 (d, 1 H), 7.49 (d, 1 H), 7.35 - 7.40 (m, 1 H), 7.29 (s, 1 H), 7.27 (br. s, 2 H), 6.99 (br. s., 2 H), 6.78 - 6.85 (m, 1 H), 6.65 (s, 1 H), 6.57 - 6.63 (m, 1 H), 6.42 (q, 1 H), 1.88 (d, 3 H).

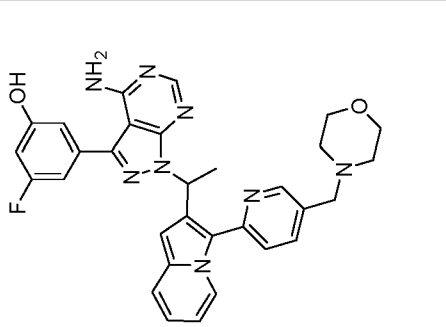
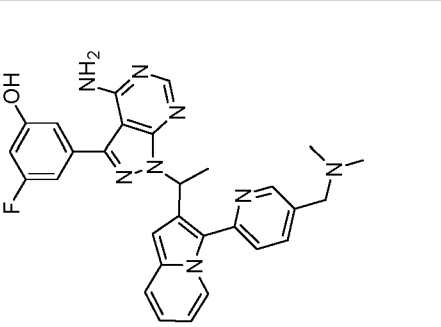
Examples 104-116, 118-123, 125-142, 146-148 and 150 found in the table below may be prepared from suitable intermediates reported below following similar procedures as for Example 85.

Example	Name and Molecular Structure		Reagent	Analytical data
104	3-(4-amino-1-({1-[7-chloro-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol		W20 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 500.3 [MH] ⁺ , Rt 1.01 min (Method A). 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.23 (br. s., 1 H), 8.71 - 8.75 (m, 1 H), 8.65 (d, 1 H), 8.18 (s, 1 H), 7.94 (td, 1 H), 7.78 (d, 1 H), 7.67 (d, 1 H), 7.36 - 7.41 (m, 1 H), 6.90 - 6.92 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.72 (s, 1 H), 6.61 - 6.70 (m, 2 H), 6.47 (q, 1 H), 6.00 - 8.00 (m, 2 H), 1.91 (d, 3 H).
105	3-(4-amino-1-({1-[7-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol		W21 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 480.3 [MH] ⁺ , Rt 0.87 min (Method A). 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.19 (br. s., 1 H), 8.67 - 8.73 (m, 1 H), 8.58 (d, 1 H), 8.17 (s, 1 H), 7.89 (td, 1 H), 7.68 - 7.75 (m, 1 H), 7.29 - 7.35 (m, 1 H), 7.22 - 7.26 (m, 1 H), 6.89 - 6.93 (m, 1 H), 6.82 - 6.89 (m, 1 H), 6.63 - 6.69 (m, 1 H), 6.54 (s, 1 H), 6.42 - 6.51 (m, 2 H), 6.15 - 7.50 (m, 2 H), 2.23 (s, 3 H), 1.90 (d, 3 H).

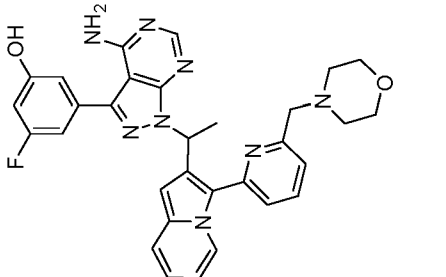
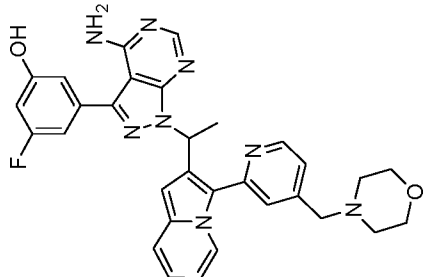
(continued)

106	3-(4-amino-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol		W22 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 480.2 [MH] ⁺ , Rt 0.67 min (Method A). ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.16 (br. s., 1 H), 8.46 - 8.50 (m, 1 H), 8.21 (s, 1 H), 8.00 - 8.04 (m, 1 H), 7.48 - 7.52 (m, 1 H), 7.25 - 7.30 (m, 2 H), 6.86 - 6.90 (m, 1 H), 6.75 - 6.85 (m, 3 H), 6.65 (dt, 1 H), 6.53 - 6.59 (m, 1 H), 6.27 (q, 1 H), 6.00 - 7.55 (m, 2 H), 2.45 (s, 3 H), 1.86 (d, 3 H).
107	5-(4-amino-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-3-ol		W22 and 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ol	MS/ESI ⁺ 463.3 [MH] ⁺ , Rt 0.67 min (Method C) ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.14 (bs, 1 H), 8.46 - 8.49 (m, 1 H), 8.26 (d, 1 H), 8.22 (s, 1 H), 8.20 (d, 1 H), 8.00 - 8.04 (m, 1 H), 7.47 - 7.52 (m, 1 H), 7.34 - 7.36 (m, 1 H), 7.26 - 7.29 (m, 2 H), 6.75 - 6.80 (m, 2 H), 6.54 - 6.58 (m, 1 H), 6.25 - 6.32 (m, 1 H), 6.20 - 7.55 (m, 2 H), 2.45 (s, 3 H), 1.87 (d, 3 H).

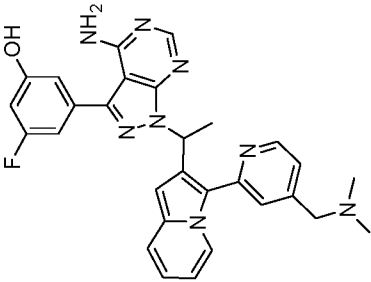
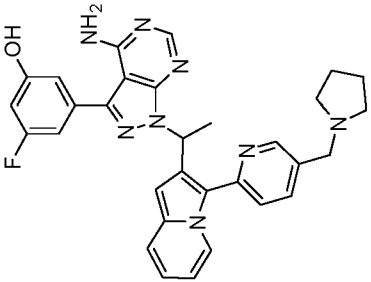
(continued)

108	3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W23 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 565.3 [MH] ⁺ , Rt 0.64 min (Method A) ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.18 (s, 1 H), 8.57 - 8.63 (m, 2 H), 8.18 (s, 1 H), 7.74 - 7.80 (m, 1 H), 7.65 - 7.71 (m, 1 H), 7.48 - 7.53 (m, 1 H), 6.87 - 6.91 (m, 1 H), 6.77 - 6.86 (m, 2 H), 6.71 (s, 1 H), 6.67 (dt, 1 H), 6.57 - 6.63 (m, 1 H), 6.53 (q, 1 H), 6.10 - 7.44 (m, 2 H), 3.58 - 3.67 (m, 4 H), 3.51 - 3.59 (m, 2 H), 2.36 - 2.46 (m, 4 H), 1.92 (d, 3 H).
109	3-{4-amino-1-[1-(3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W24 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 523.3 [MH] ⁺ , Rt 0.63 min (Method A) ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.20 (br. s., 2 H), 8.58 - 8.64 (m, 2 H), 8.17 (s, 1 H), 7.79 (dd, 1 H), 7.68 - 7.73 (m, 1 H), 7.48 - 7.53 (m, 1 H), 6.89 - 6.92 (m, 1 H), 6.78 - 6.87 (m, 2 H), 6.70 (s, 1 H), 6.64 - 6.69 (m, 1 H), 6.57 - 6.62 (m, 1 H), 6.52 (q, 1 H), 6.00 - 7.50 (m, 2 H), 3.48 (s, 2 H), 2.21 (s, 6 H), 1.92 (d, 3 H).

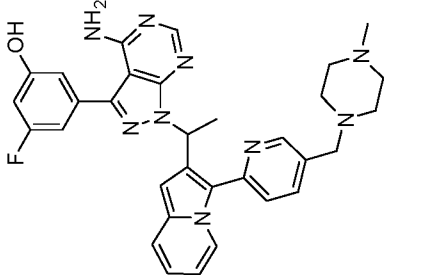
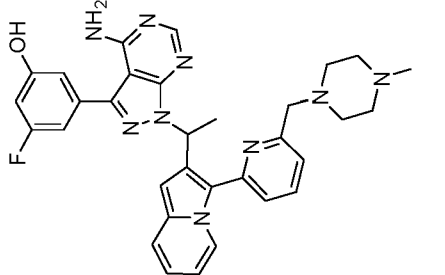
(continued)

110	3-[4-amino-1-(1-{3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W25 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 565.4 [MH] ⁺ , Rt 0.66 min (Method A) ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.21 (br. s., 1 H), 8.59 - 8.65 (m, 1 H), 8.14 (s, 1 H), 7.87 (t, 1 H), 7.60 (d, 1 H), 7.47 - 7.52 (m, 1 H), 7.38 (d, 1 H), 6.88 - 6.92 (m, 1 H), 6.77 - 6.87 (m, 2 H), 6.70 (s, 1 H), 6.63 - 6.69 (m, 1 H), 6.57 - 6.62 (m, 1 H), 6.51 (q, 1 H), 6.00 - 7.70 (m, 2 H), 3.57 - 3.68 (m, 6 H), 2.40 - 2.47 (m, 4 H), 1.92 (d, 3 H).
111	3-[4-amino-1-(1-{3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W26 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 565.5 [MH] ⁺ , Rt 0.66 min (Method A) ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.18 (br. s., 1 H), 8.62 - 8.67 (m, 2 H), 8.18 (s, 1 H), 7.48 - 7.54 (m, 2 H), 7.26 - 7.30 (m, 1 H), 6.88 - 6.91 (m, 1 H), 6.78 - 6.86 (m, 2 H), 6.76 (s, 1 H), 6.65 (dt, 1 H), 6.57 - 6.62 (m, 1 H), 6.44 (q, 1 H), 6.00 - 7.48 (m, 2 H), 3.45 - 3.58 (m, 6 H), 2.32 - 2.42 (m, 4 H), 1.90 (d, 3 H).

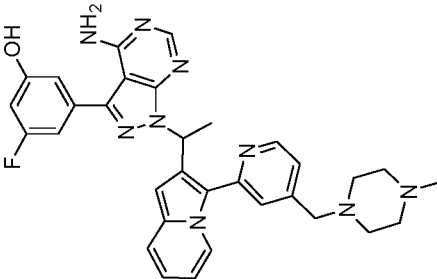
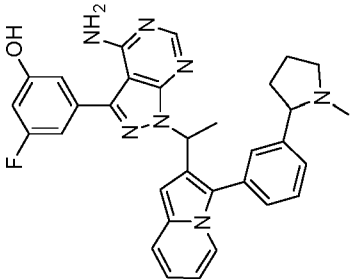
(continued)

112	3-[4-amino-1-[1-(3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W27 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 523.5 [MH] ⁺ , Rt 0.64 min (Method A) ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.18 (br. s., 1 H), 8.59 - 8.66 (m, 2 H), 8.19 (s, 1 H), 7.47 - 7.54 (m, 2 H), 7.24 - 7.29 (m, 1 H), 6.87 - 6.91 (m, 1 H), 6.77 - 6.86 (m, 2 H), 6.75 (s, 1 H), 6.65 (dt, 1 H), 6.56 - 6.62 (m, 1 H), 6.39 - 6.47 (m, 1 H), 6.00 - 7.70 (m, 2 H), 3.41 (s, 2 H), 2.16 (s, 6 H), 1.89 (d, 3 H).
113	3-[4-amino-1-(1-{3-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W28 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 549.4 [MH] ⁺ , Rt 0.65 min (Method A) ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.18 (br. s., 1 H), 8.57 - 8.62 (m, 2 H), 8.16 (s, 1 H), 7.78 (dd, 1 H), 7.67 (d, 1 H), 7.46 - 7.51 (m, 1 H), 6.87 - 6.91 (m, 1 H), 6.76 - 6.86 (m, 2 H), 6.63 - 6.70 (m, 2 H), 6.55 - 6.61 (m, 1 H), 6.50 (q, 1 H), 6.00 - 7.30 (m, 2 H), 3.60 - 3.69 (m, 2 H), 2.42 - 2.52 (m, 4 H), 1.90 (d, 3 H), 1.68 - 1.77 (m, 4 H).

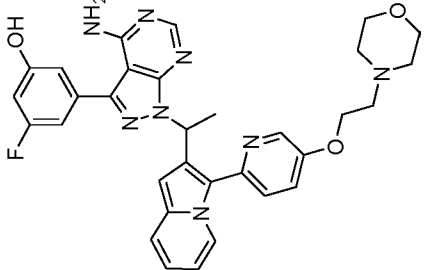
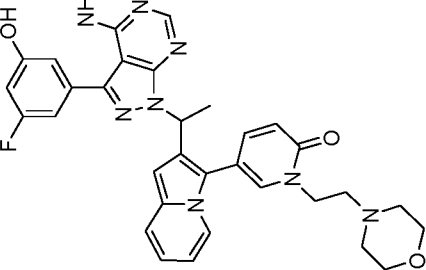
(continued)

114	3-{{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W29 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 578.4 [MH]⁺, Rt 0.62 min (Method A) ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (br. s, 1 H), 8.54 - 8.61 (m, 2 H), 8.15 (s, 1 H), 7.72 (dd, 1 H), 7.64 (d, 1 H), 7.47 - 7.52 (m, 1 H), 6.86 - 6.90 (m, 1 H), 6.76 - 6.85 (m, 2 H), 6.69 (s, 1 H), 6.65 (dt, 1 H), 6.55 - 6.61 (m, 1 H), 6.51 (q, 1 H), 6.10 - 7.30 (m, 2 H), 3.48 - 3.58 (m, 2 H), 2.22 - 2.49 (m, 8 H), 2.16 (s, 3 H), 1.90 (d, 3 H).
115	3-{{4-amino-1-[1-(3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W30 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 578.5 [MH]⁺, Rt 0.63 min (Method A) ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (br.s., 1 H), 8.59 - 8.65 (m, 1 H), 8.14 (s, 1 H), 7.81 - 7.88 (m, 1 H), 7.58 (d, 1 H), 7.47 - 7.51 (m, 1 H), 7.33 (d, 1 H), 6.87 - 6.92 (m, 1 H), 6.76 - 6.87 (m, 2 H), 6.69 (s, 1 H), 6.65 (dt, 1 H), 6.55 - 6.61 (m, 1 H), 6.50 (q, 1 H), 6.10 - 7.40 (m, 2 H), 3.57 - 3.66 (m, 2 H), 2.19 - 2.47 (m, 8 H), 2.15 (s, 3 H), 1.92 (d, 3 H).

