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(54) Title: DNA POLYMERASE THETA INHIBITORS

(57) Abstract: The invention relates to heterocyclic derivatives and their use in the treatment and prophylaxis of cancer, and to compositions containing said derivatives and processes for their preparation.

DNA POLYMERASE THETA INHIBITORS

FIELD OF THE INVENTION

The invention relates to heterocyclic derivatives and their use in the treatment and prophylaxis of cancer, and to compositions containing said derivatives and processes for their preparation.

BACKGROUND OF THE INVENTION

Robust repair of DNA double-strand breaks (DSBs) is essential for the maintenance of genome stability and cell viability. DSBs can be repaired by one of three main pathways: homologous recombination (HR), non-homologous end-joining (NHEJ) and alternative NHEJ (alt-NHEJ). Microhomology-mediated end-joining (MMEJ) is the most well characterised alt-NHEJ mechanism. HR-mediated repair is a high-fidelity mechanism essential for accurate error-free repair, preventing cancer-predisposing genomic stability. Conversely, NHEJ and MMEJ are error-prone pathways that can leave mutational scars at the site of repair. MMEJ can function parallel to both HR and NHEJ pathways (Truong *et al.* PNAS 2013, 110 (19), 7720-7725).

The survival of cancer cells, unlike normal cells, is often dependent on the mis-regulation of DNA damage response (DDR) pathways. For example, an increased dependency on one pathway (often mutagenic) to cope with either the inactivation of another one, or the enhanced replication stress resulting from increased proliferation. An aberrant DDR can also sensitise cancer cells to specific types of DNA damage, thus, defective DDR can be exploited to develop targeted cancer therapies. Crucially, cancer cells with impairment or inactivation of HR and NHEJ become hyper-dependent on MMEJ-mediated DNA repair. Genetic, cell biological and biochemical data have identified Polθ (UniProtKB - O75417 (DPOLQ_HUMAN) as the key protein in MMEJ (Kent *et al.* Nature Structural & Molecular Biology (2015), 22(3), 230-237, Mateos-Gomez *et al.* Nature (2015), 518(7538), 254-257). Polθ is multifunctional enzyme, which comprises an N-terminal helicase domain (SF2 HEL308-type) and a C-terminal low-fidelity DNA polymerase domain (A-type) (Wood & Doublé DNA Repair (2016), 44, 22-32). Both domains have been shown to have concerted mechanistic functions in MMEJ. The helicase domain mediates the removal of RPA protein from ssDNA ends and stimulates annealing. The polymerase domain extends the ssDNA ends and fills the remaining gaps.

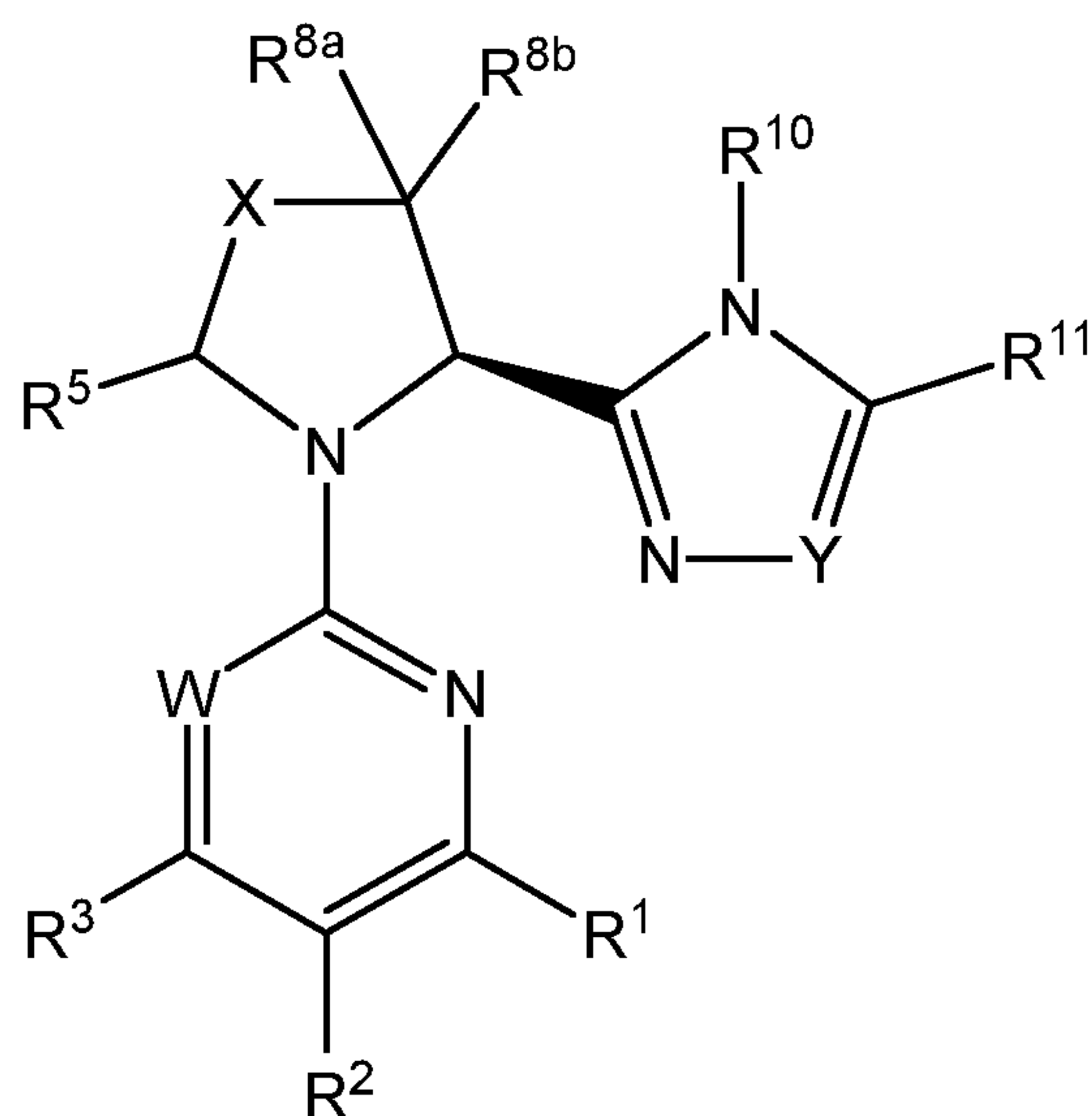
Therapeutic inactivation of Polθ would thus disable the ability of cells to perform MMEJ and provide a novel targeted strategy in an array of defined tumour contexts. Firstly, Polθ has

been shown to be essential for the survival of HR-defective (HRD) cells (e.g. synthetic lethal with FA/BRCA-deficiency) and is up-regulated in HRD tumour cell lines (Ceccaldi *et al.* Nature (2015), 518(7538), 258-262). *In vivo* studies also show that Polθ is significantly over-expressed in subsets of HRD ovarian, uterine and breast cancers with associated poor prognosis (Higgins *et al.* Oncotarget (2010), 1, 175-184, Lemée *et al.* PNAS (2010), 107(30), 13390-13395, Ceccaldi *et al.* (2015), *supra*). Importantly, Polθ is largely repressed in normal tissues but has been shown to be upregulated in matched cancer samples thus correlating elevated expression with disease (Kawamura *et al.* International Journal of Cancer (2004), 109(1), 9-16). Secondly, its suppression or inhibition confers radio-sensitivity in tumour cells. Finally, Polθ inhibition could conceivably prevent the MMEJ-dependent functional reversion of BRCA2 mutations that underlies the emergence of cisplatin and PARPi resistance in tumours.

There is therefore a need to provide effective Polθ inhibitors for the treatment of cancer.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a compound of formula (I):



(I)

or a tautomeric or a stereochemically isomeric form, a pharmaceutically acceptable salt or a solvate thereof, wherein:

W represents =C(R⁴)- or =N-;

R¹, R², R³ and R⁴ independently represent hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, haloC₁₋₆ alkyl, C₃₋₈ cycloalkyl, cyano or -NR^xR^y;

X represents -C(R^{6a})(R^{6b})-, -N(R⁷)- or -O-;

R⁵ represents hydrogen, -CH₂-R^z or oxo, or together with R^{6b} may join to form a bridged group, such that when X represents -N(R⁷)- or -O-, R⁵ represents oxo and such that when R⁴ represents cyano, R⁵ represents a group other than oxo;

R^{6a} represents hydrogen, hydroxy, C₁₋₆ alkyl, haloC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanol, C₃₋₈

5 cycloalkyl, halogen, -NR^vR^w or heterocyclyl;

R^{6b} represents hydrogen, or together with R⁵ may join to form a bridged group, or together with R^{6a} may join to form a C₃₋₈ cycloalkyl group;

R⁷ represents hydrogen, C₁₋₆ alkyl, haloC₁₋₆ alkyl, C₃₋₈ cycloalkyl, heterocyclyl, C₁₋₆ alkylsulfonimidoyl or C₁₋₆ alkylamino optionally substituted by one or more (e.g. 1 or 2)

10 hydroxyl groups;

R^{8a} represents hydrogen, -CH₂-R^z or hydroxy;

R^{8b} represents hydrogen or hydroxy, such that when X represents -N(R⁷)- or -O-, R^{8b} represents hydrogen;

Y represents -C(R⁹)= or -N=;

15 R⁹ represents hydrogen, halogen or C₁₋₆ alkyl;

R¹⁰ represents phenyl or a 5 or 6 membered heteroaryl ring optionally fused to a 5 membered heteroaryl ring, wherein said phenyl or heteroaryl rings may optionally each be substituted by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanol, -CONR^tR^u, -CH₂-NR^tR^u, C₃₋₈ cycloalkyl, halogen, cyano or haloC₁₋₆ alkyl groups;

20 R¹¹ represents hydrogen, halogen or C₁₋₆ alkyl;

R^t, R^u, R^v, R^w, R^x and R^y independently represent hydrogen, C₁₋₆ alkyl, haloC₁₋₆ alkyl, C₃₋₈ cycloalkyl, -COC₁₋₆ alkyl or heterocyclyl, wherein said alkyl groups may be optionally substituted with or more hydroxy, amino or sulfone groups and said heterocyclyl ring may be optionally substituted by one or more oxo or -COC₁₋₆ alkyl groups; and

25 R^z represents hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy or C₁₋₆ alkanol.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term 'halo' or 'halogen' as used herein refers to fluorine, chlorine, bromine or iodine.

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The term 'cyano' as used herein refers to a group where a carbon atom is triple bonded to a nitrogen atom.

The term 'C₁₋₆ alkyl' as used herein as a group or part of a group refers to a linear or

35 branched saturated hydrocarbon group containing from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, *iso*-propyl, butyl, *iso*-butyl, *tert*-butyl, pentyl, hexyl and the like.

The term 'C₁₋₆ alkoxy' as used herein as a group or part of a group refers to a C₁₋₆ alkyl group which contains an oxygen atom wherein C₁₋₆ alkyl is as defined herein. Examples of such groups include methoxy, ethoxy or propoxy.

5

The term 'C₁₋₆ alkanol' as used herein as a group or part of a group refers to a C₁₋₆ alkyl group which contains an oxygen atom wherein C₁₋₆ alkyl is as defined herein.

10 The term 'haloC₁₋₆ alkyl' as used herein as a group or part of a group refers to a C₁₋₆ alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. The term 'haloC₁₋₆ alkyl' therefore includes monohaloC₁₋₆ alkyl and also polyhaloC₁₋₆ alkyl. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the haloC₁₋₆ alkyl may have one, two, three or more halogens. Examples of such groups include fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

15

The term "C₃₋₈ cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

20 The term 'oxo' as used herein refers to the group =O.

The term 'amino' as used herein refers to the group -NR'R'', wherein R' and R'' independently represent a hydrogen or C₁₋₆ alkyl group.

25 The term 'C₁₋₆ alkylamino' as used herein refers to a C₁₋₆ alkyl group as defined hereinbefore which is substituted with a -NR'R'' group, wherein R' and R'' independently represent a hydrogen or C₁₋₆ alkyl group.

30 The term 'C₁₋₆ alkylsulfonimidoyl' as used herein refers to a C₁₋₆ alkyl group as defined hereinbefore which is substituted with a -S(=O)(=NR') group, wherein R' represents a hydrogen or C₁₋₆ alkyl group.

35 The term 'heterocyclyl' as used herein refers to a monocyclic or bicyclic non-aromatic, partially saturated or fully saturated ring system containing for example 3 to 12 ring members. Each ring may contain up to five heteroatoms typically selected from nitrogen, sulfur and oxygen.

Particular examples of 'heterocyclyl' include morpholine, piperidine (e.g. piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and piperidin-4-yl), piperidinone, pyrrolidine (e.g. pyrrolidin-1-yl, pyrrolidin-2-yl and pyrrolidin-3-yl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. tetrahydropyran-4-yl), imidazoline, imidazolidinone, oxazoline, thiazoline, pyrazolin-2-yl, pyrazolidine, piperazinone and piperazine.

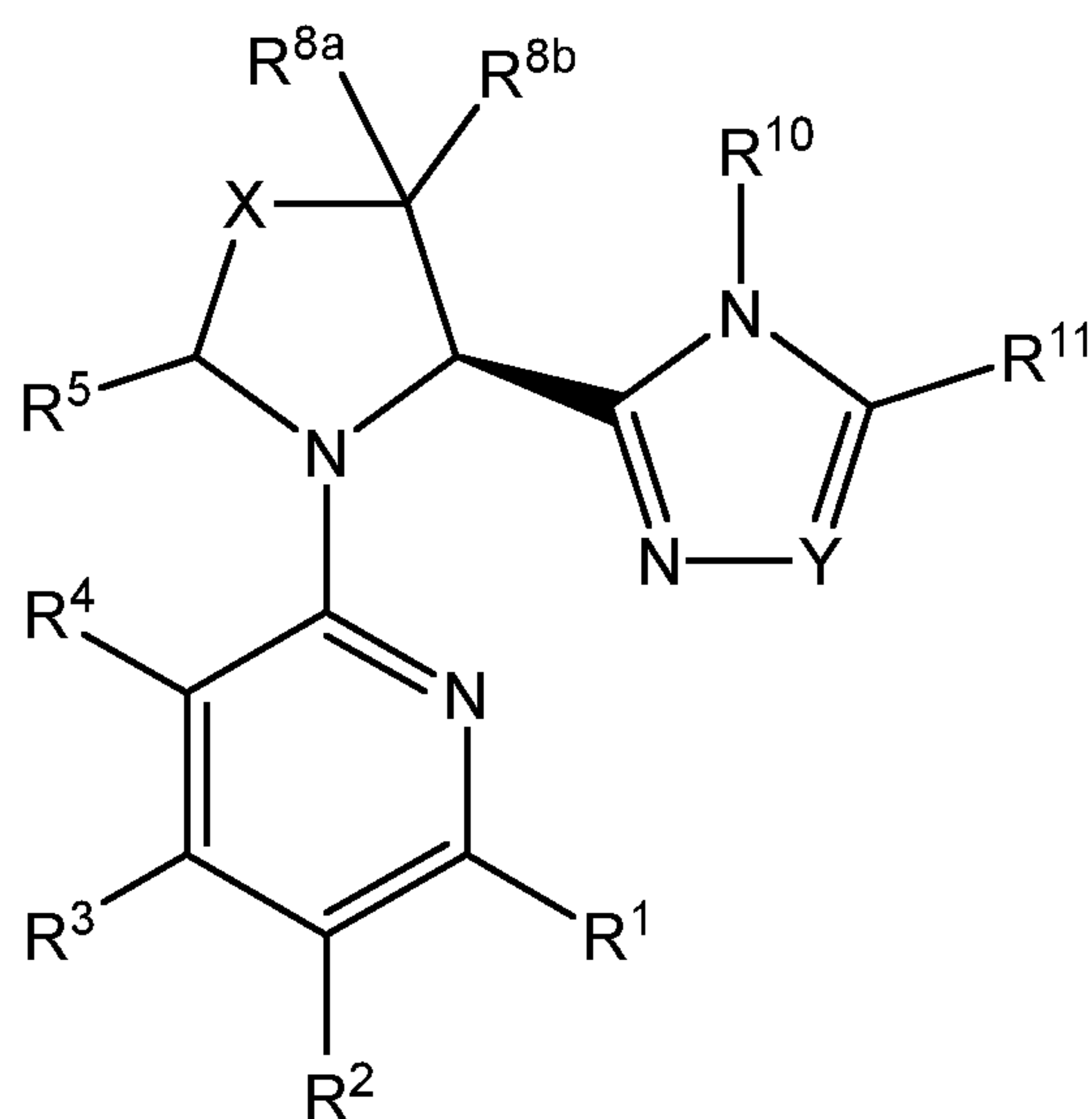
It will be appreciated that the term 'heterocyclyl' includes reference to spiro and bridged heterocyclic derivatives. Examples of such spiro and bridged heterocyclic derivatives include: hexahydropyrrolo[2,3-c]pyrrolidinyl, diazaspiro[3.4]octanyl, diazaspiro[4.4]nonyl, oxa-azaspiro[3.4]octanyl, oxa-azaspiro[4.4]nonyl, tetrahydrofuro[3,4-c]pyrrolidinyl, oxa-azaspiro[3.3]heptyl, diazaspiro[4.5]decanyl, diazaspiro[3.4]octanyl, octahydro-naphthyridinyl, tetrahydropyrazino-oxazinyl, oxadiazospiro[5.5]undecanyl and oxabicyclo[2.2.1]heptanyl.

The term '5 or 6 membered heteroaryl ring' as used herein refers to a monocyclic aromatic ring system containing 5 or 6 ring members. Each ring may contain up to three heteroatoms typically selected from nitrogen, sulfur and oxygen. Examples of five membered heteroaryl rings include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, thiadiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered heteroaryl rings include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

The term 'optionally substituted' as used herein refers to a group which may be substituted or unsubstituted by a substituent as herein defined.

Embodiments

In one embodiment, the compound of formula (I) is a compound of formula (I)^a:

(I)^a

wherein R¹, R², R³, R⁴, R⁵, X, R^{8a}, R^{8b}, Y, R¹⁰ and R¹¹ are as defined herein.

- 5 In one embodiment, R¹ represents hydrogen or C₁₋₆ alkyl (such as methyl). In a further embodiment, R¹ represents C₁₋₆ alkyl (such as methyl). In a yet further embodiment, R¹ represents hydrogen or methyl. In a still yet further embodiment, R¹ represents methyl.

- 10 In one embodiment, R² represents hydrogen or C₁₋₆ alkyl (such as methyl). In a further embodiment, R² represents hydrogen or methyl. In a still yet further embodiment, R² represents hydrogen.

- 15 In one embodiment, R³ represents C₁₋₆ alkyl (such as methyl or ethyl) or haloC₁₋₆ alkyl (such as trifluoromethyl). In a further embodiment, R³ represents methyl, ethyl or trifluoromethyl. In a yet further embodiment, R³ represents haloC₁₋₆ alkyl (such as trifluoromethyl).

In one embodiment, W represents =C(R⁴)-.

- 20 In one embodiment, R⁴ represents hydrogen or cyano. In a further embodiment, R⁴ represents cyano.

In one embodiment, W represents C(R⁴)- and:

R¹ represents C₁₋₆ alkyl (such as methyl), R² represents hydrogen, R³ represents haloC₁₋₆ alkyl (such as trifluoromethyl) and R⁴ represents cyano; or

- 25 R¹ represents C₁₋₆ alkyl (such as methyl), R² represents hydrogen, R³ represents C₁₋₆ alkyl (such as methyl) and R⁴ represents cyano; or

R^1 represents hydrogen, R^2 represents C_{1-6} alkyl (such as methyl), R^3 represents C_{1-6} alkyl (such as ethyl) and R^4 represents cyano; or

R^1 represents C_{1-6} alkyl (such as methyl), R^2 represents hydrogen, R^3 represents halo C_{1-6} alkyl (such as trifluoromethyl) and R^4 represents hydrogen.

5

In one embodiment, R^5 represents hydrogen, oxo, or R^5 together with R^7 joins to form a bridged group.

In one embodiment, X represents $-C(R^{6a})(R^{6b})-$. In an alternative embodiment, X represents -
10 O-. In a further alternative embodiment, X represents $-N(R^7)-$.

When X represents $-C(R^{6a})(R^{6b})-$, in one embodiment, R^{6a} represents hydrogen, C_{1-6} alkyl (such as methyl), hydroxy, C_{1-6} alkanol (such as CH_2OH) or $-NR^vR^w$ (such as $-NHCOMe$).

15 When X represents $-C(R^{6a})(R^{6b})-$, in one embodiment, R^{6b} represents hydrogen. When X represents $-C(R^{6a})(R^{6b})-$, in an alternative embodiment, R^{6b} together with R^5 joins to form a bridged group. When X represents $-C(R^{6a})(R^{6b})-$, in a further alternative embodiment, R^{6b} together with R^{6a} joins to form a C_{3-8} cycloalkyl group (such as a cyclopropyl group).

20 When X represents $-N(R^7)-$, in one embodiment. R^7 represents hydrogen, C_{1-6} alkylsulfonimidoyl (such as $-(CH_2)_2-S(=O)(=NH)(Me)$) or C_{1-6} alkylamino optionally substituted by one or more (e.g. 1 or 2) hydroxyl groups (such as $-CH_2-CH_2OH-CH_2-N(Me)_2$).

In one embodiment, R^{8a} and R^{8b} both represent hydrogen, or R^{8a} represents hydroxy and R^{8b}
25 represents hydrogen, or R^{8a} represents $-CH_2-R^z$ (such as methyl) and R^{8b} represents hydroxy, or R^{8a} represents $-CH_2-R^z$ (such as $-CH_2-OH$) and R^{8b} represents hydrogen or hydroxy.

In one embodiment, X represents $-C(R^{6a})(R^{6b})-$ and:

30 R^5 represents hydrogen, R^{6a} represents hydrogen, R^{6b} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R^5 represents hydrogen, R^{6a} represents hydroxy, R^{6b} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R^5 represents hydrogen, R^{6a} represents hydroxy, R^{6b} represents hydrogen, R^{8a}
35 represents hydroxy and R^{8b} represents hydrogen; or

R^5 together with R^{6b} joins to form a bridged group, R^{6a} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ together with R^{6b} joins to form a bridged group, R^{6a} represents C₁₋₆ alkanol (such as CH₂OH) and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents hydrogen, R^{6a} represents NR^vR^w (such as -NHCOMe), R^{6b} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

5 R⁵ represents oxo, R^{6a} represents C₁₋₆ alkyl (such as methyl), R^{6b} represents hydrogen, R^{8a} represents -CH₂-R^z (such as methyl) and R^{8b} represents hydroxy; or

R⁵ represents oxo, R^{6a} and R^{6b} both represent hydrogen, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydroxy; or

10 R⁵ represents oxo, R^{6a} represents C₁₋₆ alkyl (such as methyl), R^{6b} represents hydrogen, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydroxy; or

R⁵ represents oxo, R^{6a} and R^{6b} join to form a C₃₋₈ cycloalkyl group (such as a cyclopropyl group), R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydroxy.

In an alternative embodiment, X represents -O- and:

15 R⁵ represents oxo and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents oxo, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydrogen.

In an alternative embodiment, X represents -N(R⁷)- and:

20 R⁵ represents oxo, R⁷ represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents oxo, R⁷ represents hydrogen, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydrogen; or

25 R⁵ represents oxo, R⁷ represents C₁₋₆ alkylamino optionally substituted by one or more (e.g. 1 or 2) hydroxyl groups (such as -CH₂-CH₂OH-CH₂-N(Me)₂) and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents oxo, R⁷ represents C₁₋₆ alkylsulfonimidoyl (such as -(CH₂)₂-S(=O)(=NH)(Me)) and R^{8a} and R^{8b} both represent hydrogen.

30 In one embodiment, Y represents -C(R⁹)=. In an alternative embodiment, Y represents -N=.

In one embodiment, R⁹ represents hydrogen, halogen (such as fluorine or chlorine) or C₁₋₆ alkyl (such as methyl). In a further embodiment, R⁹ represents hydrogen.

35 In one embodiment, R¹⁰ represents phenyl or a 5 or 6 membered heteroaryl ring (such as pyridyl or pyrazolyl) optionally fused to a 5 membered heteroaryl ring (such as pyrrolopyridinyl) wherein said phenyl or heteroaryl rings may optionally each be substituted

by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl (such as methyl or isopropyl), C₁₋₆ alkoxy (such as methoxy), C₁₋₆ alkanol (such as CH₂OH), -CONR^tR^u (such as -CONH₂), -CH₂-NR^tR^u (such as -CH₂-NH₂), halogen (such as fluorine or chlorine), cyano or haloC₁₋₆ alkyl (such as trifluoromethyl).

5

In a further embodiment, R¹⁰ represents:

phenyl optionally substituted by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl (such as methyl or isopropyl), C₁₋₆ alkoxy (such as methoxy), C₁₋₆ alkanol (such as CH₂OH), -CONR^tR^u (such as -CONH₂), -CH₂-NR^tR^u (such as -CH₂-NH₂), halogen (such as fluorine or chlorine) or cyano; or

10

a 5 or 6 membered heteroaryl ring (such as pyridyl or pyrazolyl) optionally fused to a 5 membered heteroaryl ring (such as pyrrolopyridinyl) wherein said heteroaryl rings may optionally each be substituted by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl (such as methyl), halogen (such as fluorine or chlorine) or haloC₁₋₆ alkyl (such as trifluoromethyl).

15

In a further embodiment, R¹⁰ represents phenyl optionally substituted by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl (such as methyl or isopropyl), C₁₋₆ alkoxy (such as methoxy), C₁₋₆ alkanol (such as CH₂OH), -CONR^tR^u (such as -CONH₂), -CH₂-NR^tR^u (such as -CH₂-NH₂), halogen (such as fluorine or chlorine) and cyano.

20

In an alternative embodiment, R¹⁰ represents a 5 or 6 membered heteroaryl ring (such as pyridyl or pyrazolyl) optionally fused to a 5 membered heteroaryl ring (such as pyrrolopyridinyl) wherein said heteroaryl rings may optionally each be substituted by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl (such as methyl), halogen (such as fluorine or chlorine) or haloC₁₋₆ alkyl (such as trifluoromethyl).

25

In one embodiment, R¹¹ represents hydrogen, halogen (such as chlorine) or C₁₋₆ alkyl (such as methyl). In a further embodiment, R¹¹ represents hydrogen or methyl. In a yet further embodiment, R¹¹ represents hydrogen.

30

In one embodiment, the invention provides a compound of formula (I) which is the free base of a compound of Examples 1-66 or a pharmaceutically acceptable salt or solvate thereof.

A reference to a compound of the formula (I) and sub-groups thereof also includes ionic forms, salts, solvates, isomers (including geometric and stereochemical isomers), tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof, for example, as discussed below; preferably, the salts or tautomers or isomers or N-oxides or solvates thereof; and

35

more preferably, the salts or tautomers or N-oxides or solvates thereof, even more preferably the salts or tautomers or solvates thereof. Hereinafter, compounds and their ionic forms, salts, solvates, isomers (including geometric and stereochemical isomers), tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof as defined in any aspect of the invention (except intermediate compounds in chemical processes) are referred to as "compounds of the invention".

Salts

Certain compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulfonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

The salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used.

Acid addition salts (*mono-* or *di-*salts) may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include *mono-* or *di-*salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulfonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrohalic acids (e.g. hydrobromic, hydrochloric, hydriodic), isethionic, lactic (e.g. (+)-L-lactic, ($\pm$)-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic, ($\pm$)-DL-mandelic, methanesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, pyruvic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, (+)-L-tartaric, thiocyanic, p-toluenesulfonic, undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

One particular group of salts consists of salts formed from acetic, hydrochloric, hydriodic, phosphoric, nitric, sulfuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulfonic, toluenesulfonic, methanesulfonic (mesylate), ethanesulfonic, naphthalenesulfonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids. One particular salt is the hydrochloride salt.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

The compounds of the invention may exist as *mono*- or *di*-salts depending upon the pK_a of the acid from which the salt is formed.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.* **1977**, 66, pp. 1-19. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates or formates may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Solvates

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a

complex with water is known as a "hydrate". Pharmaceutically acceptable solvates of the compound of the invention are within the scope of the invention. In one embodiment, the pharmaceutically acceptable solvates of the compounds of the invention include the hydrate thereof.

5

In one embodiment, said crystalline form of the compounds of formula (I) is a cocrystal or coformer. Such a cocrystal or coformer may be prepared using water-soluble molecules such as saccharin, caffeine, nicotinamide or carboxylic acids. Coformers may be prepared as described in Emami S *et al* (2018) *BiolImpacts* 8(4), 305-320, the techniques of which are

10

herein incorporated by reference.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

15

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

20

N-Oxides

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

25

Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

30

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a *per*-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Commun.* **1977**, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

35

Prodrugs

It will be appreciated by those skilled in the art that certain protected derivatives of compounds of formula (I), which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All such prodrugs of compounds of the invention are included within the scope of the invention. Examples of pro-drug functionality suitable for the compounds of the present invention are described in *Drugs of Today*, 19, 9, 1983, 499-538 and in *Topics in Chemistry*, Chapter 31, pp. 306-316 and in “*Design of Prodrugs*” by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as “pro-moieties”, for example as described by H. Bundgaard in “*Design of Prodrugs*” (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within compounds of the invention.

Also included within the scope of the compound and various salts of the invention are polymorphs thereof.

Enantiomers

Where chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible enantiomers and diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. The invention also extends to any tautomeric forms or mixtures thereof.

Isotopes

The subject invention also includes all pharmaceutically acceptable isotopically-labelled compounds which are identical to those recited in formula (I) but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention comprise isotopes of hydrogen, such as ^2H (D) and ^3H (T), carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I , ^{125}I and ^{131}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S .

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The compounds of formula (I) can also have valuable diagnostic properties in that they can be used for detecting or identifying the formation of a complex between a labelled compound and other molecules, peptides, proteins, enzymes or receptors. The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances (for example, luminol, luminol derivatives, luciferin, aequorin and luciferase) *etc.* The radioactive isotopes tritium, *i.e.* ^3H (T), and carbon-14, *i.e.* ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^2H (D), may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining target occupancy.

Isotopically-labelled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using appropriate isotopically-labelled reagents in place of the non-labelled reagent previously employed.

Purity

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are given on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

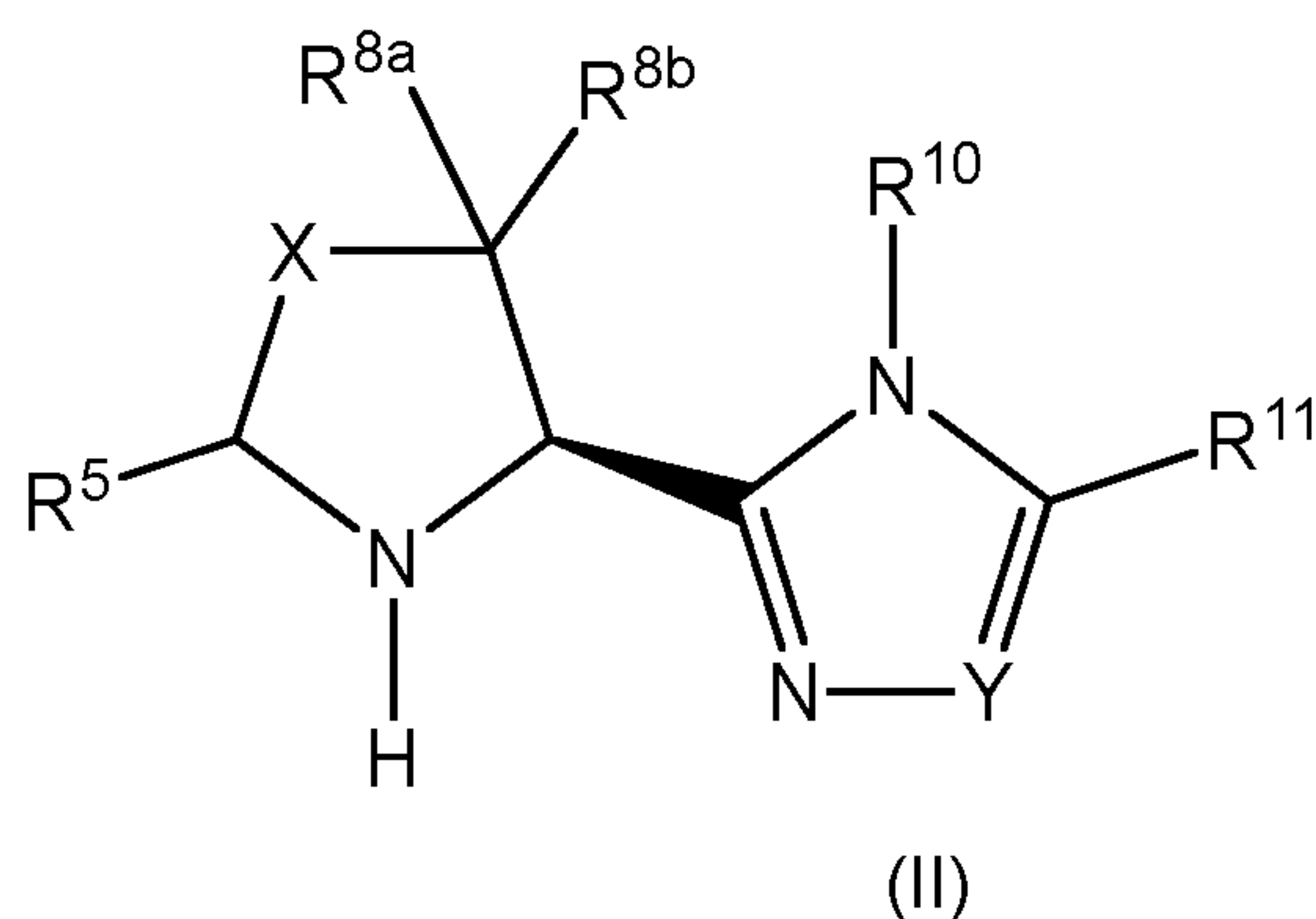
Processes

According to a further aspect of the present invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes are examples of synthetic schemes that may be used to synthesise the compounds of the

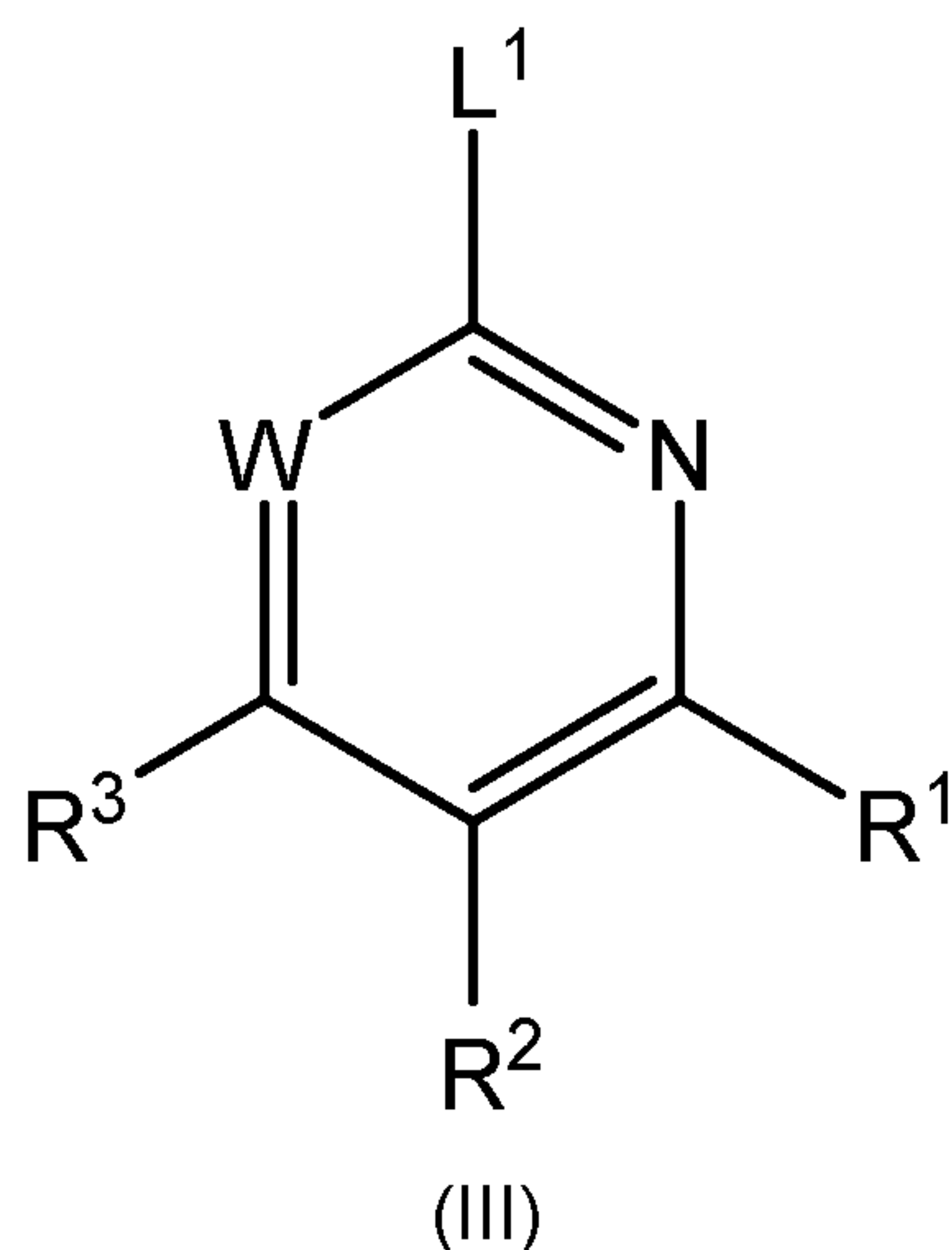
invention. In the following schemes reactive groups can be protected with protecting groups and de-protected according to well established techniques.

According to a further aspect of the invention there is provided a process for preparing a compound of formula (I) as herein defined which comprises:

(a) reacting a compound of formula (II):

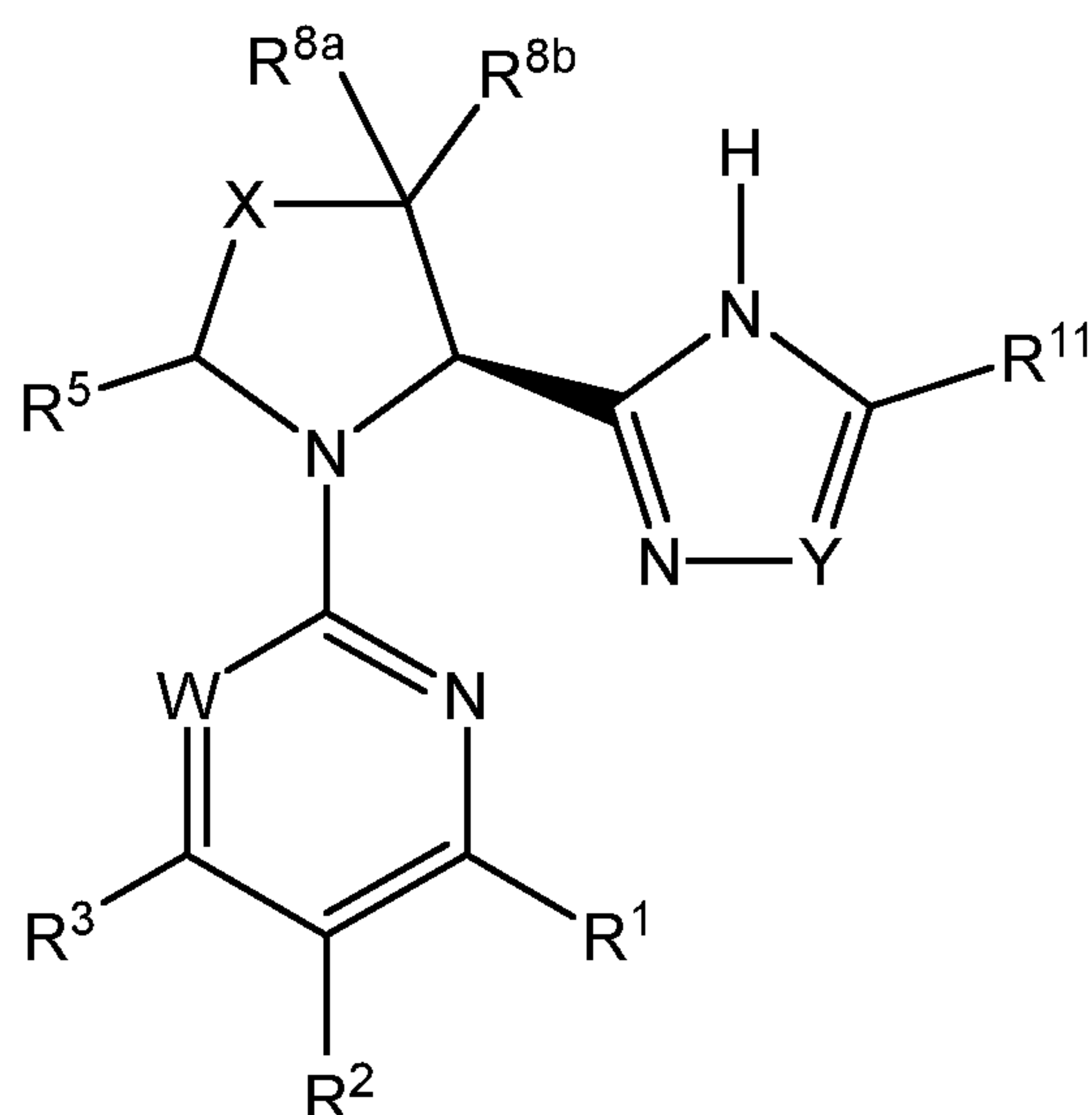


wherein R^5 , X , R^{8a} , R^{8b} , Y , R^{10} and R^{11} are as defined herein, with a compound of formula (III):



wherein R^1 , R^2 , R^3 and W are as defined herein and L^1 represents a suitable leaving group, such as a halogen atom (e.g. chlorine);

(b) reacting a compound of formula (IV):



(IV)

wherein R¹, R², R³, W, R⁵, X, R^{8a}, R^{8b}, Y and R¹¹ are as defined herein, with a compound of formula R¹⁰-L², wherein R¹⁰ is as defined herein and L² represents a suitable leaving group, such as boronic acid or a halogen atom (e.g. fluorine);

(c) deprotection of a protected derivative of a compound of formula (I);

(d) interconversion of a compound of formula (I) or protected derivative thereof to a further compound of formula (I) or protected derivative thereof; and

(e) optional formation of a pharmaceutically acceptable salt of a compound of formula (I).