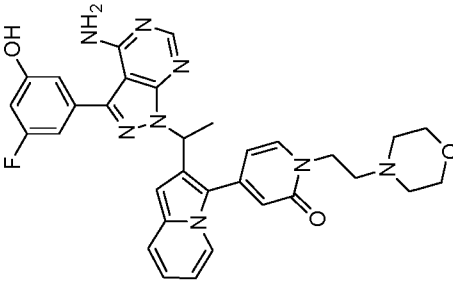
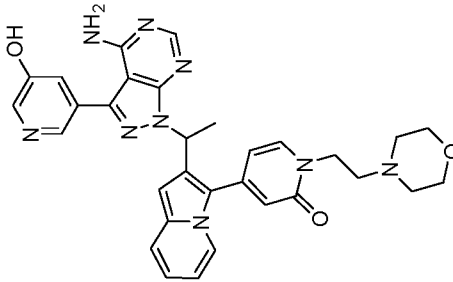
(continued)

116	3-{{4-amino-1-[1-(3-{4-[4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W31 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 578.5 [MH] ⁺ , Rt 0.60 min (Method A) 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.18 (br.s., 1 H), 8.60 - 8.67 (m, 2 H), 8.18 (s, 1 H), 7.46 - 7.54 (m, 2 H), 7.22 - 7.28 (m, 1 H), 6.88 - 6.91 (m, 1 H), 6.78 - 6.86 (m, 2 H), 6.76 (s, 1 H), 6.62 - 6.68 (m, 1 H), 6.56 - 6.62 (m, 1 H), 6.44 (q, 1 H), 6.10 - 7.45 (m, 2 H), 3.42 - 3.54 (m, 2 H), 2.16 - 2.45 (m, 8 H), 2.11 (s, 3 H), 1.89 (d, 3 H).
118	3-[4-amino-1-(1-{3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W33 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 548.4 [MH] ⁺ , Rt 0.70 min (Method A) (mixture of diastereoisomers) 1H NMR (500 MHz, DMSO-d ₆) δ ppm 1.48 - 1.78 (m, 3 H), 1.79 - 1.87 (m, 3 H), 2.00 - 2.11 (m, 3 H), 2.10 - 2.17 (m, 1 H), 2.17 - 2.25 (m, 1 H), 2.98 - 3.07 (m, 1 H), 3.07 - 3.18 (m, 1 H), 6.07 - 7.68 (m, 2 H), 6.13 - 6.23 (m, 1 H), 6.47 - 6.55 (m, 1 H), 6.61 - 6.74 (m, 3 H), 6.80 - 6.87 (m, 1 H), 6.87 - 6.93 (m, 1 H), 7.27 - 7.39 (m, 3 H), 7.40 - 7.49 (m, 2 H), 7.77 - 7.86 (m, 1 H), 8.13 (s, 1 H), 10.17 (s, 1 H).

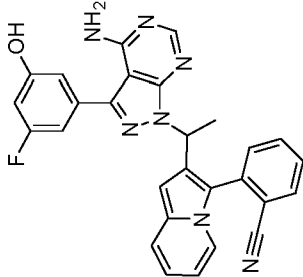
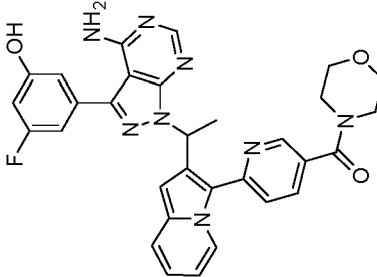
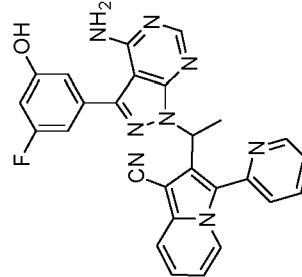
(continued)

119	3-{{4-amino-1-[1-(3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W34 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 595.2 [MH]⁺, Rt 0.90 min (Method C) ¹H NMR (400 MHz, DMSO-<i>d</i>6) δ ppm 10.19 (br. s., 1 H), 8.37 - 8.45 (m, 2 H), 8.18 (s, 1 H), 7.65 (d, 1 H), 7.51 (dd, 1 H), 7.43 - 7.48 (m, 1 H), 6.91 (s, 1 H), 6.82 - 6.87 (m, 1 H), 6.72 - 6.78 (m, 1 H), 6.63 - 6.69 (m, 2 H), 6.52 - 6.57 (m, 1 H), 6.41 (q, 1 H), 6.00 - 8.00 (m, 2 H), 4.20 - 4.27 (m, 2 H), 3.57 - 3.65 (m, 4 H), 2.72 - 2.79 (m, 2 H), 2.51 - 2.56 (m, 4 H), 1.89 (d, 3 H).
120	5-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one		W35 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 595.2 [MH]⁺, Rt 0.85 min (Method C) ¹H NMR (400 MHz, DMSO-<i>d</i>6) δ ppm 10.20 (br. s., 1 H), 8.19 (s, 1 H), 7.76 - 7.83 (m, 2 H), 7.41 - 7.48 (m, 1 H), 7.28 - 7.37 (m, 1 H), 6.88 - 6.92 (m, 1 H), 6.82 - 6.87 (m, 1 H), 6.70 - 6.75 (m, 1 H), 6.63 - 6.69 (m, 2 H), 6.50 - 6.56 (m, 1 H), 6.42 (d, 1 H), 6.22 (q, 1 H), 6.00 - 8.00 (m, 2 H), 3.91 - 4.06 (m, 2 H), 3.44 - 3.55 (m, 4 H), 2.54 - 2.64 (m, 2 H), 2.35 - 2.46 (m, 4 H), 1.89 (d, 3 H).

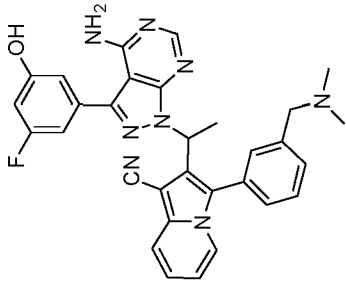
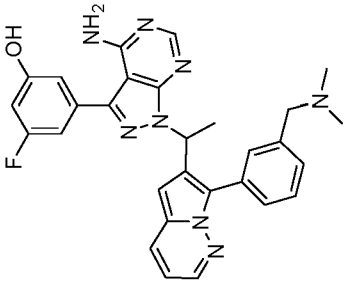
(continued)

121	4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one		W36 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 595.3 [MH] ⁺ , Rt 0.79 min (Method C)
122	4-(2-{1-[4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one		W36 and 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ol	MS/ESI ⁺ 578.4 [MH] ⁺ , Rt 0.60 min (Method J) ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 10.24 (bs, 1 H), 8.28 - 8.31 (m, 1 H), 8.20 (d, 1 H), 8.17 (s, 1 H), 8.04 (d, 1 H), 7.73 (d, 1 H), 7.45 - 7.50 (m, 1 H), 7.35 - 7.41 (m, 1 H), 6.73 - 6.82 (m, 1 H), 6.70 (s, 1 H), 6.56 - 6.64 (m, 1 H), 6.43 - 6.47 (m, 1 H), 6.27 - 6.39 (m, 2 H), 6.02 - 7.95 (m, 2 H), 3.98 - 4.06 (m, 2 H), 3.54 - 3.62 (m, 4 H), 2.54 - 2.62 (m, 2 H), 2.42 - 2.48 (m, 4 H), 1.89 (d, 3 H).

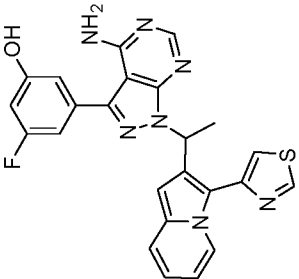
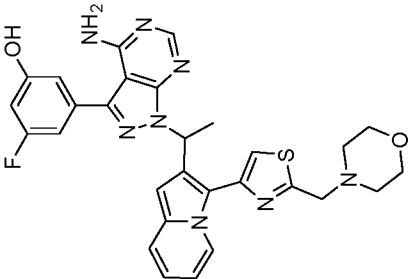
(continued)

123	2-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)benzonitrile		W37 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 490.3 [MH] ⁺ , Rt 0.96 and 0.97 min (Method A) (mixture of isomers ≈ 45/55 by ¹ H NMR) ¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 1.86 - 1.98 (m, 3 H), 6.71 (br. s, 2 H), 6.09 - 6.24 (m, 1 H), 6.45 - 6.98 (m, 6 H), 7.20 - 7.94 (m, 6 H), 7.96 - 8.10 (m, 1 H), 10.16 (br. s., 1 H).
125	3-[4-amino-1-(1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W38 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 579.3 [MH] ⁺ , Rt 0.86 min (Method A) ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.16 (br. s., 1 H), 8.66 - 8.78 (m, 2 H), 8.17 (s, 1 H), 7.87 (dd, 1 H), 7.75 - 7.80 (m, 1 H), 7.49 - 7.55 (m, 1 H), 6.76 - 6.90 (m, 3 H), 6.73 (s, 1 H), 6.60 - 6.69 (m, 2 H), 6.56 (q, 1 H), 6.00 - 8.00 (m, 2 H), 3.32 - 3.76 (m, 8 H), 1.92 (d, 3 H).
126	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-(pyridin-2-yl)indolizine-1-carbonitrile		W39 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 491.3 [MH] ⁺ , Rt 0.85 min (Method A) ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.19 (s, 1 H), 8.75 - 8.80 (m, 1 H), 8.52 (d, 1 H), 8.12 (s, 1 H), 7.99 (td, 1 H), 7.76 (d, 1 H), 7.70 (d, 1 H), 7.47 - 7.53 (m, 1 H), 7.28 - 7.34 (m, 1 H), 6.92 - 6.97 (m, 3 H), 6.66 (dt, 1 H), 6.42 (q, 1 H), 6.00 - 7.95 (m, 2 H), 2.01 (d, 3 H).

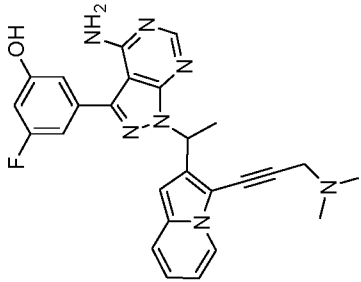
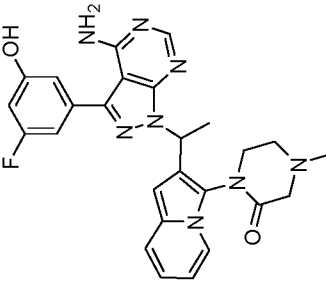
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127	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile		W40 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 547.0 [MH] ⁺ , Rt 0.64 min (Method A)
128	3-{4-amino-1-[1-(7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazin-6-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W41 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 523.5 [MH] ⁺ , Rt 0.62 min (Method A) 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.16 (br. s., 1 H), 8.17 (s, 1 H), 8.08 (dd, 1 H), 7.98 (dd, 1 H), 7.41 - 7.46 (m, 1 H), 7.35 - 7.41 (m, 1 H), 7.30 - 7.33 (m, 1 H), 7.25 - 7.29 (m, 1 H), 6.88 - 6.91 (m, 1 H), 6.81 - 6.86 (m, 2 H), 6.63 - 6.70 (m, 2 H), 6.27 - 6.33 (m, 1 H), 6.26 - 7.95 (m, 2 H), 3.30 - 3.38 (m, 2 H), 2.11 (s, 6 H), 1.85 (d, 3 H).

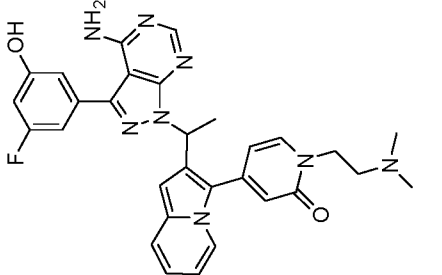
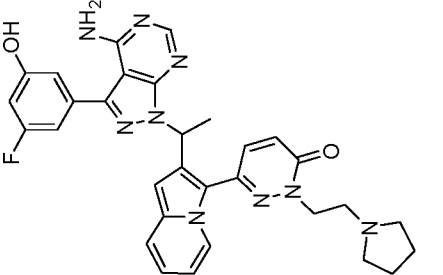
(continued)

129	3-(4-amino-1- $\{1-[3-(1,3\text{-thiazol-4-yl})\text{indolizin-2-yl}]\text{ethyl}\}$ -1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol		W42 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 472.3 [MH] ⁺ , Rt 0.95 min (Method A). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.19 (br. s., 1 H), 9.35 (d, 1 H), 8.34 - 8.42 (m, 1 H), 8.19 (s, 1 H), 8.16 (d, 1 H), 7.44 - 7.50 (m, 1 H), 6.92 - 6.95 (m, 1 H), 6.83 - 6.90 (m, 1 H), 6.73 - 6.80 (m, 1 H), 6.63 - 6.70 (m, 2 H), 6.58 - 6.62 (m, 1 H), 6.48 (q, 1 H), 6.30 - 7.30 (m, 2 H), 1.91 (d, 3 H).
130	3-[4-amino-1-(1-{3-[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W43 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 571.3 [MH] ⁺ , Rt 0.73 min (Method A). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.17 (s, 1 H), 8.31 (d, 1 H), 8.17 (s, 1 H), 7.96 (s, 1 H), 7.47 (d, 1 H), 6.87 - 6.91 (m, 1 H), 6.80 - 6.86 (m, 1 H), 6.73 - 6.79 (m, 1 H), 6.63 - 6.68 (m, 2 H), 6.56 - 6.62 (m, 1 H), 6.47 (q, 1 H), 6.00 - 7.80 (m, 2 H), 3.81 - 3.92 (m, 2 H), 3.59 - 3.65 (m, 4 H), 2.48 - 2.54 (m, 4 H), 1.90 (d, 3 H).

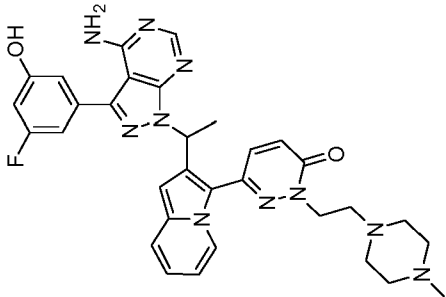
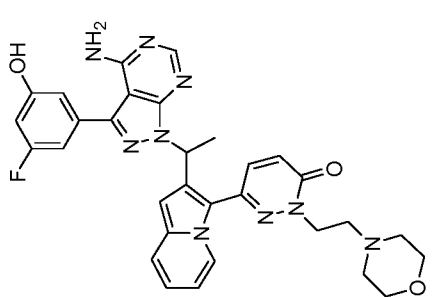
(continued)

131	3-[4-amino-1-(1-{3-[3-(dimethylamino)prop-1-yn-1-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol		W44 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 470.2 [MH] ⁺ , Rt 0.97 min (Method C). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.17 (s, 1 H), 8.25 (s, 1 H), 8.12 - 8.16 (m, 1 H), 7.49 (d, 1 H), 6.91 - 6.95 (m, 1 H), 6.84 - 6.90 (m, 2 H), 6.75 - 6.81 (m, 1 H), 6.64 - 6.70 (m, 1 H), 6.47 (s, 1 H), 6.39 (q, 1 H), 6.20 - 7.50 (m, 2 H), 3.44 - 3.55 (m, 2 H), 2.20 (s, 6 H), 1.95 (d, 3 H).
132	1-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-4-methylpiperazin-2-one		W45 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 501.3 [MH] ⁺ , Rt 0.74 and 0.77 min (Method C) mixture of isomers ≈ 65/35 by ¹ H NMR ¹ H NMR (500 MHz, DMSO-d ₆) δ ppm 10.10 - 10.23 (m, 1 H), 8.25 (s, 1 H), 7.62 - 7.75 (m, 1 H), 7.40 - 7.47 (m, 1 H), 6.80 - 6.96 (m, 2 H), 6.71 - 6.78 (m, 1 H), 6.52 - 6.69 (m, 3 H), 6.05 - 6.29 (m, 1 H), 5.92 - 8.00 (m, 2 H), 3.30 - 3.77 (m, 2 H), 3.04 - 3.28 (m, 2 H), 2.71 - 2.85 (m, 1 H), 2.47 - 2.59 (m, 1 H), 2.24 - 2.34 (m, 3 H), 1.81 - 1.95 (m, 3 H).