Process (a) typically comprises reacting a compound of formula (II) with a compound of formula (III) in the presence of suitable reagents, such as DIPEA in NMP, under suitable conditions, such as heating to a suitable temperature (such as 70 °C).

Process (b) typically comprises reacting a compound of formula (IV) with a compound of formula R¹⁰-L² in a suitable solvent, such as DCM, in the presence of a suitable reagent, such as Cu(OAc)₂·H₂O and a suitable base, such as pyridine.

Compounds of formula (II) and (IV) may be prepared in accordance with the procedures described herein. For example, compounds of formula (II) may be prepared in accordance with the experimental procedure described in Example 1 and compounds of formula (IV) may be prepared in accordance with the experimental procedure described in Example 9.

Compounds of formula (III) and $R^{10}-L^2$ are either known or may be prepared in accordance with known procedures.

A wide range of well known functional group interconversions for process (d) are known by a person skilled in the art for converting a precursor compound to a compound of formula (I) and are described in Advanced Organic Chemistry by Jerry March, 4th Edition, John Wiley & Sons, 1992. For example possible metal catalysed functionalisations such as using organotin reagents (the Stille reaction), Grignard reagents and reactions with nitrogen nucleophiles are described in 'Palladium Reagents and Catalysts' [Jiro Tsuji, Wiley, ISBN 0-470-85032-9] and Handbook of OrganoPalladium Chemistry for Organic Synthesis [Volume 1, Edited by Ei-ichi Negishi, Wiley, ISBN 0-471-31506-0].

If appropriate, the reactions described herein are followed or preceded by one or more reactions known to the skilled of the art and are performed in an appropriate order to achieve the requisite substitutions on R^1 , R^2 , R^3 , R^4 , R^5 , R^{6a} , R^{6b} , R^7 , R^{8a} , R^{8b} , R^9 , R^{10} and R^{11} defined herein to afford other compounds of formula (I). Non-limiting examples of such reactions whose conditions can be found in the literature include:

protection of reactive functions,
deprotection of reactive functions,
halogenation,
dehalogenation,
dealkylation,
alkylation of amine, aniline, alcohol and phenol,
Mitsunobu reaction on hydroxyl groups,
cycloaddition reactions on appropriate groups,
reduction of nitro, esters, cyano, aldehydes,
transition metal-catalyzed coupling reactions,
acylation,
sulfonylation/introduction of sulfonyl groups,
saponification/hydrolysis of esters groups,
amidification or transesterification of ester groups,
esterification or amidification of carboxylic groups,
halogen exchange,
nucleophilic substitution with amine, thiol or alcohol,
reductive amination,
oxime formation on carbonyl and hydroxylamine groups,
S-oxidation,

N-oxidation,
salification.

It is recognised that the sequence of reactions involving aryl coupling and reduction may be varied. It is also recognised that a wide range of palladium based catalysts are suitable for conducting aryl coupling reactions.

It may also be recognised that isomer separation may occur at any suitable stage in the synthetic sequence. It should be stressed that such chiral separation forms a key aspect of the invention and that such separation may be conducted in accordance with the methodology described herein or may be conducted in accordance with known methodology. It is also recognised that it may be beneficial to temporarily form a protected derivative of an intermediate in the synthesis, for example, a Boc-protected amine, or SEM-protected amide, in order to facilitate chromatographic separation, chiral resolution or to give improved solubility or yields in particular steps.

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and de-protecting functional groups, can be found in Protective Groups in Organic Synthesis (T. Green and P. Wuts; 4th Edition; John Wiley and Sons, 2007).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a *tert*-butyl ether; a tetrahydropyranyl (THP) ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or *tert*-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃).

An amine group may be protected, for example, as an amide (-NRCO-R) or a carbamate (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH₃); a benzyl carbamate (-NHCO-OCH₂C₆H₅, -NH-Cbz or NH-Z); as a *tert*-butyl carbamate (-NHCOOC(CH₃)₃, NH-Boc); a 2-biphenyl-2-propyl carbamate (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, NH-Boc), as a 9-fluorenylmethyl carbamate (-NH-Fmoc), as a 6-nitroveratryl carbamate (-NH-Nvoc), as a 2-trimethylsilylethyl carbamate (-NH-Teoc), as a 2,2,2-trichloroethyl carbamate (-NH-Troc), as an allyl carbamate (-NH-Alloc), or as a 2(-phenylsulfonyl)ethyl carbamate (-NH-Psec).

Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulfonyl (tosyl) and methanesulfonyl (mesyl) groups, benzyl groups such as a *para*-methoxybenzyl (PMB) group and tetrahydropyranyl (THP) groups.

5 A carboxylic acid group may be protected as an ester for example, as: an C₁₋₇ alkyl ester (e.g. a methyl ester; a *tert*-butyl ester); a C₁₋₇ haloalkyl ester (e.g. a C₁₋₇ trihaloalkyl ester); a triC₁₋₇ alkylsilyl-C₁₋₇ alkyl ester; or a C₅₋₂₀ aryl-C₁₋₇ alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester; *para*-methoxybenzyl ester).

10 It will be understood by those skilled in the art that certain compounds of the invention can be converted into other compounds of the invention according to standard chemical methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the
15 appropriate acid or acid derivative.

Therapeutic Utility

The compounds of the invention, subgroups and examples thereof, are inhibitors of Polθ polymerase activity, and which may be useful in preventing or treating disease states or
20 conditions described herein. In addition the compounds of the invention, and subgroups thereof, will be useful in preventing or treating diseases or condition mediated by Polθ. References to the preventing or prophylaxis or treatment of a disease state or condition such as cancer include within their scope alleviating or reducing the incidence of cancer.

25 Thus, for example, it is envisaged that the compounds of the invention will be useful in alleviating or reducing the incidence of cancer.

The compounds of the present invention may be useful for the treatment of the adult population. The compounds of the present invention may be useful for the treatment of the
30 pediatric population.

As a consequence of their inhibition of Polθ, the compounds will be useful in providing a means of disabling the ability of cells to perform MMEJ. It is therefore anticipated that the compounds may prove useful in treating or preventing proliferative disorders such as
35 cancers. In addition, the compounds of the invention may be useful in the treatment of diseases in which there is a disorder associated with cell accumulation.

Without being bound by theory it is expected that the Polθ inhibitors of the present invention will demonstrate certain properties for them to be of particular utility in the therapeutic treatment of certain cancers. For example, in one embodiment, the Polθ inhibitors of the present invention are suitably lethal in BRCA1 and BRCA2 deficient primary and secondary
5 solid tumours, including breast, ovarian, prostate and pancreas.

In a further embodiment, the Polθ inhibitors of the present invention are suitably lethal in a variety of primary and secondary solid tumours which are HRD by mechanisms other than BRCA deficiency, such as those with promoter hypermethylation. In these tumours where
10 no DSB repair pathway may be fully down regulated the Polθi may be given along with another DDR modulator such as a PARP inhibitor, a DNA-PK inhibitor, an ATR inhibitor, an ATM inhibitor, a wee1 inhibitor or a CHK1 inhibitor.

In a further embodiment, the Polθ inhibitors of the present invention are suitably lethal in
15 primary and secondary breast, ovarian, prostate and pancreatic tumours retaining BRCA1 deficiency but which, following or not following exposure to PARPi medication, are resistant to PARPi treatment.

In a further embodiment, the Polθ inhibitors of the present invention suitably increase the ORR
20 including CRR, will delay the onset of PARPi resistance, will increase the time to relapse and DFS, and will increase the OS of HRD (BRCA1/2 deficient and other HRD mechanisms) primary and secondary tumours (breast, ovarian, prostate and pancreas) when given with PARPi treatment programmes.

In a further embodiment, the Polθ inhibitors of the present invention suitably show synthetic
25 sickness and/or synthetic lethality in a variety of tumours with loss of ATM activity (ATM^{-/-}) particularly in the context of WT p53. Tumour types will include around 10% of all solid tumours including gastric, lung, breast, and CRC, along with CLL. Co-medicating with another DDR modifier, such as a DNA-PK inhibitor, PARP inhibitor or ATR inhibitor, may
30 further enhance such activity. Polθ inhibitors will resensitise CLL to classical chemotherapy and chemo-immunotherapy where drug resistance has emerged. Thus, according to a further embodiment, the pharmaceutical composition of the present invention additionally comprises a DNA-PK inhibitor, PARP inhibitor, or ATR inhibitor.

In a further embodiment, the Polθ inhibitors of the present invention suitably show synthetic
35 sickness and/or synthetic lethality in a variety of tumours deficient in the DNA double strand break repair process of non-homologous end-joining (NHEJ-D). Tumour types will include

approximately 2-10% of all solid tumours including prostate, pancreatic, cervical, breast, lung, bladder and oesophageal. Co-medicating with another DDR modifier, such as a PARP inhibitor, ATM inhibitor, wee1 inhibitor, CHK inhibitor, or ATR inhibitor, may further enhance such activity. Polθ inhibitors will further sensitise NHEJD cancer cells to DNA DSB inducing chemotherapies and to ionising radiation based therapies. Thus, according to a further embodiment, the pharmaceutical composition of the present invention additionally comprises a PARP inhibitor, ATM inhibitor, wee1 inhibitor, CHK inhibitor, or ATR inhibitor.

In a further embodiment, the Polθ inhibitors of the present invention suitably reduce the DNA replication stress response during the chemotherapy of HR proficient tumours such as ovarian, NSCL and breast tumours over expressing Polθ. This will increase the ORR to treatment and increase OS. Such effects are particularly likely with cytarabine (Ara-C) and hydroxyurea used in a wide variety of leukemias including CML, and the management of squamous cell carcinomas.

In a further embodiment, the Polθ inhibitors of the present invention suitably selectively sensitise solid tumours to radiotherapy, including EBRT and brachytherapy, with little or no sensitisation of normal tissues. In a fractionated curative-intent setting this will increase loco-regional control driving increased survival. This will be particularly evident in the management of NSCLC, SCCH&N, rectal cancer, prostate cancer and pancreatic cancer.

In a further embodiment, the Polθ inhibitors of the present invention suitably show synthetic sickness and/or synthetic lethality in PTEN deleted tumours such as CaP, with or without comedication with a PARPi. Furthermore, such tumours will exhibit exquisite sensitivity to radiotherapy both by dint of the PTEN deletion as well as the Polθ inhibitor induced radiosensitivity.

In a further embodiment, the Polθ inhibitors of the present invention suitably suppress TLS polymerase activity, sensitising primary and secondary solid tumours (e.g. breast, lung, ovarian, CRC) to drugs (e.g. cisplatin, mitomycin and cyclophosphamide) as well as reducing the acquisition of drug-induced mutations implicated in tumour resistance leading to prolongation of remission and increased TTR.

In a further embodiment, the Polθ inhibitors of the present invention suitably resensitise BCR-ABL-positive CML which has developed imatinib resistance, as well as other solid tumours with elevated ligase IIIα levels, reduced ligase IV levels and increased dependence upon altEJ DSB repair.

In a further embodiment, the Polθ inhibitors of the present invention suitably show synthetic sickness and/or synthetic lethality in aromatase inhibitor resistant ER⁻ primary and secondary breast cancers, again showing elevated ligase IIIα levels, reduced ligase IV levels and increased dependence upon altEJ DSB repair.

According to a further aspect of the invention there is provided a compound of formula (I) as defined herein for use in the treatment of tumours characterised by a deficiency in homologous recombination (HRD).

It will be appreciated that references herein to “deficiency in homologous recombination (HRD)” refer to any genetic variation which results in a deficiency or loss of function of the resultant homologous recombination gene. Examples of said genetic variation include mutations (e.g. point mutations), substitutions, deletions, single nucleotide polymorphisms (SNPs), haplotypes, chromosome abnormalities, Copy Number Variation (CNV), epigenetics, DNA inversions, reduction in expression and mis-localisation.

In one embodiment, said homologous recombination genes are selected from any of: ATM, ATR, BRCA1, BRCA2, BARD1, RAD51C, RAD50, CHEK1, CHEK2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, PALB2 (FANCN), FANCP (BTBD12), ERCC4 (FANQ), PTEN, CDK12, MRE11, NBS1, NBN, CLASPIN, BLM, WRN, SMARCA2, SMARCA4, LIG1, RPA1, RPA2, BRIP1 and PTEN.

It will be appreciated that references herein to “non-homologous end-joining deficiency (NHEJD)” refer to any genetic variation which results in a deficiency or loss of function of the resultant homologous recombination gene. Examples of said genetic variation include mutations (e.g. point mutations), substitutions, deletions, single nucleotide polymorphisms (SNPs), haplotypes, chromosome abnormalities, Copy Number Variation (CNV), epigenetics, DNA inversions, reduction in expression and mis-localisation.

In one embodiment, said non-homologous end-joining genes are selected from any one or more of: LIG4, NHEJ1, POLL, POLM, PRKDC, XRCC4, XRCC5, XRCC6, and DCLRE1C.

According to a further aspect of the invention there is provided a compound of formula (I) as defined herein for use in the treatment of tumours which overexpress Polθ.

According to a further aspect of the invention there is provided a compound of formula (I) as defined herein for use in the treatment of tumours which have elevated ligase III α levels, reduced ligase IV levels and increased dependence upon altEJ DSB repair.

- 5 Examples of cancers (and their benign counterparts) which may be treated (or inhibited) include, but are not limited to tumours of epithelial origin (adenomas and carcinomas of various types including adenocarcinomas, squamous carcinomas, transitional cell carcinomas and other carcinomas) such as carcinomas of the bladder and urinary tract, breast, gastrointestinal tract (including the esophagus, stomach (gastric), small intestine,
- 10 colon, rectum and anus), liver (hepatocellular carcinoma), gall bladder and biliary system, exocrine pancreas, kidney, lung (for example adenocarcinomas, small cell lung carcinomas, non-small cell lung carcinomas, bronchioalveolar carcinomas and mesotheliomas), head and neck (for example cancers of the tongue, buccal cavity, larynx, pharynx, nasopharynx, tonsil, salivary glands, nasal cavity and paranasal sinuses), ovary, fallopian tubes, peritoneum,
- 15 vagina, vulva, penis, cervix, myometrium, endometrium, thyroid (for example thyroid follicular carcinoma), adrenal, prostate, skin and adnexae (for example melanoma, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, dysplastic naevus); haematological malignancies (i.e. leukemias, lymphomas) and premalignant haematological disorders and disorders of borderline malignancy including haematological malignancies and related
- 20 conditions of lymphoid lineage (for example acute lymphocytic leukemia [ALL], chronic lymphocytic leukemia [CLL], B-cell lymphomas such as diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, MALT lymphoma, T-cell lymphomas and leukaemias, natural killer [NK] cell lymphomas, Hodgkin's lymphomas, hairy cell leukaemia, monoclonal gammopathy of uncertain significance,
- 25 plasmacytoma, multiple myeloma, and post-transplant lymphoproliferative disorders), and haematological malignancies and related conditions of myeloid lineage (for example acute myelogenous leukemia [AML], chronic myelogenous leukemia [CML], chronic myelomonocytic leukemia [CMML], hypereosinophilic syndrome, myeloproliferative disorders such as polycythaemia vera, essential thrombocythaemia and primary myelofibrosis,
- 30 myeloproliferative syndrome, myelodysplastic syndrome, and promyelocytic leukemia); tumours of mesenchymal origin, for example sarcomas of soft tissue, bone or cartilage such as osteosarcomas, fibrosarcomas, chondrosarcomas, rhabdomyosarcomas, leiomyosarcomas, liposarcomas, angiosarcomas, Kaposi's sarcoma, Ewing's sarcoma, synovial sarcomas, epithelioid sarcomas, gastrointestinal stromal tumours, benign and
- 35 malignant histiocytomas, and dermatofibrosarcoma protuberans; tumours of the central or peripheral nervous system (for example astrocytomas, gliomas and glioblastomas, meningiomas, ependymomas, pineal tumours and schwannomas); endocrine tumours (for

example pituitary tumours, adrenal tumours, islet cell tumours, parathyroid tumours, carcinoid tumours and medullary carcinoma of the thyroid); ocular and adnexal tumours (for example retinoblastoma); germ cell and trophoblastic tumours (for example teratomas, seminomas, dysgerminomas, hydatidiform moles and choriocarcinomas); and paediatric and embryonal tumours (for example medulloblastoma, neuroblastoma, Wilms tumour, and primitive neuroectodermal tumours); or syndromes, congenital or otherwise, which leave the patient susceptible to malignancy (for example Xeroderma Pigmentosum).

Many diseases are characterized by persistent and unregulated angiogenesis. Chronic proliferative diseases are often accompanied by profound angiogenesis, which can contribute to or maintain an inflammatory and/or proliferative state, or which leads to tissue destruction through the invasive proliferation of blood vessels. Tumour growth and metastasis have been found to be angiogenesis-dependent. Compounds of the invention may therefore be useful in preventing and disrupting initiation of tumour angiogenesis. In particular, the compounds of the invention may be useful in the treatment of metastasis and metastatic cancers.

Metastasis or metastatic disease is the spread of a disease from one organ or part to another non-adjacent organ or part. The cancers which can be treated by the compounds of the invention include primary tumours (i.e. cancer cells at the originating site), local invasion (cancer cells which penetrate and infiltrate surrounding normal tissues in the local area), and metastatic (or secondary) tumours i.e. tumours that have formed from malignant cells which have circulated through the bloodstream (haematogenous spread) or via lymphatics or across body cavities (trans-coelomic) to other sites and tissues in the body.

Particular cancers include hepatocellular carcinoma, melanoma, oesophageal, renal, colon, colorectal, lung e.g. mesothelioma or lung adenocarcinoma, breast, bladder, gastrointestinal, ovarian and prostate cancers.

A further aspect provides the use of a compound for the manufacture of a medicament for the treatment of a disease or condition as described herein, in particular cancer.

The compounds may also be useful in the treatment of tumour growth, pathogenesis, resistance to chemo- and radio-therapy by sensitising cells to chemotherapy and as an anti-metastatic agent.

The potency of the compounds of the invention as inhibitors of Polθ can be measured using the biological and biophysical assays set forth in the examples herein and the level of affinity exhibited by a given compound can be defined in terms of the IC₅₀ value. Particular compounds of the present invention are compounds having an IC₅₀ value of less than 1 μM, more particularly less than 0.1 μM.

A role for the loss of Polθ enhancing the efficacy of CRISPR mediated gene editing has been described in WO 2017/062754. Thus, Polθ inhibitory compounds are likely to be useful in enhancing the efficiency of CRISPR based editing methodologies and/or CRISPR based editing therapeutics. Furthermore, compound mediated Polθ inhibition is likely to reduce the frequency of random integration events and thus provide a route to ameliorate any safety concerns of CRISPR mediated technology. Thus, according to a further aspect of the invention, there is provided the use of a compound of formula (I) as defined herein in a CRISPR based editing methodology and/or CRISPR based editing therapeutics, such as the enhancement of efficiency of CRISPR based editing methodology and/or CRISPR based editing therapeutics.

Pharmaceutical Compositions

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation). In one embodiment this is a sterile pharmaceutical composition.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising (e.g admixing) at least one compound of formula (I) (and sub-groups thereof as defined herein), together with one or more pharmaceutically acceptable excipients and optionally other therapeutic or prophylactic agents, as described herein.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents, fillers or bulking agents, granulating agents, coating agents, release-controlling agents, binding agents, disintegrants, lubricating agents, preservatives, antioxidants, buffering agents, suspending agents, thickening agents, flavouring agents, sweeteners, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions. Examples of excipients for various types of pharmaceutical compositions are set out in more detail below.

The term “pharmaceutically acceptable” as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intrabronchial, sublingual, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery. The delivery can be by bolus injection, short term infusion or longer term infusion and can be via passive delivery or through the utilisation of a suitable infusion pump or syringe driver.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, co-solvents, surface active agents, organic solvent mixtures, cyclodextrin complexation agents, emulsifying agents (for forming and stabilizing emulsion formulations), liposome components for forming liposomes, gellable polymers for forming polymeric gels, lyophilisation protectants and combinations of agents for, *inter alia*, stabilising the active ingredient in a soluble form and rendering the formulation isotonic with the blood of the intended recipient. Pharmaceutical formulations for parenteral administration may also take the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents (R. G. Strickly, Solubilizing Excipients in oral and injectable formulations, Pharmaceutical Research, Vol 21(2) 2004, p 201-230).

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules, vials and prefilled syringes, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. In one embodiment, the formulation is provided as an active pharmaceutical ingredient in a bottle for subsequent reconstitution using an

appropriate diluent.

The pharmaceutical formulation can be prepared by lyophilising a compound of formula (I), or sub-groups thereof. Lyophilisation refers to the procedure of freeze-drying a composition.

5 Freeze-drying and lyophilisation are therefore used herein as synonyms.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

10 Pharmaceutical compositions of the present invention for parenteral injection can also comprise pharmaceutically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use.

15 Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as sunflower oil, safflower oil, corn oil or olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of thickening or coating
20 materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The compositions of the present invention may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the
25 action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include agents to adjust tonicity such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate
30 and gelatin.

In one particular embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion. For intravenous administration, the solution can be dosed as is, or can be injected into an infusion bag
35 (containing a pharmaceutically acceptable excipient, such as 0.9% saline or 5% dextrose), before administration.

In another particular embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or
5 uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

Thus, tablet compositions can contain a unit dosage of active compound together with an
10 inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and
15 granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

20

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the
25 active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated. Coatings may act either as a protective film (e.g. a polymer, wax or varnish) or as a mechanism for
30 controlling drug release or for aesthetic or identification purposes. The coating (e.g. a Eudragit TM type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum, duodenum, jejunum or colon.

35

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to

release the compound in a controlled manner in the gastrointestinal tract. Alternatively the drug can be presented in a polymer coating e.g. a polymethacrylate polymer coating, which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. In another alternative, the coating can be designed to disintegrate under microbial action in the gut. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations (for example formulations based on ion exchange resins) may be prepared in accordance with methods well known to those skilled in the art.

The compound of formula (I) may be formulated with a carrier and administered in the form of nanoparticles, the increased surface area of the nanoparticles assisting their absorption. In addition, nanoparticles offer the possibility of direct penetration into the cell. Nanoparticle drug delivery systems are described in "Nanoparticle Technology for Drug Delivery", edited by Ram B Gupta and Uday B. Kompella, Informa Healthcare, ISBN 9781574448573, published 13th March 2006. Nanoparticles for drug delivery are also described in J. Control. Release, 2003, 91 (1-2), 167-172, and in Sinha *et al.*, Mol. Cancer Ther. August 1, (2006) 5, 1909.

The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient or combination of excipients. Particularly, the compositions comprise from approximately 20% (w/w) to approximately 90%, % (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically acceptable excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, particularly from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, tablets or capsules.

The pharmaceutically acceptable excipient(s) can be selected according to the desired physical form of the formulation and can, for example, be selected from diluents (e.g solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), disintegrants, buffering agents, lubricants, flow aids, release controlling (e.g.

release retarding or delaying polymers or waxes) agents, binders, granulating agents, pigments, plasticizers, antioxidants, preservatives, flavouring agents, taste masking agents, tonicity adjusting agents and coating agents.

- 5 The skilled person will have the expertise to select the appropriate amounts of ingredients for use in the formulations. For example tablets and capsules typically contain 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition contain 0-99%
10 (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

- Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents,
15 and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

- Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the
20 mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragee cores or capsules. It is also possible for them to be incorporated into a polymer or waxy matrix that allow the active ingredients to diffuse or be released in measured amounts.

- The compounds of the invention can also be formulated as solid dispersions. Solid
25 dispersions are homogeneous extremely fine disperse phases of two or more solids. Solid solutions (molecularly disperse systems), one type of solid dispersion, are well known for use in pharmaceutical technology (see (Chiou and Riegelman, J. Pharm. Sci., 60, 1281-1300 (1971)) and are useful in increasing dissolution rates and increasing the bioavailability of poorly water-soluble drugs.

30

- This invention also provides solid dosage forms comprising the solid solution described above. Solid dosage forms include tablets, capsules, chewable tablets and dispersible or effervescent tablets. Known excipients can be blended with the solid solution to provide the desired dosage form. For example, a capsule can contain the solid solution blended with (a)
35 a disintegrant and a lubricant, or (b) a disintegrant, a lubricant and a surfactant. In addition a capsule can contain a bulking agent, such as lactose or microcrystalline cellulose. A tablet can contain the solid solution blended with at least one disintegrant, a lubricant, a surfactant,

a bulking agent and a glidant. A chewable tablet can contain the solid solution blended with a bulking agent, a lubricant, and if desired an additional sweetening agent (such as an artificial sweetener), and suitable flavours. Solid solutions may also be formed by spraying solutions of drug and a suitable polymer onto the surface of inert carriers such as sugar beads ('non-pareils'). These beads can subsequently be filled into capsules or compressed into tablets.

The pharmaceutical formulations may be presented to a patient in "patient packs" containing an entire course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in patient prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

Compositions for topical use and nasal delivery include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound. Solutions of the active compound may also be used for rectal administration.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administered in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the formula (I) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to

20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

10

Methods of Treatment

The compounds of the formula (I) and sub-groups as defined herein may be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by Polθ. Thus, according to a further aspect of the invention there is provided a method of treating a disease state or condition mediated by Polθ (e.g. cancer) which comprises administering to a subject in need thereof a compound of formula (I) as described herein. Examples of such disease states and conditions are set out above, and in particular include cancer.

The compounds are generally administered to a subject in need of such administration, for example a human or animal patient, particularly a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a continuous manner or in a manner that provides intermittent dosing (e.g. a pulsatile manner).

A typical daily dose of the compound of formula (I) can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 5 nanograms to 25 milligrams per kilogram of bodyweight, and more usually 10 nanograms to 15 milligrams per kilogram (e.g. 10 nanograms to 10 milligrams, and more typically 1 microgram per kilogram to 20

milligrams per kilogram, for example 1 microgram to 10 milligrams per kilogram) per kilogram of bodyweight although higher or lower doses may be administered where required. The compound of the formula (I) can be administered on a daily basis or on a repeat basis every 2, or 3, or 4, or 5, or 6, or 7, or 10 or 14, or 21, or 28 days for example.

5

The compounds of the invention may be administered orally in a range of doses, for example 1 to 1500 mg, 2 to 800 mg, or 5 to 500 mg, e.g. 2 to 200 mg or 10 to 1000 mg, particular examples of doses including 10, 20, 50 and 80 mg. The compound may be administered once or more than once each day. The compound can be administered continuously (i.e.

10 taken every day without a break for the duration of the treatment regimen). Alternatively, the compound can be administered intermittently (i.e. taken continuously for a given period such as a week, then discontinued for a period such as a week and then taken continuously for another period such as a week and so on throughout the duration of the treatment regimen).

Examples of treatment regimens involving intermittent administration include regimens

15 wherein administration is in cycles of one week on, one week off; or two weeks on, one week off; or three weeks on, one week off; or two weeks on, two weeks off; or four weeks on two weeks off; or one week on three weeks off - for one or more cycles, e.g. 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more cycles.

20 In one particular dosing schedule, a patient will be given an infusion of a compound of the formula (I) for periods of one hour daily for up to ten days in particular up to five days for one week, and the treatment repeated at a desired interval such as two to four weeks, in particular every three weeks.

25 More particularly, a patient may be given an infusion of a compound of the formula (I) for periods of one hour daily for 5 days and the treatment repeated every three weeks.

In another particular dosing schedule, a patient is given an infusion over 30 minutes to 1 hour followed by maintenance infusions of variable duration, for example 1 to 5 hours, e.g. 3
30 hours.

In a further particular dosing schedule, a patient is given a continuous infusion for a period of 12 hours to 5 days, in particular a continuous infusion of 24 hours to 72 hours.

35 In another particular dosing schedule, a patient is given the compound orally once a week.

In another particular dosing schedule, a patient is given the compound orally once-daily for between 7 and 28 days such as 7, 14 or 28 days.

5 In another particular dosing schedule, a patient is given the compound orally once-daily for 1 day, 2 days, 3 days, 5 days or 1 week followed by the required amount of days off to complete a one or two week cycle.

In another particular dosing schedule, a patient is given the compound orally once-daily for 2 weeks followed by 2 weeks off.

10

In another particular dosing schedule, a patient is given the compound orally once-daily for 2 weeks followed by 1 week off.

15

In another particular dosing schedule, a patient is given the compound orally once-daily for 1 week followed by 1 week off.

Ultimately, however, the quantity of compound administered and the type of composition used will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

20

It will be appreciated that Polθ inhibitors can be used as a single agent or in combination with other anticancer agents. Combination experiments can be performed, for example, as described in Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. Adv Enzyme Regulat 1984;22: 27–
25 55.

30

The compounds as defined herein can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds (or therapies) for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents or adjuvants (supporting agents in the therapy) in cancer therapy. Examples of other therapeutic agents or treatments that may be administered together (whether concurrently or at different time intervals) with the compounds
35 of the formula (I) include but are not limited to:

- Topoisomerase I inhibitors;
- Antimetabolites;

- Tubulin targeting agents;
- DNA binder and topoisomerase II inhibitors;
- Alkylating Agents;
- Monoclonal Antibodies;
- 5 • Anti-Hormones;
- Signal Transduction Inhibitors;
- Proteasome Inhibitors;
- DNA methyl transferase inhibitors;
- Cytokines and retinoids;
- 10 • Chromatin targeted therapies;
- Radiotherapy; and
- Other therapeutic or prophylactic agents.

Particular examples of anti-cancer agents or adjuvants (or salts thereof), include but are not
 15 limited to any of the agents selected from groups (i)-(xlvii), and optionally group (xlviii), below:

- (i) Platinum compounds, for example cisplatin (optionally combined with amifostine),
 carboplatin or oxaliplatin;
- (ii) Taxane compounds, for example paclitaxel, paclitaxel protein bound particles
 (Abraxane™), docetaxel, cabazitaxel or larotaxel;
- 20 (iii) Topoisomerase I inhibitors, for example camptothecin compounds, for example
 camptothecin, irinotecan(CPT11), SN-38, or topotecan;
- (iv) Topoisomerase II inhibitors, for example anti-tumour epipodophyllotoxins or
 podophyllotoxin derivatives for example etoposide, or teniposide;
- (v) Vinca alkaloids, for example vinblastine, vincristine, liposomal vincristine (Onco-TCS),
 vinorelbine, vindesine, vinflunine or vinvesir;
- 25 (vi) Nucleoside derivatives, for example 5-fluorouracil (5-FU, optionally in combination with
 leucovorin), gemcitabine, capecitabine, tegafur, UFT, S1, cladribine, cytarabine (Ara-C,
 cytosine arabinoside), fludarabine, clofarabine, or nelarabine;
- (vii) Antimetabolites, for example clofarabine, aminopterin, or methotrexate, azacitidine,
 cytarabine, floxuridine, pentostatin, thioguanine, thiopurine, 6-mercaptopurine, or
 hydroxyurea (hydroxycarbamide);
- 30 (viii) Alkylating agents, such as nitrogen mustards or nitrosourea, for example
 cyclophosphamide, chlorambucil, carmustine (BCNU), bendamustine, thiotepa,
 melphalan, treosulfan, lomustine (CCNU), altretamine, busulfan, dacarbazine,
 estramustine, fotemustine, ifosfamide (optionally in combination with mesna),
- 35

pipobroman, procarbazine, streptozocin, temozolomide, uracil, mechlorethamine, methylcyclohexylchloroethylnitrosurea, or nimustine (ACNU);

- (ix) Anthracyclines, anthracenediones and related drugs, for example daunorubicin, doxorubicin (optionally in combination with dexrazoxane), liposomal formulations of doxorubicin (eg. Caelyx™, Myocet™, Doxil™), idarubicin, mitoxantrone, epirubicin, amsacrine, or valrubicin;
- (x) Epothilones, for example ixabepilone, patupilone, BMS-310705, KOS-862 and ZK-EPO, epothilone A, epothilone B, desoxyepothilone B (also known as epothilone D or KOS-862), aza-epothilone B (also known as BMS-247550), aulimalide, isolaulimalide, or luetherobin;
- (xi) DNA methyl transferase inhibitors, for example temozolomide, azacytidine or decitabine, or SGI-110;
- (xii) Antifolates, for example methotrexate, pemetrexed disodium, or raltitrexed;
- (xiii) Cytotoxic antibiotics, for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, or mithramycin;
- (xiv) Tubulin-binding agents, for example combrestatin, colchicines or nocodazole;
- (xv) Signal Transduction inhibitors such as Kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, VEGFR (vascular endothelial growth factor receptor) inhibitors, PDGFR (platelet-derived growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), Raf inhibitors, mTOR inhibitors for example imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, dovotinib, axitinib, nilotinib, vandetanib, vatalinib, pazopanib, sorafenib, sunitinib, temsirolimus, everolimus (RAD 001), vemurafenib (PLX4032/RG7204), dabrafenib, encorafenib or an IκB kinase inhibitor such as SAR-113945, bardoxolone, BMS-066, BMS-345541, IMD-0354, IMD-2560, or IMD-1041, or MEK inhibitors such as Selumetinib (AZD6244) and Trametinib (GSK121120212);
- (xvi) Aurora kinase inhibitors for example AT9283, barasertib (AZD1152), TAK-901, MK0457 (VX680), cenisertib (R-763), danusertib (PHA-739358), alisertib (MLN-8237), or MP-470;
- (xvii) CDK inhibitors for example AT7519, roscovitine, seliciclib, alvocidib (flavopiridol), dinaciclib (SCH-727965), 7-hydroxy-staurosporine (UCN-01), JNJ-7706621, BMS-387032 (a.k.a. SNS-032), PHA533533, PD332991, ZK-304709, or AZD-5438;
- (xviii) PKA/B inhibitors and PKB (akt) pathway inhibitors for example AKT inhibitors such as KRX-0401 (perifosine/ NSC 639966), ipatasertib (GDC-0068; RG-7440), afuresertib (GSK-2110183; 2110183), MK-2206, MK-8156, AT13148, AZD-5363, triciribine phosphate (VQD-002; triciribine phosphate monohydrate (API-2; TCN-P; TCN-PM; VD-0002), RX-0201, NL-71-101, SR-13668, PX-316, AT13148, AZ-5363, Semaphore, SF1126, or Enzastaurin HCl (LY317615) or mTOR inhibitors such as rapamycin

- analogues such as RAD 001 (everolimus), CCI 779 (temsirolemus), AP23573 and ridaforolimus, sirolimus (originally known as rapamycin), AP23841 and AP23573, calmodulin inhibitors e.g. CBP-501 (forkhead translocation inhibitors), enzastaurin HCl (LY317615) or PI3K Inhibitors such as dactolisib (BEZ235), buparlisib (BKM-120; NVP-BKM-120), BYL719, copanlisib (BAY-80-6946), ZSTK-474, CUDC-907, apitolisib (GDC-0980; RG-7422), pictilisib (pictrelisib, GDC-0941, RG-7321), GDC-0032, GDC-0068, GSK-2636771, idelalisib (formerly CAL-101, GS 1101, GS-1101), MLN1117 (INK1117), MLN0128 (INK128), IPI-145 (INK1197), LY-3023414, ipatasertib, afuresertib, MK-2206, MK-8156, LY-3023414, LY294002, SF1126 or PI-103, or sonolisib (PX-866);
- 5 (xix) Hsp90 inhibitors for example AT13387, herbimycin, geldanamycin (GA), 17-allylamino-17-desmethoxygeldanamycin (17-AAG) e.g. NSC-330507, Kos-953 and CNF-1010, 17-dimethylaminoethylamino-17-demethoxygeldanamycin hydrochloride (17-DMAG) e.g. NSC-707545 and Kos-1022, NVP-AUY922 (VER-52296), NVP-BEP800, CNF-2024 (BIIB-021 an oral purine), ganetespib (STA-9090), SNX-5422 (SC-102112) or IPI-504;
- 10 (xx) Monoclonal Antibodies (unconjugated or conjugated to radioisotopes, toxins or other agents), antibody derivatives and related agents, such as anti-CD, anti-VEGFR, anti-HER2, anti-CTLA4, anti-PD-1 or anti-EGFR antibodies, for example rituximab (CD20), ofatumumab (CD20), ibritumomab tiuxetan (CD20), GA101 (CD20), tositumomab (CD20), epratuzumab (CD22), lintuzumab (CD33), gemtuzumab ozogamicin (CD33),
- 15 alemtuzumab (CD52), galiximab (CD80), trastuzumab (HER2 antibody), pertuzumab (HER2), trastuzumab-DM1 (HER2), ertumaxomab (HER2 and CD3), cetuximab (EGFR), panitumumab (EGFR), necitumumab (EGFR), nimotuzumab (EGFR), bevacizumab (VEGF), catumaxumab (EpCAM and CD3), abagovomab (CA125), farletuzumab (folate receptor), elotuzumab (CS1), denosumab (RANK ligand),
- 20 figitumumab (IGF1R), CP751,871 (IGF1R), mapatumumab (TRAIL receptor), metMAB (met), mitumomab (GD3 ganglioside), naptumomab estafenatox (5T4), siltuximab (IL6), or immunomodulating agents such as CTLA-4 blocking antibodies and/or antibodies against PD-1 and PD-L1 and/or PD-L2 for example ipilimumab (CTLA4), MK-3475 (pembrolizumab, formerly lambrolizumab, anti-PD-1), nivolumab (anti-PD-1), BMS-
- 25 936559 (anti- PD-L1), MPDL320A, AMP-514 or MEDI4736 (anti-PD-L1), or tremelimumab (formerly ticilimumab, CP-675,206, anti-CTLA-4);
- (xxi) Estrogen receptor antagonists or selective estrogen receptor modulators (SERMs) or inhibitors of estrogen synthesis, for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, or raloxifene;
- 30 (xxii) Aromatase inhibitors and related drugs, such as exemestane, anastrozole, letrozole, testolactone aminoglutethimide, mitotane or vorozole;

- (xxiii) Antiandrogens (i.e. androgen receptor antagonists) and related agents for example bicalutamide, nilutamide, flutamide, cyproterone, or ketoconazole;
- (xxiv) Hormones and analogues thereof such as medroxyprogesterone, diethylstilbestrol (a.k.a. diethylstilboestrol) or octreotide;
- 5 (xxv) Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), fluoxymestrone or gossypol,
- (xxvi) Steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone;
- (xxvii) Gonadotropin releasing hormone agonists or antagonists (GnRAs) for example
- 10 abarelix, goserelin acetate, histrelin acetate, leuprolide acetate, triptorelin, buserelin, or deslorelin;
- (xxviii) Glucocorticoids, for example prednisone, prednisolone, dexamethasone;
- (xxix) Differentiating agents, such as retinoids, rexinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane, alitretinoin,
- 15 bexarotene, or tretinoin;
- (xxx) Farnesyltransferase inhibitors for example tipifarnib;
- (xxxi) Chromatin targeted therapies such as histone deacetylase (HDAC) inhibitors for example panobinostat, resminostat, abexinostat, vorinostat, romidepsin, belinostat, entinostat, quisinostat, pracinostat, tefinostat, mocetinostat, givinostat, CUDC-907,
- 20 CUDC-101, ACY-1215, MGCD-290, EVP-0334, RG-2833, 4SC-202, romidepsin, AR-42 (Ohio State University), CG-200745, valproic acid, CKD-581, sodium butyrate, suberoylanilide hydroxamide acid (SAHA), depsipeptide (FR 901228), dacinostat (NVP-LAQ824), R306465/ JNJ-16241199, JNJ-26481585, trichostatin A, chlamydocin, A-173, JNJ-MGCD-0103, PXD-101, or apicidin;
- 25 (xxxii) Proteasome Inhibitors for example bortezomib, carfilzomib, delanzomib (CEP-18770), ixazomib (MLN-9708), oprozomib (ONX-0912) or marizomib;
- (xxxiii) Photodynamic drugs for example porfimer sodium or temoporfin;
- (xxxiv) Marine organism-derived anticancer agents such as trabectedin;
- (xxxv) Radiolabelled drugs for radioimmunotherapy for example with a beta particle-emitting
- 30 isotope (e.g. , Iodine -131, Yttrium -90) or an alpha particle-emitting isotope (e.g., Bismuth-213 or Actinium-225) for example ibritumomab or Iodine tositumomab;
- (xxxvi) Telomerase inhibitors for example telomestatin;
- (xxxvii) Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat or metastat;
- 35 (xxxviii) Recombinant interferons (such as interferon- γ and interferon α) and interleukins (e.g. interleukin 2), for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, or peginterferon alfa 2b;

- (xxxix) Selective immunoresponse modulators for example thalidomide, or lenalidomide;
- (xl) Therapeutic Vaccines such as sipuleucel-T (Provenge) or OncoVex;
- (xli) Cytokine-activating agents include Picibanil, Romurtide, Sizofiran, Virulizin, or Thymosin;
- 5 (xlii) Arsenic trioxide;
- (xliii) Inhibitors of G-protein coupled receptors (GPCR) for example atrasentan;
- (xliv) Enzymes such as L-asparaginase, pegaspargase, rasburicase, or pegademase;
- (xlv) DNA repair inhibitors such as PARP inhibitors for example, olaparib, velaparib, iniparib, rucaparib (AG-014699 or PF-01367338), talazoparib or AG-014699;
- 10 (xlvii) DNA damage response inhibitors such as ATM inhibitors AZD0156 MS3541, ATR inhibitors AZD6738, M4344, M6620 wee1 inhibitor AZD1775;
- (xlviii) Agonists of Death receptor (e.g. TNF-related apoptosis inducing ligand (TRAIL) receptor), such as mapatumumab (formerly HGS-ETR1), conatumumab (formerly AMG 655), PRO95780, lexatumumab, dulanermin, CS-1008, apomab or recombinant TRAIL
- 15 ligands such as recombinant Human TRAIL/Apo2 Ligand;
- (xlviii) Prophylactic agents (adjuncts); i.e. agents that reduce or alleviate some of the side effects associated with chemotherapy agents, for example
- anti-emetic agents,
 - agents that prevent or decrease the duration of chemotherapy-associated

20 neutropenia and prevent complications that arise from reduced levels of platelets, red blood cells or white blood cells, for example interleukin-11 (e.g. oprelvekin), erythropoietin (EPO) and analogues thereof (e.g. darbepoetin alfa), colony-stimulating factor analogs such as granulocyte macrophage-colony stimulating factor (GM-CSF) (e.g. sargramostim), and granulocyte-colony stimulating factor (G-CSF)

25 and analogues thereof (e.g. filgrastim, pegfilgrastim),

 - agents that inhibit bone resorption such as denosumab or bisphosphonates e.g. zoledronate, zoledronic acid, pamidronate and ibandronate,
 - agents that suppress inflammatory responses such as dexamethasone, prednisone, and prednisolone,

30 – agents used to reduce blood levels of growth hormone and IGF-I (and other hormones) in patients with acromegaly or other rare hormone-producing tumours, such as synthetic forms of the hormone somatostatin e.g. octreotide acetate,

 - antidote to drugs that decrease levels of folic acid such as leucovorin, or folinic acid,
 - agents for pain e.g. opiates such as morphine, diamorphine and fentanyl,

35 – non-steroidal anti-inflammatory drugs (NSAID) such as COX-2 inhibitors for example celecoxib, etoricoxib and lumiracoxib,

 - agents for mucositis e.g. palifermin,

- agents for the treatment of side-effects including anorexia, cachexia, oedema or thromboembolic episodes, such as megestrol acetate.