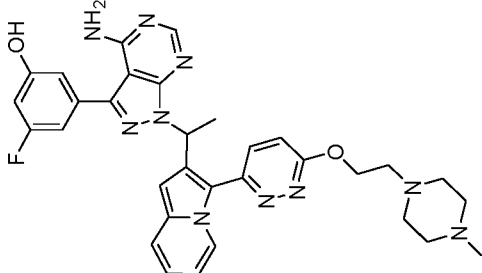
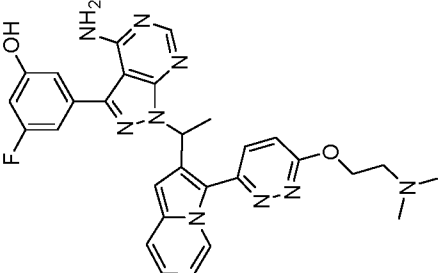
(continued)

133	4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one		W46 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 553.4 [MH]⁺, Rt 0.80 min (Method J). ¹H NMR (400 MHz, DMSO-<i>d</i>6) δ ppm 10.21 (br. s., 1 H), 8.16 (s, 1 H), 8.04 (d, 1 H), 7.72 (d, 1 H), 7.44 - 7.50 (m, 1 H), 6.90 - 6.92 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.75 - 6.81 (m, 1 H), 6.63 - 6.70 (m, 2 H), 6.57 - 6.62 (m, 1 H), 6.45 (d, 1 H), 6.28 - 6.37 (m, 2 H), 6.00 - 7.40 (m, 2 H), 3.99 (t, 2 H), 2.52 - 2.56 (m, 2 H), 2.22 (s, 6 H), 1.89 (d, 3 H).
134	6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(pyrrolidin-1-yl)ethyl]-2,3-dihydropyridazin-3-one		W47 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 580.4 [MH]⁺, Rt 0.65 min (Method A). ¹H NMR (400 MHz, DMSO-<i>d</i>6) δ ppm 10.17 (br.s, 1H), 8.28 - 8.33 (m, 1H), 8.18 (s, 1 H), 7.73 (d, 1 H), 7.49 - 7.55 (m, 1 H), 6.97 (d, 1 H), 6.88 - 6.91 (m, 1 H), 6.79 - 6.87 (m, 2 H), 6.59 - 6.73 (m, 3 H), 6.39 (q, 1 H), 6.10 - 7.45 (m, 2 H), 4.10 - 4.26 (m, 2 H), 2.73 - 2.84 (m, 2 H), 2.43 - 2.55 (m, 4 H), 1.93 (d, 3 H), 1.62 - 1.73 (m, 4 H).

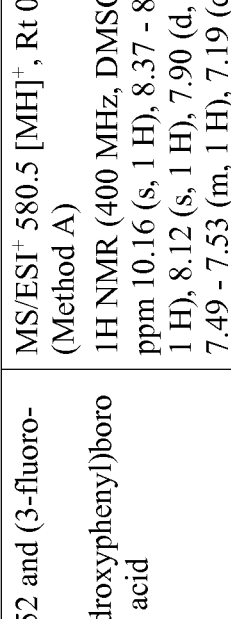
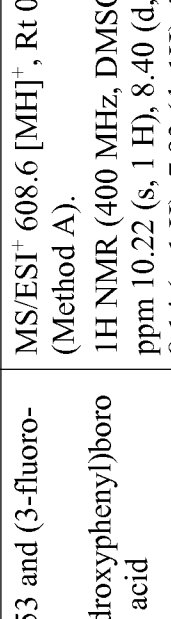
(continued)

135	6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(4-methylpiperazin-1-yl)ethyl]-2,3-dihydropyridazin-3-one		W48 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 609.7 [MH] ⁺ , Rt 0.63 min (Method A). 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.23 (br. s., 1 H), 8.26 - 8.31 (m, 1 H), 8.17 (s, 1 H), 7.72 (d, 1 H), 7.50 - 7.55 (m, 1 H), 6.97 (d, 1 H), 6.80 - 6.91 (m, 3 H), 6.59 - 6.73 (m, 3 H), 6.39 (q, 1 H), 6.00 - 8.00 (m, 2 H), 4.10 - 4.27 (m, 2 H), 2.62 - 2.72 (m, 2 H), 2.36 - 2.49 (m, 4 H), 2.20 - 2.33 (m, 4 H), 2.12 (s, 3 H), 1.93 (d, 3 H).
136	6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(morpholin-4-yl)ethyl]-2,3-dihydropyridazin-3-one		W49 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 596.3 [MH] ⁺ , Rt 0.65 min (Method A). 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.19 (bs, 1 H), 8.26 - 8.30 (m, 1 H), 8.17 (s, 1 H), 7.73 (d, 1 H), 7.50 - 7.55 (m, 1 H), 6.98 (d, 1 H), 6.89 - 6.92 (m, 1 H), 6.81 - 6.88 (m, 2 H), 6.60 - 6.74 (m, 3 H), 6.39 (q, 1 H), 6.00 - 7.40 (m, 2 H), 4.12 - 4.30 (m, 2 H), 3.50 - 3.58 (m, 4 H), 2.65 - 2.73 (m, 2 H), 2.37 - 2.47 (m, 4 H), 1.93 (d, 3 H).

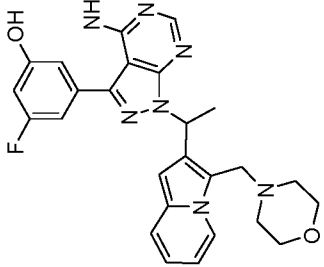
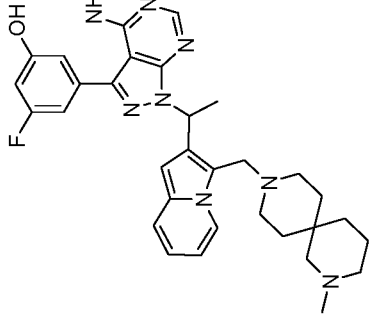
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137	3-{4-amino-1-[1-(3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W50 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 609.5 [MH] ⁺ , Rt 0.63 min (Method A). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.19 (br. s., 1 H), 8.39 - 8.43 (m, 1 H), 8.15 (s, 1 H), 7.94 (d, J=8 Hz, 1 H), 7.51 - 7.55 (m, 1 H), 7.28 (d, 1 H), 6.88 - 6.91 (m, 1 H), 6.81 - 6.87 (m, 2 H), 6.73 (s, 1 H), 6.67 (dt, 1 H), 6.60 - 6.64 (m, 1 H), 6.40 (q, 1 H), 6.00 - 7.90 (m, 2 H), 4.58 - 4.65 (m, 2 H), 2.79 (t, 2 H), 2.29 - 2.60 (m, 8 H), 2.17 (s, 3 H), 1.94 (d, 3 H).
138	3-{4-amino-1-[1-(3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W51 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 554.4 [MH] ⁺ , Rt 0.65 min (Method A). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.23 (br. s., 1 H), 8.38 - 8.42 (m, 1 H), 8.14 (s, 1 H), 7.94 (d, 1 H), 7.50 - 7.54 (m, 1 H), 7.27 (d, 1 H), 6.88 - 6.90 (m, 1 H), 6.80 - 6.86 (m, 2 H), 6.72 (s, 1 H), 6.66 (dt, 1 H), 6.59 - 6.64 (m, 1 H), 6.39 (q, 1 H), 6.30 - 8.37 (m, 2 H), 4.57 - 4.61 (m, 2 H), 2.72 (t, 2 H), 2.26 (s, 6 H), 1.93 (d, 3 H).

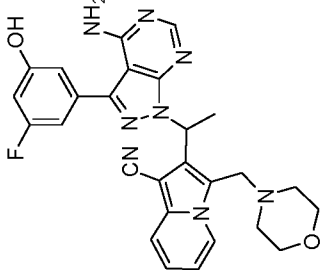
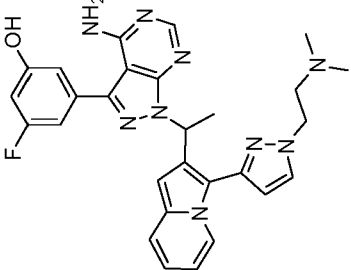
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139	3-{4-amino-1-[1-(3-{6-[1-methylpiperidin-4-yloxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol 	W52 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 580.5 [MH]⁺, Rt 0.66 min (Method A) ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (s, 1 H), 8.37 - 8.40 (m, 1 H), 8.12 (s, 1 H), 7.90 (d, 1 H), 7.49 - 7.53 (m, 1 H), 7.19 (d, 1 H), 6.86 - 6.89 (m, 1 H), 6.78 - 6.85 (m, 2 H), 6.71 (s, 1 H), 6.65 (dt, 1 H), 6.57 - 6.62 (m, 1 H), 6.36 - 6.42 (m, 1 H), 5.90 - 7.86 (m, 2 H), 5.19 - 5.27 (m, 1 H), 2.65 - 2.73 (m, 2 H), 2.15 - 2.26 (m, 5 H), 2.02 - 2.13 (m, 2 H), 1.92 (d, 3 H), 1.70 - 1.82 (m, 2 H).
140	3-{4-amino-1-[1-(3-{6-[2-(1-methylpiperidin-4-yloxy)pyridazin-3-yl]indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol 	W53 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 608.6 [MH]⁺, Rt 0.68 min (Method A) ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.22 (s, 1 H), 8.40 (d, 1 H), 8.14 (s, 1 H), 7.93 (d, 1 H), 7.50 - 7.54 (m, 1 H), 7.25 (d, 1 H), 6.87 - 6.90 (m, 1 H), 6.79 - 6.86 (m, 2 H), 6.72 (s, 1 H), 6.58 - 6.69 (m, 2 H), 6.38 (q, 1 H), 6.00 - 7.80 (m, 2 H), 4.49 - 4.59 (m, 2 H), 2.72 - 2.79 (m, 2 H), 2.14 (s, 3 H), 1.93 (d, 3 H), 1.66 - 1.89 (m, 6 H), 1.39 - 1.51 (m, 1 H), 1.18 - 1.31 (m, 2 H).

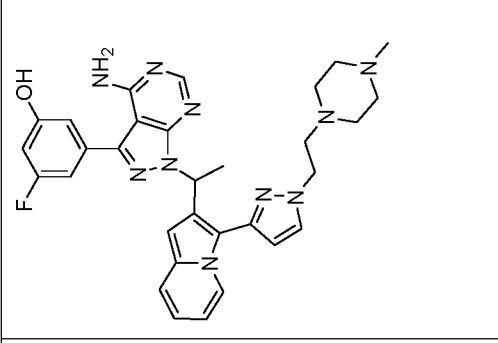
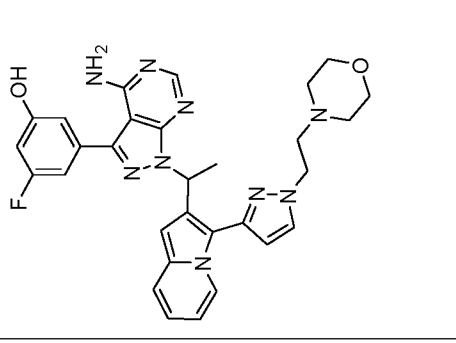
(continued)

141	3-(4-amino-1-{1-[3-(morpholin-4-ylmethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol		W54 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 488.4 [MH] ⁺ , Rt 0.92 min (Method J). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.16 (br. s., 1 H), 8.28 (s, 1 H), 8.11 - 8.15 (m, 1 H), 7.37 - 7.42 (m, 1 H), 6.85 - 6.88 (m, 1 H), 6.79 - 6.84 (m, 1 H), 6.61 - 6.72 (m, 2 H), 6.54 - 6.61 (m, 2 H), 6.36 (q, 1 H), 6.00 - 7.30 (m, 2 H), 3.73 - 3.88 (m, 2 H), 3.34 - 3.50 (m, 4 H), 2.12 - 2.23 (m, 4 H), 1.90 (d, 3 H).
142	3-(4-amino-1-{1-[3-(2-methyl-2,9-diazaspiro[5.5]undecan-9-yl)methyl]indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol		W55 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 569.5 [MH] ⁺ , Rt 1.18 min (Method J). ¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 10.12 (br. s., 1 H), 8.28 (s, 1 H), 8.07 - 8.11 (m, 1 H), 7.37 - 7.41 (m, 1 H), 6.83 - 6.87 (m, 1 H), 6.77 - 6.82 (m, 1 H), 6.61 - 6.70 (m, 2 H), 6.60 (s, 1 H), 6.52 - 6.57 (m, 1 H), 6.36 (q, 1 H), 6.00 - 7.70 (m, 2 H), 3.66 - 3.85 (m, 2 H), 2.06 (s, 3 H), 1.90 (d, 3 H), 1.83 - 2.24 (m, 8 H), 1.05 - 1.45 (m, 8 H).

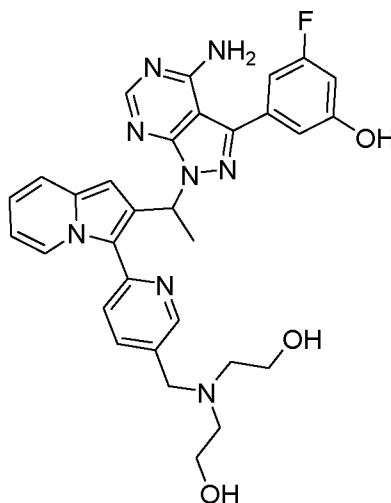
(continued)

146	2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-(morpholin-4-ylmethyl)indolizine-1-carbonitrile		W59 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 513.4 [MH] ⁺ , Rt 0.64 min (Method A) 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.19 (s, 1 H), 8.44 (d, 1 H), 8.26 (s, 1 H), 7.57 - 7.63 (m, 1 H), 7.20 - 7.26 (m, 1 H), 6.89 - 6.99 (m, 3 H), 6.64 (dt, 1 H), 6.42 (q, 1 H), 6.00 - 7.66 (m, 2 H), 3.84 - 4.00 (m, 2 H), 3.37 - 3.48 (m, 4 H), 2.19 - 2.28 (m, 4 H), 2.05 (d, 3 H).
147	3-{4-amino-1-[1-(3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl]indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W60 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI ⁺ 526.4 [MH] ⁺ , Rt 0.65 min (Method A) 1H NMR (400 MHz, DMSO-d ₆) δ ppm 10.24 (br. s., 1 H), 8.72 - 8.75 (m, 1 H), 8.21 (s, 1 H), 7.94 (d, 1 H), 7.42 - 7.45 (m, 1 H), 6.93 - 6.96 (m, 1 H), 6.86 - 6.91 (m, 1 H), 6.77 (d, 1 H), 6.70 - 6.75 (m, 1 H), 6.66 (dt, 1 H), 6.57 - 6.62 (m, 2 H), 6.50 (q, 1 H), 6.45 - 7.40 (m, 2 H), 4.30 (t, 2 H), 2.73 (t, 2 H), 2.20 (s, 6 H), 1.89 (d, 3 H)

(continued)

148	3-{4-amino-1-[1-(3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W61 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 580.9 [MH]⁺, Rt 0.66 min (Method A) ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.20 (br. s., 1 H), 8.70 - 8.74 (m, 1 H), 8.21 (s, 1 H), 7.94 (d, 1 H), 7.41 - 7.46 (m, 1 H), 6.93 - 6.96 (m, 1 H), 6.87 - 6.92 (m, 1 H), 6.77 (d, 1 H), 6.70 - 6.75 (m, 1 H), 6.67 (dt, 1 H), 6.56 - 6.62 (m, 2 H), 6.50 (q, 1 H), 6.10 - 7.30 (m, 2 H), 4.32 (t, 2 H), 2.79 (t, 2 H), 2.39 - 2.51 (m, 4 H), 2.23 - 2.37 (m, 4 H), 2.13 (s, 3 H), 1.89 (d, 3 H).
150	3-{4-amino-1-[1-(3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol		W63 and (3-fluoro-5-hydroxyphenyl)boronic acid	MS/ESI⁺ 568.4 [MH]⁺, Rt 0.70 min (Method A) ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.31 - 8.35 (m, 1 H), 8.22 (s, 1 H), 7.76 (d, 1 H), 7.38 - 7.43 (m, 1 H), 6.92 - 6.94 (m, 1 H), 6.87 - 6.91 (m, 1 H), 6.70 - 6.75 (m, 2 H), 6.66 (dt, 1 H), 6.50 - 6.59 (m, 3 H), 4.29 - 4.35 (m, 2 H), 3.68 - 3.72 (m, 4 H), 2.84 (t, 2 H), 2.51 - 2.55 (m, 4 H), 1.98 (d, 3 H).

Example 117: 3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

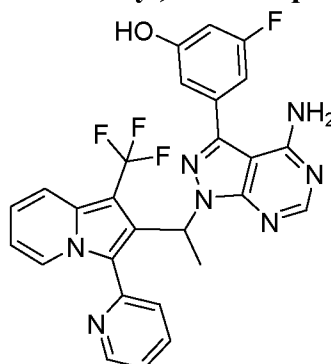


5 A mixture of crude 3-iodo-1-[1-(3-{5-[(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-7-aza-3,11-disilatridecan-7-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine W32 (0.214), (3-fluoro-5-hydroxyphenyl)boronic acid (0.044 g, 0.285 mmol) and Pd(PPh₃)₄ (0.015 g, 0.013 mmol), in DME (9.3 ml), EtOH (1.7 mL) and saturated aqueous Na₂CO₃ (3.5 ml) was heated at 80°C for 3 h. The mixture was
10 partitioned between water and DCM and the aqueous phase was extracted with DCM; the combined organic layers were washed with brine and dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in a 1M solution of aqueous HCl in EtOH (prepared from aqueous 37% HCl in EtOH) (3.5 mL) and the mixture was stirred at r.t. for 3 h. The volatiles were removed under reduced pressure and
15 the crude was dissolved in MeOH, charged on a SCX cartridge (1 g) washing with MeOH, and then eluted with 1M NH₃ in MeOH. The basic fractions were evaporated and the residue was purified by flash chromatography on silica gel cartridge (DCM to DCM : MeOH = 85 : 15) to afford title compound as a yellow solid (0.040 g). MS/ESI⁺ 583.3 [MH]⁺, Rt 0.62 min (Method A).

20 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.18 (s, 1 H), 8.65 - 8.68 (m, 1 H), 8.60 (d, 1 H), 8.17 (s, 1 H), 7.87 (dd, 1 H), 7.70 (d, 1 H), 7.46 - 7.50 (m, 1 H), 6.90 - 6.93 (m, 1

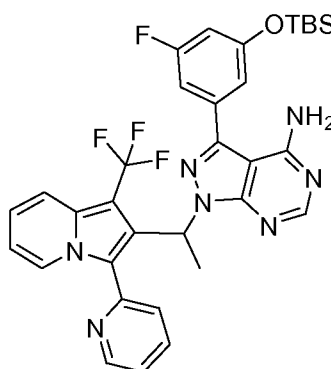
H), 6.83 - 6.89 (m, 1 H), 6.76 - 6.82 (m, 1 H), 6.64 - 6.69 (m, 2 H), 6.55 - 6.61 (m, 1 H), 6.49 (q, 1 H), 6.20 - 7.30 (m, 2 H), 4.43 (t, 2 H), 3.76 (s, 2 H), 3.46 - 3.56 (m, 4 H), 2.60 (t, 4 H), 1.90 (d, 3 H).

Example 124: 3-(4-amino-1-{1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



Step 1: 3-{3-[(tert-butyldimethylsilyl)oxy]-5-fluorophenyl}-1-{1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine

124a



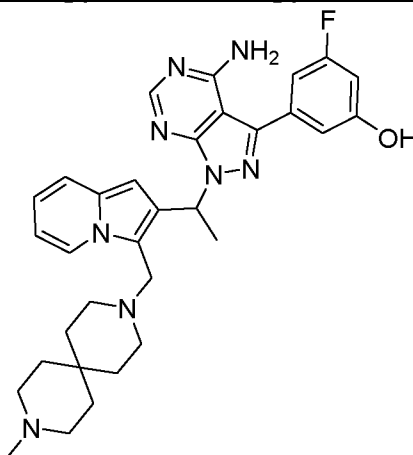
To a mixture of 1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethan-1-ol M41 (0.065 g, 0.21 mmol), 3-{3-[(tert-butyldimethylsilyl)oxy]-5-fluorophenyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine AA7 (0.091 g, 0.25 mmol) and PPh₃ (0.072 g, 0.27 mmol) in dry THF (3 mL), a solution of DIAD (0.049 mL, 0.25 mmol) in THF (1 mL) was added drop-wise and the reaction was stirred at RT for 1 h. The solvent was removed and the crude was purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : MeOH = 95 : 5) to afford crude title compound (0.100 g) which was used without any additional purification. MS/ESI⁺ 648.4 [MH]⁺, Rt 1.56 (Method A).

Step 2: 3-(4-amino-1-{1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol 124

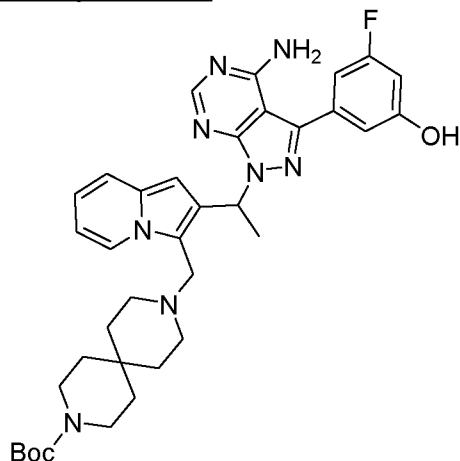
To a solution of crude 3-{3-[(tert-butyldimethylsilyl)oxy]-5-fluorophenyl}-1-{1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine 124a (0.100 g) in THF (1.7 ml), a solution of tetrabutylammonium fluoride 1M in THF (0.23 ml, 0.23 mmol) was added and the resulting mixture was stirred at RT for 30 minutes, then diluted with DCM and quenched with a saturated aqueous solution of NH₄Cl. The phases were separated, the organic layer was dried over sodium sulfate, filtered and concentrated. The crude was purified by flash chromatography on Biotage silica gel cartridge (DCM to DCM : MeOH = 98 : 3). The obtained product was further purified by preparative TLC (DCM : MeOH = 95 : 5) to obtain title compound (4.5 mg). MS/ESI⁺ 534.3 [MH]⁺, Rt 1.00 (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.23 (br. s., 1 H), 8.58 - 8.61 (m, 1 H), 8.12 (s, 1 H), 7.74 - 7.83 (m, 2 H), 7.64 - 7.69 (m, 1 H), 7.47 - 7.51 (m, 1 H), 7.29 - 7.34 (m, 1 H), 7.13 - 7.18 (m, 1 H), 6.73 - 6.81 (m, 2 H), 6.67 - 6.72 (m, 1 H), 6.64 (dt, 1 H), 6.31 (q, 1 H), 6.00 - 7.73 (m, 2 H), 1.91 (d, 3 H).

Example 143: 3-(4-amino-1-{1-[3-(9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)methyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



Step 1: tert-butyl 9-[(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate 143a



5 Prepared similarly to Example 85, starting from crude tert-butyl 9-[(2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate W56 (0.370 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.129 g, 0.828 mmol) and Pd(PPh₃)₄ (0.032 g, 0.028 mmol), in DME (18 ml), EtOH (3 mL) and saturated aqueous Na₂CO₃ (5.5 ml), heating at 80°C
10 overnight; after work-up the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 95 : 5) to afford title compound (0.017 g, 0.026 mmol). MS/ESI⁺ 655.5 [MH]⁺, Rt 1.46 min (Method J).

Step 2: 3-(4-amino-1-{1-[3-({9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)methyl}indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol

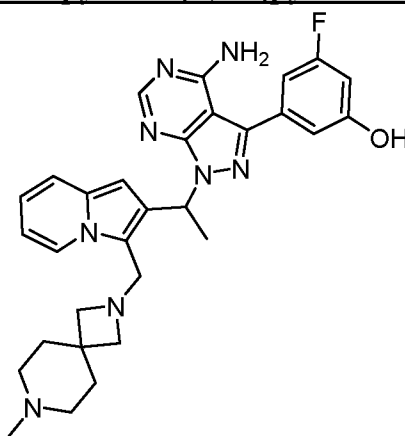
15 **143**

A mixture of tert-butyl 9-[(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)methyl]-3,9-diazaspiro[5.5]undecane-3-carboxylate 143a (17 mg, 0.026 mmol) and 1M in THF LiAlH₄ (0.156 mL, 0.156 mmol) in dry THF (8 mL) was stirred at 65 °C under nitrogen for 2 h. The reaction was cooled to
20 0 °C, sodium sulphate decahydrate was added and the mixture was stirred at RT for 0.5 h, then the solid was filtered off and the filtrate was evaporated. The resulting crude was purified by chromatography on silica NH cartridge (DCM to DCM : MeOH = 90 : 10) to

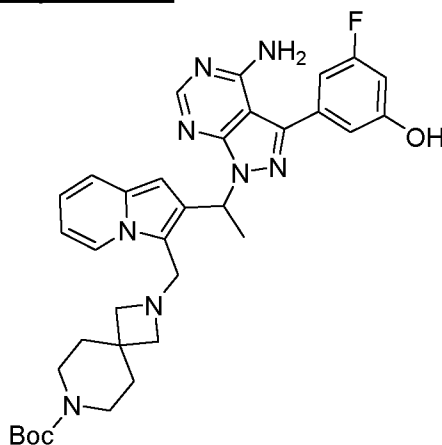
affords title compound as a white solid (5 mg). MS/ESI⁺ 569.6 [MH]⁺, Rt 1.09 min (Method J).

¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.20 (br. s., 1 H), 8.29 (s, 1 H), 8.08 (d, 1 H), 7.39 (d, 1 H), 6.75 - 6.87 (m, 2 H), 6.60 - 6.71 (m, 3 H), 6.55 (t, 1 H), 6.36 (q, 1 H),
5 6.85 (br. s, 2 H), 3.82 (d, 1 H), 3.67 (d, 1 H), 2.12 - 2.22 (m, 4 H), 2.09 (s, 3 H), 1.90 (d, 3 H), 1.85 - 2.03 (m, 4 H), 1.10 - 1.29 (m, 8 H).

Example 144: 3-(4-amino-1-{1-[3-(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)methyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



10 **Step1:** tert-butyl 2-[(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate 144a



Prepared similarly to Example 85, starting from crude tert-butyl 2-{[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate W57 (0.056 g), (3-fluoro-5-hydroxyphenyl)boronic
15

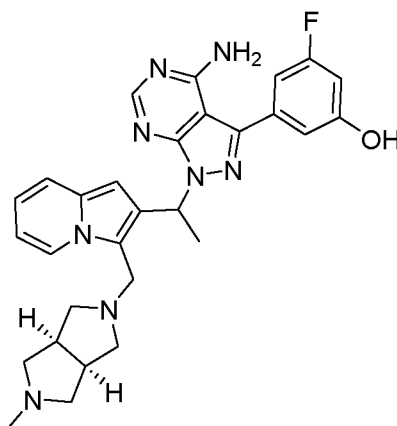
acid (0.027 g, 0.174 mmol) and Pd(PPh₃)₄ (0.010 g, 0.0087 mmol), in DME (4 ml), EtOH (0.5 mL) and saturated aqueous Na₂CO₃ (1.4 ml), heating at 80°C overnight; after work-up the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 85 : 15) to afford title compound as a pale brown solid (0.024 g, 0.038 mmol). MS/ESI⁺ 627.6 [MH]⁺, Rt 0.77 min (Method A).

Step 2: 3-(4-amino-1-{1-[3-({7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)methyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol
144

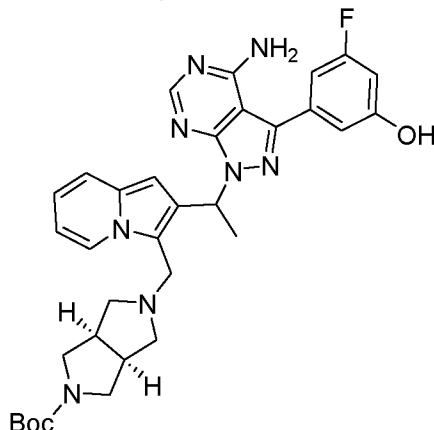
Prepared similarly to Example 143 Step2, starting from tert-butyl 2-[(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl}indolizin-3-yl)methyl]-2,7-diazaspiro[3.5]nonane-7-carboxylate 144a (24 mg, 0.038 mmol), heating at 65°C overnight, and purified by chromatography on silica-NH cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as a white solid (6 mg). MS/ESI⁺ 541.5 [MH]⁺, Rt 0.88 min (Method J).

¹H NMR (500 MHz, DMSO-d₆) δ ppm 10.15 (br. s., 1 H), 8.30 (s, 1 H), 8.11 (d, 1 H), 7.39 (d, 1 H), 6.85 - 6.91 (m, 1 H), 6.78 - 6.83 (m, 1 H), 6.60 - 6.71 (m, 3 H), 6.51 - 6.57 (m, 1 H), 6.41 (q, 1 H), 6.32 - 8.39 (m, 2 H), 3.69 - 4.07 (m, 2 H), 2.52 - 2.63 (m, 4 H), 1.80 - 2.22 (m, 10 H), 1.36 - 1.51 (m, 4 H).

Example 145: 3-{1-[1-(3-[(3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl)methyl}indolizin-2-yl)ethyl]-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol



Step1: tert-butyl (3aR,6aS)-5-[(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)methyl]-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate 145a



5 Prepared similarly to Example 85, starting from crude tert-butyl (3aR,6aS)-5-{[2-(1-{4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl)indolizin-3-yl)methyl}-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate W58 (0.152 g), (3-fluoro-5-hydroxyphenyl)boronic acid (0.041 g, 0.266 mmol) and Pd(PPh₃)₄ (0.014 g, 0.012 mmol), in DME (8.6 ml), EtOH (1.6 mL) and saturated aqueous Na₂CO₃ (3.3 ml), heating at 80°C
10 for 3 h; after work-up the crude was purified by flash chromatography on Biotage silica-NH SNAP cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as a yellow solid (0.032 g). MS/ESI⁺ 613.3 [MH]⁺, Rt 1.23 min (Method C).

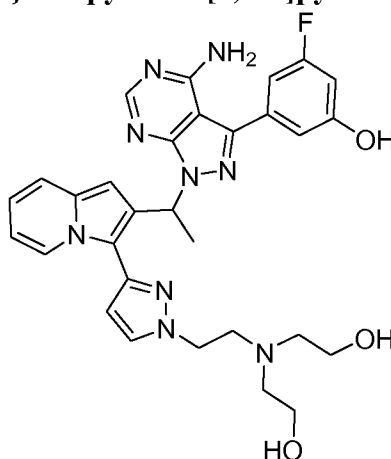
Step 2: 3-{1-[1-(3-{[(3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl]methyl}indolizin-2-yl)ethyl]-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol 145

15 Prepared similarly to Example 143 Step 2, starting from tert-butyl (3aR,6aS)-5-[(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)methyl]-octahydropyrrolo[3,4-c]pyrrole-2-carboxylate 145a (18 mg, 0.029 mmol), heating at 65°C overnight, and purified by chromatography on silica-NH
20 cartridge (DCM : MeOH = 99 : 1 to 90 : 10) to afford title compound as a vitreous solid (2.8 mg). MS/ESI⁺ 527.3 [MH]⁺, Rt 0.99 min (Method C).

¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.28 (s, 1 H), 8.17 (d, 1 H), 7.34 (d,

1 H), 6.86 - 6.89 (m, 1 H), 6.80 - 6.85 (m, 1 H), 6.59 - 6.71 (m, 3 H), 6.42 - 6.53 (m, 2 H), 3.84 - 4.09 (m, 2 H), 2.74 - 2.88 (m, 2 H), 2.52 - 2.69 (m, 2 H), 2.28 - 2.39 (m, 2 H), 2.27 (s, 3 H), 2.18 - 2.24 (m, 1 H), 1.99 (d, 3 H), 1.96 - 2.16 (m, 3 H).