In one embodiment the anticancer is selected from recombinant interferons (such as
5 interferon- γ and interferon α) and interleukins (e.g. interleukin 2), for example aldesleukin,
denileukin diftitox, interferon alfa 2a, interferon alfa 2b, or peginterferon alfa 2b; interferon- α 2
(500 μ /ml) in particular interferon- β ; and signal transduction inhibitors such as kinase
inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, VEGFR (vascular
endothelial growth factor receptor) inhibitors, PDGFR (platelet-derived growth factor
10 receptor) inhibitors, MTKI (multi target kinase inhibitors), Raf inhibitors, mTOR inhibitors for
example imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, dovotinib, axitinib,
nilotinib, vandetanib, vatalinib, pazopanib, sorafenib, sunitinib, temsirolimus, everolimus
(RAD 001), vemurafenib (PLX4032/RG7204), dabrafenib, encorafenib or an I κ B kinase
inhibitor such as SAR-113945, bardoxolone, BMS-066, BMS-345541, IMD-0354, IMD-2560,
15 or IMD-1041, or MEK inhibitors such as Selumetinib (AZD6244) and Trametinib
(GSK121120212), in particular Raf inhibitors (e.g. vemurafenib) or MEK inhibitors (e.g.
trametinib).

Each of the compounds present in the combinations of the invention may be given in
20 individually varying dose schedules and via different routes. As such, the posology of each
of the two or more agents may differ: each may be administered at the same time or at
different times. A person skilled in the art would know through his or her common general
knowledge the dosing regimes and combination therapies to use. For example, the
compound of the invention may be using in combination with one or more other agents
25 which are administered according to their existing combination regimen. Examples of
standard combination regimens are provided below.

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per
square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2 , particularly for
30 paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2
per course of treatment.

The camptothecin compound is advantageously administered in a dosage of 0.1 to
400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2 ,
35 particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about
1 to 2 mg/m^2 per course of treatment.

The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250 mg/m^2 , particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

5

The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2 , for vincristine in a dosage of about 1 to 2 mg/m^2 , and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

10

The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to 1500 mg/m^2 , particularly for 5-FU in a dosage of 200 to 500 mg/m^2 , for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 2500 mg/m^2 per course of treatment.

15

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2 , particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

20

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2 , particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2 , for daunorubicin in a dosage of about 25 to 45 mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

25

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, particularly 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a

30

35

day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

- 5 Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m^2) of body surface area, or as known in the art, if different. Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m^2) of body surface area, particularly 2 to 4mg/m^2 per course of treatment.
- 10 Where the compound of the formula (I) is administered in combination therapy with one, two, three, four or more other therapeutic agents (particularly one or two, more particularly one), the compounds can be administered simultaneously or sequentially. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. When
- 15 administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s). These dosages may be administered for example once, twice or more per course of treatment, which may be
- 20 repeated for example every 7, 14, 21 or 28 days.

In one embodiment is provided a compound of formula (I) for the manufacture of a medicament for use in therapy wherein said compound is used in combination with one, two, three, or four other therapeutic agents. In another embodiment is provided a medicament for

25 treating cancer which comprises a compound of formula (I) wherein said medicament is used in combination with one, two, three, or four other therapeutic agents. The invention further provides use of a compound of formula (I) for the manufacture of a medicament for enhancing or potentiating the response rate in a patient suffering from a cancer where the patient is being treated with one, two, three, or four other therapeutic agents.

30

It will be appreciated that the particular method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the

35 particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends
5 on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the
10 effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

15 The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

20 The compounds of the present invention also have therapeutic applications in sensitising tumour cells for radiotherapy and chemotherapy. Hence the compounds of the present invention can be used as "radiosensitizer" and/or "chemosensitizer" or can be given in combination with another "radiosensitizer" and/or "chemosensitizer". In one embodiment the compound of the invention is for use as chemosensitiser.

25 The term "radiosensitizer" is defined as a molecule administered to patients in therapeutically effective amounts to increase the sensitivity of the cells to ionizing radiation and/or to promote the treatment of diseases which are treatable with ionizing radiation.

30 The term "chemosensitizer" is defined as a molecule administered to patients in therapeutically effective amounts to increase the sensitivity of cells to chemotherapy and/or promote the treatment of diseases which are treatable with chemotherapeutics.

In one embodiment the compound of the invention is administered with a "radiosensitizer"
35 and/or "chemosensitizer". In one embodiment the compound of the invention is administered with an "immune sensitizer".

The term “immune sensitizer” is defined as a molecule administered to patients in therapeutically effective amounts to increase the sensitivity of cells to a Polθ inhibitor.

Many cancer treatment protocols currently employ radiosensitizers in conjunction with radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylnisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, tin etioporphyrin, pheorbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds of the invention; compounds which promote the incorporation of radiosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour with or without additional radiation; or other therapeutically effective compounds for treating cancer or other diseases.

Chemosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds of the invention; compounds which promote the incorporation of chemosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour or other therapeutically effective compounds for treating cancer or other disease. Calcium antagonists, for example verapamil, are found useful in combination with antineoplastic agents to establish chemosensitivity in tumor cells resistant to accepted chemotherapeutic agents and to potentiate the efficacy of such compounds in drug-sensitive malignancies.

Examples of immune sensitizers include the following, but are not limited to: immunomodulating agents, for example monoclonal antibodies such as immune checkpoint antibodies [e.g. CTLA-4 blocking antibodies and/or antibodies against PD-1 and PD-L1

and/or PD-L2 for example ipilimumab (CTLA4), MK-3475 (pembrolizumab, formerly
lambrolizumab, anti-PD-1), nivolumab (anti-PD-1), BMS-936559 (anti- PD-L1), MPDL320A,
AMP-514 or MEDI4736 (anti-PD-L1), or tremelimumab (formerly ticilimumab, CP-675,206,
anti-CTLA-4)]; or Signal Transduction inhibitors; or cytokines (such as recombinant
5 interferons); or oncolytic viruses; or immune adjuvants (e.g. BCG).

Immune sensitizers may be administered in conjunction with a therapeutically effective
amount of one or more other compounds, including but not limited to: compounds of the
invention; compounds which promote the incorporation of immune sensitizers to the target
10 cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the
target cells; therapeutic agents which act on the tumour or other therapeutically effective
compounds for treating cancer or other disease.

For use in combination therapy with another chemotherapeutic agent, the compound of the
15 formula (I) and one, two, three, four or more other therapeutic agents can be, for example,
formulated together in a dosage form containing two, three, four or more therapeutic agents
i.e. in a unitary pharmaceutical composition containing all agents. In an alternative
embodiment, the individual therapeutic agents may be formulated separately and presented
together in the form of a kit, optionally with instructions for their use.

20 In one embodiment is provided a combination of a compound of formula (I) with one or more
(e.g. 1 or 2) other therapeutic agents (e.g. anticancer agents as described above). In a
further embodiment is provided a combination of a Polθ inhibitor as described herein and a
PI3K/AKT pathway inhibitor selected from: apitolisib, buparlisib, Copanlisib, pictilisib, ZSTK-
25 474, CUDC-907, GSK-2636771, LY-3023414, ipatasertib, afuresertib, MK-2206, MK-8156,
Idelalisib, BEZ235 (dactolisib), BYL719, GDC- 0980, GDC-0941, GDC-0032 and GDC-0068.

In another embodiment is provided a compound of formula (I) in combination with one or
more (e.g. 1 or 2) other therapeutic agents (e.g. anticancer agents) for use in therapy, such
30 as in the prophylaxis or treatment of cancer.

In one embodiment the pharmaceutical composition comprises a compound of formula (I)
together with a pharmaceutically acceptable carrier and optionally one or more therapeutic
agent(s).

In another embodiment the invention relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting the growth of tumour cells.

- 5 In a further embodiment the invention relates to a product containing a compound of formula (I) and one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

EXAMPLES

- 10 The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

Abbreviations

	aq.	Aqueous
15	BOC	<i>tert</i> -Butyloxycarbonyl
	CDI	1,1'-Carbonyldiimidazole
	DCM	Dichloromethane
	DIBAL-H	Diisobutylaluminium hydride
	DIPEA	<i>N,N</i> -Diisopropylethylamine
20	DMF	<i>N,N</i> -Dimethylformamide
	DMF-DMA	<i>N,N</i> -Dimethylformamide dimethyl acetal
	DMSO	Dimethylsulfoxide
	ES	Electrospray
	EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
25	EtOH	Ethanol
	EtOAc	Ethyl acetate
	h	hour(s)
	HATU	1-[Bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxid hexafluorophosphate
30	HPLC	High-performance liquid chromatography
	MeCN	Acetonitrile
	MeOH	Methanol
	min	minutes
	NMO	4-Methylmorpholine 4-oxide
35	NMP	<i>N</i> -Methylpyrrolidinone
	NMR	Nuclear magnetic resonance
	OAc	Acetate

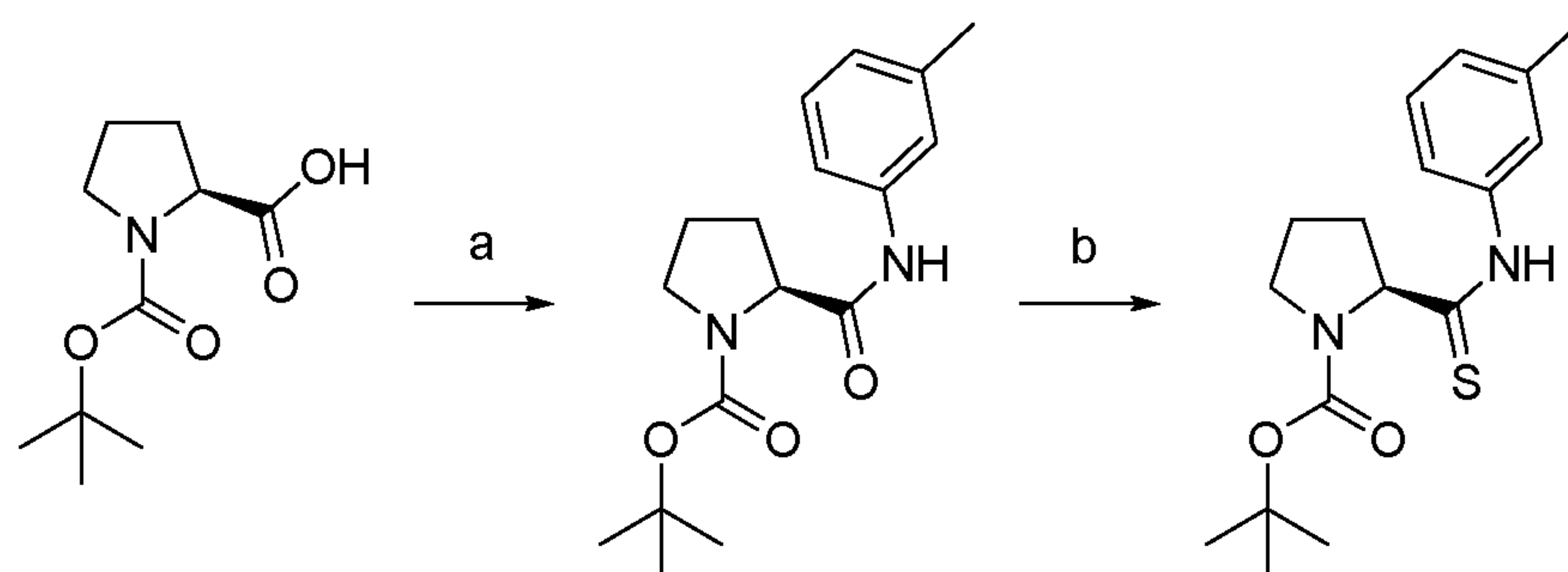
	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
	PE	Petroleum ether
	RuPhos-Pd-G2	Chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
5	rt	Room temperature or ambient temperature
	SFC	Supercritical Fluid Chromatography
	TBAF	Tetra- <i>n</i> -butylammonium fluoride
	TBDPSCI	tert-Butyl(chloro)diphenylsilane
	TEA	Triethylamine
10	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography (silica plates)
	XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

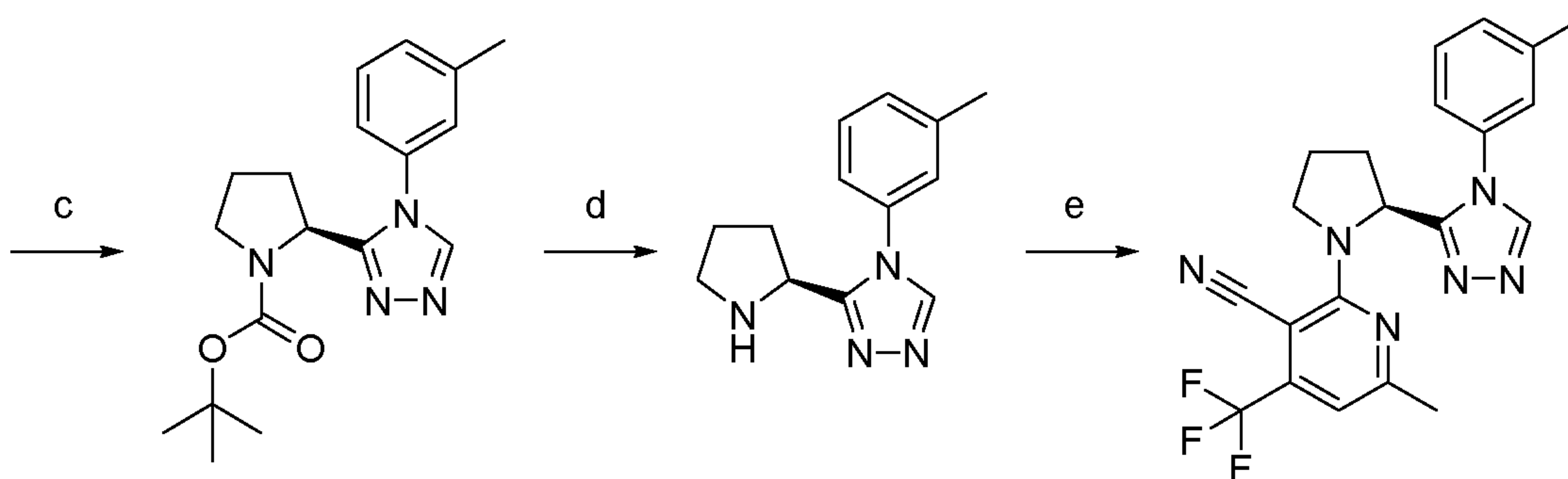
15 Typical Preparative HPLC method

For purification of samples by prep-HPLC the following columns were typically used; Waters XBridge, Xtimate C18, Phenomenex Gemini, Phenomenex Synergi C18, Luna C18 and Shim-pack C18. Typical mobile phases used were water and MeCN, with either acidic or basic additives (typically at 0.05 – 0.1% v/v), such as formic acid, TFA, ammonium bicarbonate or ammonium hydroxide. A typical method started with 95% water:5% MeCN and decreasingly polar ratios of water and MeCN over a period of 5 to 12 min, with a typical flow rate of 25 mL/min. For mass-directed HPLC the typical mass spectrometer used was a Waters 3100 which detected masses between 100 and 700 g/mol.

25 Example 1

(S)-6-Methyl-2-(2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)-nicotinonitrile





Step a. To a solution of (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.00 g, 4.65 mmol), 3-methylaniline (547 mg, 5.11 mmol) in DMF (15 mL) was added HATU (1.94 g, 5.11 mmol) and DIPEA (1.80 g, 13.9 mmol). The mixture was stirred at rt for 12 h. The reaction mixture was quenched by addition of water (110 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/1) to give compound (*S*)-*tert*-butyl 2-(*m*-tolylcarbamoyl)pyrrolidine-1-carboxylate (1.42 g, 95% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 305.2

Step b. To a solution of (*S*)-*tert*-butyl 2-(*m*-tolylcarbamoyl)pyrrolidine-1-carboxylate (1.00 g, 3.29 mmol) in toluene (20 mL) was added Lawesson's reagent (1.46 g, 3.61 mmol). The mixture was stirred at 90°C for 2 h. Upon completion, the reaction mixture was quenched by addition of water (60 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 3/1) to give (*S*)-*tert*-butyl 2-(*m*-tolylcarbamothioyl)pyrrolidine-1-carboxylate (1.23 g, 95% yield) as a brown solid.

m/z ES⁺ [M+H]⁺ 321.2

Step c. To a solution of (*S*)-*tert*-butyl 2-(*m*-tolylcarbamothioyl)pyrrolidine-1-carboxylate (500 mg, 1.56 mmol), formohydrazide (187 mg, 3.12 mmol) in MeCN (10 mL) was added Hg(OAc)₂ (994 mg, 3.12 mmol). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to EtOAc/MeOH = 5/1) to give (*S*)-*tert*-butyl 2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (620 mg, crude) as a brown solid.

m/z ES⁺ [M+H]⁺ 329.2

Step d. To a solution of (*S*)-*tert*-butyl 2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (620 mg, 1.89 mmol) in dioxane (2 mL) was added HCl/dioxane (4 M, 4.72 mL). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was evaporated to give compound (*S*)-3-(pyrrolidin-2-yl)-4-(*m*-tolyl)-4*H*-1,2,4-triazole (520 mg, crude, HCl salt) as a light yellow solid.

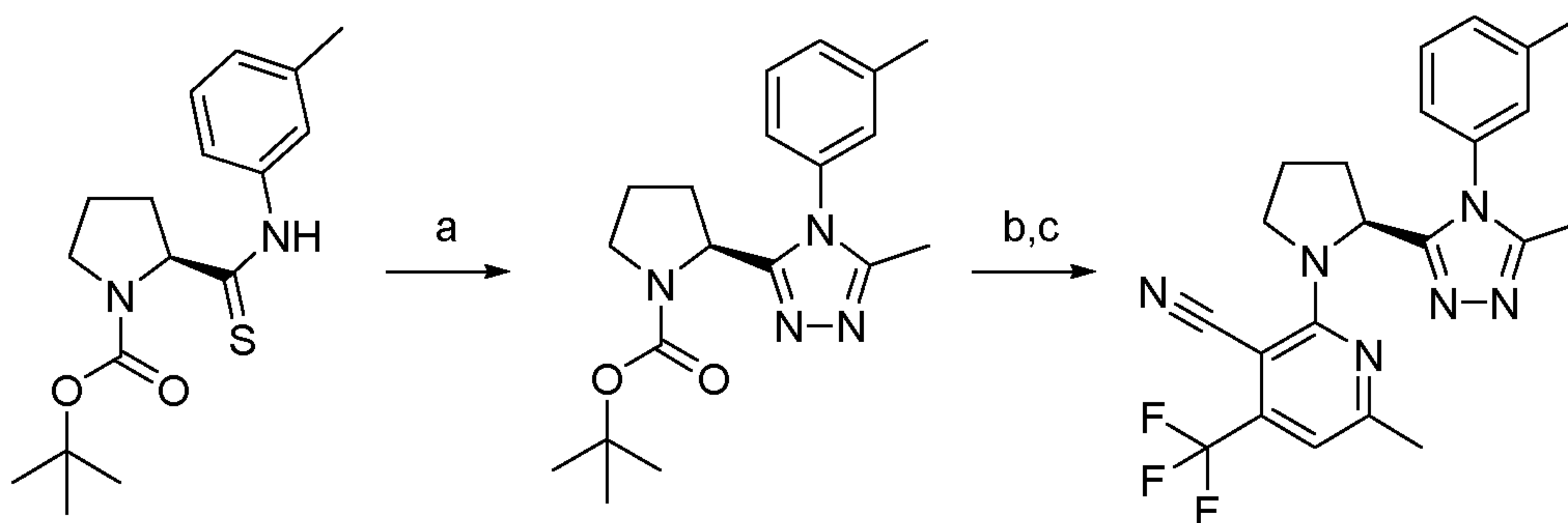
m/z ES⁺ [M+H]⁺ 229.2

Step e. To a solution of (S)-3-(pyrrolidin-2-yl)-4-(*m*-tolyl)-4*H*-1,2,4-triazole (520 mg, 1.96 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (650 mg, 2.95 mmol) in NMP (8 mL) was added DIPEA (761 mg, 5.89 mmol). The mixture was stirred at 70°C for 12 h. Upon completion, the reaction mixture was quenched by addition of water (120 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (39 mg, 5% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 413.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.88 (s, 1H), 7.52 - 7.43 (m, 1H), 7.40 - 7.28 (m, 3H), 7.05 (s, 1H), 5.44 - 5.35 (m, 1H), 4.08 - 3.96 (m, 1H), 3.94 - 3.84 (m, 1H), 2.50 (s, 3H), 2.27 (s, 3H), 2.25 - 2.15 (m, 2H), 2.10 - 2.02 (m, 2H).

Example 2

(S)-6-Methyl-2-(2-(5-methyl-4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile



Step a. To a solution of (S)-*tert*-butyl 2-(*m*-tolylcarbamothioyl)pyrrolidine-1-carboxylate (320 mg, 1.00 mmol), acetohydrazide (148 mg, 2.00 mmol) in MeCN (15 mL) was added Hg(OAc)₂ (477 mg, 1.50 mmol). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to EtOAc/MeOH = 5/2) to give (S)-*tert*-butyl 2-(5-methyl-4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate as a light yellow solid.

m/z ES⁺ [M+H]⁺ 343.2

Step b. To a solution of (S)-*tert*-butyl 2-(5-methyl-4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (300 mg, 0.88 mmol) in MeOH (3 mL) was added HCl/dioxane (4 M, 2.19 mL). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was evaporated to give compound (S)-3-methyl-5-(pyrrolidin-2-yl)-4-(*m*-tolyl)-4*H*-1,2,4-triazole (240 mg, 98% yield, HCl salt) as a light yellow solid which was used in the next step directly.

m/z ES⁺ [M+H]⁺ 243.2

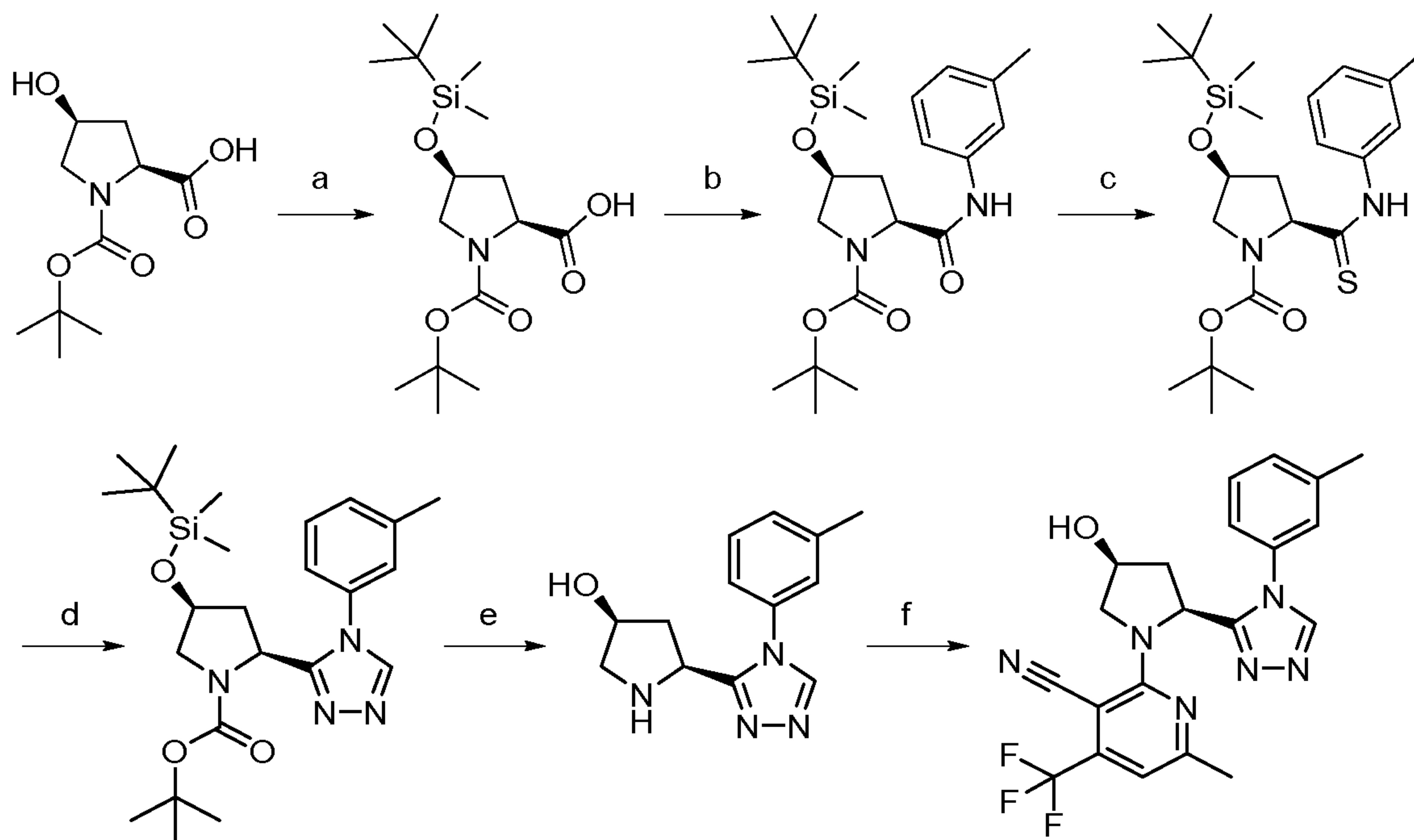
Step c. To a solution of (S)-3-methyl-5-(pyrrolidin-2-yl)-4-(*m*-tolyl)-4*H*-1,2,4-triazole (240 mg, 0.99 mmol), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (284 mg, 1.29 mmol) in DMF (10 mL) was added DIPEA (384 mg, 2.97 mmol). The mixture was stirred at 90°C for 12 h.

Upon completion, the reaction mixture was quenched by addition of water (120 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (83 mg, 19% yield) as a yellow solid.

5 m/z ES+ [M+H]⁺ 427.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.60 - 7.25 (m, 4H), 7.12 (s, 1H), 5.33 - 5.20 (m, 1H), 4.01 - 3.78 (m, 2H), 2.38 (s, 6H), 2.32 (s, 3H), 2.24 - 1.99 (m, 4H).

Example 3

10 **2-((2S,4S)-4-Hydroxy-2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile**



15 **Step a.** A mixture of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (5.00 g, 21.6 mmol), *tert*-butylchlorodimethylsilane (3.91 g, 25.9 mmol), imidazole (2.21 g, 32.4 mmol) in DCM (30 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at rt for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by addition of aq. NH₄Cl solution (60 mL) and water (100 mL), and then extracted with DCM (200 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated to give (2S,4S)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid (7.2 g, crude) as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 4.42 - 4.20 (m, 1H), 4.26 - 4.07 (m, 1H), 3.64 - 3.44 (m, 1H), 3.14 - 2.99 (m, 1H), 2.43 - 2.31 (m, 1H), 1.91 - 1.76 (m, 1H), 1.40 - 1.33 (m, 9H), 0.85 - 0.76 (m, 9H), 0.23 - 0.16 (m, 6H).

25 **Step b.** To a solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid (1 g, 2.89 mmol), 3-methylaniline (376 mg, 3.47 mmol) in

pyridine (2 mL) was added propylphosphonic anhydride (5.53 g, 50% wt. % in DMF). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was evaporated to give a residue. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 5/1) to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(*m*-tolyl/carbamoyl)pyrrolidine-1-carboxylate (688 mg, 49% yield) as a yellow oil.

m/z ES+ [M+H]⁺ 436.3

Step c. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(*m*-tolyl/carbamoyl)pyrrolidine-1-carboxylate (1.00 g, 3.29 mmol) in toluene (20 mL) was added Lawesson's reagent (1.46 g, 3.61 mmol). The mixture was stirred at 90°C for 2 h. Upon completion, the reaction mixture was quenched by addition of water (60 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 3/1) to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(*m*-tolyl/carbamothioyl)pyrrolidine-1-carboxylate (550 mg, 45% yield) as a brown solid.

m/z ES+ [M+H]⁺ 451.3

Step d. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(*m*-tolyl/carbamothioyl)pyrrolidine-1-carboxylate (500 mg, 1.11 mmol), formohydrazide (200 mg, 3.33 mmol) in MeCN (10 mL) was added Hg(OAc)₂ (707 mg, 2.22 mmol). The mixture was stirred at rt for 12 h. The reaction mixture was filtered and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 5/1) to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (288 mg, crude) as a red solid.

m/z ES+ [M+H]⁺ 459.2

Step e. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (300 mg, 0.88 mmol) in MeOH (3 mL) was added HCl/dioxane (4 M, 2.19 mL). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was evaporated to give (3*S*,5*S*)-5-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)-pyrrolidin-3-ol (240 mg, 98% yield, HCl salt) as a yellow solid which was used in the next step directly.

m/z ES+ [M+H]⁺ 245.2

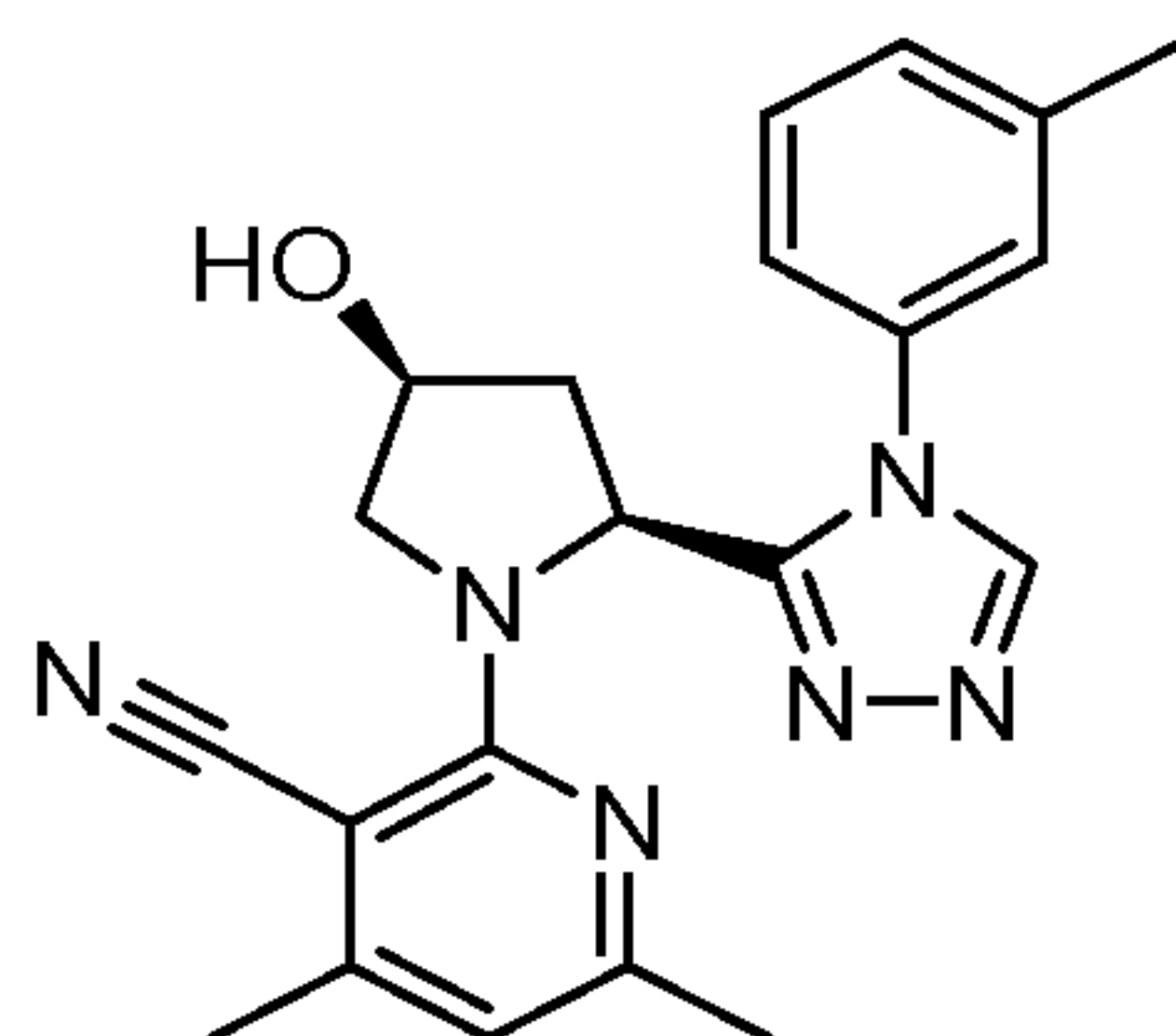
Step f. To a solution of (3*S*,5*S*)-5-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-3-ol (140 mg, 0.57 mmol), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (190 mg, 0.86 mmol) in NMP (10 mL) was added DIPEA (222 mg, 1.72 mmol). The mixture was stirred at 60°C for 12 h. Upon completion, the reaction mixture was quenched by addition of water (120 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (5 mg, 20% yield) as a yellow solid.

m/z ES+ [M+H]⁺ 429.2; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.95 – 8.90 (m, 1H), 7.53 – 7.46 (m, 1H), 7.43 – 7.38 (m, 1H), 7.36 – 7.28 (m, 2H), 7.08 (s, 1H), 5.45 (t, *J* = 7.2 Hz, 1H), 4.48 – 4.35 (m, 1H), 4.01 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.77 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.58 – 2.54 (m, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.17 – 2.06 (m, 1H).

5

Example 4

2-((2*S*,4*S*)-4-Hydroxy-2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-4,6-dimethylnicotinonitrile



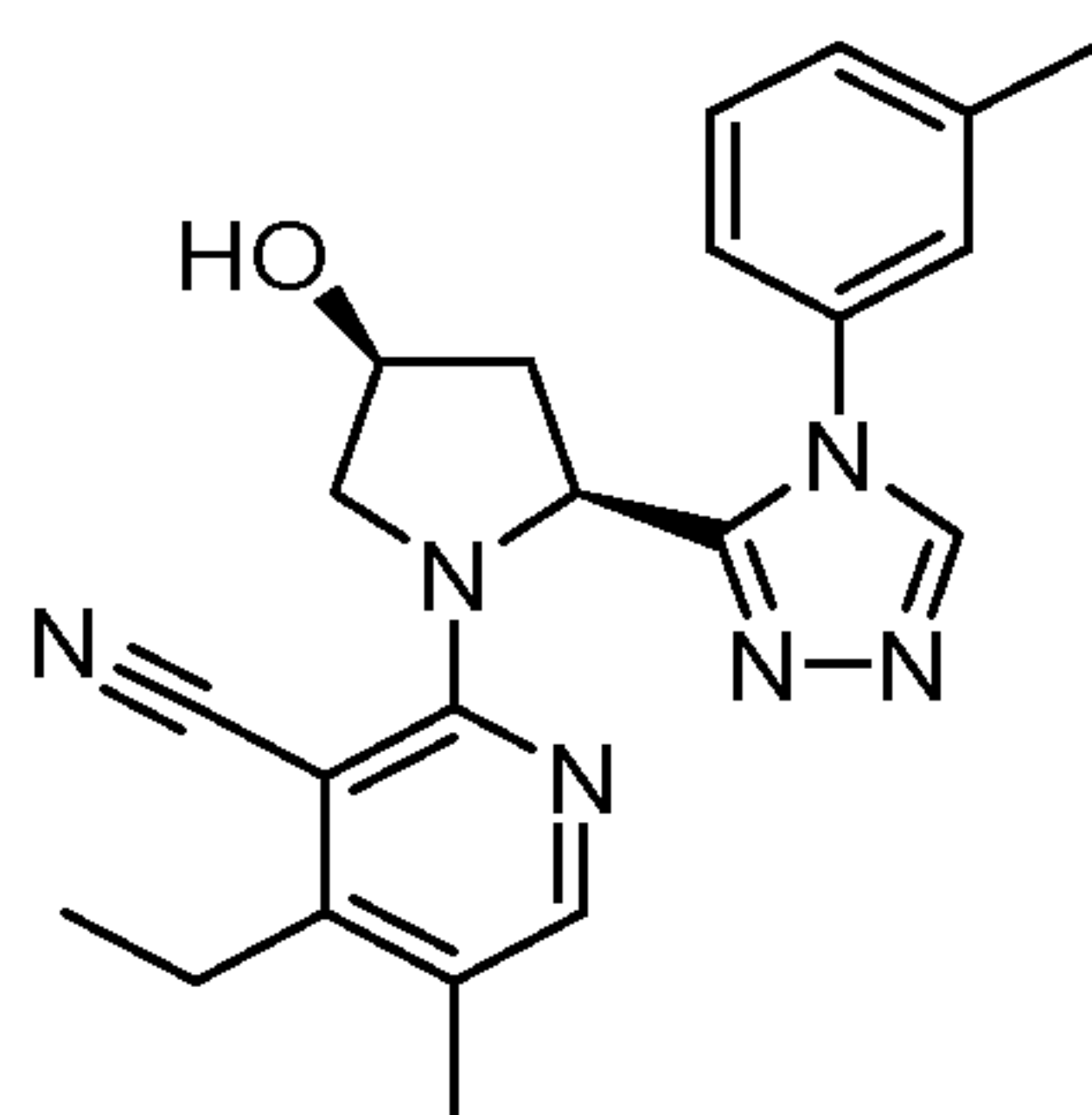
10 The title compound was prepared in a similar manner to **Example 3**, using 2-chloro-4,6-dimethylnicotinonitrile in step f.

m/z ES+ [M+H]⁺ 375.0; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.60 (s, 1H), 7.52 – 7.46 (m, 1H), 7.42 – 7.37 (m, 1H), 7.36 – 7.31 (m, 1H), 7.30 – 7.27 (m, 1H), 6.58 (s, 1H), 5.54 (s, 1H), 5.37 (t, *J* = 7.6 Hz, 1H), 4.45 – 4.35 (m, 1H), 4.03 – 3.95 (m, 1H), 3.78 – 3.71 (m, 1H), 2.57 – 2.56 (m, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 2.11 (s, 3H), 2.09 – 2.04 (m, 1H).

15

Example 5

4-Ethyl-2-((2*S*,4*S*)-4-hydroxy-2-(4-(*m*-tolyl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-5-methylnicotinonitrile

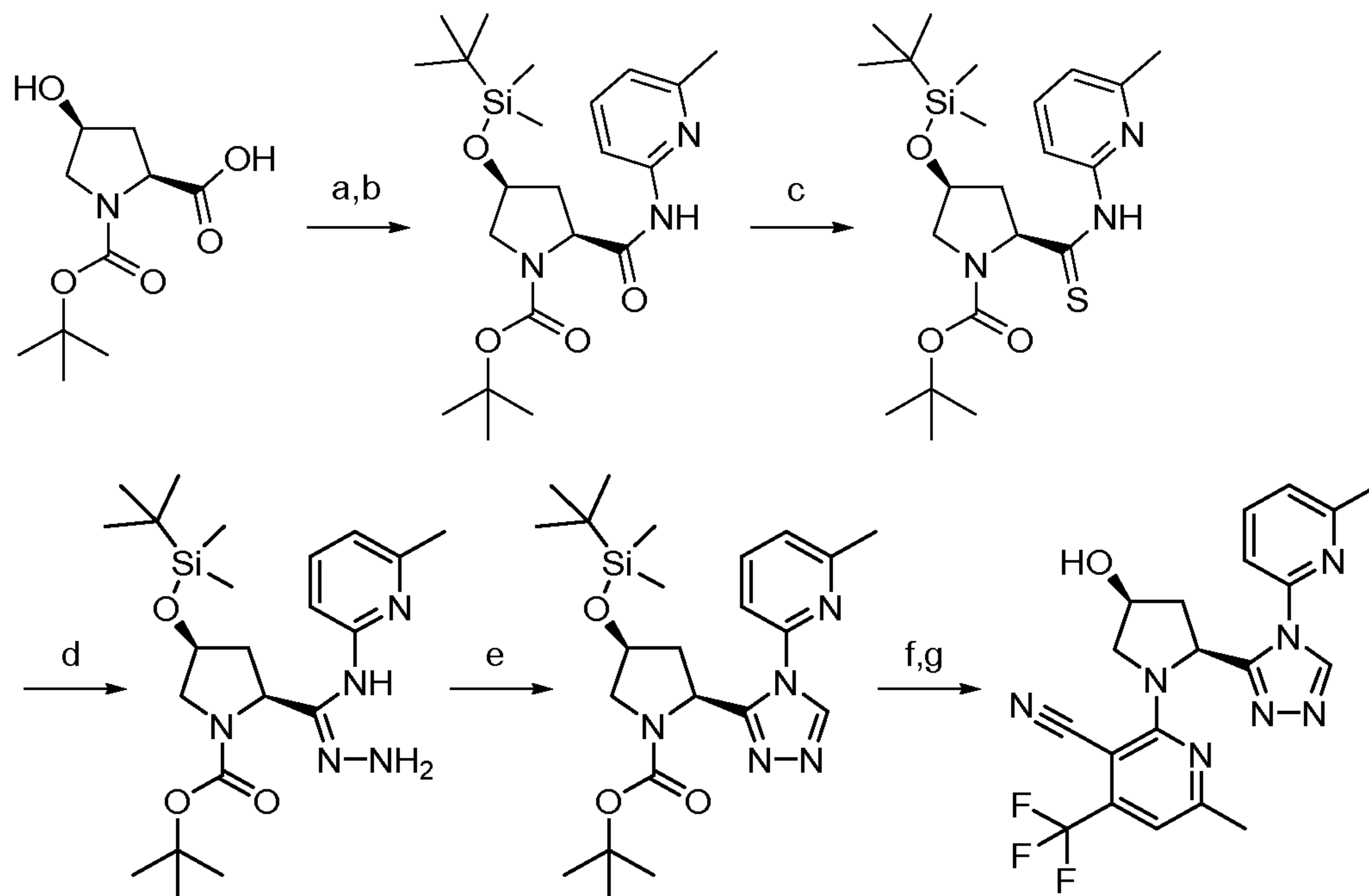


20

The title compound was prepared in a similar manner to **Example 3**, using 2-chloro-4-ethyl-5-methyl-3-pyridinecarbonitrile (CAS Number 125731-31-9, prepared as described in European Journal of Medicinal Chemistry, 85, 450-457; 2014) in step f.

m/z ES+ [M+H]⁺ 389.1; ¹H NMR (400MHz, CD₃OD) δ ppm 9.15 (s, 1H), 8.01 (s, 1H), 7.62 – 7.46 (m, 4H), 5.68 – 5.64 (m, 1H), 4.67 – 4.59 (m, 1H), 4.27 – 4.20 (m, 1H), 4.08 – 4.04 (m, 1H), 2.88 – 2.82 (m, 2H), 2.49 (s, 3H), 2.47 – 2.41 (m, 1H), 2.22 (s, 3H), 2.21 – 2.15 (m, 1H), 1.22 (t, *J* = 7.6 Hz, 3H).

25

Example 6**2-((2S,4S)-4-Hydroxy-2-(4-(6-methylpyridin-2-yl)-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile**

Step a. A mixture of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (20.00 g, 86.5 mmol), *tert*-butylchlorodimethylsilane (18.25 g, 121.1 mmol) and imidazole (8.83 g, 129.7 mmol) in DCM (150 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at rt for 36 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by addition of aq. NH₄Cl solution (200 mL) and water (200 mL), and then extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated to give compound (2S,4S)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid (32 g, crude) as a colorless oil.

Step b. To a solution of (2S,4S)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid (5.00 g, 14.5 mmol), 6-methylpyridin-2-amine (1.88 g, 17.37 mmol) in pyridine (50 mL) was added propylphosphonic anhydride (27.63 g, 43.41 mmol, 50% wt.% in DMF). The mixture was stirred at 30°C for 12 h. Upon completion, the reaction mixture was quenched by addition of water (250 mL) and extracted with EtOAc (250 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/1) to give (2S,4S)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((6-methylpyridin-2-yl)carbamoyl)pyrrolidine-1-carboxylate (4.3 g, 65% yield) as a yellow oil.

m/z ES⁺ [M+H]⁺ 436.1

Step c. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((6-methylpyridin-2-yl)carbamoyl)pyrrolidine-1-carboxylate (0.50 g, 1.15 mmol) in *o*-xylene (20 mL) was added Lawesson's reagent (696 mg, 1.72 mmol). The mixture was stirred at 120°C for 2 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by prep-HPLC to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((6-methylpyridin-2-yl)carbamothioyl)pyrrolidine-1-carboxylate (300 mg, 58% yield) as a brown solid.

m/z ES⁺ [M+H]⁺ 452.2

Step d. A mixture of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((6-methylpyridin-2-yl)carbamothioyl)pyrrolidine-1-carboxylate (320 mg, 0.71 mmol), hydrazine hydrate (71 mg, 1.42 mmol) in THF (5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at rt for 1.5 h under N₂ atmosphere. Upon completion, the reaction mixture was filtered and evaporated to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((*Z*)-*N*-(6-methylpyridin-2-yl)carbamohydrazonoyl)pyrrolidine-1-carboxylate (300 mg, crude) as a brown solid which was used in the next step directly.

m/z ES⁺ [M+H]⁺ 450.2

Step e. A mixture of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-((*Z*)-*N*-(6-methylpyridin-2-yl)carbamohydrazonoyl)pyrrolidine-1-carboxylate (318 mg, 0.71 mmol), diethoxymethoxyethane (314 mg, 2.12 mmol) in EtOH (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 80°C for 12 h under N₂ atmosphere.

Upon completion, the reaction mixture was evaporated. The obtained residue was purified by prep-HPLC to give compound (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(6-methylpyridin-2-yl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (100 mg, 31% yield) as a brown solid.

m/z ES⁺ [M+H]⁺ 460.1

Step f. A solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(6-methylpyridin-2-yl)-4*H*-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (100 mg, 0.22 mmol) in HCl/dioxane (4 M, 3 mL) was stirred at rt for 2 h. Upon completion, the reaction mixture was evaporated to give (3*S*,5*S*)-5-(4-(6-methylpyridin-2-yl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-3-ol (60 mg, crude, HCl salt) as a brown solid which was used in the next step directly.

m/z ES⁺ [M+H]⁺ 246.2

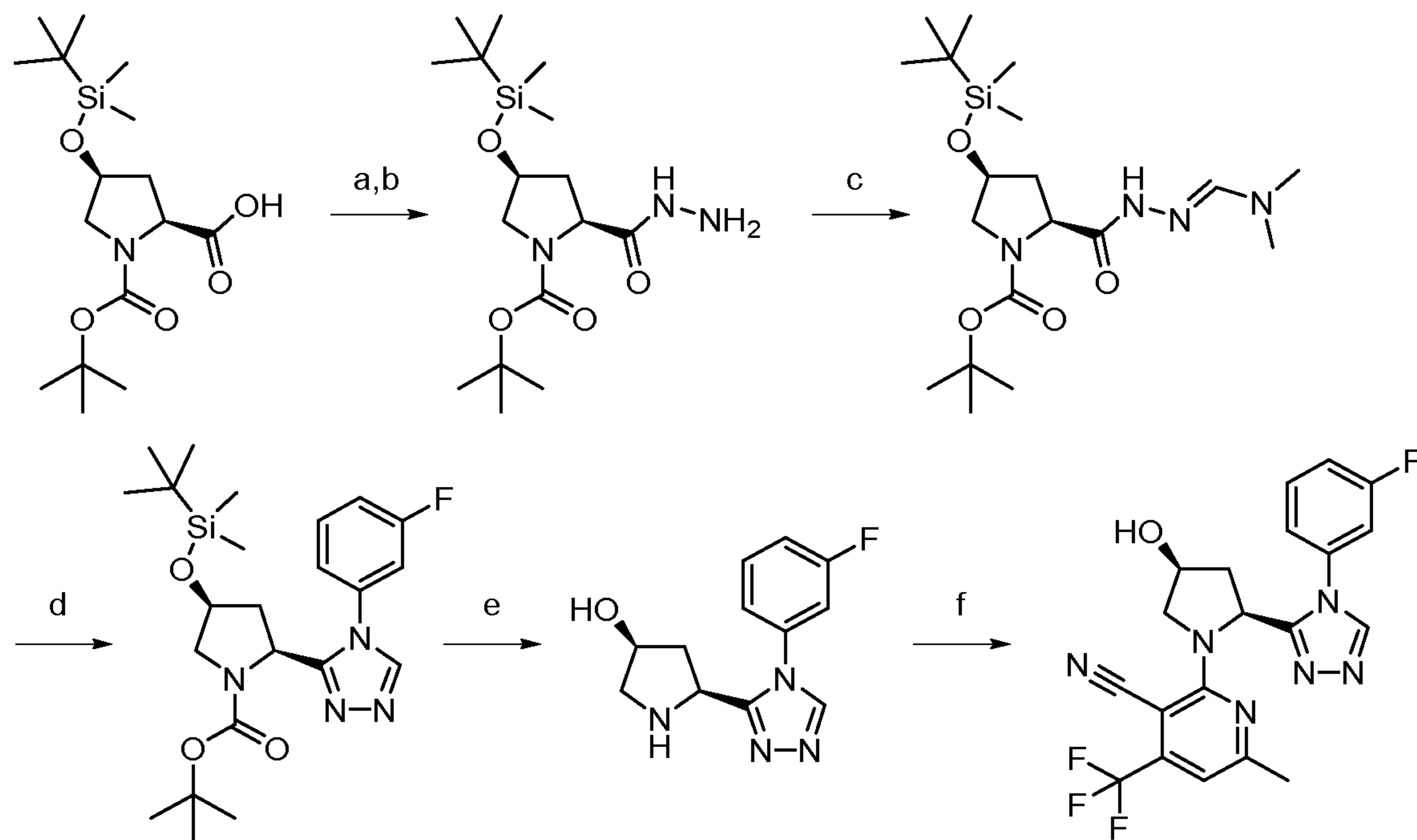
Step g. To a solution of (3*S*,5*S*)-5-(4-(6-methylpyridin-2-yl)-4*H*-1,2,4-triazol-3-yl)pyrrolidin-3-ol (60 mg, 0.22 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile in NMP (5 mL) was added DIPEA (84 mg, 0.65 mmol). The mixture was stirred at 60°C for 12 h. Upon completion, the reaction mixture was evaporated. The obtained residue was purified by prep-HPLC to give the title compound (12 mg, 13% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 430.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.25 (s, 1H), 8.05 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 5.78 (t, *J* = 7.6 Hz,

1H), 4.55 – 4.40 (m, 1H), 3.93 – 3.85 (m, 3H), 2.80 – 2.70 (m, 1H), 2.56 (s, 3H), 2.30 -2.20 (m, 1H), 2.12 (s, 3H).

Example 7

5 2-((2S,4S)-2-(4-(3-Fluorophenyl)-4H-1,2,4-triazol-3-yl)-4-hydroxypyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile



Step a. To a solution of (2S,4S)-1-*tert*-butoxycarbonyl-4-[(*tert*-butyl(dimethyl)silyl)oxy]pyrrolidine-2-carboxylic acid (5.00 g, 14.5 mmol) and benzyl hydrazinecarboxylate (2.89 g, 17.4 mmol) in DCM (125 mL) was added EDCI (3.33 g, 17.4 mmol), hydroxybenzotriazole (2.74 g, 20.3 mmol) and TEA (2.93 g, 29 mmol). The mixture was stirred at rt for 12 h. On completion, the reaction mixture was diluted with water (100 mL) and extracted with DCM (80 mL × 2). The combined organic layers were washed with brine (80 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 8/1 to 1/1) to afford *tert*-butyl (2S,4S)-2-(benzyloxycarbonylaminocarbamoyl)-4-[(*tert*-butyl(dimethyl)silyl)oxy]pyrrolidine-1-carboxylate (3.5 g, 49% yield) as colorless oil.

m/z ES+ [M+H]⁺ 494.2;

Step b. To a solution of *tert*-butyl (2S,4S)-2-(benzyloxycarbonylaminocarbamoyl)-4-[(*tert*-butyl(dimethyl)silyl)oxy]pyrrolidine-1-carboxylate (3.50 g, 7.09 mmol) in MeOH (20 mL) was added Pd/C (150 mg, 10% purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) atmosphere at rt for 1 h. The reaction mixture was filtered and evaporated to afford *tert*-butyl (2S,4S)-4-[(*tert*-

butyl(dimethyl)silyl]oxy-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate (2.5 g, 98% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.53-7.50 (m, 1H), 4.38 (m, 2H), 3.83-3.74 (m, 1H), 3.58-3.21 (m, 2H), 2.40-2.10 (m, 2H), 1.47 (s, 9H), 0.88 (s, 9H), 0.07 (d, J = 7.2 Hz, 6H).

5 **Step c.** To a solution of *tert*-butyl (2*S*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-(hydrazinecarbonyl)pyrrolidine-1-carboxylate (1.00 g, 2.78 mmol) in MeCN (25 mL) was added DMF-DMA (365 mg, 3.06 mmol). The mixture was stirred at 50°C for 30 minutes. On completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (15 mL × 2). The combined organic
10 layers were washed with brine (15 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 3/1 followed by DCM/MeOH = 10/1) to afford *tert*-butyl (2*S*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-[[*(Z)*-dimethylaminomethyleneamino]carbonyl]pyrrolidine-1-carboxylate (1.1 g, 95% yield) as a white solid.

15 ¹H NMR (400 MHz, CDCl₃) δ ppm 8.53-8.19 (m, 1H), 7.95-7.65 (m, 1H), 4.42-4.26 (m, 2H), 3.58-3.51 (m, 1H), 3.49-3.39 (m, 1H), 2.89 (s, 6H), 2.45-2.15 (m, 2H), 1.46 (s, 9H), 0.87 (s, 9H), 0.07 (d, J=4.4 Hz, 6H).

Step d. To a solution of *tert*-butyl (2*S*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-[[*(Z)*-dimethylaminomethyleneamino]carbonyl]pyrrolidine-1-carboxylate (300 mg, 0.72 mmol) and 3-
20 fluoroaniline (402 mg, 3.62 mmol) in toluene (5 mL) was added acetic acid (217 mg, 3.62 mmol). The mixture was stirred at 150°C under microwave irradiation for 2 h. On completion, the reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC to give compound *tert*-butyl (2*S*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-[4-(3-fluorophenyl)-1,2,4-triazol-3-yl]pyrrolidine-1-carboxylate (70 mg, 15% yield) as a yellow oil.

25 **Step e.** A solution of *tert*-butyl (2*S*,4*S*)-4-[*tert*-butyl(dimethyl)silyl]oxy-2-[4-(3-fluorophenyl)-1,2,4-triazol-3-yl]pyrrolidine-1-carboxylate (70 mg, 0.11 mmol) in HCl/dioxane (4 M, 2 mL) was stirred at rt for 2 h. The mixture was concentrated in vacuo to give compound (3*S*,5*S*)-5-[4-(3-fluorophenyl)-1,2,4-triazol-3-yl]pyrrolidin-3-ol (80 mg, crude, HCl) as a yellow solid.

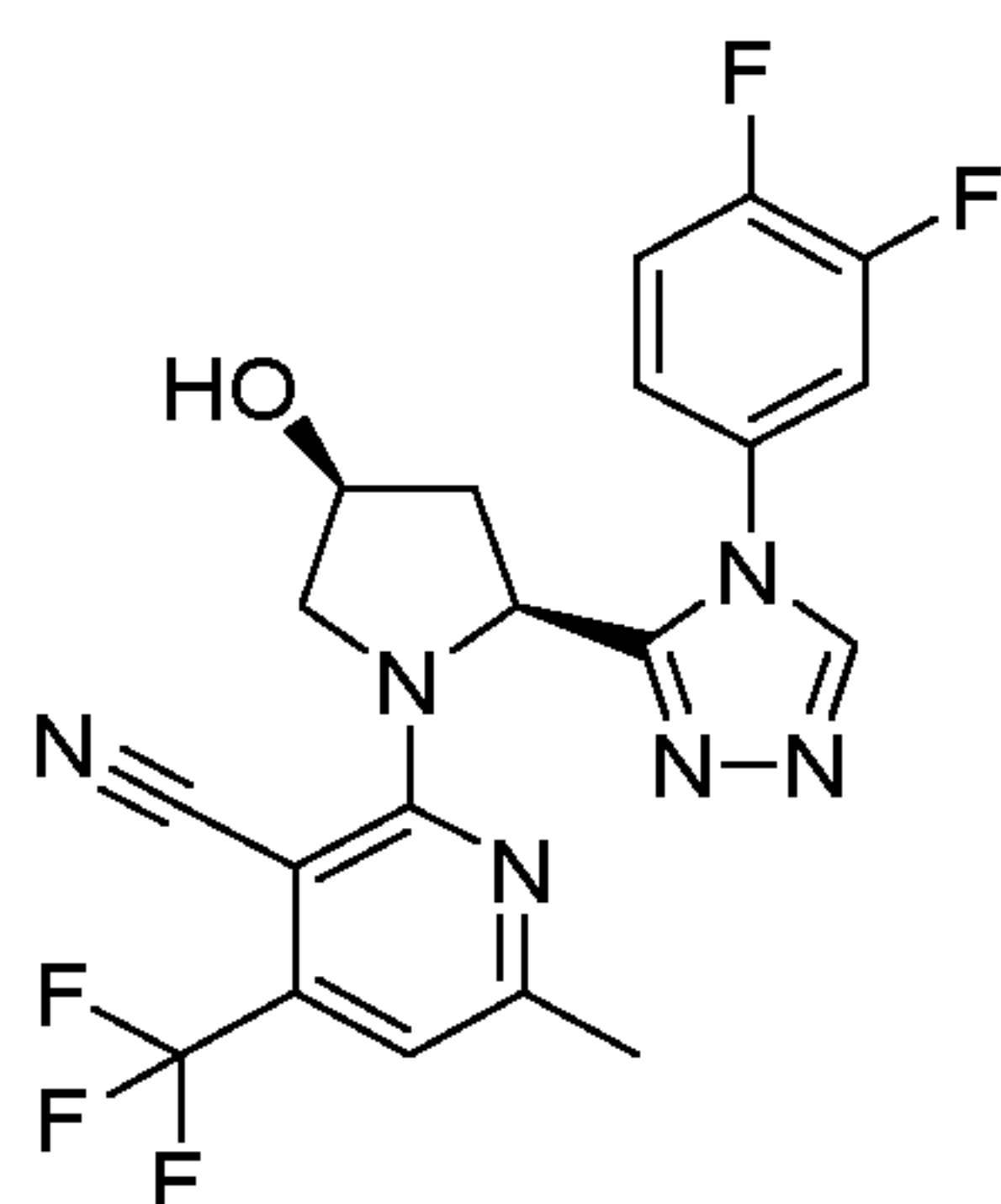
Step f. A solution of (3*S*,5*S*)-5-[4-(3-fluorophenyl)-1,2,4-triazol-3-yl]pyrrolidin-3-ol (75 mg, 0.26 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (58 mg, 0.26 mmol) and DIPEA (102 mg, 0.79 mmol) in NMP (2 mL) was stirred at 100°C for 12 h
30 under N₂. On completion, the mixture was purified by prep-HPLC to give the title compound (20 mg, 17% yield) as a white solid.

m/z ES+ [M+H]⁺ 433.1; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.22 (s, 1H), 7.64-7.55 (m, 1H),
35 7.34-7.28 (m, 3H), 6.76 (s, 1H), 5.68 (d, J = 12 Hz, 1H), 5.61 (d, J = 8.4 Hz, 1H), 4.76-4.68

(m, 1H), 4.56-4.50 (m, 1H), 4.45-4.38 (m, 1H), 2.49-2.40 (m, 1H), 2.33-2.27 (m, 1H), 2.21 (s, 3H)

Example 8

- 5 **2-((2*S*,4*S*)-2-(4-(3,4-Difluorophenyl)-4*H*-1,2,4-triazol-3-yl)-4-hydroxypyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile**

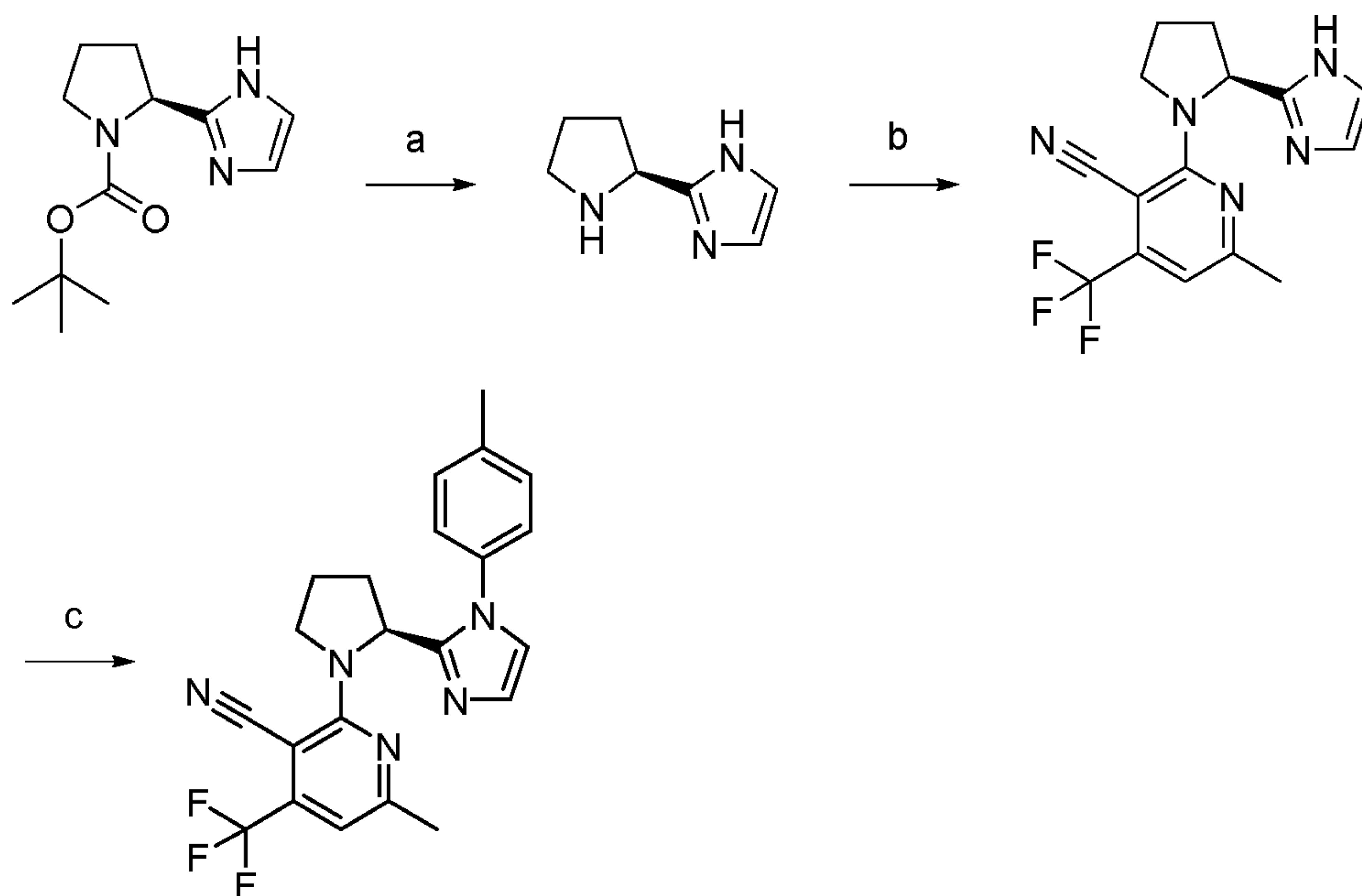


The title compound was prepared in a similar manner to **Example 7**, using 3,4-difluoroaniline in step d.

- 10 m/z ES⁺ [M+H]⁺ 451.1; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.20 (s, 1H), 7.52-7.37 (m, 2H), 7.32-7.27 (m, 1H), 6.79 (s, 1H), 5.60-5.50 (m, 2H), 4.76-4.68 (m, 1H), 4.54-4.48 (m, 1H), 4.44-4.37 (m, 1H), 2.47-2.38 (m, 1H), 2.29~2.25 (m, 1H), 2.24 (s, 3H)

Example 9

- 15 **(*S*)-6-Methyl-2-(2-(1-(*p*-tolyl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile**



Step a. A solution of *tert*-butyl (2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (2.00 g, 8.43 mmol) in HCl/MeOH (4 M, 10 mL) was stirred at rt for 1 h. The mixture was then concentrated in vacuo to afford compound 2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole (1.73 g, crude, HCl salt) as a brown solid.

5 ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.44 (s, 1H), 7.72 (s, 2H), 5.03 (t, *J* = 8.4 Hz, 1H), 3.31 - 3.46 (m, 2H), 2.37 - 2.49 (m, 2H), 2.13 - 2.24 (m, 1H), 1.92 - 2.04 (m, 1H).

Step b. To a solution of 2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole (1.00 g, 5.76 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (1.27 g, 5.76 mmol) in NMP (10 mL) was added DIPEA (2.23 g, 17.28 mmol). The reaction mixture was stirred at 60°C for 12 h.

10 Upon completion, the mixture was added water (20 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (15 mL x 3) and then evaporated. The residue was purified by column chromatography (PE/EtOAc = 6/1 to 0/1) to afford compound 2-[(2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidin-1-yl]-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (1.9 g, 92% yield) as a brown solid.

15 ¹H NMR (400 MHz, CDCl₃) δ ppm 6.97 (s, 2H), 6.83 (s, 1H), 5.63 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.29 (ddd, *J* = 10.4, 7.6, 4.8 Hz, 1H), 3.95 (dt, *J* = 10.4, 7.2 Hz, 1H), 2.78 - 2.70 (m, 1H), 2.52 (s, 3H), 2.40 - 2.25 (m, 2H), 2.19 - 2.12 (m, 1H).

Step c. To a solution of 2-[(2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidin-1-yl]-6-methyl-4-

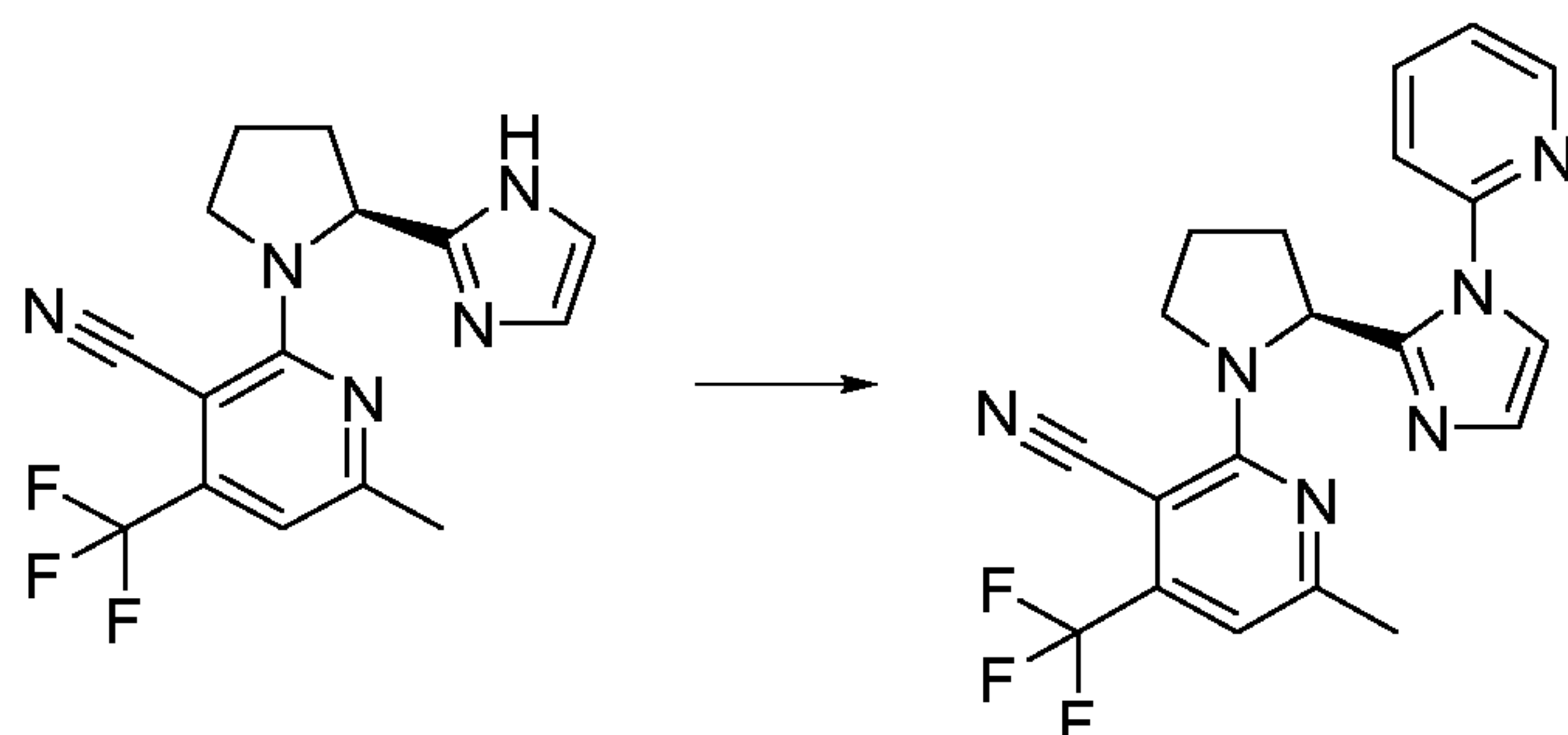
20 (trifluoromethyl)pyridine-3-carbonitrile (100 mg, 0.31 mmol), *p*-tolylboronic acid (63.5 mg, 0.47 mmol) in DCM (2 mL) was added Cu(OAc)₂·H₂O (57 mg, 0.31 mmol) and pyridine (50 mg, 0.62 mmol). The reaction mixture was stirred at rt for 16 h under O₂ balloon (15 psi).

Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by prep-HPLC to give the title compound (9 mg, 7% yield) as a yellow solid.

25 *m/z* ES⁺ [M+H]⁺ 412.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.42 - 7.34 (m, 4H), 7.20 (d, *J* = 0.96 Hz, 1H), 6.95 (s, 1H), 6.87 (s, 1H), 5.34 (d, *J* = 7.6 Hz, 1H), 4.11 - 4.03 (m, 1H), 3.87 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.39 (s, 3H), 2.29 - 2.16 (m, 5H), 2.06 - 1.92 (m, 2H).

Example 10

30 **(*S*)-6-Methyl-2-(2-(1-(pyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)-nicotinonitrile**

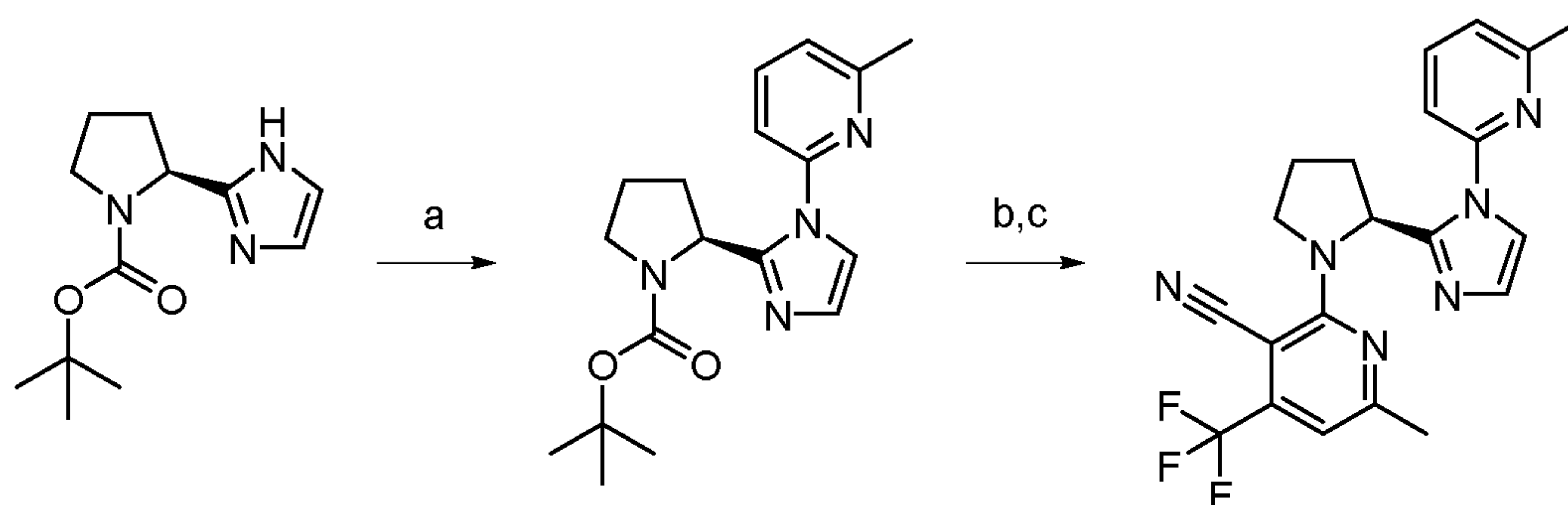


To a solution of 2-[(2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidin-1-yl]-6-methyl-4-(trifluoromethyl)-pyridine-3-carbonitrile (100 mg, 0.31 mmol) in DMF (2.5 mL) was added Cs₂CO₃ (202 mg, 0.62 mmol) and 2-fluoropyridine (45 mg, 0.47 mmol). The mixture was stirred at 100°C for 12 h. Upon completion, the reaction mixture was quenched by addition of water (5 mL), and then extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (PE/EtOAc = 1/1) to give the title compound (49 mg, 39% yield) as a yellow solid.

m/z ES+ [M+H]⁺ 399.1; ¹H NMR (400 MHz, CDCl₃) δ ppm 8.63 - 8.57 (m, 1H), 7.91 - 7.85 (m, 1H), 7.43 - 7.39 (m, 1H), 7.37 - 7.32 (m, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.03 (d, *J* = 1.6 Hz, 1H), 6.60 (s, 1H), 5.84 - 5.78 (m, 1H), 4.36 - 4.30 (m, 1H), 4.08 - 4.01 (m, 1H), 2.51 - 2.40 (m, 2H), 2.39 - 2.32 (m, 1H), 2.13 (s, 3H), 2.10 - 2.03 (m, 1H)

Example 11

(*S*)-6-Methyl-2-(2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile



Step a. A mixture of (*S*)-*tert*-butyl 2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (500 mg, 2.11 mmol), 2-bromo-6-methyl-pyridine (725 mg, 4.21 mmol), CuI (441 mg, 2.32 mmol) and Cs₂CO₃ (2.06 g, 6.32 mmol) in DMSO (15 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120°C for 16 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by addition of water (60 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 3/1 to 0/1) to give (*S*)-*tert*-butyl 2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (427 mg, 93% yield) as a light yellow oil.

m/z ES+ [M+H]⁺ 329.2

Step b. To a solution of (*S*)-*tert*-butyl 2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (380 mg, 1.16 mmol) in dioxane (10 mL) was added HCl/dioxane (4 M, 2.89 mL). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was evaporated to provide (*S*)-2-methyl-6-(2-(pyrrolidin-2-yl)-1*H*-imidazol-1-yl)pyridine (300 mg, crude, HCl salt) as a light yellow oil, which was used for the next step directly.

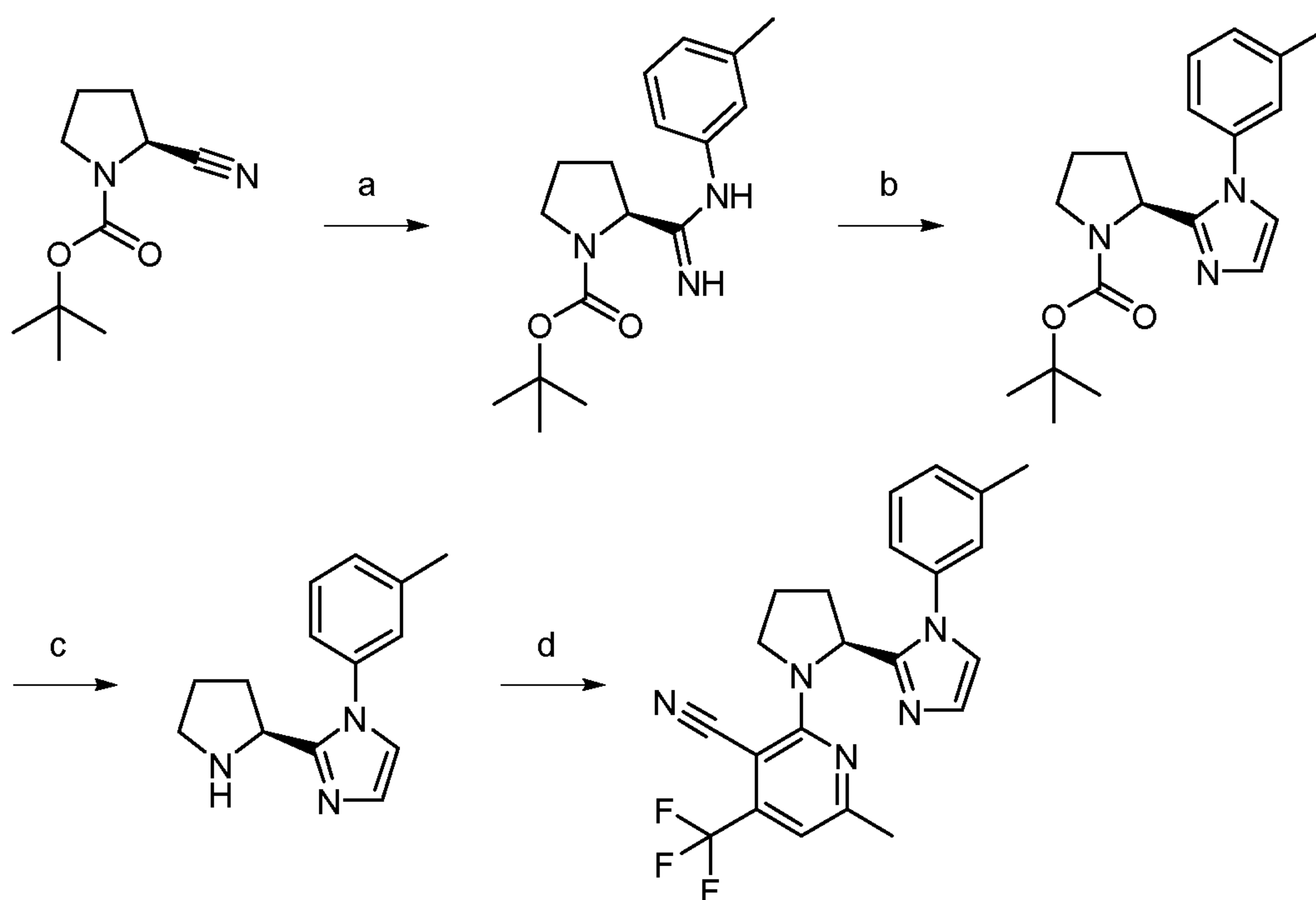
m/z ES+ [M+H]⁺ 229.1

Step c. To a solution of (S)-2-methyl-6-(2-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridine (300 mg, 1.13 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (300 mg, 1.36 mmol) in NMP (10 mL) was added DIPEA (440 mg, 3.40 mmol). The mixture was stirred at 70°C for 12 h. Upon completion, the reaction mixture was quenched by addition of water (60 mL), and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (14 mg, 14% yield) as a light brown solid.

m/z ES+ [M+H]⁺ 413.2; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.16 - 8.07 (m, 2H), 7.78 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 5.54 (t, J = 7.2 Hz, 1H), 4.42 - 4.29 (m, 1H), 3.95 - 3.84 (m, 1H), 2.68 - 2.59 (m, 1H), 2.42 - 2.31 (m, 1H), 2.57 (s, 3H), 2.18 - 2.06 (m, 4H), 2.30 - 2.20 (m, 1H).

Example 12

(S)-6-Methyl-2-(2-(1-(*m*-tolyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)-nicotinonitrile



Step a. To a solution of *tert*-butyl (2S)-2-cyanopyrrolidine-1-carboxylate (300 mg, 1.53 mmol) and 3-methylaniline (180 mg, 1.68 mmol) in toluene (8 mL) was added trimethylaluminium (2 M in toluene, 0.84 mL, 1.68 mmol) at 0°C. The mixture was stirred at 90°C for 2 h. On completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 3/1 to 0/1) to

afford compound *tert*-butyl (2*S*)-2-[*N*-(*m*-tolyl)carbamimidoyl]pyrrolidine-1-carboxylate (150 mg, 32% yield) as a brown oil.

m/z ES⁺ [M+H]⁺ 304.1

Step b. To a solution of *tert*-butyl (2*S*)-2-[*N*-(*m*-tolyl)carbamimidoyl]pyrrolidine-1-carboxylate (150 mg, 0.49 mmol) and Na₂CO₃ (157 mg, 1.48 mmol) in isopropanol (8 mL) was added 2-chloroacetaldehyde (194 mg, 0.99 mmol). The mixture was stirred at 100°C for 12 h under N₂ atmosphere in a sealed tube. On completion, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 5/1 to 0/1) to afford compound *tert*-butyl (2*S*)-2-[1-(*m*-tolyl)imidazol-2-yl]pyrrolidine-1-carboxylate (100 mg, 62% yield) as a brown oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.42 - 7.29 (m, 2H), 7.27 - 7.20 (m, 1H), 7.18 - 6.93 (m, 3H), 5.01 - 4.73 (m, 1H), 3.74 - 3.62 (m, 1H), 3.53 - 3.36 (m, 1H), 2.44 (s, 3H), 2.21 - 2.12 (m, 1H), 2.04 - 1.97 (m, 1H), 1.86 - 1.81 (m, 1H), 1.69 - 1.58 (m, 1H), 1.47 - 1.26 (m, 9H).

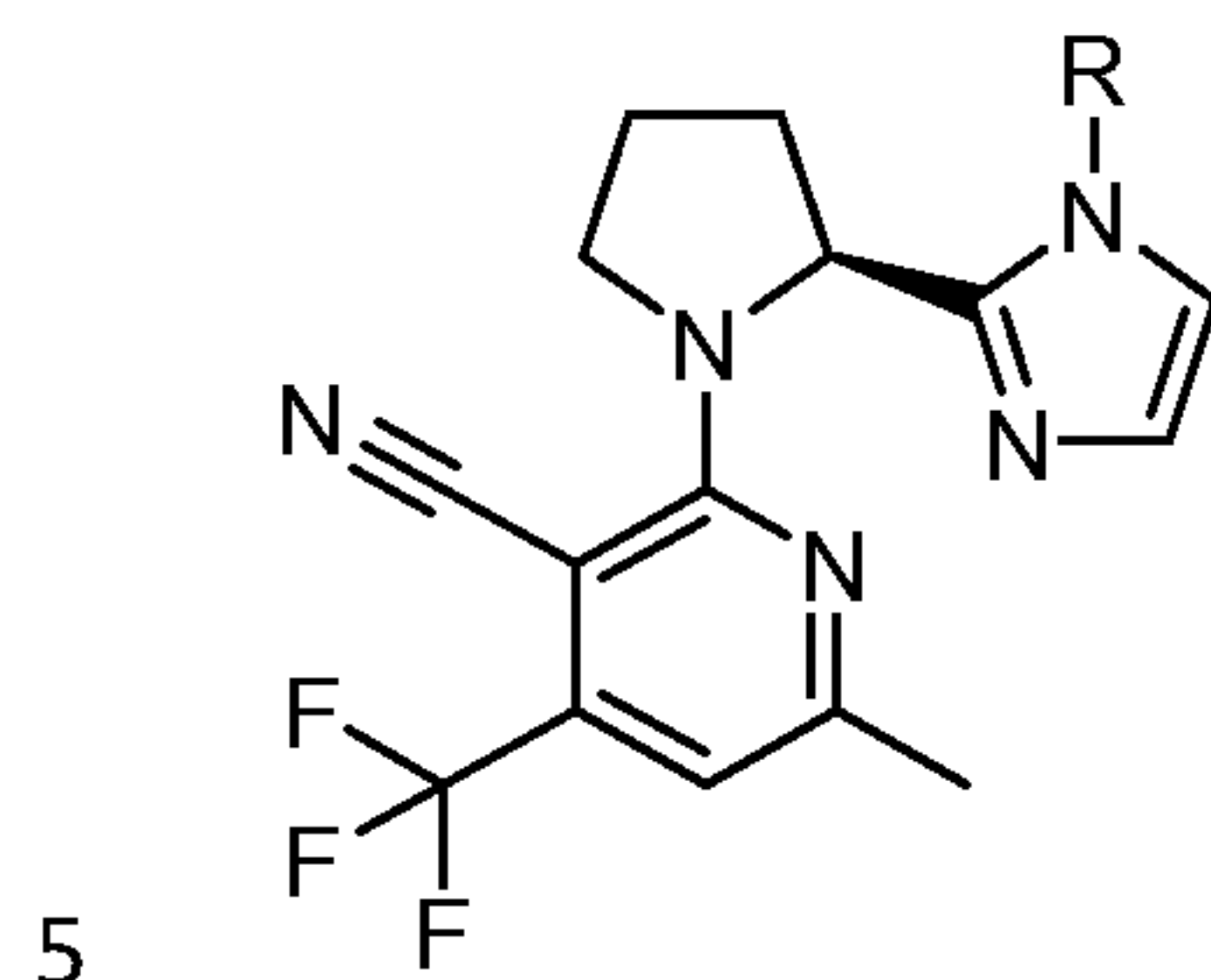
Step c. A solution of *tert*-butyl (2*S*)-2-[1-(*m*-tolyl)imidazol-2-yl]pyrrolidine-1-carboxylate (90 mg, 0.28 mmol) in TFA (5 mL) and DCM (5 mL) was stirred at rt for 1 h. The reaction mixture was evaporated to afford compound 1-(*m*-tolyl)-2-[(2*S*)-pyrrolidin-2-yl]imidazole (50 mg, 80% yield, TFA salt) as a brown oil.