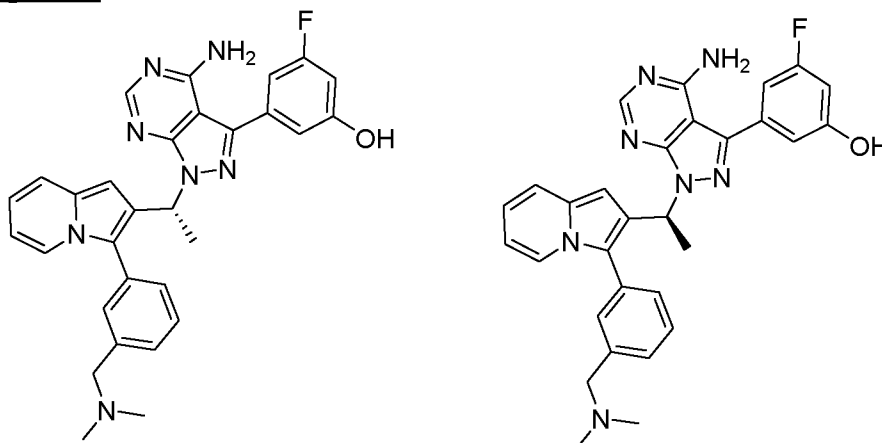
Example 149: 3-(4-amino-1-{1-[3-(1-{2-[bis(2-hydroxyethyl)amino]ethyl}-1H-pyrazol-3-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



Prepared similarly to Example 117, starting from 3-iodo-1-[1-(3-{1-[2-(2,2,3,3,11,11,12,12-octamethyl-4,10-dioxo-7-aza-3,11-disilatridecan-7-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine W62 (0.180 g) and (3-fluoro-5-hydroxyphenyl)boronic acid (39.7 mg, 0.25 mmol). After work-up the crude was dissolved in MeOH and charged on a SCX cartridge (10 g) washing with MeOH, and then eluted with 1M NH₃ in MeOH. The basic fractions were evaporated and the residue was purified by flash chromatography on silica gel cartridge (DCM to DCM : MeOH = 90 : 10) to afford title compound as a yellow solid (8.7 mg). MS/ESI⁺ 586.5 [MH]⁺, Rt 0.63 min (Method A).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.69 - 8.73 (m, 1H), 8.22 (s, 1H), 7.97 (d, 1 H), 7.41 - 7.45 (m, 1H), 6.94 - 6.97 (m, 1 H), 6.87 - 6.92 (m, 1 H), 6.78 (d, 1 H), 6.69 - 6.75 (m, 1 H), 6.66 (dt, 1 H), 6.56 - 6.62 (m, 2 H), 6.50 (q, 1 H), 6.46 - 7.30 (m, 2 H), 4.19 - 4.43 (m, 4 H), 3.39 (t, 4 H), 2.99 (t, 2 H), 2.60 (t, 4 H), 1.88 (d, 3 H).

Example 93a (enantiomer 1) and example 93b (enantiomer 2) : 3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-

3-yl]-5-fluorophenol

Racemate 3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol described in Example 93
 5 (0.330 g) was dissolved in EtOH/MeOH 1/1 (140 ml) and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak AD-H (25 x 3.0 cm), 5 μ ; Mobile phase: n-Hexane/(Ethanol + 0.1% isopropylamine) 85/15 % v/v; UV detection: 220 nm; Flow Rate: 34 mL/min; Injection: 10.8 mg.

Compound 93a was obtained as the first eluted enantiomer as a pale brown solid
 10 (0.105 g). MS/ESI⁺ 522.3 [MH]⁺, Rt 0.70 min (Method A). Chiral HPLC Method K: Rt = 7.3 min, 100% ee.

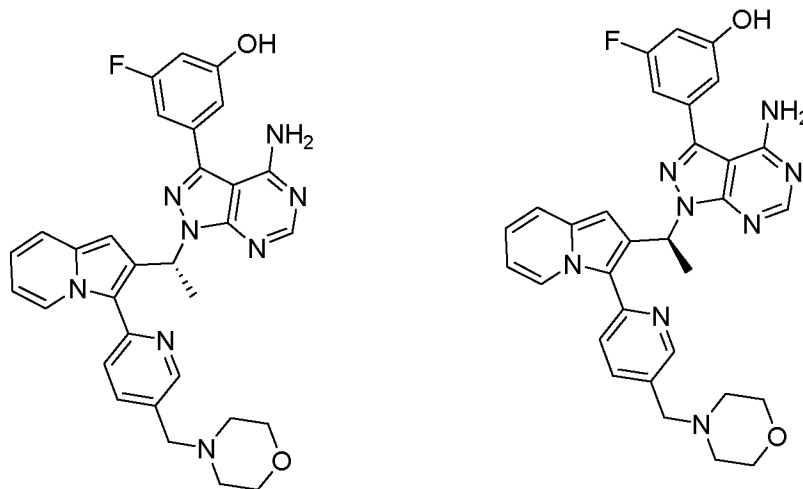
¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.16 (br. s., 1 H), 8.14 (s, 1 H), 7.78 - 7.83 (m, 1 H), 7.40 - 7.48 (m, 2 H), 7.28 - 7.34 (m, 2 H), 7.22 (s, 1 H), 6.88 - 6.92 (m, 1 H), 6.80 - 6.87 (m, 1 H), 6.62 - 6.74 (m, 3 H), 6.54 - 8.10 (m, 2 H), 6.47 - 6.53 (m, 1 H), 6.20 (q, 1
 15 H), 3.32 - 3.40 (m, 2 H), 2.12 (s, 6 H), 1.83 (d, 3 H).

Compound 93b was obtained as the second eluted enantiomer as a pale brown solid (0.103 g). MS/ESI⁺ 522.3 [MH]⁺, Rt 0.69 min (Method A). Chiral HPLC Method K: Rt = 10.5 min, 100% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.15 (br. s., 1 H), 8.14 (s, 1 H), 7.78 - 7.83 (m, 1 H), 7.40 - 7.48 (m, 2 H), 7.28 - 7.34 (m, 2 H), 7.22 (s, 1 H), 6.88 - 6.92 (m, 1 H), 6.80 - 6.87 (m, 1 H), 6.62 - 6.74 (m, 3 H), 6.54 - 8.10 (m, 2 H), 6.47 - 6.53 (m, 1 H), 6.20 (q, 1
 20 H), 3.32 - 3.40 (m, 2 H), 2.12 (s, 6 H), 1.83 (d, 3 H).

Example 108a (enantiomer 1) and

Example 108b (enantiomer 2) : 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol



5

Racemate 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol described in Example 108 (0.063 g) was dissolved in EtOH (8 ml) and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak AD-H (25 x 2 cm), 5
10 um; Mobile phase: n-Hexane/(Ethanol + 0.1% isopropylamine) 70/30 % v/v; UV detection: 220 nm; Flow Rate: 14 mL/min; Injection: 9 mg.

Compound 108a was obtained as the first eluted enantiomer (23 mg) MS/ESI⁺ 565.4 [MH]⁺, Rt 0.65 min (Method A). Chiral HPLC Method L: Rt = 12.8 min, 100% ee.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.18 (br. s., 1 H), 8.57 - 8.62 (m, 2 H), 8.17
15 (s, 1 H), 7.77 (dd, 1 H), 7.68 (d, 1 H), 7.48 - 7.53 (m, 1 H), 6.86 - 6.90 (m, 1 H), 6.77 - 6.86 (m, 2 H), 6.71 (s, 1 H), 6.66 (dt, 1 H), 6.57 - 6.63 (m, 1 H), 6.52 (q, 1 H), 6.10 - 7.44 (m, 2 H), 3.59 - 3.65 (m, 4 H), 3.51 - 3.59 (m, 2 H), 2.36 - 2.44 (m, 4 H), 1.92 (d, 3 H).

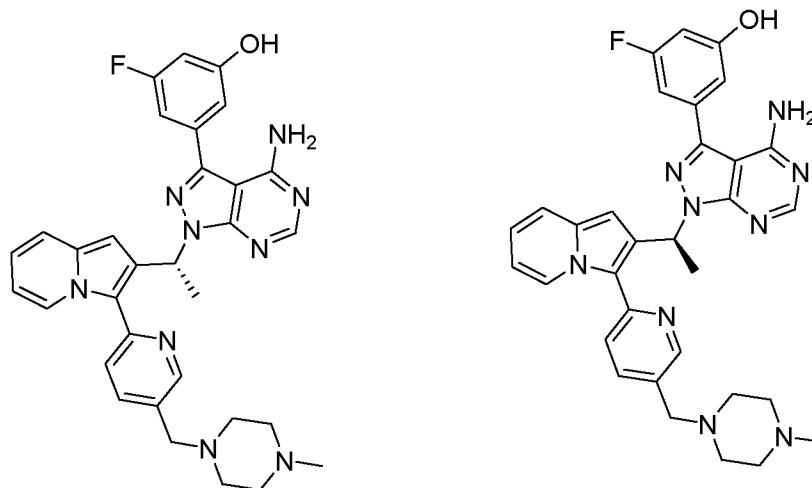
Compound 108b was obtained as the second eluted enantiomer (19 mg). MS/ESI⁺ 565.4 [MH]⁺, Rt 0.64 min (Method A). Chiral HPLC Method L: Rt = 16.0 min, 97.6 % ee.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.20 (br. s., 1 H), 8.57 - 8.62 (m, 2 H), 8.17
20 (s, 1 H), 7.77 (dd, 1 H), 7.68 (d, 1 H), 7.48 - 7.53 (m, 1 H), 6.86 - 6.90 (m, 1 H), 6.77 - 6.86

(m, 2 H), 6.71 (s, 1 H), 6.66 (dt, 1 H), 6.57 - 6.63 (m, 1 H), 6.52 (q, 1 H), 6.10 - 7.44 (m, 2 H), 3.59 - 3.66 (m, 4 H), 3.51 - 3.59 (m, 2 H), 2.36 - 2.45 (m, 4 H), 1.92 (d, 3 H).

Example 114a (enantiomer 1) and

Example 114b (enantiomer 2) : 3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol



Racemate 3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol described in Example 114 (0.266 g) was dissolved in 10 ml Ethanol+4 ml n-Hexane and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak AD-H (25 x 2.0 cm), 5 μ m; Mobile phase: n-Hexane/(Ethanol+ 0.1% isopropylamine) 80/20 % v/v; UV detection: 220 nm; Flow Rate: 18 mL/min; Injection: 28.5 mg.

Compound 114a was obtained as the first eluted enantiomer as a yellow solid (0.091 g). MS/ESI⁺ 578.4 [MH]⁺, Rt 0.64 min (Method A). Chiral HPLC Method M: Rt = 8.8 min, 100% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.18 (br. s., 1 H), 8.54 - 8.60 (m, 2 H), 8.15 (s, 1 H), 7.72 (dd, 1 H), 7.64 (d, 1 H), 7.47 - 7.51 (m, 1 H), 6.86 - 6.89 (m, 1 H), 6.76 - 6.84 (m, 2 H), 6.69 (s, 1 H), 6.64 (dt, 1 H), 6.55 - 6.60 (m, 1 H), 6.51 (q, 1 H), 6.10 - 7.30 (m, 2 H), 3.48 - 3.58 (m, 2 H), 2.22 - 2.49 (m, 8 H), 2.16 (s, 3 H), 1.90 (d, 3 H).

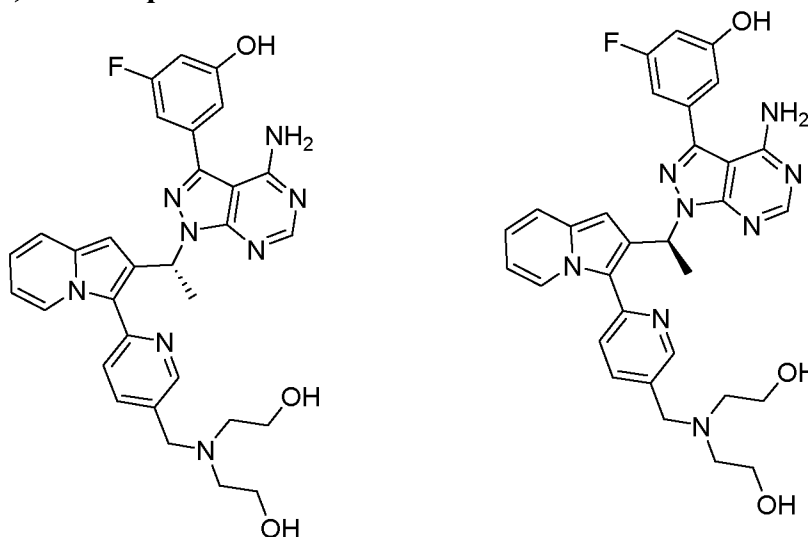
Compound 114b was obtained as the second eluted enantiomer as a yellow solid (0.091 g). MS/ESI⁺ 578.4 [MH]⁺, Rt 0.64 min (Method A). Chiral HPLC Method M: Rt = 15.3 min, 100% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (br. s., 1 H), 8.54 - 8.60 (m, 2 H), 8.15 (s, 1 H), 7.72 (dd, 1 H), 7.64 (d, 1 H), 7.47 - 7.51 (m, 1 H), 6.86 - 6.89 (m, 1 H), 6.76 - 6.84 (m, 2 H), 6.69 (s, 1 H), 6.64 (dt, 1 H), 6.55 - 6.60 (m, 1 H), 6.51 (q, 1 H), 6.10 - 7.30 (m, 2 H), 3.48 - 3.58 (m, 2 H), 2.22 - 2.49 (m, 8 H), 2.16 (s, 3 H), 1.90 (d, 3 H).

Example 117a (enantiomer 1) and

example 117b (enantiomer 2): 3-(4-amino-1-{1-[3-(5-{[bis(2-

hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol



Racemate 3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol described in Example 117 (0.030 g) was dissolved in 3 ml of (Ethanol/n-Hexane 1/1) and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak AD-H (25 x 2.0 cm), 5 μm; Mobile phase: n-Hexane/(Ethanol/Methanol 1/1+ 0.1% isopropylamine) 75/25 % v/v; UV detection: 220 nm; Flow Rate: 17 mL/min; Injection: 8 mg.

Compound 117a was obtained as the first eluted enantiomer (0.012 g). MS/ESI⁺ 583.4 [MH]⁺, Rt 0.60 min (Method A). Chiral HPLC Method N: Rt = 5.3 min, 100% ee.

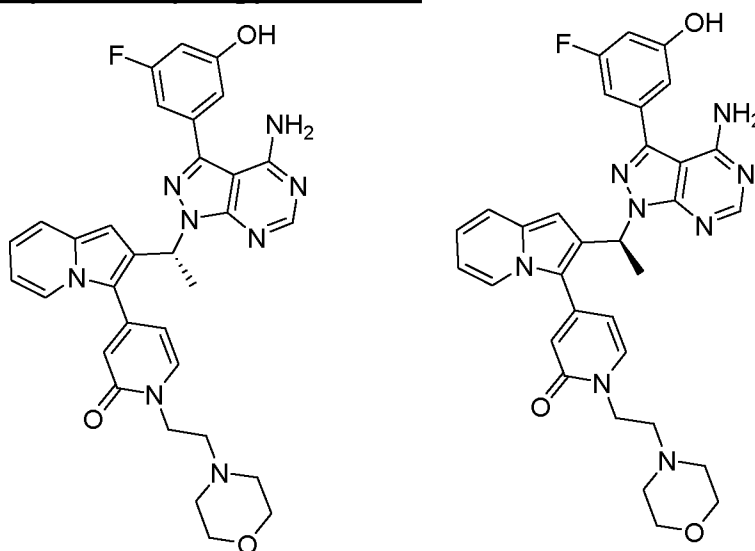
¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.75 - 10.50 (m, 1 H), 8.65 - 8.68 (m, 1 H), 8.58 - 8.62 (m, 1 H), 8.17 (s, 1 H), 7.87 (dd, 1 H), 7.70 (d, 1 H), 7.46 - 7.50 (m, 1 H), 6.88 - 6.91 (m, 1 H), 6.76 - 6.86 (m, 2 H), 6.62 - 6.68 (m, 2 H), 6.55 - 6.61 (m, 1 H), 6.49 (q, 1 H), 6.20 - 7.30 (m, 2 H), 4.45 (br. s., 2 H), 3.76 (s, 2 H), 3.51 (t, 4 H), 2.60 (t, 4 H), 1.90 (d, 3 H).