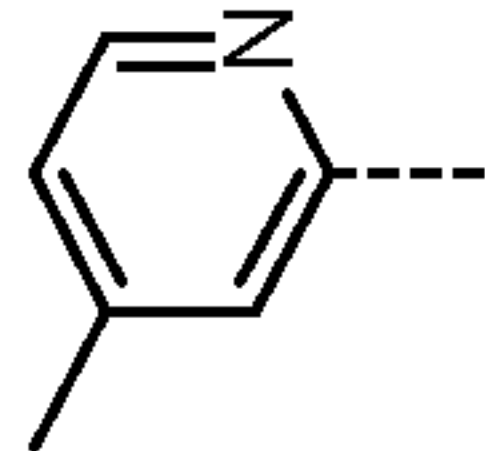
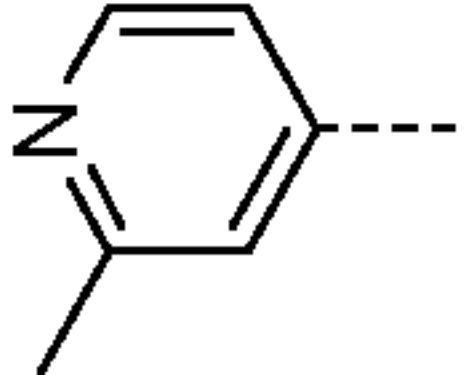
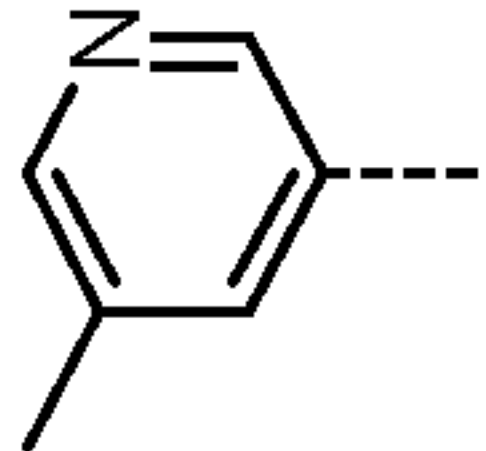
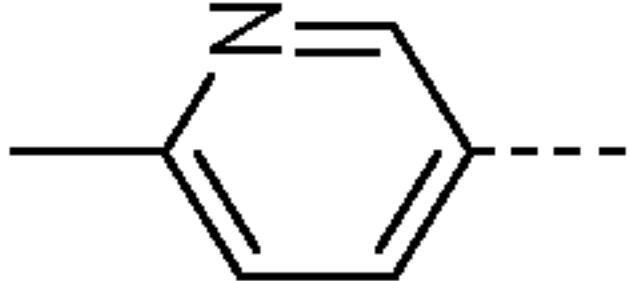
Step d. To a solution of 1-(*m*-tolyl)-2-[(2*S*)-pyrrolidin-2-yl]imidazole (50 mg, 0.22 mmol) and 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (58 mg, 0.26 mmol) in NMP (3 mL) was added DIPEA (57 mg, 0.44 mmol). The mixture was stirred at 80°C for 5 h. On completion, the reaction mixture was quenched by addition of water (5 mL) at 0°C and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (19 mg, 21% yield) as a yellow solid.

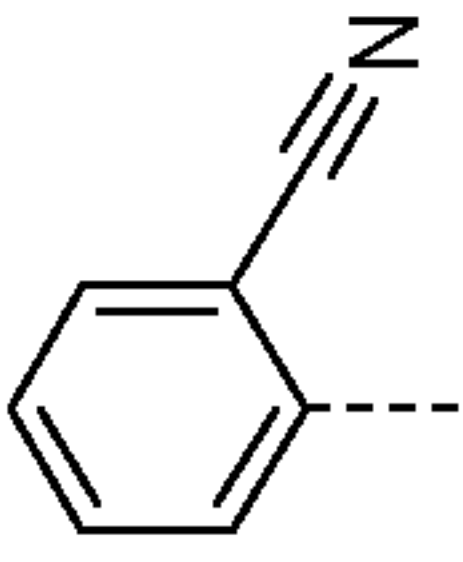
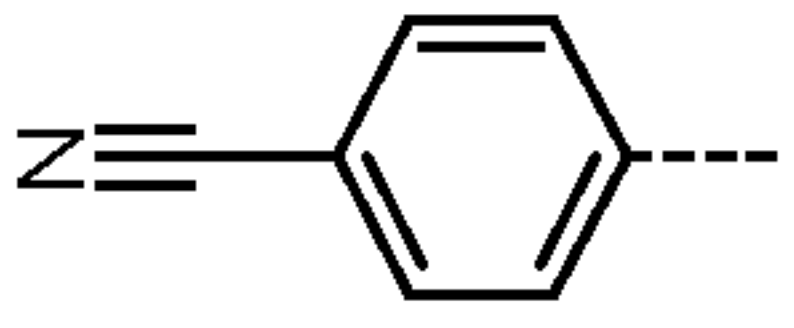
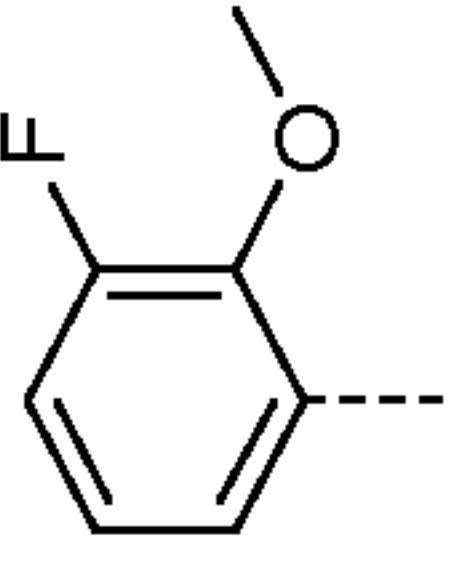
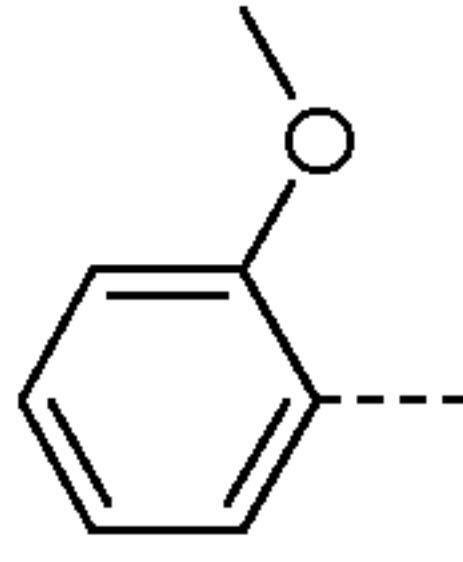
m/z ES⁺ [M+H]⁺ 412.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.49 - 7.43 (m, 1H), 7.35 - 7.28 (m, 3H), 7.24 - 7.20 (m, 1H), 6.96 (s, 1H), 6.89 - 6.86 (m, 1H), 5.40 - 5.33 (m, 1H), 4.11 - 4.01 (m, 1H), 3.93 - 3.83 (m, 1H), 2.39 (s, 3H), 2.27 - 2.18 (m, 5H), 2.04 - 1.97 (m, 2H).

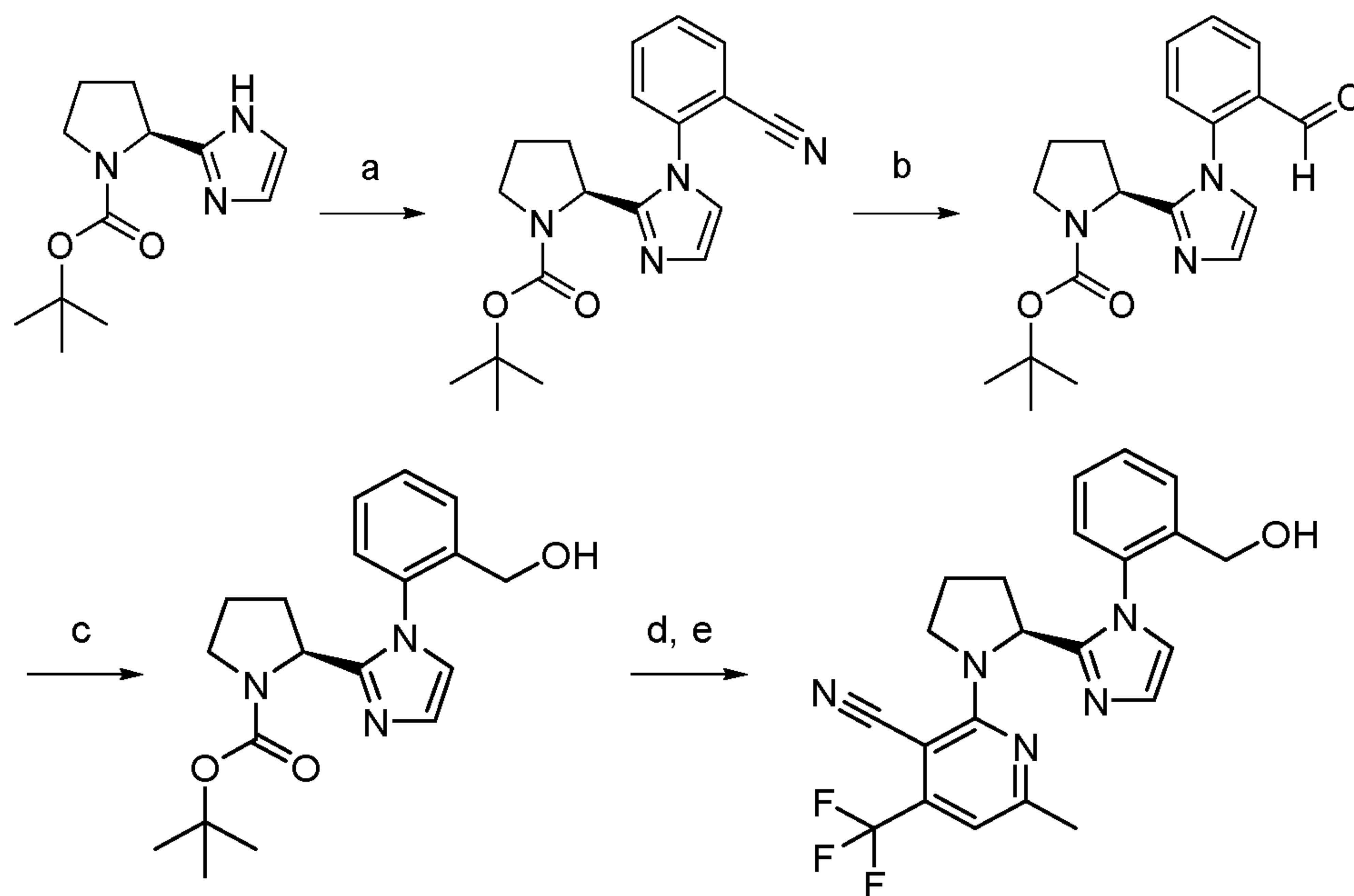
The Examples in **Table 1** were prepared using methods similar to those described in the synthesis of **Examples 9-12**.

Table 1



Example Number	R	Name	¹ H NMR (400 MHz) δ ppm	MI
13		(S)-6-Methyl-2-(2-(1-(4-methylpyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile	(CD ₃ OD) 8.56 (d, <i>J</i> = 5.2 Hz, 1H), 7.97 (d, <i>J</i> = 2 Hz, 1H), 7.65 (d, <i>J</i> = 2 Hz, 1H), 7.62 (s, 1H), 7.54 (d, <i>J</i> = 5.2 Hz, 1H), 7.03 (s, 1H), 5.77 - 5.73 (m, 1H), 4.30 - 4.26 (m, 1H), 4.03 - 4.00 (m, 1H), 2.79 - 2.74 (m, 1H), 2.55 (s, 3H), 2.44 - 2.41 (m, 1H), 2.32 - 2.29 (m, 1H), 2.23 (s, 3H), 2.25 - 2.20 (m, 1H).	413.1
14		(S)-6-Methyl-2-(2-(1-(2-methylpyridin-4-yl)-1 <i>H</i> -imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile	(DMSO-d ₆) 8.63 (d, <i>J</i> = 5.2 Hz, 1H), 7.49 - 7.33 (m, 3H), 7.01 - 6.90 (m, 2H), 5.42 (d, <i>J</i> = 6.8 Hz, 1H), 4.15 - 4.03 (m, 1H), 3.96 - 3.85 (m, 1H), 2.57 (s, 3H), 2.38 - 2.30 (m, 2H), 2.15 (s, 3H), 2.04 (d, <i>J</i> = 4.80 Hz, 2H).	413.1
15		6-Methyl-2-(2-(1-(5-methylpyridin-3-yl)-1 <i>H</i> -imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile	(DMSO-d ₆) 8.55 (d, <i>J</i> = 2.8 Hz, 2H), 7.78 (s, 1H), 7.31 (d, <i>J</i> = 1.2 Hz, 1H), 7.01 - 6.84 (m, 2H), 5.33 (t, <i>J</i> = 5.6 Hz, 1H), 4.12 - 3.99 (m, 1H), 3.86 (d, <i>J</i> = 9.6 Hz, 1H), 2.40 (s, 3 H), 2.36 - 2.29 (m, 2H), 2.21 (s, 3H), 2.10 - 1.97 (m, 2H).	413.1
16		(S)-6-Methyl-2-(2-(1-(6-methylpyridin-3-yl)-1 <i>H</i> -imidazol-2-yl)pyrrolidin-1-yl)-4-(trifluoromethyl)nicotinonitrile	(DMSO-d ₆) 8.58 (s, 1H), 7.85 (d, <i>J</i> = 5.6 Hz, 1H), 7.46 (d, <i>J</i> = 8.8 Hz, 1H), 7.28 (s, 1H), 7.01 - 6.87 (m, 2H), 5.28 (s, 1H), 4.04 (s, 1H), 3.87 (s, 1H), 2.56 (s, 3H), 2.31 - 2.35 (m, 2H), 2.21 (s, 3H), 1.95 - 2.09 (m, 2H).	413.1

Example Number	R	Name	¹ H NMR (400 MHz) δ ppm	MI
17		(S)-2-(2-(1-(2-Cyanophenyl))-1H-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile	(DMSO-d6) 8.03 (d, J = 7.6 Hz, 1H), 7.90 (t, J = 7.6 Hz, 1H), 7.83 - 7.63 (m, 2H), 7.38 (s, 1H), 7.01 (d, J = 10.4 Hz, 2H), 5.50 - 5.40 (m, 1H), 3.95 - 3.90 (m, 1H), 3.80 - 3.75 (m, 1H), 2.30 (s, 3H), 2.25 - 2.20 (m, 2H), 2.15 - 2.05 (m, 1H), 2.03 - 1.95 (m, 1H).	423.1
18		(S)-2-(2-(1-(4-Cyanophenyl))-1H-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile	(DMSO-d6) 8.08 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 1.2 Hz, 1H), 7.01 - 6.86 (m, 2H), 5.34 (t, J = 5.6 Hz, 1H), 4.11 - 3.99 (m, 1H), 3.94 - 3.82 (m, 1H), 2.34 - 2.27 (m, 2H), 2.16 (s, 3H), 2.10 - 1.97 (m, 2H).	423.1
19		(S)-2-(2-(1-(3-Fluoro-2-methoxyphenyl))-1H-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile	(DMSO-d6) 7.49 - 7.41 (m, 1H), 7.36 - 7.28 (m, 1H), 7.28 - 7.22 (m, 1H), 7.21 (d, J = 0.8 Hz, 1H), 6.98 (s, 1H), 6.93 (d, J = 1.2 Hz, 1H), 5.39 - 5.32 (m, 1H), 4.06 - 3.98 (m, 1H), 3.85 - 3.77 (m, 1H), 3.73 (s, 3H), 2.26 (s, 4H), 2.19 - 2.09 (m, 1H), 2.04 - 1.94 (m, 2H).	446.1
20		(S)-2-(2-(1-(2-Methoxyphenyl))-1H-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile	(DMSO-d6) 7.49 - 7.45 (m, 1H), 7.37 - 7.35 (m, 1H), 7.24 - 7.22 (m, 1H), 7.10 - 7.05 (m, 2H), 6.94 (s, 1H), 6.86 (s, 1H), 5.30 - 5.20 (m, 1H), 4.05 - 3.95 (m, 1H), 3.85 - 3.80 (m, 1H), 3.78 (s, 3H), 2.35 - 2.25 (m, 1H), 2.24 (s, 3H), 2.15 - 2.10 (m, 1H), 2.05 - 1.90 (m, 2H).	428.2

Example 21**(S)-2-(2-(1-(2-(Hydroxymethyl)phenyl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile**

Step a. To a solution of *tert*-butyl (2*S*)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (500 mg, 2.11 mmol), 2-fluorobenzonitrile (306 mg, 2.53 mmol) and Cs₂CO₃ (1.37 g, 4.21 mmol) in DMF (10 mL) was stirred at 100°C for 12 h under N₂ atmosphere. On completion, the mixture was diluted with water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 1/1 to 0/1) to afford *tert*-butyl (2*S*)-2-[1-(2-cyanophenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (700 mg, 94% yield) as a yellow solid.

m/z ES+ [M+H]⁺ 339.1

Step b. To a solution of *tert*-butyl (2*S*)-2-[1-(2-cyanophenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (250 mg, 0.74 mmol) in toluene (5 mL) was added DIBAL-H (1 M, 1.11 mmol) at 0°C over 30 min. The mixture was then stirred at 0°C for 1.5 h. On completion, the reaction mixture was quenched by addition of aqueous NaOH solution (1 M, 10 mL) at 0°C, and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄ and evaporated to afford *tert*-butyl (2*S*)-2-[1-(2-formylphenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (300 mg, crude) as a yellow solid.

m/z ES+ [M+H]⁺ 342.1

Step c. To a solution of *tert*-butyl (2*S*)-2-[1-(2-formylphenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (300 mg, 0.88 mmol) in MeOH (5 mL) was added NaBH₄ (66.5 mg, 1.76 mmol) portionwise at 0°C. The mixture was stirred at rt for 1 h. On completion, the reaction mixture was quenched by addition of water (10 mL) at 0°C and extracted with EtOAc (5 mL x 3). The

combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 5/1 to 0/1) to afford *tert*-butyl (2*S*)-2-[1-[2-(hydroxymethyl)phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (50 mg, 16% yield) as a brown oil.

5 m/z ES⁺ [M+H]⁺ 344.1

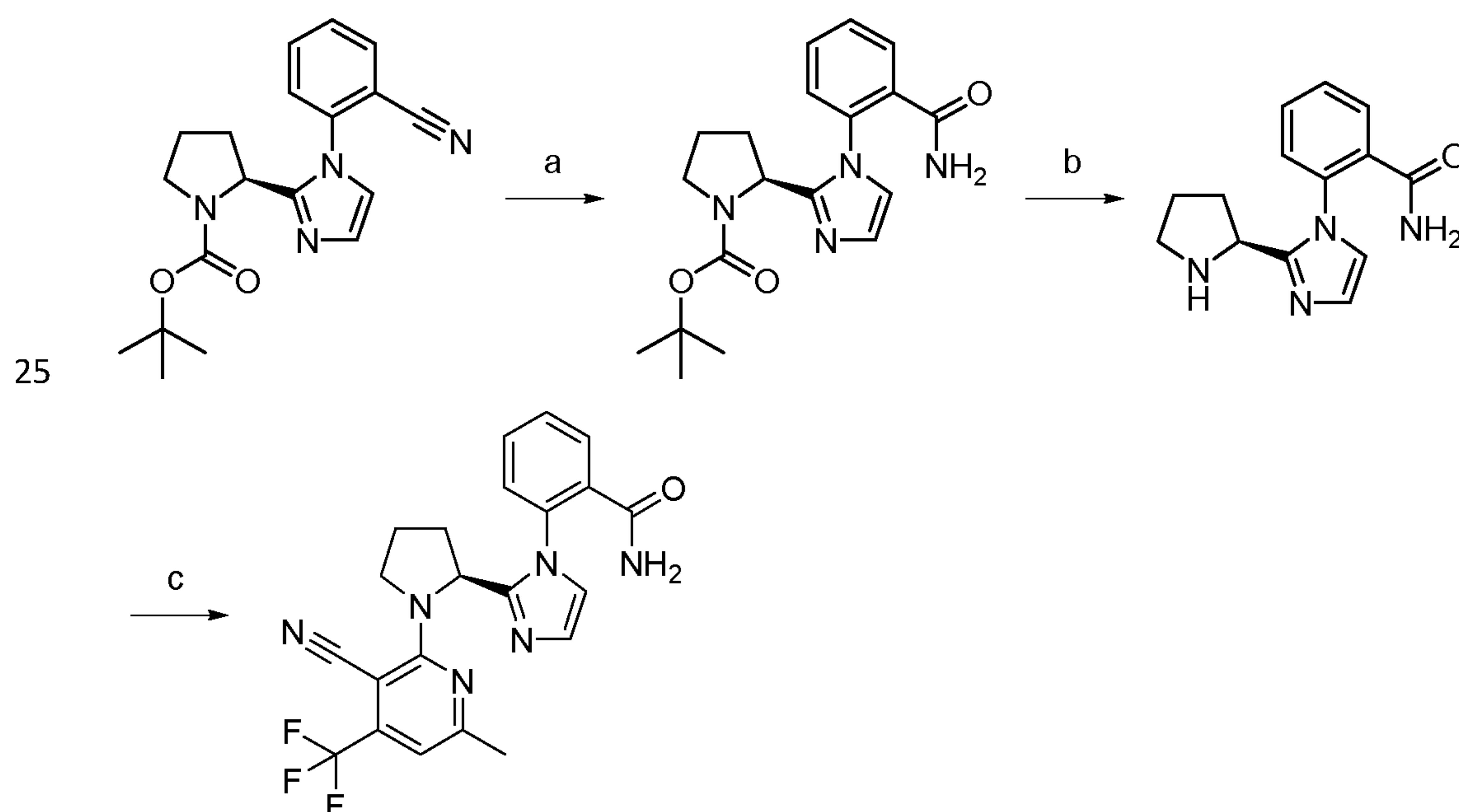
Step d. A solution of *tert*-butyl (2*S*)-2-[1-[2-(hydroxymethyl)phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (50 mg, 0.15 mmol) in HCl/dioxane (4 M, 5 mL) was stirred at rt for 1 h. The reaction mixture was evaporated to afford compound [2-[2-[(2*S*)-pyrrolidin-2-yl]imidazol-1-yl]phenyl]methanol (20 mg, 49% yield, HCl salt) as a colorless oil.

10 **Step e.** To a solution of [2-[2-[(2*S*)-pyrrolidin-2-yl]imidazol-1-yl]phenyl]methanol (20 mg, 0.072 mmol, HCl salt) and 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (16 mg, 0.072 mmol) in NMP (1.5 mL) was added DIPEA (19 mg, 0.14 mmol). The mixture was stirred at 80°C for 6 h. On completion, the reaction mixture was diluted with water (8 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine
15 (5 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (6 mg, 18% yield) as a brown gum.

m/z ES⁺ [M+H]⁺ 428.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.73 - 7.49 (m, 3H), 7.48 - 7.30 (m, 1H), 7.21 - 7.16 (m, 1H), 7.04 - 6.97 (m, 1H), 6.90 (d, *J* = 1.2 Hz, 1H), 5.44 - 5.19 (m, 2H), 4.51 - 4.32 (m, 1H), 4.30 - 3.97 (m, 2H), 3.89 - 3.76 (m, 1H), 2.42 - 2.25 (m, 3H),
20 2.21 - 2.00 (m, 2H), 1.98 - 1.74 (m, 2H).

Example 22

(*S*)-2-(2-(1-(3-Cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-yl)-1*H*-imidazol-1-yl)benzamide



Step a. A solution of *tert*-butyl (2*S*)-2-[1-(2-cyanophenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (200 mg, 0.59 mmol) and K₂CO₃ (163 mg, 1.18 mmol) in DMSO (5 mL) was treated dropwise with aq. H₂O₂ (335 mg, 2.96 mmol, 30%) at 0°C. The mixture was warmed to rt and stirred for 8 h under N₂ atmosphere. The mixture was quenched with water (15 mL) and extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (15 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (PE/EtOAc = 3/1) to afford compound *tert*-butyl (2*S*)-2-[1-(2-carbamoylphenyl)-imidazol-2-yl]pyrrolidine-1-carboxylate (300 mg, 90% yield) as a colorless oil.

m/z ES+ [M+H]⁺ 357.1; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.83 - 7.70 (m, 2H), 7.55 - 7.45 (m, 2H), 7.04 (s, 1H), 6.91 (s, 1H), 5.56 (s, 1H), 3.73 - 3.61 (m, 1H), 3.43 - 3.31 (m, 1H), 2.30 - 2.10 (m, 2H), 1.90 (td, *J* = 12.0, 6.4 Hz, 2H), 1.27 (s, 9H).

Step b. A solution of *tert*-butyl (2*S*)-2-[1-(2-carbamoylphenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (300 mg, 0.53 mmol) in HCl/MeOH (5 mL) was stirred at rt for 2 h. The mixture was then evaporated. The residue was dissolved in sat. Na₂CO₃ solution (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na₂SO₄ and evaporated. The obtained residue was purified by column chromatography (PE/EtOAc = 1/1 to 0/1) to afford 2-[2-[(2*S*)-pyrrolidin-2-yl]imidazol-1-yl]benzamide (140 mg, 97% yield) as a yellow oil.

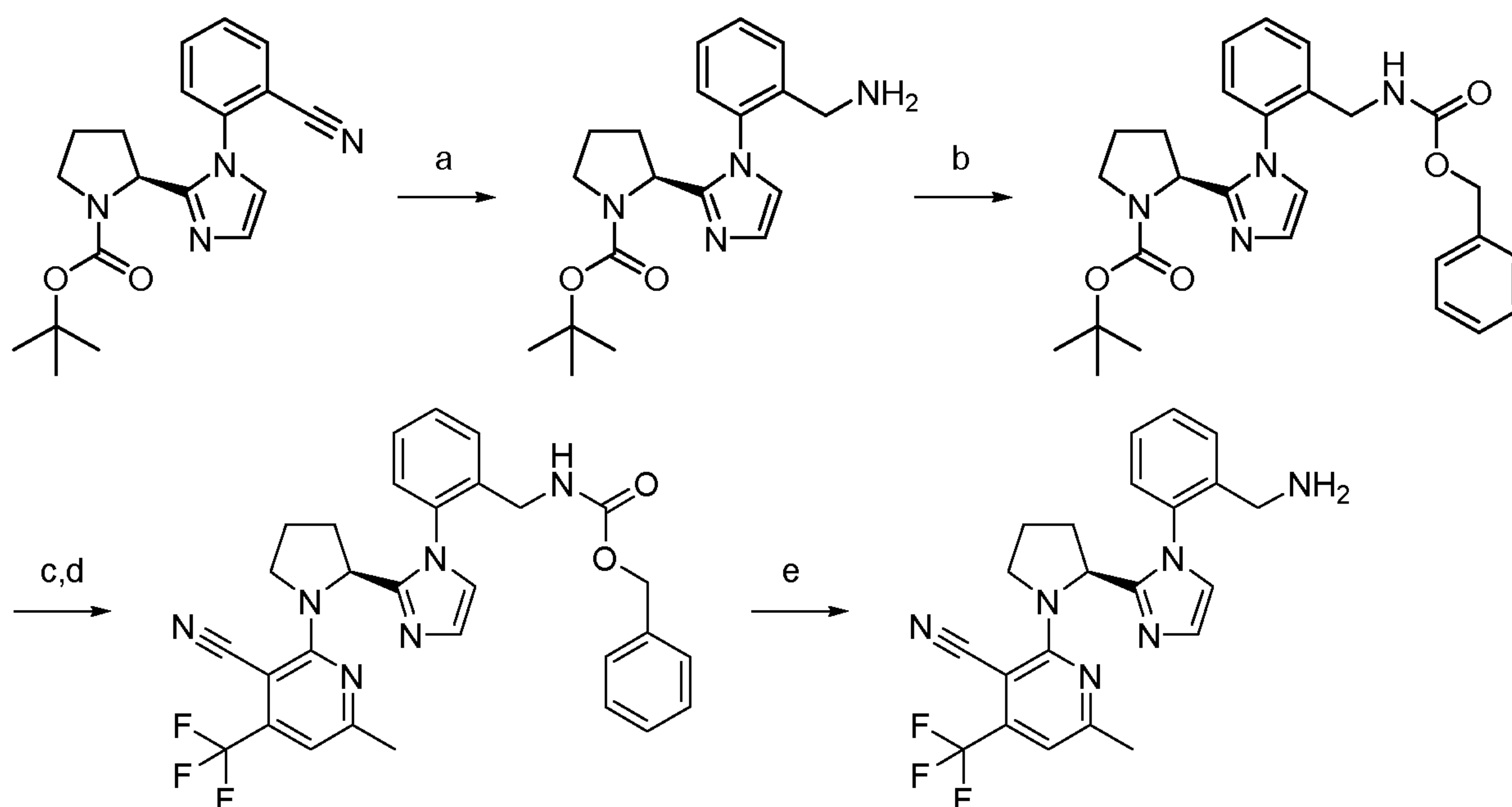
m/z ES+ [M+H]⁺ 257.0

Step c. A solution of 2-[2-[(2*S*)-pyrrolidin-2-yl]imidazol-1-yl]benzamide (140 mg, 0.52 mmol), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (127 mg, 0.57 mmol) and DIPEA (135 mg, 1.04 mmol) in DMF (2 mL) was stirred at 100°C for 12 h. The reaction mixture was evaporated and the residue was purified by prep-HPLC to give the title compound (39 mg, 16% yield) as a red solid.

m/z ES+ [M+H]⁺ 441.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.72 (s, 1H), 7.67 - 7.60 (m, 3H), 7.59 (s, 1H), 7.12 (s, 1H), 7.46 (s, 1H), 7.00 (s, 1H), 6.85 (s, 1H), 5.40 - 5.35 (m, 1H), 4.15 - 4.05 (m, 1H), 3.87 - 3.75 (m, 1H), 2.34 (s, 3H), 2.24 - 2.14 (m, 1H), 2.07 - 1.96 (m, 2H), 1.94 - 1.85 (m, 1H).

Example 23

(*S*)-2-(2-(1-(2-(Aminomethyl)phenyl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile



Step a. To a solution of *tert*-butyl (2S)-2-[1-(2-cyanophenyl)imidazol-2-yl]pyrrolidine-1-carboxylate (200 mg, 0.59 mmol) in MeOH (10 mL) and ammonium hydroxide (1 mL) was added Raney-Ni (101 mg, 1.18 mmol). The mixture was stirred at rt for 2 h under 15 psi H₂. On completion, the reaction mixture was evaporated to afford *tert*-butyl (2S)-2-[1-[2-(aminomethyl)-phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (130 mg, 64% yield) as a brown oil.

m/z ES+ [M+H]⁺ 343.2

Step b. To a solution of *tert*-butyl (2S)-2-[1-[2-(aminomethyl)phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (130 mg, 0.38 mmol) in THF (8 mL) was added NaHCO₃ (1 M, 2 mL) and benzyl chloroformate (78 mg, 0.46 mmol) dropwise at 0°C. The mixture was stirred at rt for 12 h. On completion, the reaction mixture was diluted with water (8 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/1) to afford *tert*-butyl (2S)-2-[1-[2-(benzyloxycarbonylaminomethyl)-phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (100 mg, 55% yield) as a colorless oil.

m/z ES+ [M+H]⁺ 477.2

Step c. A solution of *tert*-butyl (2S)-2-[1-[2-(benzyloxycarbonylaminomethyl)phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (80 mg, 0.17 mmol) in HCl/MeOH (4 M, 5 mL) was stirred at rt for 2 h. Then the reaction mixture was evaporated to afford benzyl *N*-[[2-[2-[(2S)-pyrrolidin-2-yl]imidazol-1-yl]phenyl]methyl]carbamate (60 mg, 87% yield, HCl) as a white solid.

m/z ES+ [M+H]⁺ 377.1

Step d. To a solution of benzyl *N*-[[2-[2-[(2S)-pyrrolidin-2-yl]imidazol-1-yl]phenyl]methyl]carbamate (60 mg, 0.15 mmol, HCl) and 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (35 mg, 0.16 mmol) in NMP (3 mL) was added DIPEA (38 mg, 0.29 mmol). The

mixture was stirred at 80°C for 5 h. On completion, the reaction mixture was poured into water (6 mL), and then extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL x 2), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 5/1 to 1/1) to afford benzyl N-[[2-[2-[(2S)-1-[3-cyano-6-methyl-4-(trifluoromethyl)-2-pyridyl]pyrrolidin-2-yl]imidazol-1-yl]phenyl]methyl]-carbamate (60 mg, 74% yield) as a white solid.

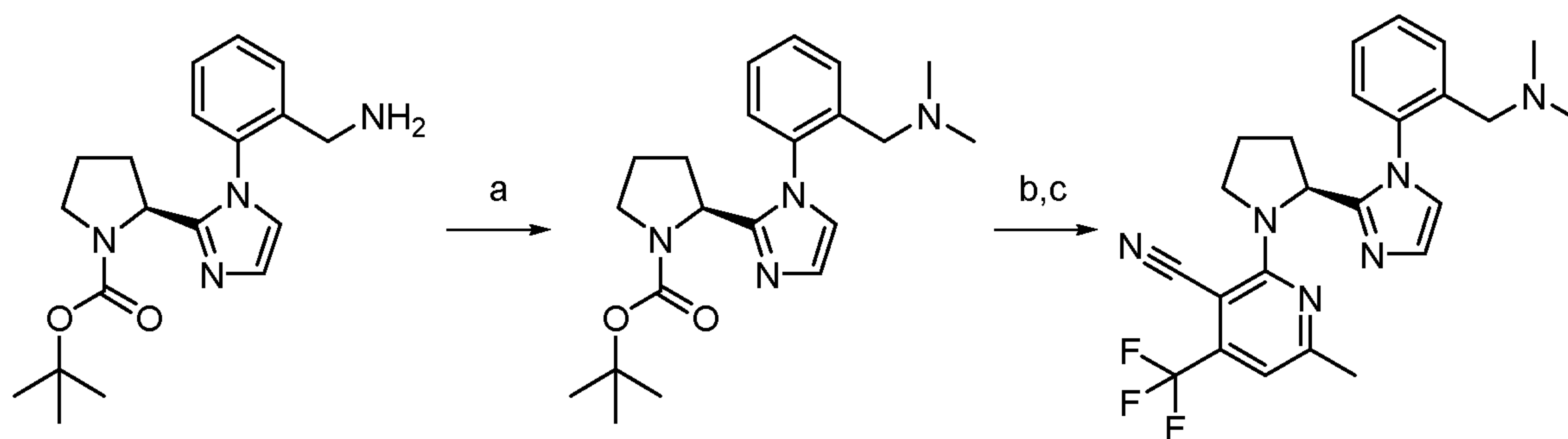
m/z ES+ [M+H]⁺ 561.2

Step e. To a solution of benzyl N-[[2-[2-[(2S)-1-[3-cyano-6-methyl-4-(trifluoromethyl)-2-pyridyl]pyrrolidin-2-yl]imidazol-1-yl]phenyl]methyl]carbamate (60 mg, 0.11 mmol) in EtOH (5 mL) was added Pd/C (10 mg, 10% loading) under N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was then stirred under H₂ atmosphere (15 psi) at rt for 2 h. On completion, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by prep-HPLC to give the title compound (19 mg, 39% yield) as a white solid.

m/z ES+ [M+H]⁺ 427.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.72 - 7.67 (m, 1H), 7.65 - 7.52 (m, 1H), 7.52 - 7.45 (m, 1H), 7.45 - 7.34 (m, 1H), 7.30 - 7.21 (m, 1H), 7.05 - 6.97 (m, 1H), 6.90 (s, 1H), 5.40 - 5.25 (m, 1H), 4.11 - 3.94 (m, 1H), 3.85 - 3.75 (m, 1H), 3.70 - 3.49 (m, 1H), 3.42 - 3.34 (m, 1H), 2.41 - 2.28 (m, 3H), 2.21 - 2.03 (m, 2H), 1.98 - 1.90 (m, 2H).

Example 24

(S)-2-(2-(1-(2-((Dimethylamino)methyl)phenyl)-1H-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile



Step a. To a solution of *tert*-butyl (2S)-2-[1-[2-(aminomethyl)phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (90 mg, 0.26 mmol) in THF (2 mL) and MeOH (2 mL) was added formaldehyde (19 mg, 0.63 mmol) and NaBH₃CN (40 mg, 0.63 mmol). The mixture was stirred at rt for 3 h. The mixture was evaporated, the residue was treated with water (10 mL) and extracted into EtOAc (30 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography (PE/EtOAc = 1/0 followed by EtOAc/EtOH = 20/1 with 0.1% of TEA) to

afford *tert*-butyl (2*S*)-2-[1-[2-[(dimethylamino)methyl]phenyl]imidazol-2-yl]pyrrolidine-1-carboxylate (140 mg, 84% yield) as a white solid.

m/z ES⁺ [M+H]⁺ 371.2

Step b. A solution of *tert*-butyl (2*S*)-2-[1-[2-[(dimethylamino)methyl]phenyl]imidazol-2-

5 yl]pyrrolidine-1-carboxylate (140 mg, 0.38 mmol) in HCl/dioxane (5 mL) was stirred at rt for 2 h. The reaction mixture was then evaporated to afford *N,N*-dimethyl-1-[2-[2-[(2*S*)-pyrrolidin-2-yl]imidazol-1-yl]phenyl]methanamine (90 mg, 88% yield) as a pink solid, which was used in next step without further purification.

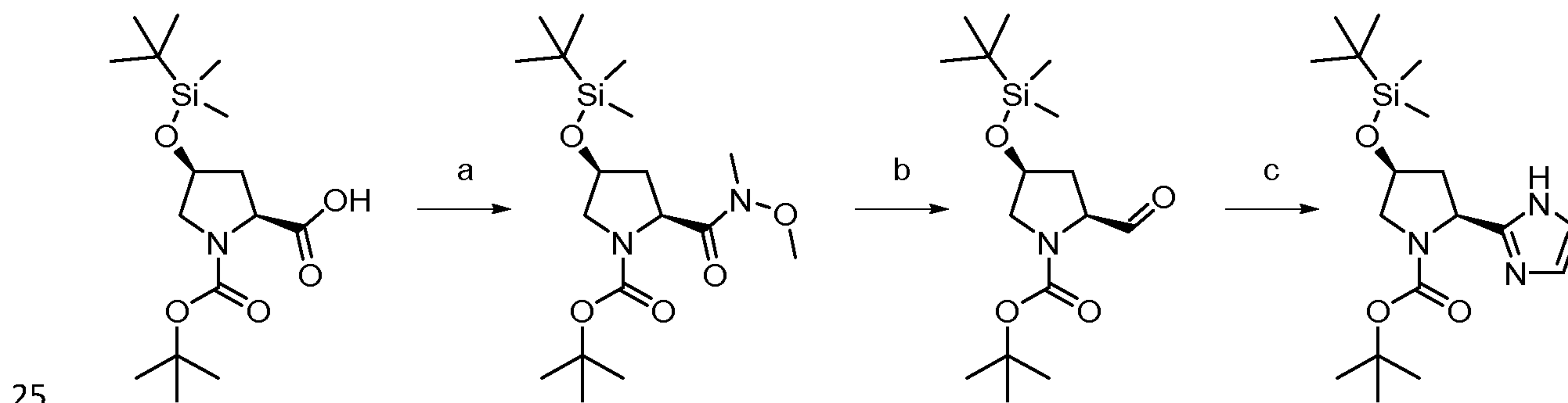
m/z ES⁺ [M+H]⁺ 271.1

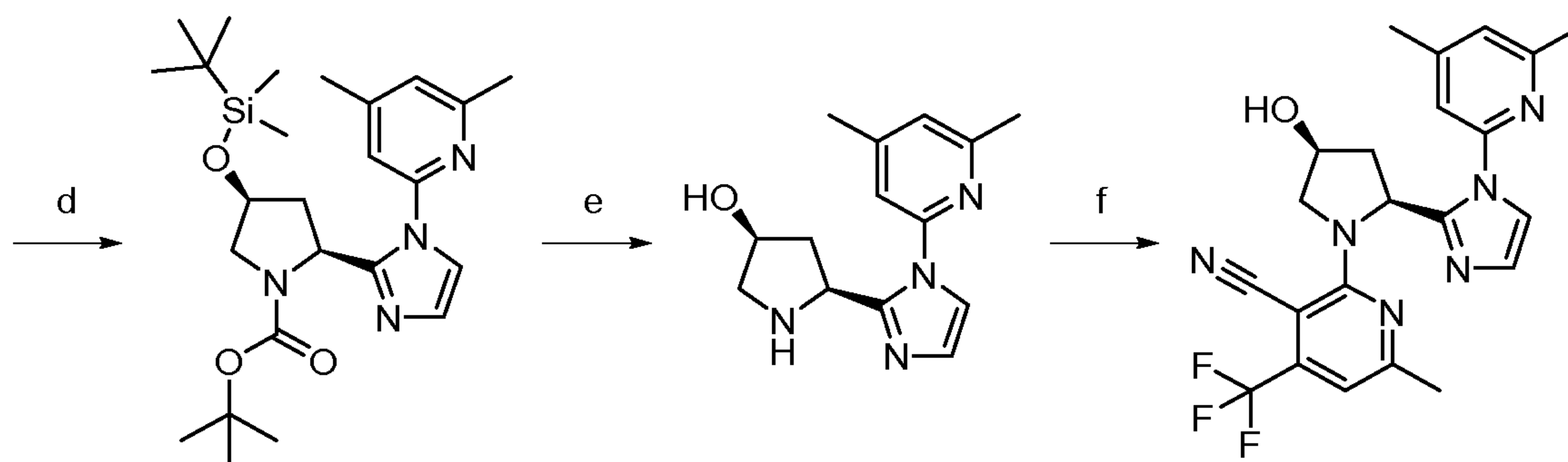
10 **Step c.** To a solution of *N,N*-dimethyl-1-[2-[2-[(2*S*)-pyrrolidin-2-yl]imidazol-1-yl]phenyl]-methanamine (90 mg, 0.30 mmol) and DIPEA (108 mg, 0.83 mmol) in NMP (2 mL) was added 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (88 mg, 0.40 mmol). The mixture was stirred at 80°C for 5 h. Upon completion, the reaction mixture was quenched with water (15 mL) and extracted into EtOAc (30 mL x 3). The combined organic layers were

15 washed with brine (15 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (21 mg, 13% yield) as a brown solid.
 m/z ES⁺ [M+H]⁺ 455.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.67 - 7.52 (m, 2H), 7.51 - 7.38 (m, 2H), 7.33 - 7.16 (m, 1H), 7.04 - 6.98 (m, 1H), 6.90 (s, 1H), 5.45 - 5.40 (m, 1H), 4.03 - 3.97 (m, 1H), 3.85 - 3.75 (m, 1H), 3.11 - 3.01 (m, 2H), 2.40 (s, 3H), 2.30 - 2.10 (m, 2H),
 20 2.07 (s, 6H), 2.00 - 1.79 (m, 2H).