Compound 117b was obtained as the second eluted enantiomer (0.012 g). MS/ESI⁺ 583.4 [MH]⁺, Rt 0.60 min (Method A). Chiral HPLC Method N: Rt = 7.7 min, 100% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (s, 1 H), 8.65 - 8.68 (m, 1 H), 8.58 - 8.62 (m, 1 H), 8.17 (s, 1 H), 7.87 (dd, 1 H), 7.70 (d, 1 H), 7.46 - 7.50 (m, 1 H), 6.90 - 6.93 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.76 - 6.82 (m, 1 H), 6.64 - 6.69 (m, 2 H), 6.55 - 6.61 (m, 1 H), 6.49 (q, 1 H), 6.20 - 7.30 (m, 2 H), 4.43 (t, 2 H), 3.76 (s, 2 H), 3.47 - 3.55 (m, 4 H), 2.60 (t, 4 H), 1.90 (d, 3 H).

Example 121a (enantiomer 1) and

Example 121b (enantiomer 2): 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one



Racemate 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one described in Example 121 (0.225 g) was dissolved in 50 ml of (Ethanol/n-Hexane 1/1)

and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak IC (25 x 2.0 cm), 5 μ m; Mobile phase: n-Hexane/(Ethanol + 0.1% isopropylamine) 75/25 % v/v; UV detection: 220 nm; Flow Rate: 19 mL/min; Injection: 22 mg.

5 Compound 121a was obtained as the first eluted enantiomer (0.074 g). MS/ESI⁺ 595.4 [MH]⁺, Rt 0.67 min (Method J). Chiral HPLC Method O: Rt = 14.9 min, 98% ee.

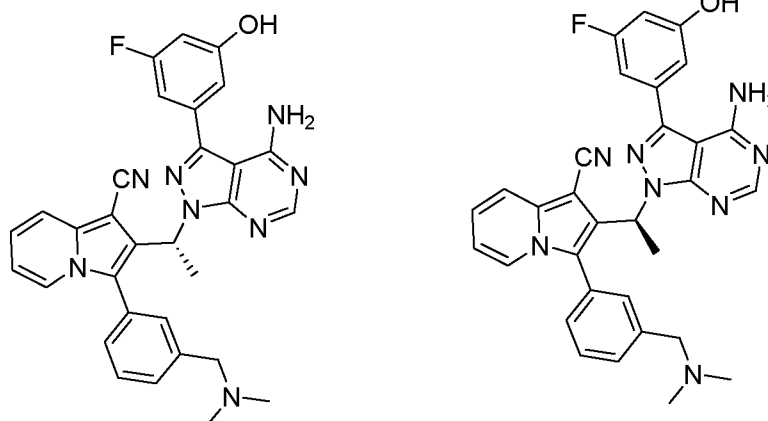
¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (br.s., 1 H), 8.16 (s, 1 H), 8.02 - 8.06 (m, 1 H), 7.73 (d, 1 H), 7.45 - 7.50 (m, 1 H), 6.89 - 6.92 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.75 - 6.81 (m, 1 H), 6.63 - 6.71 (m, 2 H), 6.57 - 6.63 (m, 1 H), 6.42 - 6.46 (m, 1 H), 6.29 - 6.37 (m, 2 H), 6.00 - 7.40 (m, 2 H), 3.98 - 4.05 (m, 2 H), 3.54 - 3.62 (m, 4 H), 2.55 - 2.61 (m, 2 H), 2.43 - 2.50 (m, 4 H), 1.89 (d, 3 H).

 Compound 121b was obtained as the second eluted enantiomer (0.076 g). MS/ESI⁺ 595.4 [MH]⁺, Rt 0.64 min (Method J). Chiral HPLC Method O: Rt = 17.9 min, 98% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (br.s., 1 H), 8.16 (s, 1 H), 8.02 - 8.06 (m, 1 H), 7.73 (d, 1 H), 7.45 - 7.50 (m, 1 H), 6.89 - 6.92 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.75 - 6.81 (m, 1 H), 6.63 - 6.71 (m, 2 H), 6.57 - 6.63 (m, 1 H), 6.42 - 6.46 (m, 1 H), 6.29 - 6.37 (m, 2 H), 6.00 - 7.40 (m, 2 H), 3.98 - 4.06 (m, 2 H), 3.54 - 3.62 (m, 4 H), 2.55 - 2.62 (m, 2 H), 2.43 - 2.50 (m, 4 H), 1.89 (d, 3 H).

Example 127a (enantiomer 1) and

Example 127b (enantiomer 2): 2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile



5

Racemate

2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-

d]pyrimidin-1-yl]ethyl}-3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile

described in Example 127 (0.146 g) was dissolved in 7 ml Ethanol/n-Hexane 1/1 and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions:

10 Column: Chiralpak AD-H (25 x 2.0 cm), 5 μ m; Mobile phase: n-Hexane/(Ethanol+ 0.1% isopropylamine) 75/25 % v/v; UV detection: 220 nm; Flow Rate: 17 mL/min; Injection: 10.4 mg.

Compound 127a was obtained as the first eluted enantiomer (53.7 mg). MS/ESI⁺ 547.4 [MH]⁺, Rt 0.64 min (Method A). Chiral HPLC Method P: Rt = 5.7 min, 100% ee.

15 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (br. s., 1 H), 8.12 (s, 1 H), 7.89 (d, 1 H), 7.67 (d, 1 H), 7.43 - 7.49 (m, 1 H), 7.37 - 7.42 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.17 - 7.26 (m, 2 H), 6.84 - 6.92 (m, 3 H), 6.64 (dt, 1 H), 6.17 (q, 1 H), 6.10 - 7.80 (m, 2 H), 3.30 - 3.40 (m, 2 H), 2.10 (s, 6 H), 1.93 (d, 3 H).

Compound 127b was obtained as the second eluted enantiomer (52.8 mg). MS/ESI⁺ 547.3 [MH]⁺, Rt 0.64 min (Method A). Chiral HPLC Method P: Rt = 7.5 min, 99.6% ee.

20

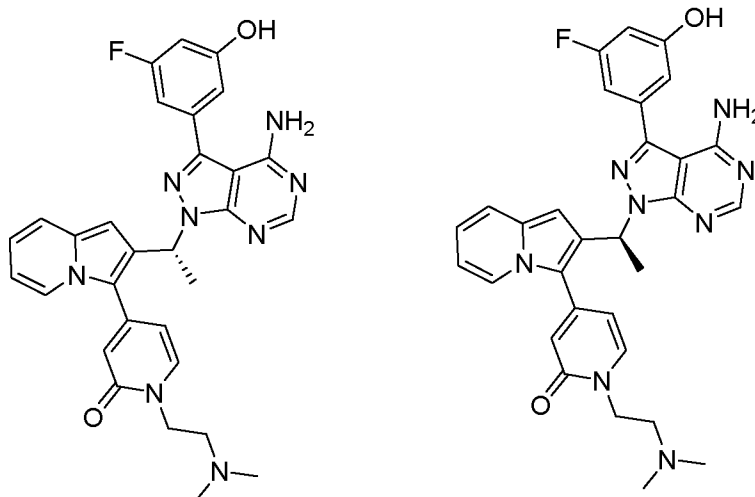
¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (br. s., 1 H), 8.12 (s, 1 H), 7.89 (d, 1 H), 7.67 (d, 1 H), 7.43 - 7.49 (m, 1 H), 7.37 - 7.42 (m, 1 H), 7.27 - 7.33 (m, 1 H), 7.17 -

7.26 (m, 2 H), 6.84 - 6.92 (m, 3 H), 6.64 (dt, 1 H), 6.17 (q, 1 H), 6.10 - 7.80 (m, 2 H), 3.30 - 3.40 (m, 2 H), 2.10 (s, 6 H), 1.93 (d, 3 H).

Example 133a (enantiomer 1) and

Example 133b (enantiomer 2): 4-(2-{1-[4-amino-3-(3-fluoro-5-

hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl}ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one



Racemate 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-

d]pyrimidin-1-yl}ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-

one described in Example 133 (55.0 mg) was dissolved in 11 ml of ethanol and submitted to chiral resolution by Chiral preparative liquid chromatography. Conditions: Column: Chiralpak IC (25 x 2.0 cm), 5 μ ; Mobile phase: n-Hexane/(Ethanol + 0.1 % isopropylamine) 70/30 % v/v; UV detection: 220 nm; Flow Rate: 15 mL/min; Injection: 5 mg.

Compound 133a was obtained as the first eluted enantiomer (17.3 mg). MS/ESI⁺

553.5 [MH]⁺, Rt 0.63 min (Method A). Chiral HPLC Method Q: Rt = 7.7 min, 100% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.17 (br. s., 1 H), 8.16 (s, 1 H), 8.04 (d, 1 H), 7.72 (d, 1 H), 7.45 - 7.49 (m, 1 H), 6.90 - 6.92 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.75 - 6.81 (m, 1 H), 6.63 - 6.70 (m, 2 H), 6.57 - 6.62 (m, 1 H), 6.45 (d, 1 H), 6.28 - 6.36 (m, 2 H), 6.00 - 7.40 (m, 2 H), 3.99 (t, 2 H), 2.51 - 2.55 (m, 2 H), 2.22 (s, 6 H), 1.89 (d, 3 H).

Compound 133b was obtained as the second eluted enantiomer (19.7 mg). MS/ESI⁺ 553.5 [MH]⁺, Rt 0.63 min (Method A). Chiral HPLC Method Q: Rt = 8.9 min, 96.8% ee.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.19 (br. s., 1 H), 8.16 (s, 1 H), 8.04 (d, 1 H), 7.72 (d, 1 H), 7.45 - 7.49 (m, 1 H), 6.90 - 6.92 (m, 1 H), 6.84 - 6.89 (m, 1 H), 6.75 - 6.81 (m, 1 H), 6.63 - 6.70 (m, 2 H), 6.57 - 6.62 (m, 1 H), 6.45 (d, 1 H), 6.28 - 6.36 (m, 2 H), 6.00 - 7.40 (m, 2 H), 3.99 (t, 2 H), 2.51 - 2.55 (m, 2 H), 2.22 (s, 6 H), 1.89 (d, 3 H).

5 **PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION.**

In vitro determination of the PI3K enzyme inhibitory activity in the cell free assay

Human recombinant proteins PI3K α , PI3K β , PI3K γ and PI3K δ were purchased
10 from Millipore Ltd (Billerica, MA). Compounds were dissolved at 0.5mM in DMSO and were tested at different concentrations for their activity against PI3Ks using the ADP-Glo™ Kinase Assay (Promega, Madison WI) according to the manufacturer's instructions.

Briefly, the kinase reactions were performed in 384-well white plates (Greiner Bio-One GmbH, Frickenhausen). Each well was loaded with 0.1μl of test compounds and 2.5μl
15 of 2x reaction buffer (40mM Tris pH7.5, 0.5mM EGTA, 0.5mM Na₃VO₄, 5mM β-glycerophosphate, 0.1mg/ml BSA, 1mM DTT), containing 50μM PI and PS substrates (L-α-phosphatidylinositol sodium salt and L-α-phosphatidyl-L-serine, Sigma-Aldrich, St. Louis MO) and the PI3K recombinant proteins (PI3K γ 0.25ng/μl, PI3K δ 1ng/μl, PI3K α 0.125ng/μl, PI3K β 1ng/μl).

20 The reactions were started by adding 2.5μl of 2x ATP solution to each well (final concentrations: PI3K γ ATP 30μM; PI3K δ ATP 80μM; PI3K α ATP 50μM; PI3K β ATP 100μM) and incubated for 60 min at room temperature. Subsequently, each kinase reaction was incubated for 40 min with 5μl ADP-Glo™ Reagent, allowing depletion of unconsumed ATP. Then, the Kinase Detection Reagent (10μl) was added in each well to convert ADP
25 to ATP and to allow the newly synthesized ATP to be measured using a luciferase/luciferin reaction. Following 60 min incubation, the luminescence signal was measured using a Wallac EnVision® multilabel reader (PerkinElmer, Waltham MA).

Curve fitting and IC₅₀ calculation were carried out using a four-parameter logistic

model in XLfit (IDBS, Guilford, UK) for Microsoft Excel (Microsoft, Redmont, WA).

Representative compounds according to the invention showed $IC_{50} < 1 \mu M$, some even lower than 10nM, particularly in the PI3Kdelta inhibitory assay herein above described.

5 The results for individual compounds are provided below in Table 1

Table 1: Results of the in vitro determination of the PI3K enzyme inhibitory activity in the cell free assay

Compound of Example N.	PI3K alpha inhibition	PI3K beta inhibition	PI3K delta inhibition	PI3K gamma inhibition
1	+	+	+	+
2	+	+	+	+
3	+	+	+	+
4	+	+	++	+
5	+	+	+	+
6	+	+	+	+
7	+	+	+	+
8	+	+	+	+
9	+	+	+	+
10	+	+	+	+
11	+	+	+	+
12	+	+	+	+
13	+	+	+	+
14	+	+	+	+
15	+	+	+	+
16	+	+	+	+
17	+	+	+	+

(continued)

18	+	+	++	+
19	+	+	+	+
20	+	+	++	+
21	+	++	++	+
22	+	+	++	+
23	+	+	++	+
24	+	+	++	+
25	+	+	++	+
26	+	+	++	+
27	+	+	+	+
28	+	+	++	+
29	+	+	++	+
30	+	+	++	+
31	+	+	++	+
32	+	+	++	+
33	+	++	++	+
34	+	++	++	++
35	+	++	++	+
36	+	++	++	++
37	+	+	++	+
38	+	+	++	+
39	+	++	+++	+
40	+	+	+++	+
41	+	+	++	+
42	+	++	++	+
43	+	++	++	+

(continued)

370

44	+	+	++	++
45	+	++	++	+
46	+	++	++	++
47	+	++	++	+
48	+	+	++	+
49	+	+	++	+
50	+	+	++	+
51	+	+	++	+
52	+	+	++	+
53	+	+	+	+
54	+	+	+	+
55	+	+	+	+
56	+	+	+	+
57	+	+	+	+
58	+	++	+++	+
59	+	+	++	+
60	+	+	++	+
61	+	++	++	++
62	+	+	++	+
63	+	+	+	+
64	+	+	++	+
65	+	++	+++	++
66	+	++	++	+
67	+	+	++	+
68	+	+	++	+
69	+	++	+++	++

(continued)

70	+	+	++	++
71	+	+	++	++
72	+	++	+++	++
73	+	+	++	+
74	+	+	++	+
75	+	+	+	+
76	+	++	++	+
77	+	++	+++	++
78	+	+	+	+
79	++	++	+++	++
80	++	++	+++	++
81	+	+	++	+
82	+	++	+++	++
83	++	++	+++	++
84	+	+	++	+
85	+	++	++	+
86	+	+	++	++
87	+	++	++	+
88	+	+	++	+
89	++	++	++	++
90	++	++	+++	++
91	+	+	++	+
92	+	++	++	+
93	++	++	++	++
93a	++	++	+++	+
93b	+	++	++	+

(continued)

94	++	++	+++	++
95	++	++	+++	++
96	+	++	+++	+
97	++	++	+++	++
98	++	++	++	++
99	++	++	+++	++
100	+	++	+++	++
101	+	++	++	+
102	+	+	++	+
103	+	++	++	++
104	++	++	+++	++
105	+	+	++	+
106	+	++	+++	++
107	+	++	+++	++
108	+	++	+++	+
108a	+	++	+++	+
108b	+	++	+++	+
109	+	++	++	+
110	+	++	+++	+
111	+	++	+++	++
112	++	++	+++	++
113	+	++	+++	+
114	+	++	+++	+
114a	++	++	+++	++
114b	++	++	+++	++
115	++	++	++	++