Example 25

2-((2*S*,4*S*)-2-(1-(4,6-Dimethylpyridin-2-yl)-1*H*-imidazol-2-yl)-4-hydroxypyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile





Step a. A mixture of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-[(*tert*-butyl(dimethyl)silyl]oxy-pyrrolidine-2-carboxylic acid (10.00 g, 28.9 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (3.11 g, 31.8 mmol), HATU (13.21 g, 34.7 mmol) and DIPEA (7.48 g, 57.9 mmol) in DCM (100 mL) was stirred at 15°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was evaporated. The obtained residue was purified by column chromatography (PE/EtOAc 10/1 to 5/1) to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxy(methyl)-carbamoyl)pyrrolidine-1-carboxylate (7.5 g, 67% yield) as a white solid.

m/z ES⁺ [M+H]⁺ 389.3

Step b. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxy(methyl)-carbamoyl)pyrrolidine-1-carboxylate (5.00 g, 12.87 mmol) in DCM (50 mL) was added DIBAL-H (1 M, 38.6 mL) dropwise at -78°C. The mixture was stirred at -78°C for 2 h. The reaction mixture was quenched by dropwise addition of MeOH (2 mL) at -78°C, warmed to rt, filtered and washed with MeOH (250 mL). The filtrate was evaporated and the residue was purified by column chromatography (PE/EtOAc = 20/1 to 4/1) to afford (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate (3.1 g, 73% yield) as a colorless oil.

Step c. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate (2.00 g, 6.07 mmol), glyoxal (3.07 g, 21.2 mmol) in MeOH (20 mL) was added ammonium hydroxide (5.60 g, 39.9 mmol, 25% aq.). The mixture was stirred at 10°C for 16 h. The reaction mixture was evaporated and the residue was purified by column chromatography (PE/EtOAc = 10/1 to 0/1) to afford (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (1.1 g, 49% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 368.3; ¹H NMR (400 MHz, CDCl₃) δ ppm 6.95 (br s, 2H), 5.07 (br d, *J* = 9.6 Hz, 1H), 4.61 - 4.34 (m, 1H), 3.79 - 3.54 (m, 1H), 3.25 (br s, 1H), 2.74 - 2.38 (m, 1H), 2.21 - 1.99 (m, 1H), 1.60 - 1.19 (m, 9H), 0.99 - 0.78 (m, 9H), 0.25 - 0.06 (m, 6H)

Step d. A mixture of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (70 mg, 0.19 mmol), 2-bromo-4,6-dimethylpyridine (71 mg, 0.38 mmol), CuI (40 mg, 0.21 mmol) and Cs₂CO₃ (187 mg, 0.57 mmol) in DMSO (1.5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120°C for 16 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by EtOAc (100

mL) and water (50 mL). The organic phase was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/3) to afford (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1-(4,6-dimethylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (60 mg, 88% yield) as a yellow oil.

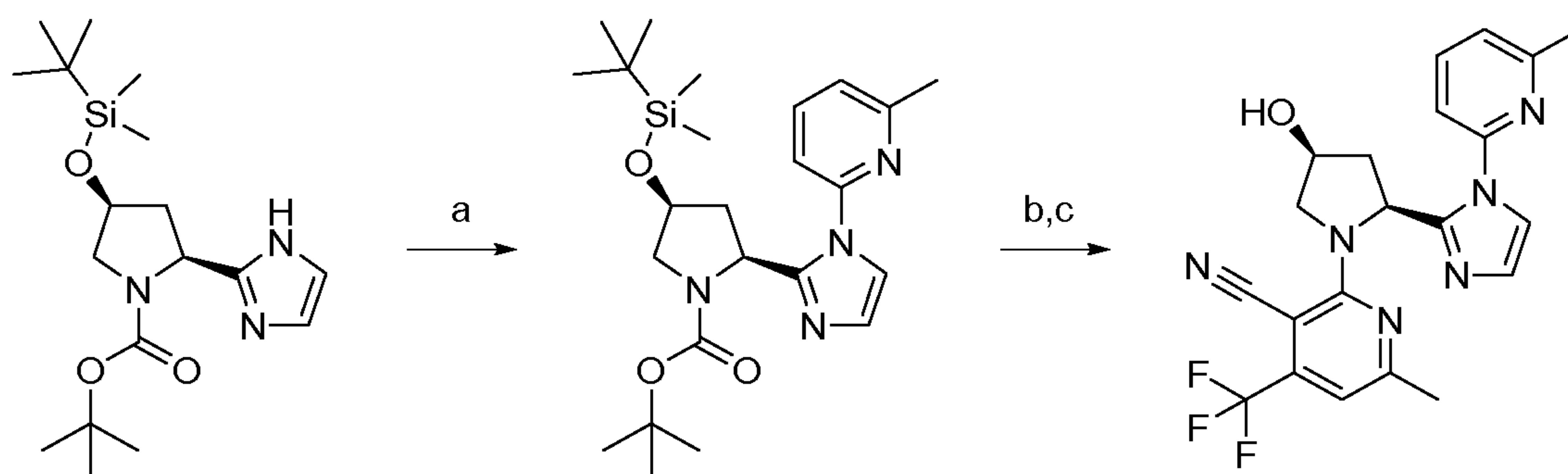
Step e. To a solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1-(4,6-dimethylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (60 mg, 0.17 mmol) in dioxane (0.5 mL) was added HCl/dioxane (4 M, 0.5 mL). The mixture was stirred at rt for 1 h. On completion, the mixture was concentrated in vacuo to afford (3*S*,5*S*)-5-(1-(4,6-dimethylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol (43 mg, crude, HCl) as a yellow oil which was used in the next step without further purification.

Step f. To a solution of (3*S*,5*S*)-5-(1-(4,6-dimethylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol (43 mg, 0.17 mmol, HCl), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (55 mg, 0.25 mmol) in NMP (0.5 mL) was added DIPEA (64 mg, 0.50 mmol). The mixture was stirred at 60°C for 16 h. On completion, the reaction mixture was quenched by EtOAc (100 mL) and water (20 mL). The organic phase was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by prep-HPLC to give the title compound (5 mg, 7% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 443.2; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.37 (br d, *J* = 16.8 Hz, 2H), 7.20 (s, 1H), 7.12 (br s, 1H), 6.78 (s, 1H), 5.80 – 5.65 (m, 1H), 5.02 (br d, *J* = 10.8 Hz, 1H), 4.78 (br s, 1H), 4.21 (br d, *J* = 10.0 Hz, 1H), 2.88 - 2.78 (m, 1H), 2.66 - 2.43 (m, 7H), 2.20 (s, 3H)

Example 26

(3*S*,5*S*)-1-(6-Methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol



Step a. A mixture of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (370 mg, 1.01 mmol), 2-bromo-6-methylpyridine (208 mg, 1.21 mmol), CuI (192 mg, 1.01 mmol), K₂CO₃ (417 mg, 3.02 mmol), *L*-proline (232 mg, 2.01 mmol) in DMSO (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100°C for 12 h under N₂ atmosphere. On completion, the reaction mixture was

quenched by aq. NH_4Cl (60 mL) at rt, diluted with water (100 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4 , filtered and evaporated. The residue was purified by prep-TLC (PE/EtOAc = 15/85)

to give (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1-(6-methylpyridin-2-yl)-1*H*-

Step b. A solution of (2*S*,4*S*)-*tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (70 mg, 0.15 mmol) in HCl/dioxane (5 mL) was stirred at rt for 2 h. Upon completion, the reaction mixture was evaporated to give

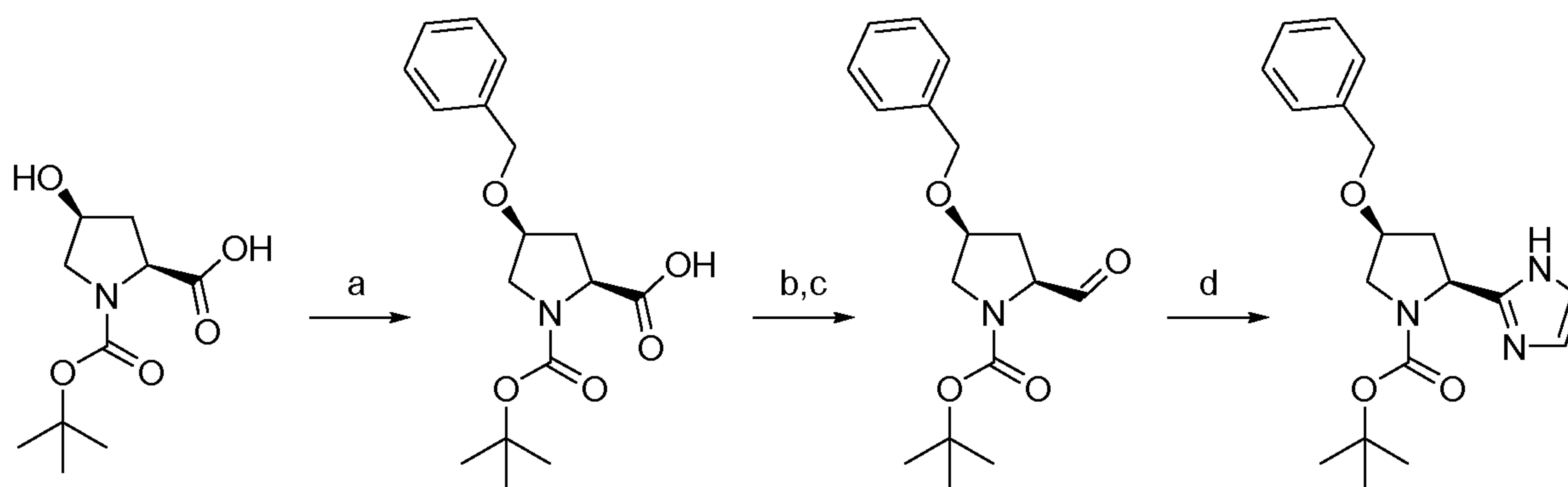
(3*S*,5*S*)-5-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol (40 mg, crude HCl salt)

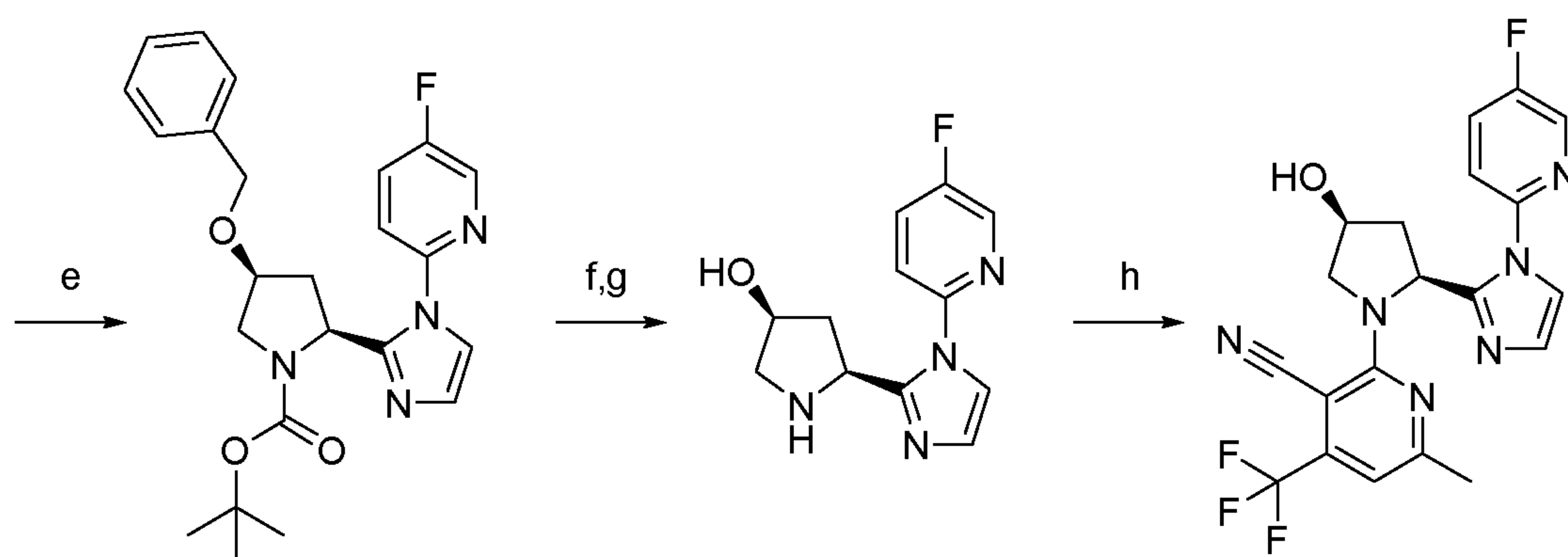
Step c. A mixture of (3*S*,5*S*)-5-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol (40 mg, 0.20 mmol, crude HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine (77 mg, 0.39 mmol), Cs_2CO_3 (255 mg, 0.78 mmol), RuPhos-Pd-G2 (15 mg, 0.020 mmol) in dioxane (2 mL) was degassed and purged with N_2 3 times, and then stirred at 70°C for 12 h under N_2 atmosphere. Upon completion, the reaction mixture was filtered and concentrated in vacuo. The obtained residue was purified by prep-HPLC to give the title compound (17 mg, 21% yield) as a white solid.

m/z ES+ $[\text{M}+\text{H}]^+$ 404.2; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.97 (dd, J = 7.6, 7.6 Hz, 1H), 7.54 - 7.47 (m, 2H), 7.38 (d, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.75 (bs, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 5.73 (d, J = 7.2 Hz, 1H), 4.50 - 4.39 (m, 1H), 3.73 - 3.67 (m, 1H), 3.65 - 3.59 (m, 1H), 2.65 - 2.55 (m, 1H), 2.54 (s, 3H), 2.20 - 2.10 (m, 1H), 1.97 (s, 3H).

Example 27

2-((2*S*,4*S*)-2-(1-(5-Fluoropyridin-2-yl)-1*H*-imidazol-2-yl)-4-hydroxypyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile





Step a. To a solution of (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (10.00 g, 43.24 mmol) in THF (150 mL) was added NaH (3.81 g, 95.1 mmol, 60% dispersion in mineral oil) portionwise at 0°C and then benzyl bromide (8.88 g, 51.89 mmol) was added. The mixture was stirred at rt for 16 h. On completion, the mixture was poured into 200 mL water slowly and carefully adjusted to pH ~ 2 with aq. HCl (2 M). The mixture was then extracted with EtOAc (400 mL x 3). The combined organic phase was dried over Na₂SO₄ and evaporated. The residue was triturated with PE/EtOAc = 10/1 (500/50 mL) for 30 min and filtered to give (2*S*,4*S*)-4-(benzyloxy)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (12.5 g, 90% yield) as a white solid.

Step b. A mixture of (2*S*,4*S*)-4-(benzyloxy)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (20 g, 62.2 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (6.68 g, 68.5 mmol), DIPEA (16.09 g, 124.5 mmol), HATU (26.03 g, 68.46 mmol) in DCM (270 mL) was stirred at rt for 12 h. The reaction mixture was concentrated and the residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/1) to give (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (20.8 g, 92% yield) as a colorless oil. *m/z* ES+ [M+H]⁺ 365.3

Step c. To a solution of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (30 g, 82.32 mmol) in DCM (300 mL) was added DIBAL-H (1 M, 247 mL) slowly at -78°C. The mixture was stirred at -78°C for 2 h. On completion, the reaction mixture was quenched by MeOH (100 mL) at -78°C, and then filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc = 15/1 to 8/1) to give (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-formylpyrrolidine-1-carboxylate (16.5 g, 66% yield) as a colorless oil.

Step d. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-formylpyrrolidine-1-carboxylate (14 g, 45.8 mmol), glyoxal (33.26 g, 229 mmol), ammonium hydroxide (38.56 g, 275 mmol, 25% aq.) in MeOH (35 mL) was stirred at rt for 16 h under N₂ atmosphere. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column

chromatography (PE/EtOAc = 5/1 to 1/2) to give (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (10.5 g, 67% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 344.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.56 (br s, 1H), 7.40 - 7.21 (m, 5H), 7.17 (br s, 1H), 6.84 (br s, 1H), 4.96 - 4.68 (m, 1H), 4.50 - 4.31 (m, 2H), 4.22 - 4.09 (m, 1H), 3.68 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.41 (dd, *J* = 11.2, 4.4 Hz, 2H), 2.07 (br s, 1H), 1.41 - 1.13 (m, 9H).

Step e. A mixture of *tert*-butyl (2*S*,4*S*)-4-benzyloxy-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (200 mg, 0.58 mmol), 2,5-difluoropyridine (80 mg, 0.70 mmol) and Cs₂CO₃ (284 mg, 0.87 mmol) in DMSO (1 mL) was stirred at 80°C for 12 h under N₂ atmosphere. On completion, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc = 3/1 to 1/1) to give (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1-(5-fluoropyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (80 mg, 30% yield) as a colorless oil.

m/z ES⁺ [M+H]⁺ 439.3

Step f. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1-(5-fluoropyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (138 mg, 0.31 mmol) and Pd/C (20 mg, 10% loading) in EtOH (1 mL) was stirred at rt for 12 h under H₂ balloon atmosphere. On completion, the reaction mixture was filtered and evaporated to give (2*S*,4*S*)-*tert*-butyl 2-(1-(5-fluoropyridin-2-yl)-1*H*-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (150 mg, crude) as a colorless oil.

m/z ES⁺ [M+H]⁺ 349.2

Step g. To a solution of (2*S*,4*S*)-*tert*-butyl 2-(1-(5-fluoropyridin-2-yl)-1*H*-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (150 mg, 0.43 mmol) in dioxane (1 mL) was added HCl/dioxane (4 M, 1 mL). The reaction mixture was stirred at rt for 2 h. On completion, the reaction mixture was evaporated to give (3*S*,5*S*)-5-(1-(5-fluoropyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol (120 mg, 90 % yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 249.1

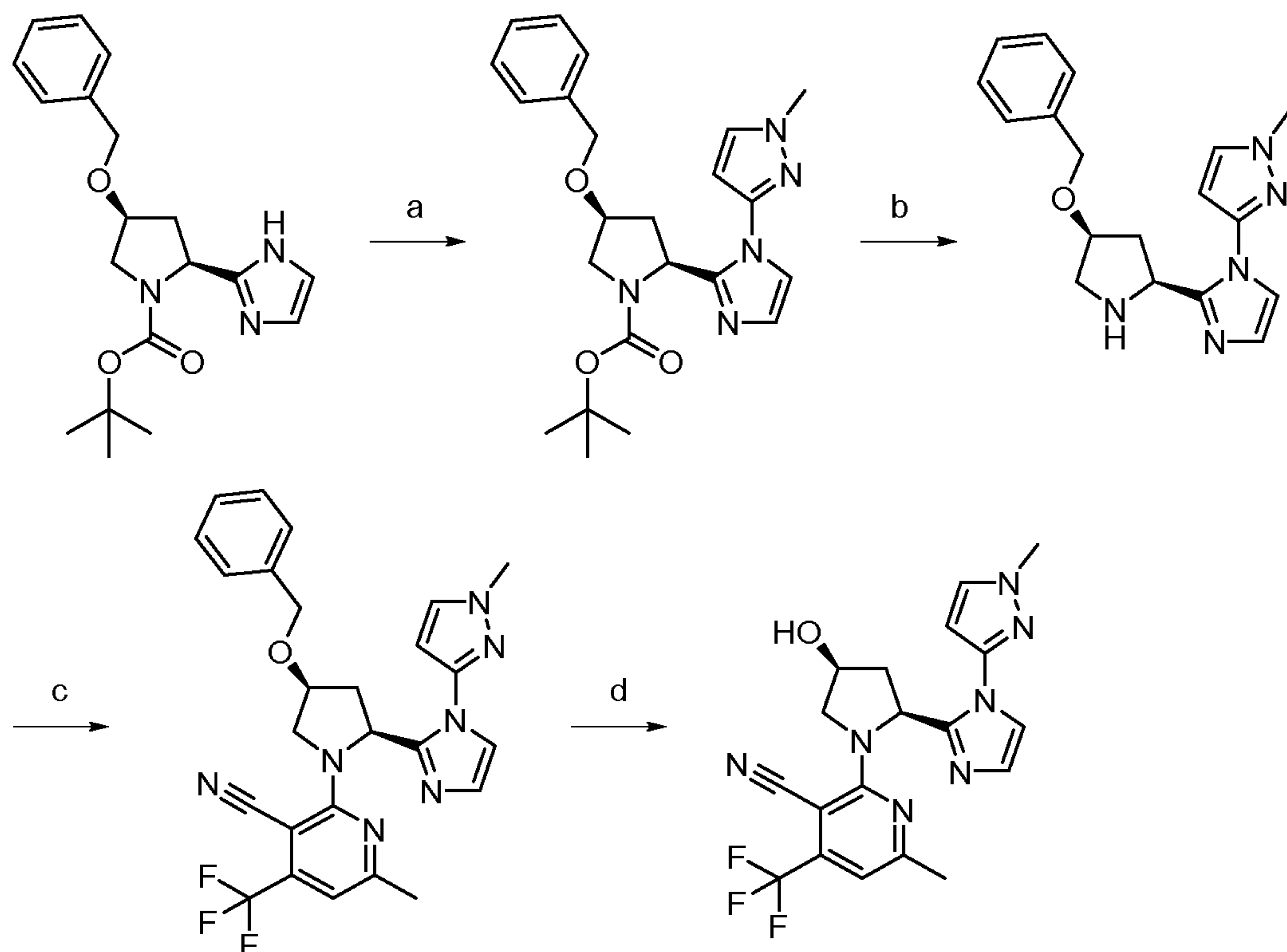
Step h. A mixture of (3*S*,5*S*)-5-(1-(5-fluoropyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-ol (100 mg, 0.35 mmol, HCl), 2-chloro-6-methyl-4-(trifluoromethyl)pyridine-3-carbonitrile (93 mg, 0.42 mmol) and DIPEA (91 mg, 0.70 mmol) in NMP (2 mL) was stirred at 60°C for 12 h. On completion, the reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC to give the title compound (30 mg, 19 % yield) as a white solid.

m/z ES⁺ [M+H]⁺ 433.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.65 (d, *J* = 2.8 Hz, 1H), 8.06 (dt, *J* = 3.2, 8.4 Hz, 1H), 7.75 (dd, *J* = 4.0, 8.8 Hz, 1H), 7.51 (s, 1H), 6.96 (d, *J* = 1.6 Hz, 1H), 6.93 (s, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.76 (t, *J* = 7.2 Hz, 1H), 4.51 - 4.36 (m, 1H), 4.09 (dd, *J*

= 6.4, 10.0 Hz, 1H), 3.92 (dd, J = 5.6, 10.4 Hz, 1H), 2.74 - 2.60 (m, 1H), 2.14 (td, J = 6.4, 12.8 Hz, 1H), 2.00 (s, 3H).

Example 28

5 2-((2*S*,4*S*)-4-Hydroxy-2-(1-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile



Step a. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (500 mg, 1.46 mmol), 3-iodo-1-methyl-1*H*-pyrazole (908 mg, 4.37 mmol), CuI (111 mg, 0.58 mmol), *L*-proline (134 mg, 1.16 mmol) and K₂CO₃ (1.01 g, 7.28 mmol) in DMSO (5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 110°C for 16 h under N₂ atmosphere. On completion, the reaction mixture was quenched by EtOAc (100 mL) and water (50 mL). The organic phase was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated. The obtained residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/3) to afford (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (140 mg, 23% yield) as a yellow solid.

Step b. (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (140 mg, 0.33 mmol) in HCl/dioxane (4 M, 2.33 mL) was stirred at rt for 2 h. On completion, the reaction mixture was concentrated in vacuo to afford 3-(2-((2*S*,4*S*)-4-(benzyloxy)pyrrolidin-2-yl)-1*H*-imidazol-1-yl)-1-methyl-1*H*-pyrazole (100 mg, crude) as a yellow oil.

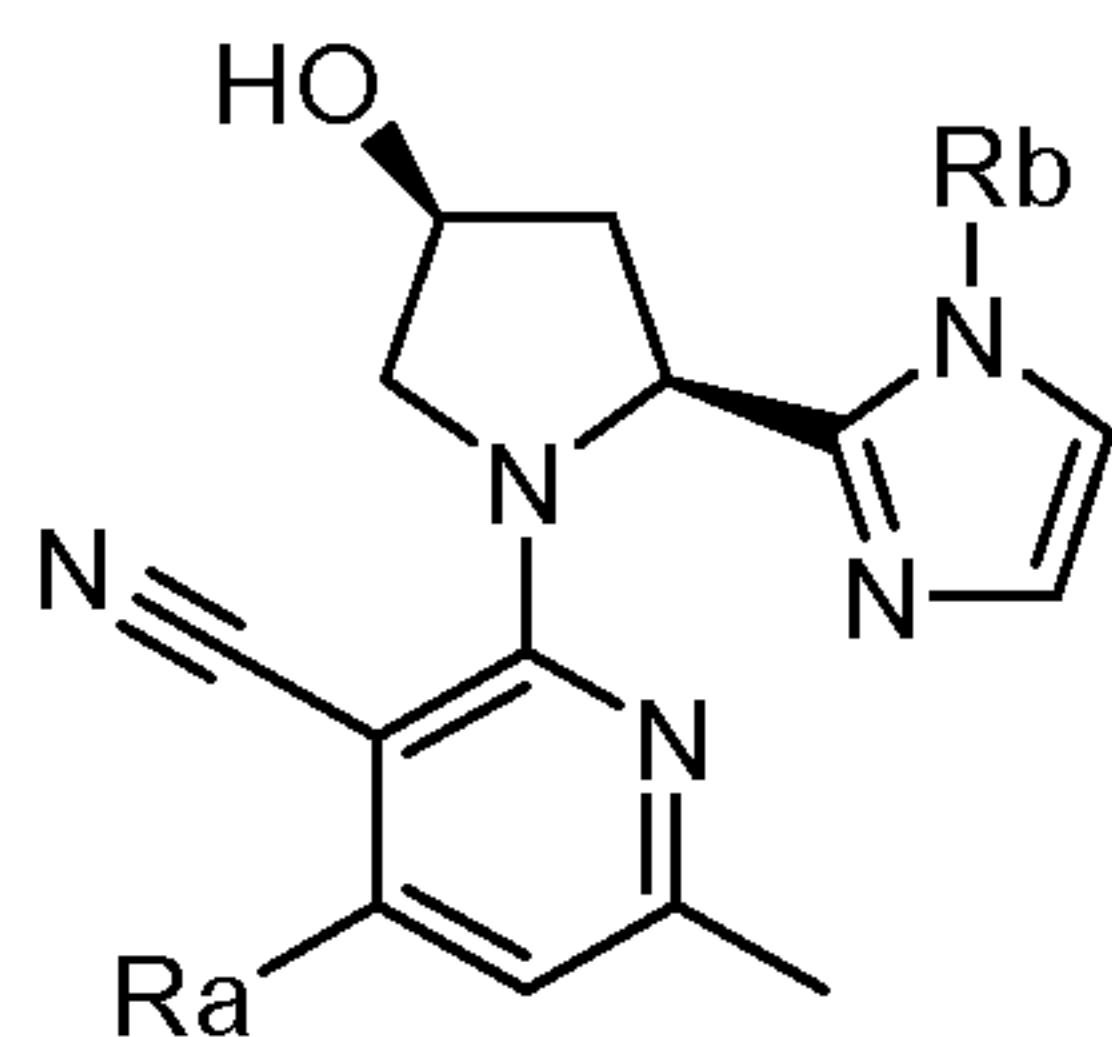
Step c. A mixture of 3-(2-((2*S*,4*S*)-4-(benzyloxy)pyrrolidin-2-yl)-1*H*-imidazol-1-yl)-1-methyl-1*H*-pyrazole (100 mg, 0.31 mmol), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (82 mg, 0.37 mmol) and DIPEA (120 mg, 0.93 mmol) in NMP (2 mL) was stirred at 60°C for 16 h. On completion, the reaction mixture was quenched by EtOAc (100 mL) and water (20 mL). The organic phase was separated, washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by prep-TLC (PE/EtOAc = 1/1) to afford 2-((2*S*,4*S*)-4-(benzyloxy)-2-(1-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (100 mg, 64% yield) as a yellow solid.

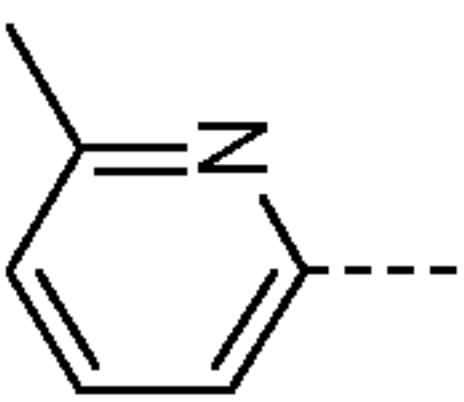
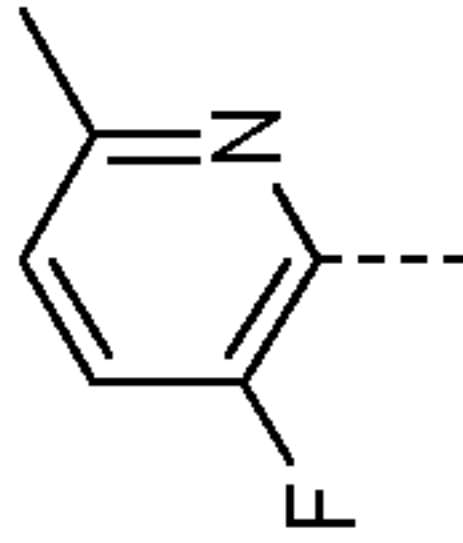
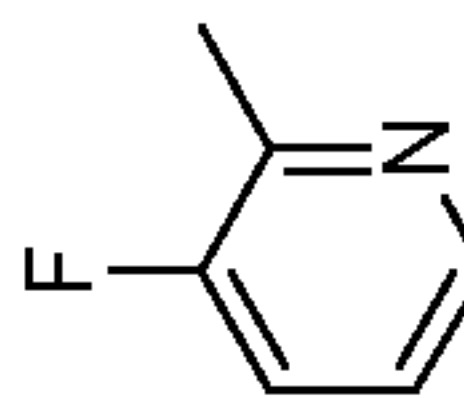
Step d. To a solution of 2-((2*S*,4*S*)-4-(benzyloxy)-2-(1-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (60 mg, 0.12 mmol) in DCM (2 mL) was added BCl₃ (1 M in toluene, 2.36 mL) dropwise at 0°C. The mixture was stirred at 0°C for 30 min. On completion, the reaction mixture was quenched by water (5 mL) at 0°C, and then adjusted to pH = 8 with aq. NaOH (5% wt). The mixture was extracted with EtOAc (25 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by prep-HPLC. The obtained product was treated with aq. HCl (2 M, 2 mL) and then lyophilized to give the hydrochloride salt of the title compound (25 mg, 46% yield) as a yellow solid.

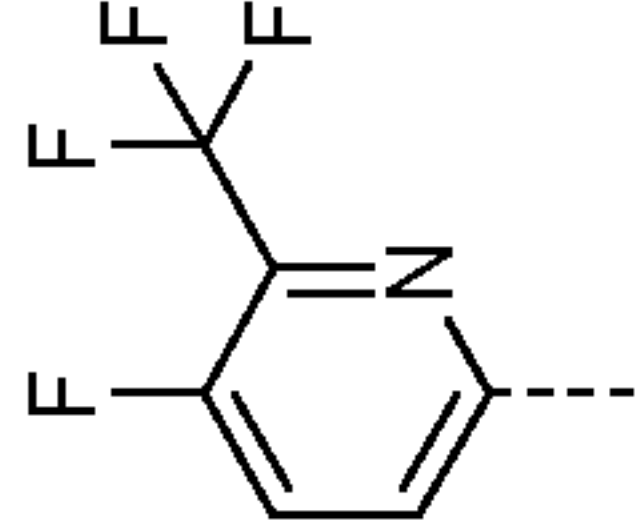
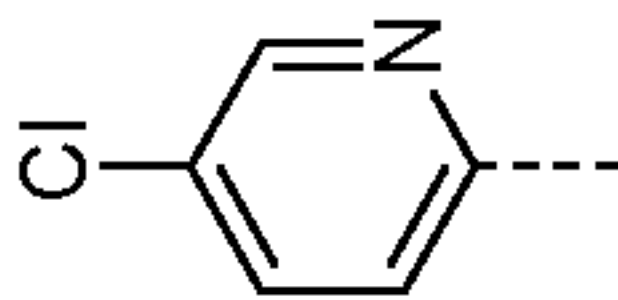
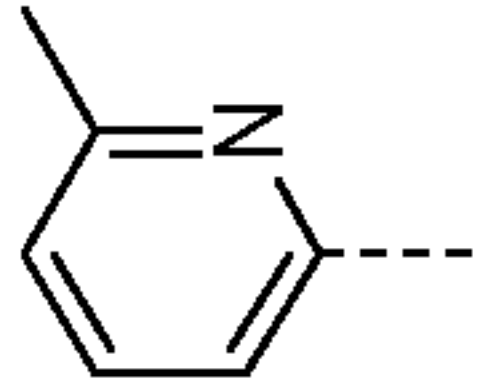
m/z ES+ [M+H]⁺ 418.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.03 (dd, *J* = 2.0, 10.4 Hz, 2H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.12 (s, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 5.68 (dd, *J* = 4.4, 8.8 Hz, 1H), 4.59 - 4.50 (m, 1H), 4.23 - 4.04 (m, 2H), 3.95 (s, 3H), 2.63 - 2.57 (m, 1H), 2.20 (s, 3H), 2.20 - 2.10 (m, 1H).

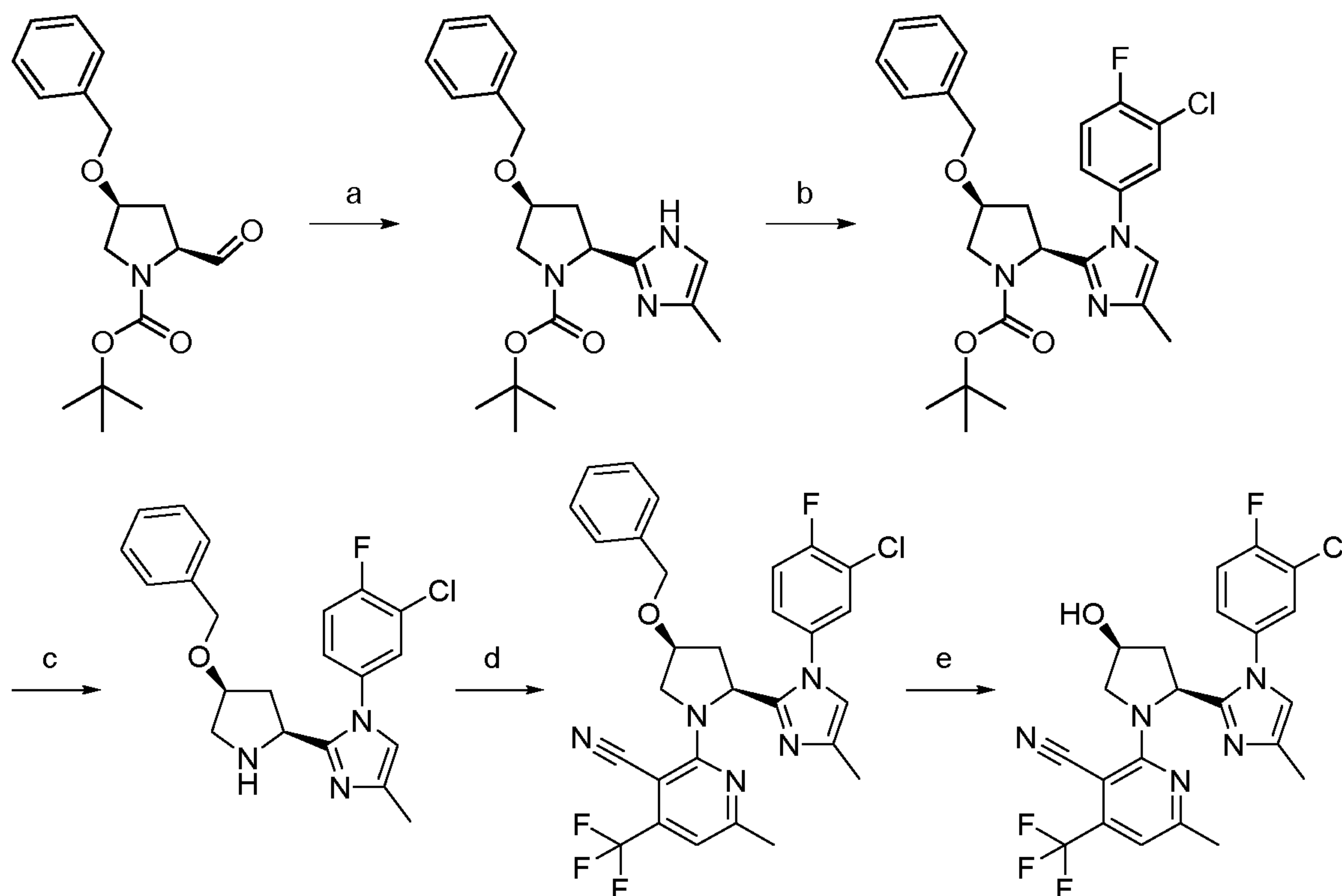
The Examples in **Table 2** were prepared using methods similar to those described in the synthesis of **Examples 25-28**.

Table 2



Example Number	Ra	Rb	Aryl halide CAS Number	Name	¹ H NMR (400 MHz) δ ppm	MI
29	CF ₃		5315-25-3	2-((2 <i>S</i> ,4 <i>S</i>)-4-Hydroxy-2-(1-(6-methylpyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)-nicotinonitrile	(DMSO-d ₆) 7.94 (t, <i>J</i> = 7.6 Hz, 1H), 7.47 (s, 1H), 7.42 (d, <i>J</i> = 8.0 Hz, 1H), 7.35 (d, <i>J</i> = 7.6 Hz, 1H), 6.91 (d, <i>J</i> = 12.8 Hz, 2H), 6.01 (d, <i>J</i> = 8.0 Hz, 1H), 5.80 (t, <i>J</i> = 7.2 Hz, 1H), 4.50 – 4.40 (m, 1H), 4.15 – 4.05 (m, 1H), 4.00 – 3.85 (m, 1H), 2.80 – 2.65 (m, 1H), 2.54 (s, 3H), 2.21 - 2.11 (m, 1H), 1.99 (s, 3H)	429.2
30	CF ₃		1227579-04-5	2-((2 <i>S</i> ,4 <i>S</i>)-2-(1-(3-Fluoro-6-methylpyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)-4-hydroxy-pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)-nicotinonitrile	(CDCl ₃) 7.71 (br t, <i>J</i> = 9.2 Hz, 1H), 7.56 - 7.42 (m, 2H), 7.37 (br s, 1H), 6.80 (s, 1H), 5.51 (br d, <i>J</i> = 8.4 Hz, 1H), 5.07 (br d, <i>J</i> = 11.2 Hz, 1H), 4.82 (br s, 1H), 4.24 (br d, <i>J</i> = 8.0 Hz, 1H), 2.88 (br d, <i>J</i> = 9.6 Hz, 1H), 2.66 (s, 3H), 2.65 – 2.55 (m, 1H), 2.20 (s, 3H)	447.2
31	CF ₃		99132-28-2	2-((2 <i>S</i> ,4 <i>S</i>)-2-(1-(5-Fluoro-6-methylpyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)-4-hydroxy-pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)-nicotinonitrile	(DMSO-d ₆) 8.19 - 8.05 (m, 2H), 7.90 - 7.66 (m, 2H), 7.10 (s, 1H), 5.69 (dd, <i>J</i> = 5.2, 8.4 Hz, 1H), 4.61 - 4.49 (m, 1H), 4.21 - 4.01 (m, 2H), 2.69 - 2.63 (m, 1H), 2.54 (d, <i>J</i> = 2.8 Hz, 3H), 2.26 (td, <i>J</i> = 4.8, 12.8 Hz, 1H), 2.18 (s, 3H)	447.0

Example Number	Ra	Rb	Aryl halide CAS Number	Name	¹ H NMR (400 MHz) δ ppm	MI
32	CF ₃		1099597-92-8	2-((2 <i>S</i> ,4 <i>S</i>)-2-(1-(5-Fluoro-6-(trifluoromethyl)pyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)-4-hydroxy-pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile	(DMSO-d ₆) 8.59 (t, <i>J</i> = 9.2 Hz, 1H), 8.41 (dd, <i>J</i> = 2.8, 9.2 Hz, 1H), 8.14 (s, 1H), 7.71 (br s, 1H), 7.09 (s, 1H), 5.72 (dd, <i>J</i> = 4.8, 8.4 Hz, 1H), 4.60 - 4.49 (m, 1H), 4.21 - 4.05 (m, 2H), 2.63 (ddd, <i>J</i> = 5.2, 8.4, 13.2 Hz, 1H), 2.27 (td, <i>J</i> = 4.8, 13.2 Hz, 1H), 2.16 (s, 3H)	501.0
33	CH ₃		1480-65-5	2-((2 <i>S</i> ,4 <i>S</i>)-2-(1-(5-Chloropyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)-4-hydroxy-pyrrolidin-1-yl)-4,6-dimethylnicotinonitrile	(CDCl ₃) 8.58 (s, 1H), 8.03 (d, <i>J</i> = 6.8 Hz, 1H), 7.75 (d, <i>J</i> = 8.8 Hz, 1H), 7.59 (s, 1H), 7.47 (s, 1H), 6.51 (s, 1H), 6.06 (br s, 1H), 4.71 (br s, 1H), 4.61 (d, <i>J</i> = 10.0 Hz, 1H), 4.20 (d, <i>J</i> = 9.6 Hz, 1H), 2.54 - 2.52 (m, 2H), 2.40 (s, 3H), 2.23 (s, 3H)	395.1
34	CH ₃		5315-25-3	2-((2 <i>S</i> ,4 <i>S</i>)-4-Hydroxy-2-(1-(6-methylpyridin-2-yl)-1 <i>H</i> -imidazol-2-yl)pyrrolidin-1-yl)-4,6-dimethylnicotinonitrile	(DMSO-d ₆) 7.93 (t, <i>J</i> = 7.8 Hz, 1H), 7.46 - 7.40 (m, 2H), 7.34 (d, <i>J</i> = 7.6 Hz, 1H), 6.91 (s, 1H), 6.40 (s, 1H), 6.22 (d, <i>J</i> = 8.4 Hz, 1H), 5.78 (dd, <i>J</i> = 8.0, 5.6 Hz, 1H), 4.50 - 4.40 (m, 1H), 4.05 - 3.90 (m, 2H), 2.70 - 2.60 (m, 1H), 2.53 (s, 3H), 2.24 (s, 3H), 2.19 - 2.07 (m, 1H), 1.80 (s, 3H)	375.2

Example 35**2-((2*S*,4*S*)-2-(1-(3-Chloro-4-fluorophenyl)-4-methyl-1*H*-imidazol-2-yl)-4-hydroxypyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile**

Step a. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-formylpyrrolidine-1-carboxylate (1.90 g, 6.22 mmol), 2-oxopropanal (1.79 g, 24.89 mmol), ammonium hydroxide (7.63 g, 43.55 mmol, 20% purity) in MeOH (30 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at rt for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was concentrated and the residue purified by prep-HPLC to give (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(4-methyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (950 mg, 33% yield) as a yellow solid.