(continued)

116	++	++	+++	++
117	+	++	+++	+
117a	++	++	+++	+
117b	++	++	+++	+
118	+	++	++	+
119	+	++	+++	+
120	+	+	+++	++
121	+	++	+++	++
121a	+	+	++	+
121b	++	++	+++	++
122	+	++	+++	+
123	+	++	+++	+
124	+	++	+++	+
125	++	++	+++	++
126	++	++	+++	++
127	+	++	+++	+
127a	++	++	+++	++
127b	+	+	+++	+
128	+	++	++	+
129	++	++	++	++
130	+	++	+++	++
131	++	++	++	++
132	++	++	+++	++
133	+	++	+++	++
133a	+	+	++	+
133b	++	++	+++	++

(continued)

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134	+	++	+++	+
135	+	++	++	+
136	++	++	++	+
137	+	++	+++	+
138	++	++	+++	++
139	+	++	++	+
140	+	++	++	+
141	++	++	+++	++
142	+	+	++	++
143	++	++	+++	++
144	++	++	++	++
145	++	++	++	++
146				
147	++	++	+++	+
148	++	++	+++	++
149	+	++	+++	++
150	+	++	+++	++

wherein the compounds are classified in term of potency with respect to their inhibitory activity on PI3K -alpha, -beta, -gamma and -delta according to the following:

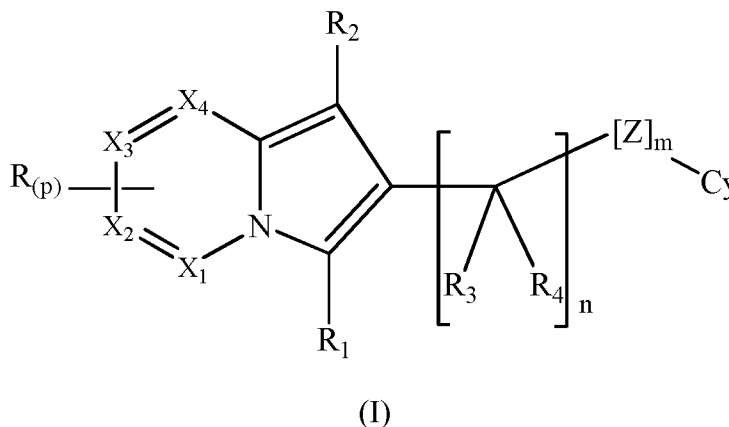
+++ : IC₅₀ < 10 nM

++ : IC₅₀ in the range 10-1000 nM

++ : IC₅₀ > 1000 nM

CLAIMS

1. A compound of formula (I)



5 wherein

X₁, **X₂**, **X₃** and **X₄** are all CH groups or at least one of **X₁**, **X₂**, **X₃** and **X₄** is a nitrogen atom and the others are CH groups.

each **R**, when present, is selected from the group consisting of: -OR₅, -SR₅, -S(O)_q-R₇, halogen, -NR₁₀R₁₁, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₂-C₆) alkenyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl; each of which being in his turn optionally and independently substituted with one or more groups selected from halogen, -OH, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₂-C₆) alkenyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

R₁ is selected from the group consisting of -H, -OR₆, -SR₆, -S(O)_q-R₈, halogen, -NR₁₂R₁₃, -CN, -C(O)NR₁₂R₁₃, -C(O)OR₁₆, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₂-C₆) alkenyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl; each of which being in his turn optionally and independently substituted with one or more groups selected from halogen, -NR₂₂R₂₃, -(CH₂)_nNR₂₂R₂₃, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, (C₁-C₆) aminoalkoxy (C₃-C₆)

heterocycloalkyloxy or (C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxy, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

R₂ is selected from the group consisting of -H, -OR₉, -SR₉, -S(O)_q-R₁₇, halogen, -NR₁₄R₁₅, -CN, -C(O)NR₁₄R₁₅, -C(O)OR₁₈, -(C₁-C₆) alkyl, -(C₁-C₆) haloalkyl, -(C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, (C₃-C₇) cycloalkyl, (C₅-C₇) cycloalkenyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl; each of which being in his turn optionally and independently substituted with one or more groups selected from halogen; -NR₂₄R₂₅, -(CH₂)_nNR₂₄R₂₅, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl ;

R₃ and **R₄**, the same or different, are selected from the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl;

Cy is selected from the group consisting of aryl, heteroaryl, and (C₃-C₆) heterocycloalkyl; each of which being optionally and independently substituted by one or more groups selected from halogen, -OH, -NR₁₉R₂₀, -CH₂NR₁₉R₂₀; -CN, -CH(O), -CH=NOH, -C(O)NR₁₉R₂₀, -C(O)OR₂₁, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl, and by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl, each of which being in his turn optionally and independently substituted with one or more groups selected from -OH, halogen, -CN, -S(O)₂NR^IR^{III}, -NR^{III}S(O)₂R^{II}, -NR^IR^{III}, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) alkoxy, aryl, heteroaryl, (C₃-C₆) heterocycloalkyl;

wherein R^I R^{II} and R^{III} the same or different, are independently selected from the group consisting of -H, (C₁-C₆) alkyl and alkanoyl;

R₅, **R₆**, **R₉**, **R₁₆**, **R₁₈**, and **R₂₁** the same or different, are independently selected from the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆) aminoalkyl, alkanoyl, and aryl alkanoyl;

R₇, **R₈** and **R₁₇**, the same or different, are independently selected from the group consisting of NR₁₂R₁₃, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆)

aminoalkyl, or by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl each of which being in his turn optionally and independently substituted with one or more groups selected from halogen, -NR₂₂R₂₃, -CH₂NR₂₂R₂₃, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl;

5 R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₉, R₂₀, R₂₂, R₂₃, R₂₄ and R₂₅, the same or different, are independently selected from the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) hydroxyalkyl and alkanoyl or, taken together with the nitrogen atom they are linked to, anyone of R₁₀ and R₁₁, R₁₂ and R₁₃, R₁₄ and R₁₅, R₁₉ and R₂₀, R₂₂ and R₂₃, R₂₄ and R₂₅ may form, a 5 to 6 membered heterocycle optionally containing one additional heteroatom or
10 heteroatomic group selected from O, S, N, NH;

 Z, when present, is an atom or a group selected from -O-, -NH-, -C(O)-, -NHC(O)-, -C(O)NH-, -S-, -S(O)-, and -S(O)₂-;

 m is zero or 1;

 n is 1 or 2,

15 p is zero or an integer ranging from 1 to 3

 q is an integer ranging from 1 to 2

 or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 present as a mixture of diastereoisomers.

3. A compound according to Claims 1 or 2 wherein:

20 R₃ is selected from H and (C₁-C₆) alkyl;

 R₄ is H;

 R, R₁, R₂, m, n, p, Z, CY and X₁₋₄ are as defined in claim 1 or pharmaceutically acceptable salt thereof.

4. A compound according to any one of Claims 1 to 3 wherein:

25 R₃ is selected from H and (C₁-C₆) alkyl;

 R₄ is H;

 CY is an heteroaryl selected from the group consisting of I-1 to I-9 wherein (I-1) is 3H-purin-3-yl, (I-2) is 9H-purin-9-yl, (I-3) is 9H-purin-6-yl, (I-4) is

1H-pyrazolo[3,4-d]pyrimidin-1-yl, (I-5) is 6-oxo-5H,6H,7H-pyrrolo[2,3-d]pyrimidin-4-yl, (I-6) is pyrimidin-4-yl, (I-7) is pyrimidin-2-yl, (I-8) is pyrazin-2-yl, (I-9) is 1,3,5-triazin-2-yl; each of which being optionally and independently substituted by one or more groups selected from halogen, -OH, -NR₁₉R₂₀, -CH₂NR₁₉R₂₀, -CN, -CH(O), -CH=NOH, -C(O)NR₁₉R₂₀, -C(O)OR₂₁, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, (C₂-C₆) hydroxyalkynyl or by a group selected from aryl, heteroaryl and (C₃-C₆) heterocycloalkyl each of which being in his turn optionally and independently substituted with one or more groups selected from -OH, halogen, -CN, -S(O)₂NR^IR^{III}, -NR^{III}S(O)₂R^{II}, -NR^IR^{III}, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl, (C₁-C₆) hydroxyalkyl, (C₁-C₆)alkoxy, aryl, heteroaryl, (C₃-C₆) heterocycloalkyl; all the other variables being as defined in claim 1, or pharmaceutically acceptable salt thereof.

5. A compound according to any of claims 1 to 4 wherein:

R₃ is methyl;

15 R₄ is H;

Cy is 1H-pyrazolo[3,4-d]pyrimidin-1-yl (I-4), which is optionally and independently substituted by one or more groups selected from -NR₁₉R₂₀ and aryl which is optionally substituted by one or more groups selected from OH and halogen; all the other variables being as defined in claim 1,

20 or pharmaceutically acceptable salt thereof.

6. A compound according to claim 5 wherein:

R₁ is selected from the group consisting of 4-morpholinomethyl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl}methyl, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl, and 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}methyl;

25

R₃ is methyl;

R₄ is H;

CY is 1H-pyrazolo[3,4-d]pyrimidin-1-yl (I-4), which is substituted in the position

4 by $-NH_2$ and in the position 3 by 3-fluoro-5-hydroxyphenyl; all the other variables being as defined in claim 1.

or pharmaceutically acceptable salt thereof.

7. A compound according to claim 1, wherein:

5 X_1 , X_2 , X_3 and X_4 are all CH groups;

R is selected from the group consisting of C_1 - C_6 alkyl, such as methyl, C_1 - C_6 haloalkyl such as trifluoromethyl, and halogen, more preferably fluoro, chloro and bromo;

R_1 is selected in the group consisting of hydrogen, C_2 - C_6 alkynyl such as 3-pent-1-yn-1-yl, C_2 - C_6 aminoalkynyl such as 3-dimethylaminoprop-1-yn-1-yl, and C_2 - C_6 hydroxyalkynyl such as 3-hydroxyprop-1-yn-1-yl, aryl, such as phenyl, heteroaryl, such as pyridyl, pyrazinyl, thienyl and thiazolyl, C_3 - C_6 heterocycloalkyl such as 3,6-dihydro-2H-pyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, pyrrolidin-1-yl-2-one, and 4-methylpiperazin-1-yl-2-one, a group $-(CH_2)_nN_{22}N_{23}$ such as 4-morpholinomethyl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-ylmethyl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl}methyl, 7-
10 methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl, and 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}methyl, wherein each aryl and heteroaryl may be optionally substituted by one or two groups independently selected from halogen such as chlorine and fluorine, cyano, (C_1 - C_6) alkyl such as methyl, $-C(O)NR_{12}R_{13}$ such as 4-morpholinocarbonyl, (C_3 - C_6) heterocycloalkyl such as 1-methylpyrrolidin-1-yl, $-NR_{22}R_{23}$ such as dimethylamino, $-(CH_2)_nR_{22}R_{23}$ such as 2-dimethylaminomethyl, N,N-bis(2-hydroxyethyl)amino, 4-morpholinomethyl, 2-(4-morpholino)ethyl, 1-pyrrolidinomethyl, and (4-methylpiperazin-
20 i-yl)methyl, (C_3 - C_6) heterocycloalkoxyl such as 1-methylpiperidin-4-yl-oxyl, (C_3 - C_6) heterocycloalkyl (C_1 - C_6) alkoxyl such as 2-(4-methylpiperazin-1-yl)ethoxyl, 2-(4-morpholino)ethoxyl, 2-dimethylaminoethoxyl and 2-(1-methylpiperidin-4-yl)ethoxyl;

25 R_2 is selected in the group consisting of hydrogen, cyano, (C_1 - C_6) haloalkyl such as trifluoromethyl, aryl such as phenyl which is optionally substituted by halogen such as fluoro and methyl, heteroaryl such as pyridinyl;

R_3 is selected from the group consisting of H and (C_1 - C_6) alkyl such as methyl and

ethyl;

R₄ is H;

Cy is an heteroaryl selected from the following group: 9H-purine-6-amine-9-yl, 3H-purine-6-amine-3-yl, 9H-purin-6-yl, 4-amino-5-cyanopyrimidin-6-yl, 4-amino-5-formylpyrimidin-6-yl, 4-amino-5-bromopyrimidin-6-yl, 4-amino-5-trifluoromethylpyrimidin-6-yl, 4-amino-5-methylpyrimidin-6-yl, 4-amino-5-(N-methylcarbamoyl)pyrimidin-6-yl, 4-amino-5-carbamoylpyrimidin-6-yl, 4-amino-5-carboxypyrimidin-6-yl, 2-amino-3-pyrazinyl, 4-amino-5-hydroxymethylpyrimidin-6-yl, 4-amino-5-(4-morpholinomethyl)pyrimidin-6-yl, 4-amino-5-(hydroxyiminomethyl)pyrimidin-6-yl, 4-amino-5-(3-hydroxypropyn-1-yl)pyrimidin-6-yl, 4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-acetylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-hydroxymethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(5-hydroxy-3-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-methanesulphonylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(5-hydroxy-3-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(4-fluoro-3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-chloro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-aminosulphonylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-sulphonylamino-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-aminosulphonyl-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-amino-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-cyano-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-5-(1H-1,2,3,4-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-hydroxypropyn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, and 4-amino-3-(2-aminothiazol-5-yl)-1H-

pyrazolo[3,4-d]pyrimidin-1-yl.

m is 1;

n is 1;

p is 1;

- 5 Z is absent or is selected from -NH- or -NHC(O)-;
and all the other variables are as defined in claim 1.