Step b. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(4-methyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (550 mg, 1.54 mmol), 2-chloro-1-fluoro-4-iodo-benzene (1.18 g, 4.62 mmol), CuI (146 mg, 0.77 mmol), quinolin-8-ol (223 mg, 1.54 mmol) and CsF (701 mg, 4.62 mmol) in DMSO (2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by aq. NH₄Cl (60 mL) at rt, further diluted with water (100 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1-(3-chloro-4-fluorophenyl)-4-methyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (135 mg, 18% yield) as a brown solid.

Step c. A solution of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1-(3-chloro-4-fluorophenyl)-4-

methyl-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (130 mg, 0.27 mmol) in HCl/dioxane (4 M, 5 mL) was stirred at rt for 2 h. Upon completion, the reaction mixture was concentrated in vacuo to give 2-((2*S*,4*S*)-4-(benzyloxy)pyrrolidin-2-yl)-1-(3-chloro-4-fluorophenyl)-4-methyl-1*H*-imidazole (110 mg, crude, HCl salt) as a yellow solid.

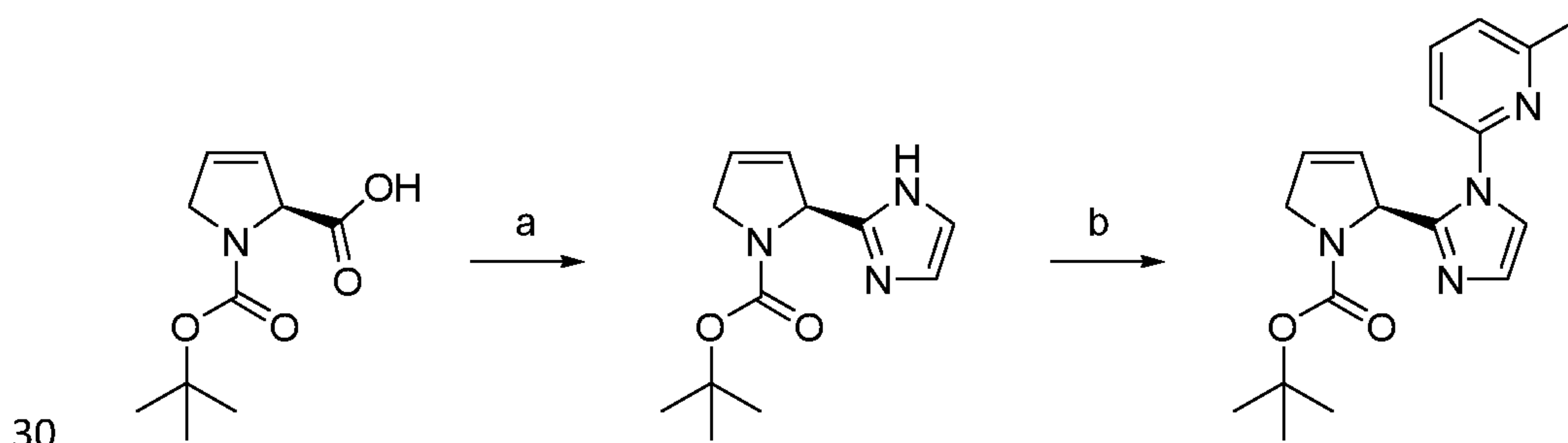
5 **Step d.** A mixture of 2-((2*S*,4*S*)-4-(benzyloxy)pyrrolidin-2-yl)-1-(3-chloro-4-fluorophenyl)-4-methyl-1*H*-imidazole (110 mg, 0.26 mmol, HCl), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (86 mg, 0.39 mmol) and DIPEA (101 mg, 0.78 mmol) in NMP (3 mL) was stirred at 60°C for 12 h. Upon completion, the reaction mixture was quenched by aq. NH₄Cl (60 mL) at rt, further diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The
10 combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 10/1 to 1/1) to give 2-((2*S*,4*S*)-4-(benzyloxy)-2-(1-(3-chloro-4-fluorophenyl)-4-methyl-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (180 mg, 78% yield) as a brown solid.

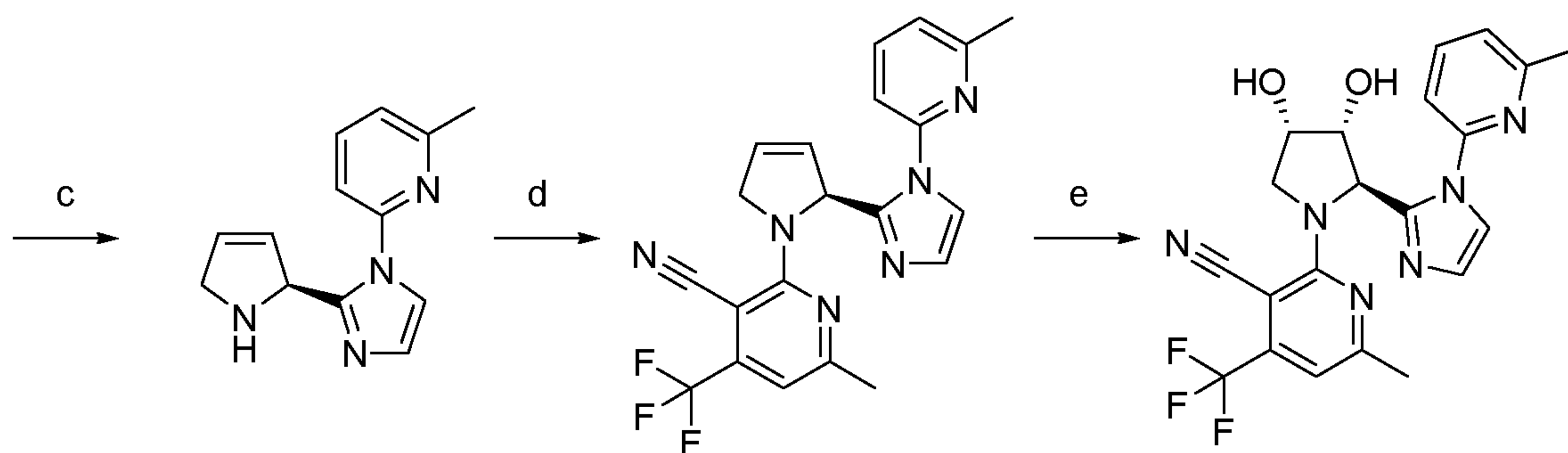
15 **Step e.** To a solution of 2-((2*S*,4*S*)-4-(benzyloxy)-2-(1-(3-chloro-4-fluorophenyl)-4-methyl-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (120 mg, 0.21 mmol) in DCM (2 mL) was added BCl₃ (1 M in toluene, 2.11 mL) dropwise at 0°C. Then the mixture was stirred at 0°C for 0.5 h. On completion, the reaction mixture was quenched by aq. NaOH solution (20 mL, 10% wt) at 0°C, further diluted with water (20 mL) and extracted
20 with DCM (50 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give the title compound (80 mg, 15% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 480.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.63 (dd, *J* = 2.8, 6.4 Hz, 1H), 7.50 - 7.35 (m, 2H), 6.91 (s, 1H), 6.83 (s, 1H), 5.44 (t, *J* = 7.2 Hz, 1H), 4.45 – 4.40 (m, 1H),
25 4.15- 3.97 (m, 2H), 2.63 - 2.48 (m, 1H), 2.29 (s, 3H), 2.21 - 2.16 (m, 1H), 2.15 (s, 3H).

Example 36

2-((2*R*,3*R*,4*S*)-3,4-Dihydroxy-2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile





Step a. (*S*)-*tert*-Butyl 2-(1*H*-imidazol-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate was prepared from (*S*)-1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid in a similar manner to the preparation of (2*S*,4*S*)-*tert*-butyl 4-(benzyloxy)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate as described in **Example 27**, steps b-d.

Step b. A mixture of (*S*)-*tert*-butyl 2-(1*H*-imidazol-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (500 mg, 2.13 mmol), 2-bromo-6-methyl-pyridine (1.10 g, 6.38 mmol), CuI (202 mg, 1.06 mmol), CsF (2.77 g, 8.50 mmol) and *L*-proline (245 mg, 2.13 mmol) in DMSO (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120°C for 12 h under N₂ atmosphere. On completion, NH₄Cl (aq, 60 mL) was added to the reaction mixture and then diluted with water (100 mL) and extracted with EtOAc (100 mL × 3). The organic phase was separated, washed with brine (90 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give (*S*)-*tert*-butyl 2-(1-(6-methyl-pyridin-2-yl)-1*H*-imidazol-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (480 mg, 59% yield) as a brown solid.

Step c. A mixture of (*S*)-*tert*-butyl 2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (320 mg, 0.98 mmol) in HCl/dioxane (4 M, 10 mL) was stirred at rt for 2 h. On completion, the reaction mixture was concentrated in vacuo to afford (*S*)-2-(2-(2,5-dihydro-1*H*-pyrrol-2-yl)-1*H*-imidazol-1-yl)-6-methylpyridine (257 mg, crude, HCl salt) as a brown solid.

Step d. A mixture of (*S*)-2-(2-(2,5-dihydro-1*H*-pyrrol-2-yl)-1*H*-imidazol-1-yl)-6-methylpyridine (257 mg, 0.98 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (323 mg, 1.47 mmol) and DIPEA (379 mg, 2.93 mmol) in NMP (10 mL) was stirred at 60°C for 12 h. On completion, the reaction mixture was quenched with NH₄Cl (60 mL, aq) and then diluted with H₂O (100 mL), then extracted with EtOAc (100 mL × 3). The organic phase was separated, washed with brine (90 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC and the desired stereoisomer was isolated by further purification using prep chiral SFC (column: DAICEL CHIRALPAK IC, 250mm x 30mm, 10μm) to give (*S*)-6-methyl-2-(2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2,5-dihydro-1*H*-pyrrol-1-yl)-4-(trifluoromethyl)-nicotinonitrile (290 mg, 71% yield) as a brown solid.

Step e. A mixture of (*S*)-6-methyl-2-(2-(1-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2,5-dihydro-1*H*-pyrrol-1-yl)-4-(trifluoromethyl)nicotinonitrile (290 mg, 0.71 mmol), OsO₄ (36 mg,

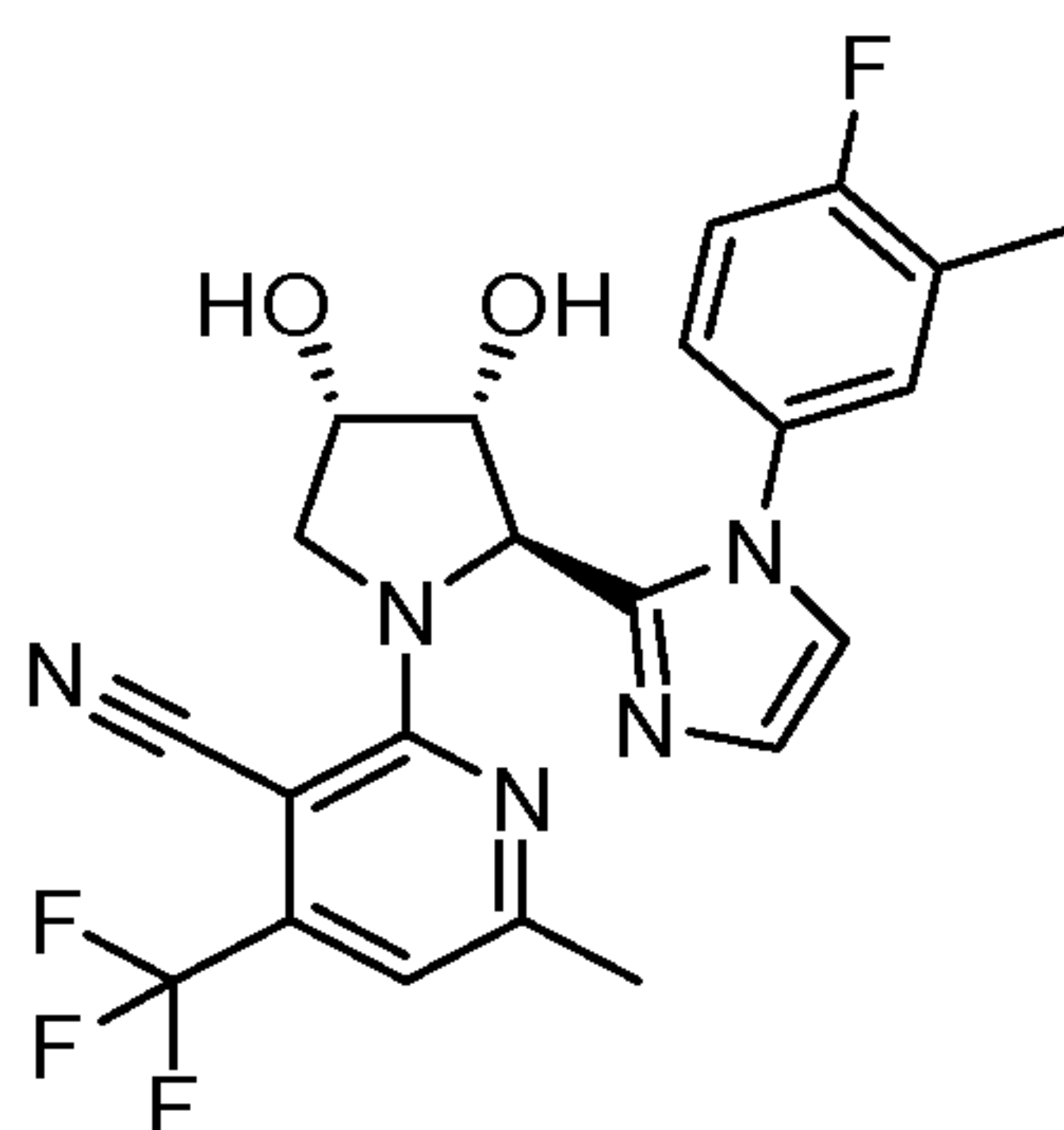
0.14 mmol), NMO (108 mg, 0.92 mmol) in water (5 mL), MeCN (5 mL), *t*-butanol (5 mL) was degassed and purged with N₂ 3 times, and stirred at rt for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by addition of aq. Na₂S₂O₃ (20 mL), filtered and concentrated. The crude product was purified by prep-HPLC to give the title compound

(150 mg, 47% yield) as a white solid.

m/z ES⁺ [M+H]⁺ 445.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.95 (t, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 5.2 Hz, 1H), 7.04 (s, 1H), 5.49 (d, *J* = 8.4 Hz, 1H), 4.45 (t, *J* = 3.2 Hz, 1H), 4.19 (d, *J* = 11.2 Hz, 1H), 3.75 (d, *J* = 11.2 Hz, 1H), 3.31 (s, 1H), 2.65 (s, 3 H), 2.24 (s, 3H).

Example 37

2-((2*R*,3*R*,4*S*)-2-(1-(4-Fluoro-3-methylphenyl)-1*H*-imidazol-2-yl)-3,4-dihydroxypyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile

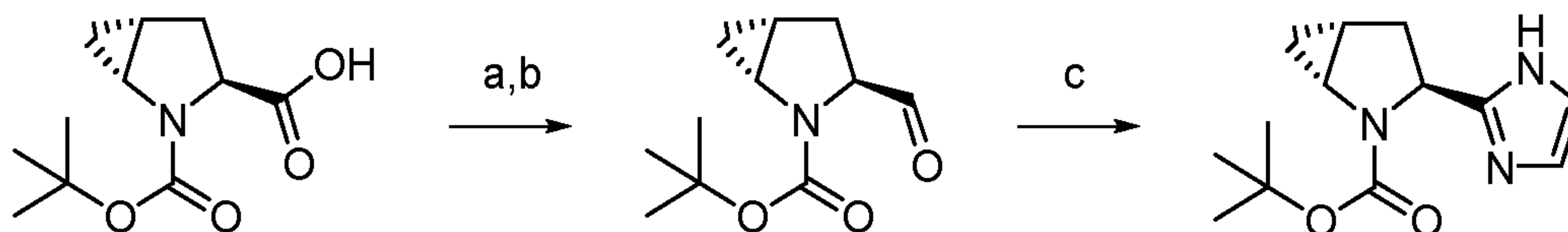


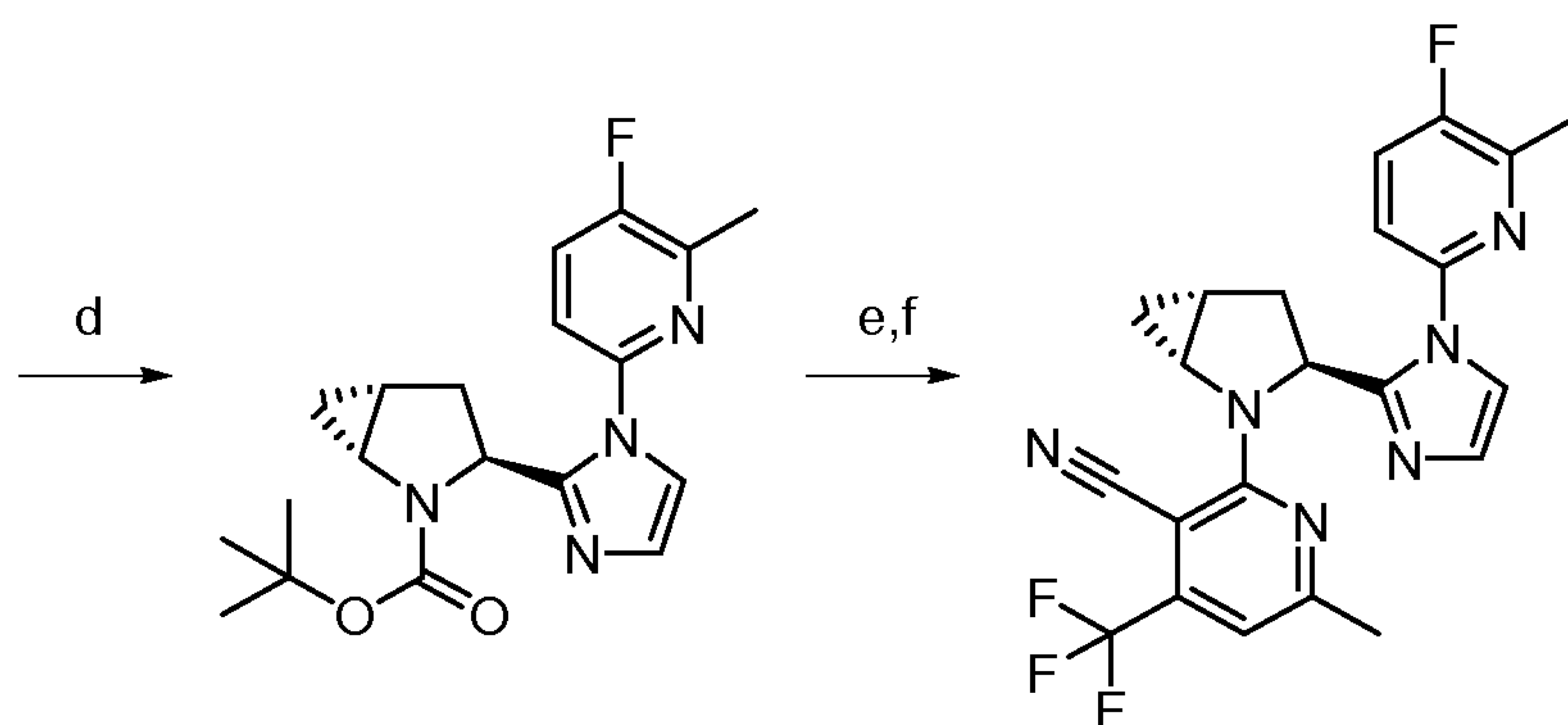
The title compound was prepared in a similar manner to **Example 36**, using 1-fluoro-4-iodo-2-methyl-benzene in step b.

m/z ES⁺ [M+H]⁺ 462.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.58-7.56 (m, 2H), 7.22 (t, *J* = 9.2 Hz, 1H), 7.18 (d, *J* = 1.2 Hz, 1H), 7.00 (s, 1H), 6.88 (s, 1H), 5.23 (d, *J* = 6.4 Hz, 1H), 4.50-4.38 (m, 3H), 3.78 (dd, *J* = 10.8 Hz, 2.8 Hz, 1H), 2.35 (s, 1H), 2.65 (s, 3 H), 2.24 (s, 3H).

Example 38

2-((1*R*,3*S*,5*R*)-3-(1-(5-Fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile





Step a. To a solution of (1*R*,3*S*,5*R*)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (CAS Number 197142-34-0; 1.00 g, 4.40 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.64 g, 6.60 mmol) in DMF (5 mL) was added HATU (2.01 g, 5.28 mmol) and DIPEA (1.71 g, 13.20 mmol). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was filtered and evaporated. The obtained residue was purified by prep-HPLC to give (1*R*,3*S*,5*R*)-*tert*-butyl 3-(methoxy(methyl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.2 g, 74% yield) as a brown solid.

Step b. To a solution of (1*R*,3*S*,5*R*)-*tert*-butyl 3-(methoxy(methyl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1.00 g, 3.70 mmol) in DCM (10 mL) was added DIBAL-H (1 M, 11.1 mL) at -78°C. The mixture was stirred at -78°C for 2 h. Upon completion, the reaction mixture was quenched by aq. NH₄Cl solution (30 mL) at rt, diluted with water (30 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 15/1 to 5/1) to give (1*R*,3*S*,5*R*)-*tert*-butyl 3-formyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (700 mg, 90% yield) as a yellow solid.

Step c. To a solution of (1*R*,3*S*,5*R*)-*tert*-butyl 3-formyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (650 mg, 3.08 mmol), glyoxal (1.79 g, 12.31 mmol) in MeOH (10 mL) was added ammonium hydroxide (3.77 g, 21.54 mmol, 20% aq.). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by prep-HPLC to give (1*R*,3*S*,5*R*)-*tert*-butyl 3-(1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (600 mg, 78% yield) as a light yellow solid.

Step d. A mixture of (1*R*,3*S*,5*R*)-*tert*-butyl 3-(1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (300 mg, 1.20 mmol), 6-bromo-3-fluoro-2-methyl-pyridine (457 mg, 2.41 mmol), Cs₂CO₃ (1.18 g, 3.61 mmol), CuI (229 mg, 1.20 mmol) and *L*-proline (277 mg, 2.41 mmol) in DMSO (15 mL) was degassed and purged with N₂ 3 times. Then the mixture was stirred at 120°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by aq. NH₄Cl (60 mL) at rt, diluted with water (100 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (PE/EtOAc = 15/85) to give

(1*R*,3*S*,5*R*)-*tert*-butyl 3-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (150 mg, 22% yield) as a brown solid.

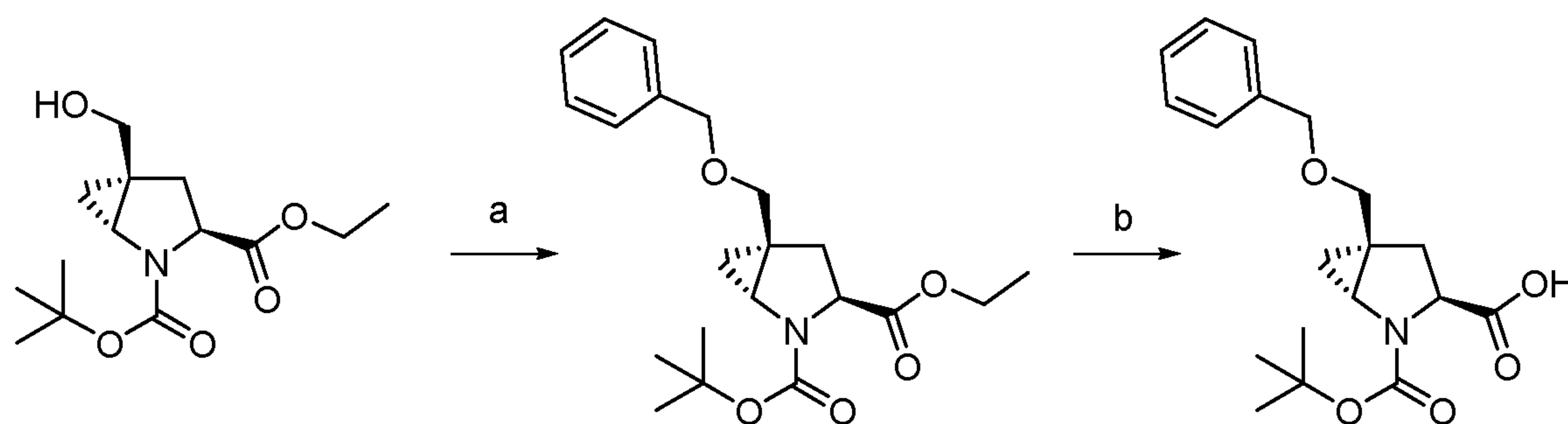
Step e. A solution of (1*R*,3*S*,5*R*)-*tert*-butyl 3-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (125 mg, 0.35 mmol) in HCl/dioxane (5 mL) was stirred at 30°C for 2 h. The reaction mixture was evaporated to give (1*R*,3*S*,5*R*)-3-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (102 mg, crude) as a brown solid which was used for the next step directly.

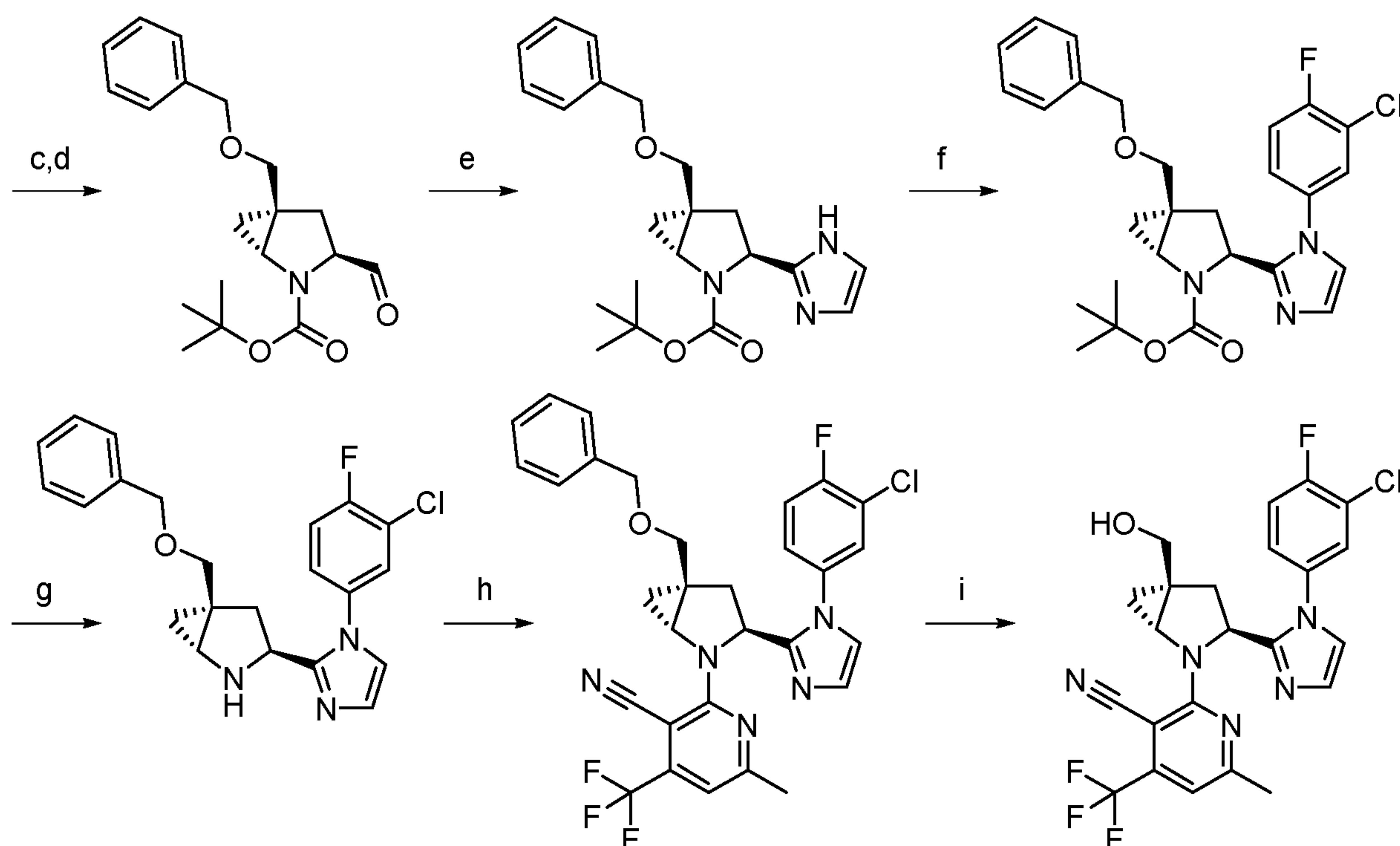
Step f. A mixture of (1*R*,3*S*,5*R*)-3-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (102 mg, 0.35 mmol, HCl), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (114 mg, 0.52 mmol) and DIPEA (134 mg, 1.04 mmol) in NMP (3 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 60°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by aq. NH₄Cl (60 mL) at rt, diluted with water (100 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and evaporated. The residue was purified by prep-HPLC to give the title compound (11 mg, 7% yield) as a brown solid.

m/z ES⁺ [M+H]⁺ 443.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.87 (t, *J* = 8.8 Hz, 1H), 7.50 - 7.45 (m, 2H), 6.94 (s, 1H), 6.91 (s, 1H), 5.73 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.95 – 3.85 (m, 1H), 2.50 – 2.45 (m, 3H), 2.45 - 2.36 (m, 2H), 2.08 (s, 3H), 2.05 – 1.95 (m, 1H), 1.09 - 0.97 (m, 1H), 0.80 – 0.70 (m, 1H).

Example 39

2-((1*R*,3*S*,5*S*)-3-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-5-(hydroxymethyl)-2-azabicyclo[3.1.0]hexan-2-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile





Step a. To a solution of 2-(*tert*-butyl) 3-ethyl (1*R*,3*S*,5*S*)-5-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (CAS Number 1386461-22-8, prepared as described in WO 2014002058 A2; 500 mg, 1.72 mmol) in DMF (5 mL) was added NaH (137 mg, 3.43 mmol, 60% dispersion in mineral oil), portionwise at 0°C. After stirring for 30 min, benzylbromide (441 mg, 2.58 mmol) was added at 0°C. The resulting suspension was allowed to warm to 30°C, and stirred at 30°C for 1.5 h. Upon completion, it was diluted with water (10 mL) and then adjusted to pH 1 with KHSO₄ (aq.), washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford the product (3*S*)-2-*tert*-butyl 3-ethyl 5-((benzyloxy)methyl)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (1.2 g, crude).

Step b. To a solution of (3*S*)-2-*tert*-butyl 3-ethyl 5-((benzyloxy)methyl)-2-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (1.20 g, crude) in THF (10 mL) and water (1 mL) and MeOH (1 mL) at 0°C was added a solution of NaOH (4.8 mL, aq. 1 M). The solution was stirred for 14 h at 30°C. Upon completion, it was concentrated to give the residue, then it was extracted with a solution (PE/EtOAc = 1/1), the aqueous phase was separated and adjusted to pH 2 with aq. KHSO₄. Then the aqueous phase was extracted with EtOAc (20 mL x 2), the organic layers were collected, dried over Na₂SO₄, filtered and concentrated to give the crude product. The crude product was purified by prep-HPLC to give (1*R*,3*S*,5*S*)-5-((benzyloxy)methyl)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (150 mg) as a white solid and (1*S*,3*S*,5*R*)-5-((benzyloxy)methyl)-2-(*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (80 mg) as a yellow oil.

m/z ES+ [M+H]⁺ 248.0; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36-7.28 (m, 5H), 4.57-4.48 (m, 2H), 4.15 (s, 1H), 3.53-3.27 (m, 3H), 2.70~2.30 (m, 2H), 1.46 (s, 9H), 0.97-0.90 (m, 1H), 0.80-0.70 (m, 1H).

Step c. A mixture of (1*R*,3*S*,5*S*)-5-((benzyloxy)methyl)-2-(*tert*-butoxycarbonyl)-2-

5 azabicyclo[3.1.0]hexane-3-carboxylic acid (500 mg, 1.44 mmol), *N*-methoxymethanamine (210 mg, 2.16 mmol, HCl), DIPEA (558 mg, 4.32 mmol) and HATU (711 mg, 1.87 mmol) in DMF (5 mL) was stirred at rt for 2 h. On completion, the reaction mixture was quenched by addition NH₄Cl (aq, 25 mL), then diluted with water (100 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine, dried over anhydrous
10 Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1 to 3/1) to give (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-(methoxy(methyl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (500 mg, 89% yield) as a brown oil.

Step d. To a solution of (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-

15 (methoxy(methyl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (670 mg, 1.72 mmol) in THF (10 mL) was added DIBAL-H (1 M, 5.15 mL) slowly at -78°C. The mixture was stirred at -78°C for 2 h. On completion, the reaction mixture was quenched by addition of MeOH (230 mL) at -78°C, and then filtered. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 10/1 to 5/1) to give (1*R*,3*S*,5*S*)-
20 *tert*-butyl 5-((benzyloxy)methyl)-3-formyl-2-azabicyclo[3.1.0]hexane-2-carboxylate (470 mg, 83% yield) as a brown oil.

Step e. A mixture of (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-formyl-2-

azabicyclo[3.1.0]hexane-2-carboxylate (470 mg, 1.42 mmol), glyoxal (1.03 g, 7.09 mmol), ammonium hydroxide (1.74 g, 9.93 mmol, 20% aq.) in MeOH (5 mL) was stirred at rt for 12
25 h. On completion, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (PE/EtOAc = 2/1 to 1/3) to give (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-(1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (270 mg, 39% yield) as a brown solid.

Step f. A mixture of (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-(1*H*-imidazol-2-yl)-2-

30 azabicyclo[3.1.0]hexane-2-carboxylate (250 mg, 0.68 mmol), 2-chloro-1-fluoro-4-iodobenzene (521 mg, 2.03 mmol), CuI (64 mg, 0.34 mmol), CsF (411 mg, 2.71 mmol) and quinolin-8-ol (98 mg, 0.68 mmol) in DMSO (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100°C for 12 h under N₂ atmosphere. On completion, NH₄Cl (aq, 60 mL) was added to the reaction mixture and then diluted with water
35 (100 mL), extracted with EtOAc (100 mL x 3). The organic phase was separated, washed with brine (90 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-

HPLC to give (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (100 mg, 19% yield) as a brown solid.

Step g. (1*R*,3*S*,5*S*)-*tert*-butyl 5-((benzyloxy)methyl)-3-(1-(3-chloro-4-fluorophenyl)-1*H*-

5 imidazol-2-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (100 mg, 0.20 mmol) in HCl/dioxane (4 M, 5 mL) was stirred at rt for 2 h. On completion, the reaction mixture was concentrated in vacuo to afford (1*R*,3*S*,5*S*)-5-((benzyloxy)methyl)-3-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (87 mg, crude, HCl) as a brown solid.

Step h. A mixture of (1*R*,3*S*,5*S*)-5-((benzyloxy)methyl)-3-(1-(3-chloro-4-fluorophenyl)-1*H*-

10 imidazol-2-yl)-2-azabicyclo[3.1.0]hexane (87 mg, 0.20 mmol, HCl), 2-chloro-6-methyl-4-(trifluoromethyl)nicotinonitrile (66 mg, 0.30 mmol) and DIPEA (78 mg, 0.60 mmol) in NMP (5 mL) was stirred at 60°C for 12 h. On completion, the reaction mixture was diluted with water (100 mL) and then extracted with EtOAc (100 mL × 3). The organic phase was separated, washed with brine (90 mL), dried over Na₂SO₄ and evaporated. The residue was purified by
15 silica gel column chromatography (PE/EtOAc = 5/1 to 3/1) to afford 2-((1*R*,3*S*,5*S*)-5-((benzyloxy)methyl)-3-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (70 mg, 77% yield) as a brown solid.

Step i. To a solution of 2-((1*R*,3*S*,5*S*)-5-((benzyloxy)methyl)-3-(1-(3-chloro-4-fluorophenyl)-

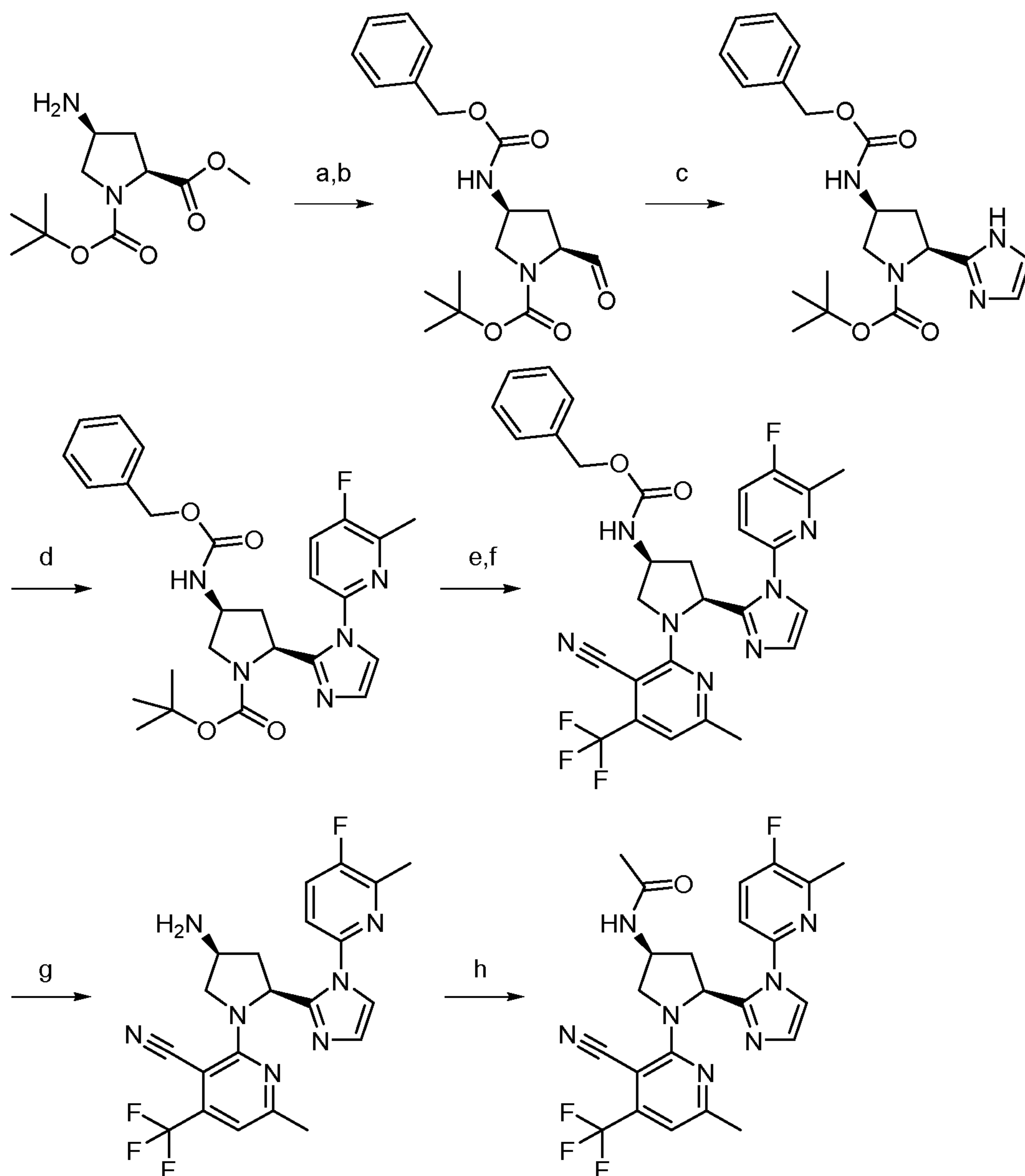
20 1*H*-imidazol-2-yl)-2-azabicyclo[3.1.0]hexan-2-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (70 mg, 0.12 mmol) in DCM (5 mL) was added BCl₃ (1 M in toluene, 1.2 mL) dropwise at 0°C. The mixture was stirred at 0°C for 15 min. On completion, the reaction mixture was quenched by NaOH (10 mL, 15%) at rt, and then diluted with water (20 mL), extracted with DCM (50 mL × 3). The combined organic layers were washed with brine (60 mL), dried over
25 Na₂SO₄ and evaporated. The residue was purified by prep-HPLC and the desired stereoisomer was isolated by further purification using prep chiral SFC (column: DAICEL CHIRALCEL OD, 250mm x 30mm, 10μm) to give the title compound (17 mg, 25% yield) as a yellow solid.

m/z ES⁺ [M+H]⁺ 492.0; ¹H NMR (400 MHz, CD₃OD) δ ppm 7.69 - 7.58 (m, 1H), 7.50 - 7.38

30 (m, 2H), 7.24 (s, 1H), 7.09 (s, 1H), 6.95 (s, 1H), 5.59~5.56 (m, 1H), 3.94~3.93 (m, 1H), 3.71 (d, *J* = 11.6 Hz, 1H), 3.61 (d, *J* = 11.6 Hz, 1H), 2.52 - 2.39 (m, 2H), 2.30 (s, 3H), 1.20 - 1.16 (m, 1H), 0.95~0.93 (m, 1H).