8. A compound according to claim 7, wherein:

X₁, X₂, X₃ and X₄ are all CH groups;

- R is selected from the group consisting of C₁-C₆ alkyl, selected from methyl, C₁-
10 C₆ haloalkyl selected from trifluoromethyl, and halogen, more preferably fluoro, chloro and
bromo;

- R₁ is selected in the group consisting of hydrogen, C₂-C₆ alkynyl which is 3-pent-
1-yn-1-yl, C₂-C₆ aminoalkynyl which is 3-dimethylaminoprop-1-yn-1-yl, and C₂-C₆
hydroxyalkynyl which is 3-hydroxyprop-1-yn-1-yl, aryl which is phenyl, heteroaryl
15 selected from pyridyl, pyrazinyl, thienyl and thiazolyl, C₃-C₆ heterocycloalkyl selected
from 3,6-dihydro-2H-pyran-4-yl, 1,2,3,6-tetrahydropyridin-4-yl, pyrrolidin-1-yl-2-one,
and 4-methylpiperazin-1-yl-2-one, a group -(CH₂)_nN₂₂N₂₃ selected from 4-
morpholinomethyl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-ylmethyl, 9-methyl-3,9-
diazaspiro[5.5]undecan-3-yl}methyl, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl, and
20 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}methyl, wherein each aryl and heteroaryl
may be optionally substituted by one or two groups independently selected from halogen
selected from chlorine and fluorine, cyano, (C₁-C₆) alkyl which is methyl, -C(O)NR₁₂R₁₃
which is 4-morpholinocarbonyl, (C₃-C₆) heterocycloalkyl which is 1-methylpyrrolidin-1-
yl, -NR₂₂R₂₃ which is dimethylamino, -(CH₂)_nR₂₂R₂₃ selected from 2-
25 dimethylaminomethyl, N,N-bis(2-hydroxyethyl)amino, 4-morpholinomethyl, 2-(4-
morpholino)ethyl, 1-pyrrolidinomethyl, and (4-methylpiperazin-i-yl)methyl, (C₃-C₆)
heterocycloalkoxyl which is 1-methylpiperidin-4-yl-oxyl, (C₃-C₆) heterocycloalkyl (C₁-C₆)
alkoxyl selected from 2-(4-methylpiperazin-1-yl)ethoxyl, 2-(4-morpholino)ethoxyl, 2-

dimethylaminoethoxyl and 2-(1-methylpiperidin-4-yl)ethoxyl;

R₂ is selected in the group consisting of hydrogen, cyano, (C₁-C₆) haloalkyl which is trifluoromethyl, aryl which is phenyl which is optionally substituted by halogen which is fluoro or methyl, heteroaryl which is pyridinyl;

5 R₃ is selected from the group consisting of H and (C₁-C₆) alkyl selected from methyl and ethyl;

R₄ is H;

Cy is an heteroaryl selected from the following group: 9H-purine-6-amine-9-yl, 3H-purine-6-amine-3-yl, 9H-purin-6-yl, 4-amino-5-cyanopyrimidin-6-yl, 4-amino-5-
 10 formylpyrimidin-6-yl, 4-amino-5-bromopyrimidin-6-yl, 4-amino-5-trifluoromethylpyrimidin-6-yl, 4-amino-5-methylpyrimidin-6-yl, 4-amino-5-(N-methylcarbamoyl)pyrimidin-6-yl, 4-amino-5-carbamoylpyrimidin-6-yl, 4-amino-5-carboxypyrimidin-6-yl, 2-amino-3-pyrazinyl, 4-amino-5-hydroxymethylpyrimidin-6-yl, 4-amino-5-(4-morpholinomethyl)pyrimidin-6-yl, 4-amino-5-
 15 (hydroxyiminomethyl)pyrimidin-6-yl, 4-amino-5-(3-hydroxypropyn-1-yl)pyrimidin-6-yl, 4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-acetylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-hydroxymethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(5-hydroxy-3-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluorophenyl)-
 20 1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-methanesulphonylamino-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(5-hydroxy-3-pyridyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(4-fluoro-3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-chloro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-aminosulphonylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-sulphonylamino-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-aminosulphonyl-5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-amino-

5-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-cyano-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-5-(1H-1,2,3,4-tetrazol-5-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, 4-amino-3-(3-hydroxypropyn-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl, and 4-amino-3-(2-aminothiazol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl.

m is 1;

n is 1;

p is 1;

10 Z is absent or is selected from -NH- or -NHC(O)-;
and all the other variables are as defined in claim 1.

9. A compound according to Claim 1 selected from:

9-[(3-phenylindolizin-2-yl)methyl]-9H-purin-6-amine,
3-[(3-phenylindolizin-2-yl)methyl]-3H-purin-6-amine,
15 9-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine,
9-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,
3-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-3H-purin-6-amine,
9-{[3-(2-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,
9-{[3-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,
20 3-{[3-(2-methylphenyl)indolizin-2-yl]methyl}-3H-purin-6-amine,
9-(indolizin-2-ylmethyl)-9H-purin-6-amine,
9-[(1-phenylindolizin-2-yl)methyl]-9H-purin-6-amine,
9-{[1-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,
9-{[1-(2-methylphenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,
25 N-[(3-phenylindolizin-2-yl)methyl]-9H-purin-6-amine,
N-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-9H-purin-6-amine,
N-{[3-(3-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,
N-{[3-(2-fluorophenyl)indolizin-2-yl]methyl}-9H-purin-6-amine,

- N-[(1-phenylindolizin-2-yl)methyl]-9H-purin-6-amine,
N-[[1-(3-fluorophenyl)indolizin-2-yl]methyl]-9H-purin-6-amine,
N-[[1-(2-methylphenyl)indolizin-2-yl]methyl]-9H-purin-6-amine,
N-[[1-(pyridin-2-yl)indolizin-2-yl]methyl]-9H-purin-6-amine,
5 N-(indolizin-2-ylmethyl)-9H-purin-6-amine,
4-amino-6-[[[(3-phenylindolizin-2-yl)methyl]amino]pyrimidine-5-carbonitrile,
4-amino-6-([[(3-(pyridin-2-yl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([[(3-(3-fluorophenyl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([[(3-(2-fluorophenyl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
10 4-amino-6-([[(3-(2-methylphenyl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-[[[(1-phenylindolizin-2-yl)methyl]amino]pyrimidine-5-carbonitrile,
4-amino-6-([[(1-(3-fluorophenyl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([[(1-(2-methylphenyl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([[(1-(pyridin-2-yl)indolizin-2-yl]methyl]amino)pyrimidine-5-carbonitrile,
15 4-amino-6-[(indolizin-2-ylmethyl)amino]pyrimidine-5-carbonitrile,
4-amino-6-[[1-(3-phenylindolizin-2-yl)ethyl]amino]pyrimidine-5-carbonitrile,
4-amino-6-([1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([1-[3-(pyridin-3-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([1-[3-(pyrazin-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile,
20 4-amino-6-([1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([1-[3-(thiophen-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([1-[3-(thiophen-3-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-carbonitrile,
4-amino-6-([1-[8-fluoro-3-(pyridin-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-
carbonitrile,
25 4-amino-6-([1-[5-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-
carbonitrile,
4-amino-6-([1-[8-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl]amino)pyrimidine-5-
carbonitrile,

- 4-amino-6-({1-[3-(3,6-dihydro-2H-pyran-4-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile,
- 4-amino-6-({1-[3-(pent-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile,
- 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]propyl}amino)pyrimidine-5-carbonitrile,
- 5 4-amino-6-({1-[3-(1,2,3,6-tetrahydropyridin-4-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile,
- 4-amino-6-({1-[3-(3-hydroxyprop-1-yn-1-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbonitrile,
- 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carbaldehyde,
- 10 5-bromo-4-N- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} pyrimidine-4,6-diamine,
- 4-N- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} -5-(trifluoromethyl)pyrimidine-4,6-diamine,
- 5-methyl-4-N- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} pyrimidine-4,6-diamine,
- 4-amino-N-methyl-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-
- 15 carboxamide,
- 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxamide,
- 4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidine-5-carboxylic acid,
- 3-amino-N- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} pyrazine-2-carboxamide,
- 3-amino-N- {[1-(pyridin-2-yl)indolizin-2-yl]methyl} pyrazine-2-carboxamide,
- 20 [4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidin-5-yl]methanol,
- 5-(morpholin-4-ylmethyl)-4-N- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} pyrimidine-4,6-diamine,
- 5-[(1E)-(hydroxyimino)methyl]-4-N- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} pyrimidine-4,6-diamine,
- 25 3-[4-amino-6-({1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}amino)pyrimidin-5-yl]prop-2-yn-1-ol,
- 3-phenyl-1- {1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl} -1H-pyrazolo[3,4-d]pyrimidin-4-amine,

- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol,
- 3-(3-fluoro-5-methoxyphenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- 5 N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]acetamide,
- [3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]methanol,
- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-(trifluoromethyl)phenol,
- 10 3-(3-fluorophenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl]methanesulfonamide,
- 15 1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- 5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-3-ol,
- 4-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol,
- 20 5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol,
- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-chlorophenol,
- 25 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzene-1-sulfonamide,
- N-[3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenyl]methanesulfonamide,

- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorobenzene-1-sulfonamide,
- 3-(3-amino-5-fluorophenyl)-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- 5 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-hydroxybenzonitrile,
- 3-[3-fluoro-5-(1H-1,2,3,4-tetrazol-5-yl)phenyl]-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-4-amine,
- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 10 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol enantiomer 1,
- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol enantiomer 2,
- 15 3-(4-amino-1-{1-[3-(pyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-{4-amino-1-[1-(3-phenylindolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 3-(4-amino-1-{1-[3-(2-fluorophenyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluoro-phenol,
- 20 3-(4-amino-1-{1-[6-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-(4-amino-1-{1-[3-(pyridin-2-yl)-6-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 25 3-(4-amino-1-{1-[1-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)thiophen-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,

- 3-[4-amino-1-(1-{3-[4-(morpholin-4-ylmethyl)phenyl]indolizin-2-yl}ethyl)-1H-indazol-3-yl]-5-fluorophenol,
- 3-{4-amino-1-[1-(3-{4-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 5 3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol enantiomer 1,
- 3-{4-amino-1-[1-(3-{3-[(dimethylamino)methyl]phenyl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol enantiomer 2,
- 10 3-(4-amino-1-{1-[3-(1,3-thiazol-5-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 1-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)pyrrolidin-2-one,
- 15 3-(4-amino-1-{1-[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-(4-amino-1-{[3-(pyridin-2-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-(4-amino-1-{[3-(pyridin-3-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 20 3-(4-amino-1-{[3-(pyridin-4-yl)indolizin-2-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-(4-amino-1-{[7-(pyridin-2-yl)pyrrolo[1,2-b]pyridazin-6-yl]methyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 25 3-(4-amino-1-{1-[3-(1,2,3,6-tetrahydropyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)prop-2-yn-1-ol,

- 5-(4-amino-1-{1-[3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3-thiazol-2-amine,
- 3-(4-amino-1-{1-[7-chloro-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 5 3-(4-amino-1-{1-[7-methyl-3-(pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 3-(4-amino-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 5-(4-amino-1-{1-[3-(2-methylpyridin-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridin-3-ol,
- 10 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
- 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol enantiomer 1,
- 15 3-[4-amino-1-(1-{3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol enantiomer 2,
- 3-{4-amino-1-[1-(3-{5-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 3-[4-amino-1-(1-{3-[6-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
- 20 3-[4-amino-1-(1-{3-[4-(morpholin-4-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
- 3-{4-amino-1-[1-(3-{4-[(dimethylamino)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 25 3-[4-amino-1-(1-{3-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
- 3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

- 3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol enantiomer 1,
- 3-{4-amino-1-[1-(3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol enantiomer 2,
- 5 3-{4-amino-1-[1-(3-{6-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 3-{4-amino-1-[1-(3-{4-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
- 10 3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol enantiomer 1,
- 3-(4-amino-1-{1-[3-(5-{[bis(2-hydroxyethyl)amino]methyl}pyridin-2-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol enantiomer 2,
- 15 3-[4-amino-1-(1-{3-[3-(1-methylpyrrolidin-2-yl)phenyl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
- 3-{4-amino-1-[1-(3-{5-[2-(morpholin-4-yl)ethoxy]pyridin-2-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
- 5-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one,
- 20 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one,
- 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one enantiomer
- 25 1,
- 4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one enantiomer
- 2,

- 4-(2-{1-[4-amino-3-(5-hydroxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(morpholin-4-yl)ethyl]-1,2-dihydropyridin-2-one;
2-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)benzotrile,
5 3-(4-amino-1-{1-[3-(pyridin-2-yl)-1-(trifluoromethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,
3-[4-amino-1-(1-{3-[5-(morpholine-4-carbonyl)pyridin-2-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-
10 3-(pyridin-2-yl)indolizine-1-carbonitrile,
2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-
3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile,
2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-
3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile enantiomer 1,
15 2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-
3-{3-[(dimethylamino)methyl]phenyl}indolizine-1-carbonitrile enantiomer 2,
3-{4-amino-1-[1-(7-{3-[(dimethylamino)methyl]phenyl}pyrrolo[1,2-b]pyridazin-6-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,
3-(4-amino-1-{1-[3-(1,3-thiazol-4-yl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-
20 3-yl)-5-fluorophenol,
3-[4-amino-1-(1-{3-[2-(morpholin-4-yl)methyl]-1,3-thiazol-4-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
3-[4-amino-1-(1-{3-[3-(dimethylamino)prop-1-yn-1-yl]indolizin-2-yl}ethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-5-fluorophenol,
25 1-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-4-methylpiperazin-2-one,
4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one,

4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one enantiomer 1,

4-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-1-[2-(dimethylamino)ethyl]-1,2-dihydropyridin-2-one enantiomer 2,

6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(pyrrolidin-1-yl)ethyl]-2,3-dihydropyridazin-3-one,

6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(4-methylpiperazin-1-yl)ethyl]-2,3-dihydropyridazin-3-one,

6-(2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}indolizin-3-yl)-2-[2-(morpholin-4-yl)ethyl]-2,3-dihydropyridazin-3-one,

3-{4-amino-1-[1-(3-{6-[2-(4-methylpiperazin-1-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

3-{4-amino-1-[1-(3-{6-[2-(dimethylamino)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

3-{4-amino-1-[1-(3-{6-[(1-methylpiperidin-4-yl)oxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

3-{4-amino-1-[1-(3-{6-[2-(1-methylpiperidin-4-yl)ethoxy]pyridazin-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

3-(4-amino-1-{1-[3-(morpholin-4-ylmethyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,

3-(4-amino-1-{1-[3-({2-methyl-2,9-diazaspiro[5.5]undecan-9-yl}methyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,

3-(4-amino-1-{1-[3-({9-methyl-3,9-diazaspiro[5.5]undecan-3-yl}methyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,

3-(4-amino-1-{1-[3-({7-methyl-2,7-diazaspiro[3.5]nonan-2-yl}methyl)indolizin-2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,

3-{1-[1-(3-{[(3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl)methyl}indolizin-2-yl)ethyl]-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

2-{1-[4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]ethyl}-3-(morpholin-4-ylmethyl)indolizine-1-carbonitrile,

5 3-{4-amino-1-[1-(3-{1-[2-(dimethylamino)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

3-{4-amino-1-[1-(3-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

3-(4-amino-1-{1-[3-(1-{2-[bis(2-hydroxyethyl)amino]ethyl}-1H-pyrazol-3-yl)indolizin-

10 2-yl]ethyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol,

3-{4-amino-1-[1-(3-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-3-yl}indolizin-2-yl)ethyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-5-fluorophenol,

and pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound as defined in any one of
15 claims 1 to 9, or a pharmaceutically acceptable salt thereof, either alone or in combination with one or more active ingredient, in admixture with one or more pharmaceutically acceptable carrier or excipient.

11. A compound according to any one of claims 1 to 9 for use as a medicament.

12. Use of a compound as defined in any one of claims 1 to 9, or a pharmaceutically
20 acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder associated by PI3K enzymes mechanisms.

13. Use according to claim 12 wherein the disorder associated by PI3K enzymes mechanisms is selected from the group consisting of respiratory diseases including idiopathic chronic cough, cough variant asthma, cough associated with thoracic tumour or
25 lung cancer, viral or post-viral cough, upper airways cough syndrome (UACS) or post nasal drip cough, or cough associated gastro oesophageal reflux disease (both acid and non acid reflux), chronic bronchitis, chronic obstructive pulmonary disease (COPD), interstitial lung disease (such as idiopathic pulmonary fibrosis (IPF)), congestive heart disease, sarcoidosis

- or infection (such as whooping cough), asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)); viral infections (including viral respiratory tract infections and viral exacerbation of respiratory diseases such as asthma and COPD); non-viral respiratory infections (including aspergillosis and leishmaniasis);
- 5 allergic diseases (including allergic rhinitis and atopic dermatitis); autoimmune diseases (including rheumatoid arthritis and multiple sclerosis); inflammatory disorders (including inflammatory bowel disease); cardiovascular diseases (including thrombosis and atherosclerosis); hematologic malignancies; neurodegenerative diseases; pancreatitis; multiorgan failure; kidney diseases; platelet aggregation; cancer; sperm motility;
- 10 transplantation rejection; graft rejection; lung injuries; and pain (including pain associated with rheumatoid arthritis or osteoarthritis, back pain, general inflammatory pain, post hepatic neuralgia, diabetic neuropathy, inflammatory neuropathic pain (trauma), trigeminal neuralgia, central pain and respiratory infections, airways damage, treatment and/or prevention of airway injury in patients with PI3K δ mutations..
- 15 14. A method according to claim 13 wherein the disorder associated by PI3K enzymes mechanisms is asthma, chronic obstructive pulmonary disease COPD idiopathic pulmonary fibrosis (IPF).