Example 40

35 N-((3*S*,5*S*)-1-(3-Cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-yl)acetamide



Step a. To a solution of (2S,4S)-1-*tert*-butyl 2-methyl 4-aminopyrrolidine-1,2-dicarboxylate (5.00 g, 17.8 mmol, HCl) and Na₂CO₃ (5.66 g, 53.4 mmol) in a mixed solvent of dioxane (80 mL) and water (40 mL) was added benzyl chloroformate (3.34 g, 19.6 mmol) dropwise at 0°C. The reaction mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (40 mL), extracted into EtOAc (100 mL), dried over Na₂SO₄ and evaporated to give (2S,4S)-1-*tert*-butyl 2-methyl 4-(((benzyloxy)carbonyl)-amino)pyrrolidine-1,2-dicarboxylate (6.7 g, 99% yield) as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.55 – 7.45 (m, 1H), 7.40 - 7.28 (m, 5H), 5.10 - 4.95 (m, 2H), 4.19 (t, *J* = 8.0 Hz, 1H), 4.12 - 4.03 (m, 1H), 3.72 - 3.58 (m, 4H), 3.07 (t, *J* = 9.2 Hz, 1H), 2.48 - 2.39 (m, 1H), 1.86 - 1.68 (m, 1H), 1.45 - 1.26 (m, 9H).

Step b. To a solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-(((benzyloxy)carbonyl)amino)-pyrrolidine-1,2-dicarboxylate (6.00 g, 15.90 mmol) in THF (100 mL) was added DIBAL-H (1 M, 47.6 mL) dropwise at -70°C. The reaction mixture was stirred at -70°C for 1 h. Upon completion, the reaction was slowly quenched with MeOH (100 mL) at -65°C. The quenched
5 reaction was warmed to rt, stirred for a further 30 min and then filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc = 1/1) to give (2*S*,4*S*)-*tert*-butyl 4-(((benzyloxy)carbonyl)amino)-2-formylpyrrolidine-1-carboxylate (2.4 g, 43% yield) as a colorless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.52 - 9.36 (m, 1H), 7.67 - 7.49 (m, 1H), 7.43 - 7.24
10 (m, 5H), 5.01 (s, 2H), 4.11 - 3.96 (m, 2H), 3.67 - 3.55 (m, 1H), 3.27 - 3.17 (m, 1H), 2.38 - 2.20 (m, 1H), 1.94 - 1.78 (m, 1H), 1.46 - 1.28 (m, 9H).

Step c. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(((benzyloxy)carbonyl)amino)-2-formylpyrrolidine-1-carboxylate (2.30 g, 6.60 mmol), glyoxal (4.79 g, 33.0 mmol) and ammonium hydroxide (5.55 g, 39.6 mmol, 25% aq.) in MeOH (20 mL) was stirred at rt for 12 h. Upon completion, the
15 reaction mixture was concentrated in vacuo. The residue was diluted with water (40 mL), extracted into EtOAc (3 x 40 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 1/1) to give (2*S*,4*S*)-*tert*-butyl 4-(((benzyloxy)-carbonyl)amino)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (1.5 g, 59% yield) as a colorless oil.

20 m/z ES+ [M+H]⁺ 387.2.

Step d. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(((benzyloxy)carbonyl)amino)-2-(1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (1.40 g, 3.62 mmol), 6-bromo-3-fluoro-2-methyl-pyridine (1.38 g, 7.25 mmol), K₂CO₃ (1.50 g, 10.9 mmol), *L*-proline (834 mg, 7.25 mmol) and CuI (690 mg, 3.62 mmol) in DMSO (10 mL) was stirred at 120°C for 12 h under N₂ atmosphere. Upon
25 completion, the reaction mixture was diluted with water (50 mL) and filtered. The filtrate was extracted with EtOAc (50 mL x 3). The combined organic layer was dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give (2*S*,4*S*)-*tert*-butyl 4-(((benzyloxy)carbonyl)amino)-2-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylate (160 mg, 6% yield) as a brown solid.

30 m/z ES+ [M+H]⁺ 496.3

Step e. A mixture of (2*S*,4*S*)-*tert*-butyl 4-(((benzyloxy)carbonyl)amino)-2-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (160 mg, 0.23 mmol) in HCl/dioxane (4 M, 3.55 mL) was stirred at rt for 30 min. Upon completion, the reaction mixture was concentrated in vacuo to give benzyl ((3*S*,5*S*)-5-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-yl)carbamate (90 mg, 91% yield, HCl salt) as a white solid
35 which was used in the next step directly.

m/z ES+ [M+H]⁺ 396.2

Step f. A mixture of benzyl ((3*S*,5*S*)-5-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-yl)carbamate (90 mg, 0.21 mmol, HCl salt), 2-chloro-6-methyl-4-(trifluoromethyl)-pyridine-3-carbonitrile (55 mg, 0.25 mmol) and DIPEA (135 mg, 1.04 mmol) in NMP (5 mL) was stirred at 60°C for 12 h. Upon completion, the reaction mixture was diluted with water (30 mL), extracted into EtOAc (3 x 30 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (PE/EtOAc = 1/1) to give benzyl ((3*S*,5*S*)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-yl)carbamate (100 mg, 82% yield) as a yellow solid.

10 m/z ES⁺ [M+H]⁺ 580.3

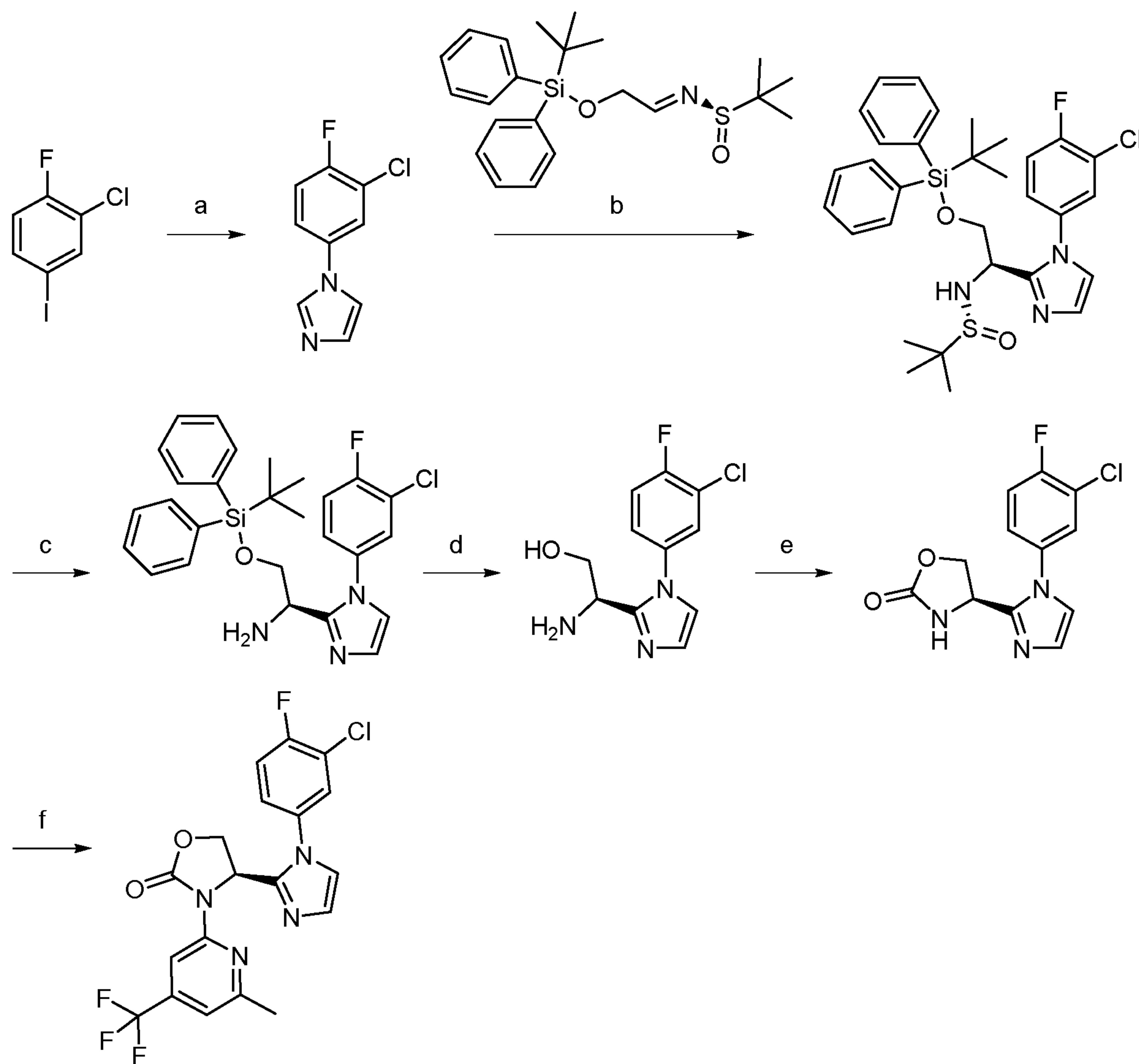
Step g. To a solution of benzyl ((3*S*,5*S*)-1-(3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-3-yl)carbamate (80 mg, 0.14 mmol) in THF (5 mL) was added Pd/C (10 mg, 10% loading). The reaction mixture was stirred at rt for 1 h under hydrogen atmosphere (15 psi). Upon completion, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by prep-TLC (PE/EtOAc = 1/1) to give 2-((2*S*,4*S*)-4-amino-2-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (50 mg, 81% yield) as a yellow solid.

Step h. To a solution of 2-((2*S*,4*S*)-4-amino-2-(1-(5-fluoro-6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-6-methyl-4-(trifluoromethyl)nicotinonitrile (15 mg, 0.034 mmol) and TEA (7 mg, 0.067 mmol) in DCM (2 mL) was added acetyl chloride (3 mg, 0.037 mmol). The reaction mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was concentrated and the crude product purified by prep-HPLC to give the title compound (7 mg, 42% yield) as a yellow solid.

25 m/z ES⁺ [M+H]⁺ 488.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.44 (d, *J* = 7.2 Hz, 1H), 7.91 (t, *J* = 8.8 Hz, 1H), 7.50 (dd, *J* = 3.2, 8.8 Hz, 1H), 7.44 (d, *J* = 1.2 Hz, 1H), 6.97 - 6.88 (m, 2H), 5.64 (t, *J* = 8.0 Hz, 1H), 4.50 - 4.36 (m, 1H), 4.20 - 4.10 (m, 1H), 3.81 - 3.69 (m, 1H), 2.86 - 2.73 (m, 1H), 2.53 - 2.51 (m, 3H), 2.22 - 2.11 (m, 1H), 2.08 (s, 3H), 1.85 (s, 3H).

Example 41

(R)-4-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)-pyridin-2-yl)oxazolidin-2-one



Step a. To a solution of imidazole (14.0 g, 206 mmol) in DMSO (300 mL) was added 2-chloro-1-fluoro-4-iodobenzene (79.1 g, 308 mmol), CuI (19.6 g, 103 mmol), CsF (93.7 g, 617 mmol, 22.8 mL) and quinolin-8-ol (29.9 g, 206 mmol) under a N₂ atmosphere. The mixture was stirred at 100°C for 12 h. On completion, the reaction mixture was diluted with water (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine (900 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (50-66% EtOAc in PE) to give 1-(3-chloro-4-fluoro-phenyl)imidazole (11.0 g, 27%) as a black-green solid.

Step b. To a solution of 1-(3-chloro-4-fluoro-phenyl)imidazole (816 mg, 4.15 mmol) in THF (10 mL) was added LDA (2 M in THF/heptane/ethylbenzene, 3.1 mL, 6.2 mmol) at -78°C under a N₂ atmosphere and the reaction mixture was stirred for 30 min. A solution of (*R*)-*N*-

(2-((*tert*-butyldiphenylsilyl)oxy)ethylidene)-2-methylpropane-2-sulfinamide (CAS Number 1029701-59-4, prepared as described in *J. Am. Chem. Soc.* **2008**, 130, 6910-6911; 2.00 g, 4.98 mmol) in THF (10 mL) was added dropwise at -78°C, then the reaction mixture was warmed to rt and stirred for 12 h. On completion, the reaction was quenched with the
5 addition of sat. aq. NH₄Cl (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 90 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (25-50% EtOAc in PE) to give (*R*)-*N*-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (1.20 g, 34%) as a yellow oil.

10 **Step c.** A solution of (*R*)-*N*-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (600 mg, 0.70 mmol) in HCl/dioxane (4 M, 6 mL) was stirred at rt for 1 h. On completion, the reaction mixture was concentrated in vacuo, diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 90 mL), dried over anhydrous Na₂SO₄, filtered
15 and concentrated in vacuo to give (*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethanamine (0.8 g, crude) as a yellow oil which was used without further purification.

Step d. To a solution of (*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethanamine (200 mg, 0.24 mmol) in THF (2 mL) was added
20 tetramethylammonium fluoride (57 mg, 0.61 mmol) at rt and stirred for 4 h. On completion, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (0-10% EtOH in EtOAc) to give (*R*)-2-amino-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethanol (50 mg, 81%) as a yellow oil.

Step e. A solution of (*R*)-2-amino-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethanol (20
25 mg, 0.078 mmol), K₂CO₃ (12 mg, 0.086 mmol) and KHCO₃ (9 mg, 0.086 mmol) in water (0.5 mL) was stirred at rt for 30 min. To the mixture was added a solution of triphosgene (12 mg, 0.039 mmol) in toluene (0.5 mL) at 0°C and the mixture was stirred at rt for 2 h. On completion, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over
30 anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by prep-TLC (100% EtOAc) to give (*R*)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)oxazolidin-2-one (20 mg, 91%) as a colorless oil.

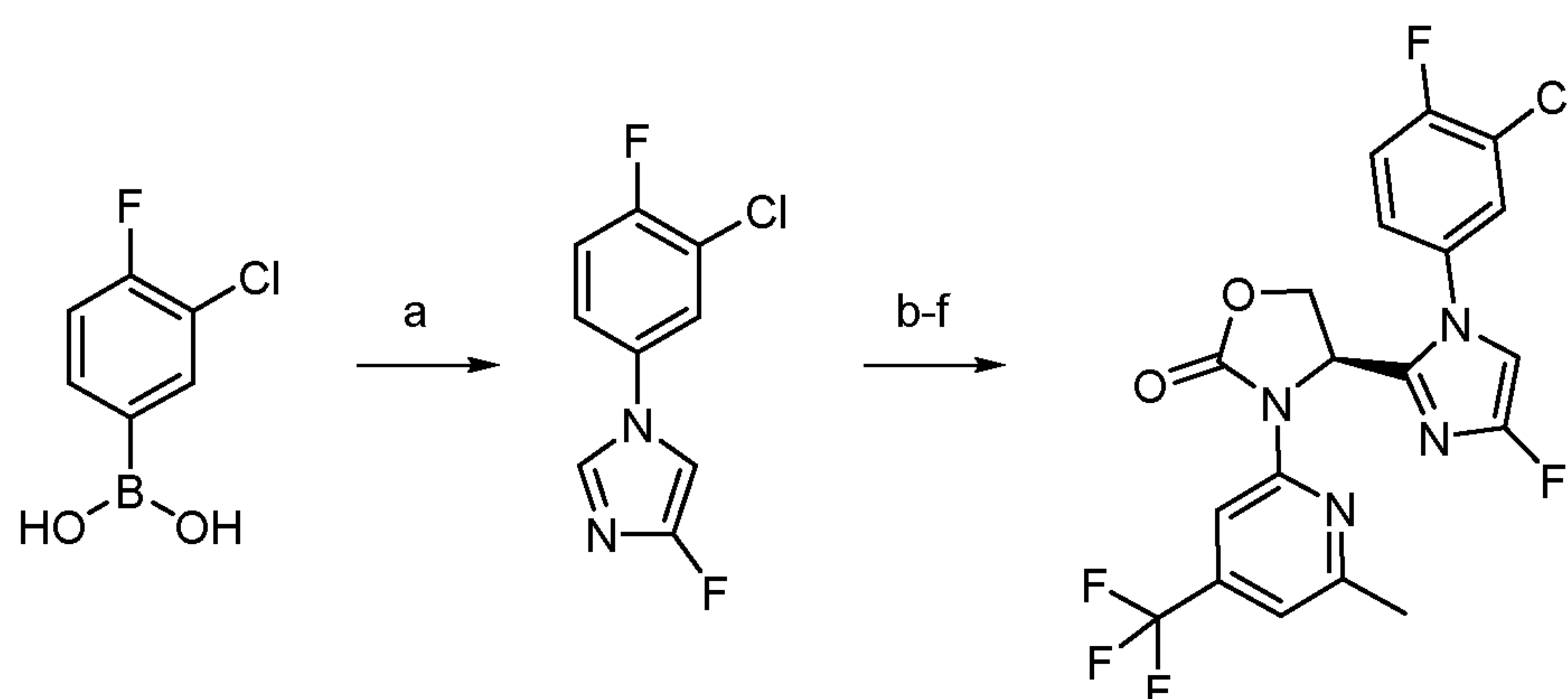
Step f. To the solution of (*R*)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)oxazolidin-2-one (40 mg, 0.14 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (51 mg, 0.21 mmol),
35 Cs₂CO₃ (93 mg, 0.28 mmol) and XantPhos (16 mg, 0.028 mmol) in dioxane (0.5 mL) was added Pd₂(dba)₃ (13 mg, 0.014 mmol) and the mixture was stirred at 80°C for 4 h under a N₂

atmosphere. On completion, the mixture was filtered, diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by prep-TLC (50% EtOAc in PE) and prep-HPLC to give the title compound (19 mg, 30%) as a yellow gum.

m/z ES+ [M+H]⁺ 441.0; ¹H NMR (400MHz, DMSO-d₆) δ ppm 8.14 (s, 1H), 7.93 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.38 (d, *J* = 1.2 Hz, 1H), 7.32 (s, 1H), 6.96 (s, 1H), 5.77 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.72 (t, *J* = 8.8 Hz, 1H), 4.53 (dd, *J* = 8.8, 3.2 Hz, 1H), 2.30 (s, 3H).

10 Example 42

(R)-4-(1-(3-Chloro-4-fluorophenyl)-4-fluoro-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one



Step a. To a solution of (3-chloro-4-fluorophenyl)boronic acid (1.22 g, 7.0 mmol), 4-fluoro-1H-imidazole (500 mg, 5.8 mmol), pyridine (1.38 g, 17.4 mmol) in DCM (10 mL) was added Cu(OAc)₂ (211 mg, 1.2 mmol). The mixture was degassed and purged with O₂ 3 times and then stirred at rt for 12 h under oxygen atmosphere. Upon completion, the mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (80 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc in PE) to give 1-(3-chloro-4-fluorophenyl)-4-fluoro-1H-imidazole (1 g, 86%) as a white solid.

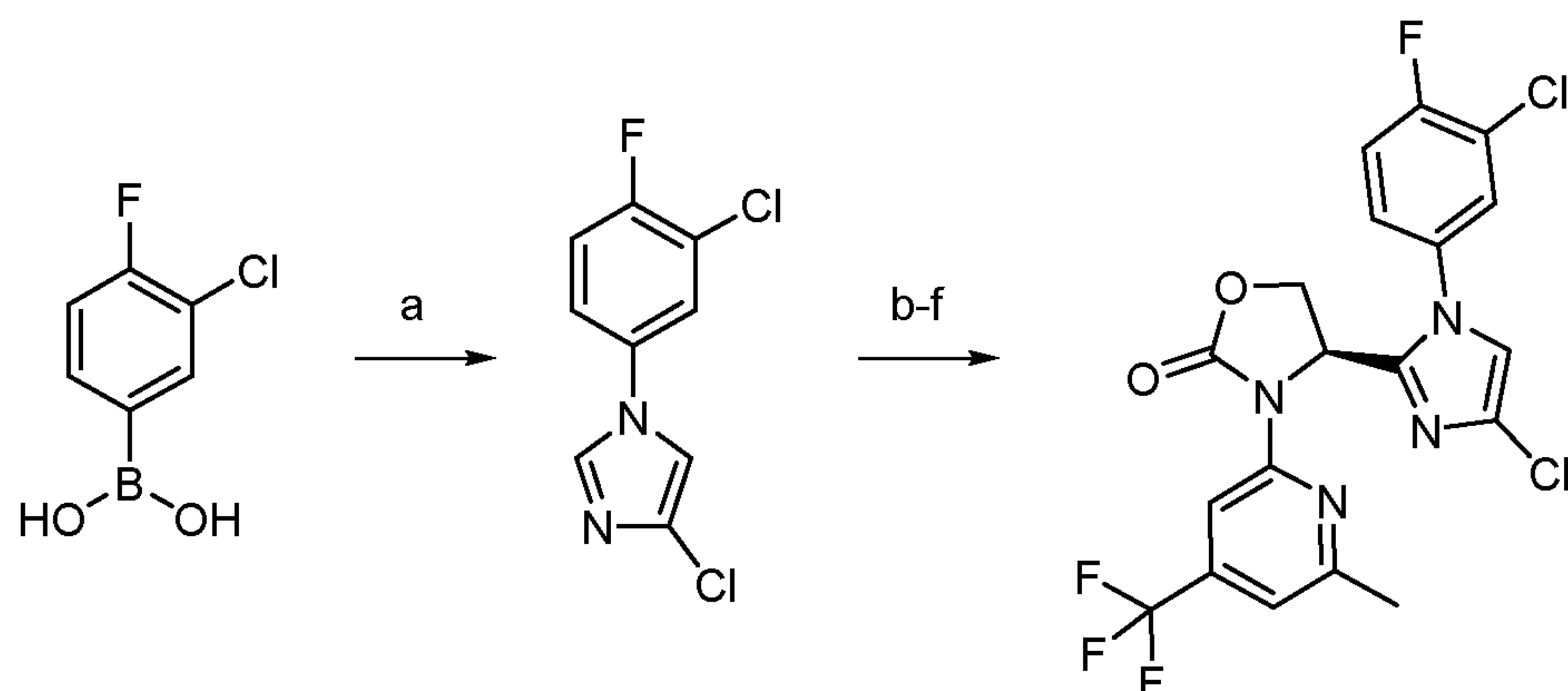
m/z ES+ [M+H]⁺ 215.0

Steps b-f. Conducted in a similar manner to **Example 41**, steps b-f.

m/z ES+ [M+H]⁺ 459.0; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.25 (s, 1H), 7.87 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.55 – 7.49 (m, 1H), 7.23 (s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.90 - 5.82 (m, 1H), 4.76 (t, *J* = 8.8 Hz, 1H), 4.53 (dd, *J* = 4.4, 8.8 Hz, 1H), 2.43 (s, 3H).

Example 43

(R)-4-(4-Chloro-1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one



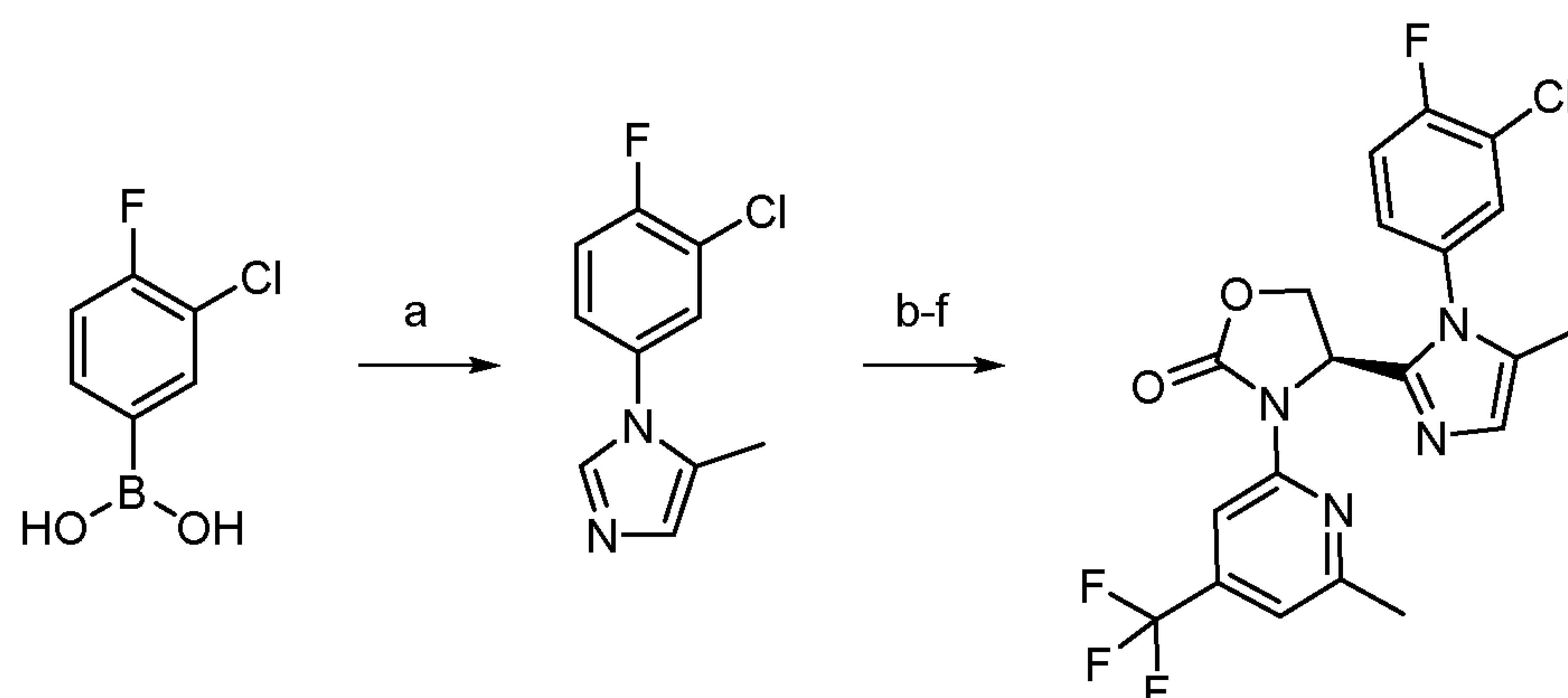
- 5 **Step a.** A mixture of 4-chloro-1*H*-imidazole (1.00 g, 9.8 mmol), (3-chloro-4-fluorophenyl)-boronic acid (2.04 g, 11.7 mmol), pyridine (2.31 g, 29.3 mmol) and Cu(OAc)₂ (354 mg, 2.0 mmol) in DCM (50 mL) was degassed and purged with O₂ 3 times, and then stirred at rt for 12 h under O₂ atmosphere. Upon completion, ammonium hydroxide (30% aq., 10 mL) was added into the reaction mixture, and stirring continued for 10 min at rt. The reaction mixture
- 10 was diluted with water (30 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by prep-HPLC to give 4-chloro-1-(3-chloro-4-fluorophenyl)-1*H*-imidazole (0.25 g, 11%) as a white solid.
- m/z ES⁺ [M+H]⁺ 230.9

- 15 **Steps b-f.** Conducted in a similar manner to **Example 41** steps b-f.

m/z ES⁺ [M+H]⁺ 475.0; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.25 (s, 1H), 7.84 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 5.88 (dd, *J* = 4.4, 9.2 Hz, 1H), 4.76 (t, *J* = 9.2 Hz, 1H), 4.53 (dd, *J* = 4.8, 8.8 Hz, 1H), 2.43 (s, 3H).

Example 44

(R)-4-(1-(3-Chloro-4-fluorophenyl)-5-methyl-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one



- 5 **Step a.** A mixture of (3-chloro-4-fluoro-phenyl)boronic acid (2 g, 11.5 mmol), 4-methyl-1*H* imidazole (785 mg, 9.6 mmol), pyridine (1.51 g, 19.1 mmol), Cu(OAc)₂ (1.74 g, 9.6 mmol) in DCM (30 mL) was degassed and purged with O₂ 3 times, and then stirred at rt for 12 h under O₂ atmosphere. On completion, the reaction mixture was diluted with ammonium hydroxide (30% aq., 50 mL) and water (50 mL). The mixture was filtered, and the filtrate was extracted
10 with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (10-50% EtOAc in PE) to give 1-(3-chloro-4-fluorophenyl)-5-methyl-1*H*-imidazole (800 mg, 40%) as a white solid.

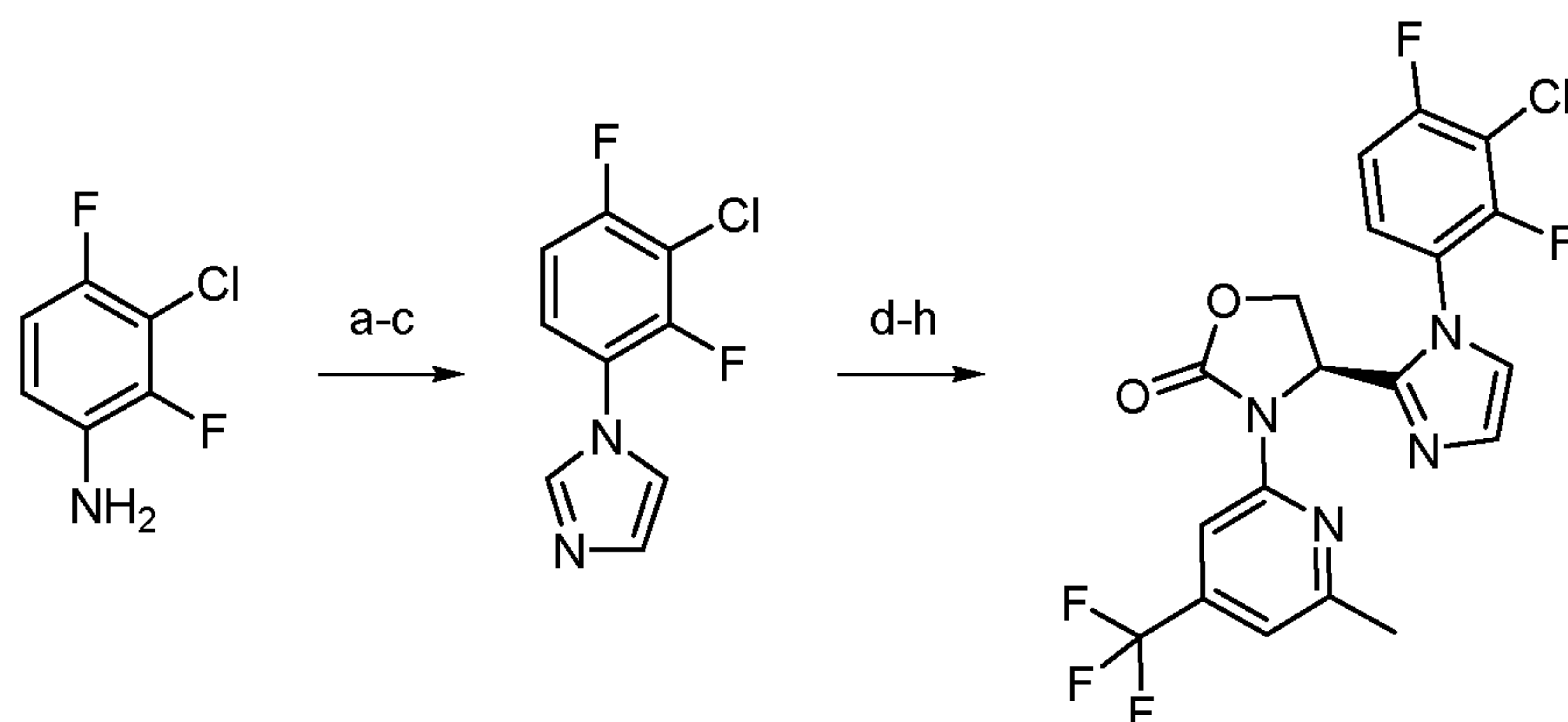
m/z ES+ [M+H]⁺ 211.0

- 15 **Steps b-f.** Conducted in a similar manner to **Example 41** steps b-f.

m/z ES+ [M+H]⁺ 455.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.28 (s, 1H), 7.85 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.64 - 7.58 (m, 1H), 7.57 (s, 1H), 7.35 (s, 1H), 6.06 (dd, *J* = 5.2, 9.6 Hz, 1H), 4.95 – 4.90 (m, 1H), 4.83 – 4.77 (m, 1H), 2.46 (s, 3H), 2.40 (m, 3H).

Example 45

(R)-4-(1-(3-Chloro-2,4-difluorophenyl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one



- 5 **Steps a-c (One-pot).** A solution of 3-chloro-2,4-difluoro-aniline (500 mg, 3.06 mmol), glyoxal (444 mg, 3.06 mmol) in MeOH (5 mL) was stirred at rt for 12 h. Then NH₄Cl (327 mg, 6.11 mmol) was added, followed by formaldehyde (496 mg, 6.11 mmol). The mixture was diluted with MeOH (20 mL) and then stirred at 70°C for 1 h. Phosphoric acid (705 mg, 6.11 mmol) was added slowly and the mixture was stirred at 70°C for 4 h. On completion, the reaction mixture was concentrated under vacuum. Then ice-cold water (30 mL) was added followed by aq. KOH solution (40% w/w) to adjust to pH 9. The mixture was then extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 120 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (30-50% EtOAc in PE) to afford 1-(3-chloro-2,4-difluorophenyl)-1H-imidazole (620 mg, 94%) as a white solid.

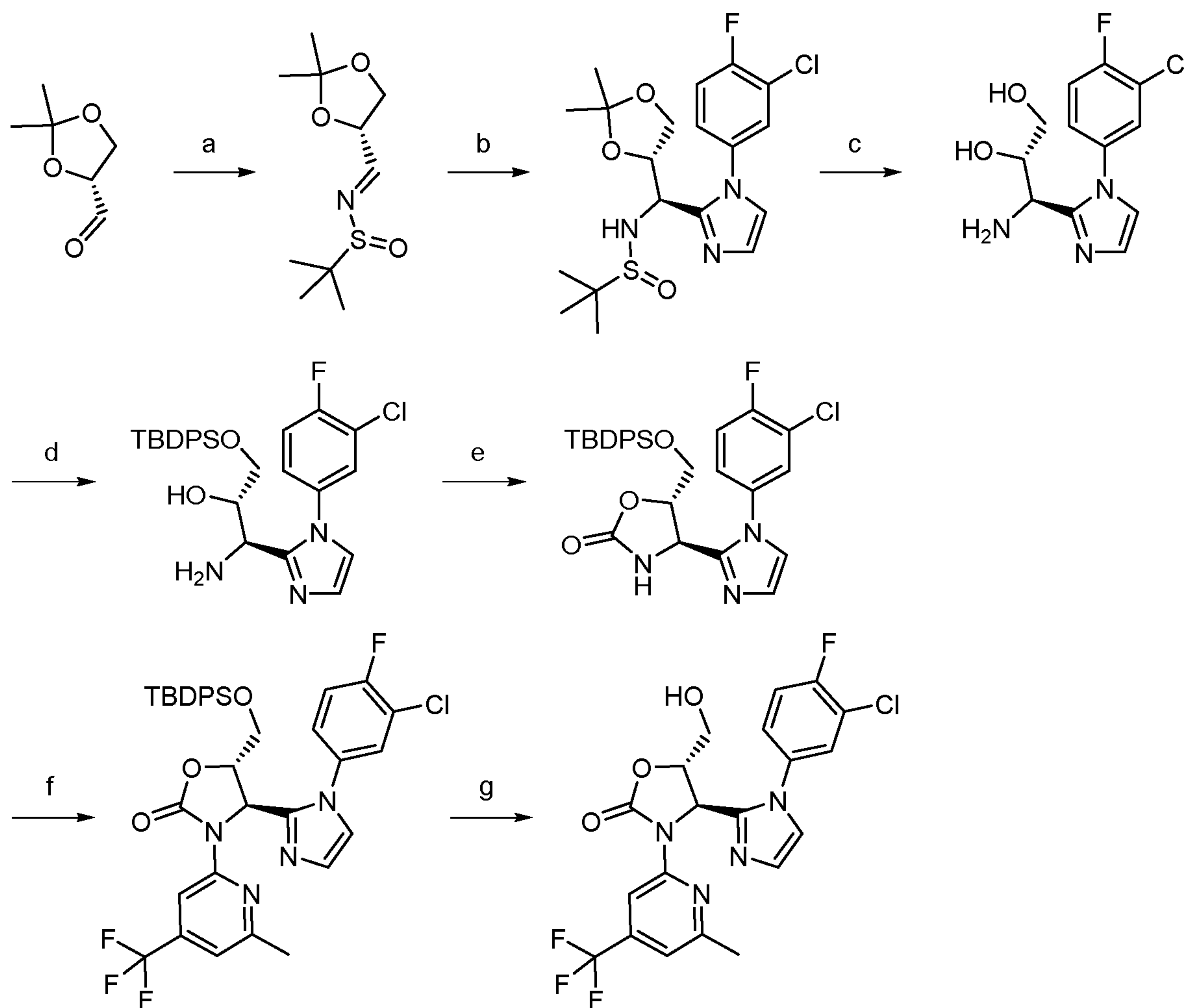
¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.04 (s, 1H), 7.76 – 7.70 (m, 1H), 7.58 (s, 1H), 7.55 – 7.50 (m, 1H), 7.14 (s, 1H).

Steps d-h. Conducted in a similar manner to **Example 41** steps b-f.

- m/z ES⁺ [M+H]⁺ 459.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.19 (s, 1H), 7.70 – 7.61 (m, 1H), 7.41 – 7.36 (m, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 5.85 – 5.81 (m, 1H), 4.80 – 4.78 (m, 1H), 4.51 – 4.48 (m, 1H), 2.33 (s, 3H).

Example 46

(4R,5S)-4-(1-(3-Chloro-4-fluorophenyl)-1H-imidazol-2-yl)-5-(hydroxymethyl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one



Step a. To a solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (2.00 g, 15.4 mmol) and (R)-2-methylpropane-2-sulfinamide (2.24 g, 18.4 mmol) in THF (50 mL) was added $\text{Ti}(\text{OEt})_4$ (10.5 g, 46.1 mmol). The reaction mixture was stirred at 15°C for 12 h. Upon completion, the reaction mixture was quenched with EtOAc (100 mL) and water (30 mL). The mixture was filtered and concentrated in vacuo. The residue was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated in vacuo. Purification by column chromatography (0-30% EtOAc in PE) gave (R)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide (1.82 g, 48%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ ppm 8.08 – 8.00 (m, 1H), 4.84 (t, $J = 4.4$ Hz, 1H), 4.30 – 4.20 (m, 1H), 4.07 – 3.98 (m, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.30 – 1.24 (m, 9H).

Step b. To a solution of 1-(3-chloro-4-fluorophenyl)-1H-imidazole (1.01 g, 5.14 mmol) in THF (20 mL) was added a solution of LDA (2 M in THF, 6.18 mmol) dropwise at -78°C . The

mixture was stirred at -78°C for 30 min before a solution of (R)-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide (1.20 g, 5.14 mmol) in THF (5 mL) was added dropwise and the mixture was stirred at -78°C for another 2.5 h. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl (5 mL), then diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by prep-HPLC to give (R)-N-((R)-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-methylpropane-2-sulfinamide (0.71 g, 31%) as a white solid.

m/z ES+ [M+H]⁺ 430.0; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.87 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.64 (t, *J* = 8.8 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.37 (s, 1H), 7.07 (s, 1H), 5.58 (d, *J* = 6.8 Hz, 1H), 4.49 (dd, *J* = 13.2, 6.4 Hz, 1H), 4.39 (t, *J* = 6.8 Hz, 1H), 3.91 (d, *J* = 6.4 Hz, 1H), 1.22 (s, 3H), 1.08 (s, 3H), 1.05 (s, 9H).

Step c. A mixture of (R)-N-((R)-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-methylpropane-2-sulfinamide (0.5 g, 1.16 mmol) in HCl/MeOH (4 M, 6 mL) was stirred at rt for 0.5 h. Upon completion, the reaction mixture was concentrated in vacuo to give (2*S*,3*R*)-3-amino-3-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)propane-1,2-diol (0.37 g, crude, HCl) as a white solid, which was used in the next step without further purification.

Step d. To a solution of (2*S*,3*R*)-3-amino-3-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)propane-1,2-diol (0.3 g, 0.93 mmol, HCl) in DCM (10 mL) was added TEA (471 mg, 4.66 mmol). Then TBDPSCI (307 mg, 1.12 mmol) in DCM (3 mL) was added at 0°C, and the mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC to give (1*R*,2*S*)-1-amino-3-((tert-butyl)di(phenyl)silyl)oxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)propan-2-ol (0.25 g, 49%) as a white solid.

m/z ES+ [M+H]⁺ 524.2

Step e. To a solution of (1*R*,2*S*)-1-amino-3-((tert-butyl)di(phenyl)silyl)oxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)propan-2-ol (0.2 g, 0.38 mmol) in water (1.5 mL) was added K₂CO₃ (60.1 mg, 0.44 mmol) and KHCO₃ (44.3 mg, 0.44 mmol). The mixture was stirred at 15°C for 0.5 h. A solution of triphosgene (60 mg, 0.20 mmol) in toluene (1.5 mL) was added at 0°C, and the reaction mixture was stirred at 15°C for 1.5 h. Upon completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (25-100% EtOAc in PE) to afford (4*R*,5*S*)-5-(((tert-butyl)di(phenyl)silyl)oxy)methyl)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)oxazolidin-2-one (0.15 g, 64%) as a white solid.

m/z ES+ [M+H]⁺ 550.2; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.59 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.40 (m, 2H), 7.39 – 7.35 (m, 5H), 7.25 – 7.13 (m, 3H), 7.06 (s, 1H),

5.75 (s, 1H), 5.10 – 5.06 (m, 1H), 5.02 (d, $J = 5.2$ Hz, 1H), 3.91 (dd, $J = 11.6, 3.2$ Hz, 1H), 3.68 (d, $J = 11.6$ Hz, 1H), 1.00 (s, 9H).

Step f. A mixture of (4R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)oxazolidin-2-one (70 mg, 0.13 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (45.8 mg, 0.19 mmol), Pd₂(dba)₃ (5.8 mg, 0.0065 mmol), XantPhos (5.9 mg, 0.01 mmol) and K₂CO₃ (35.2 mg, 0.26 mmol) in dioxane (2 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100°C for 1 h under N₂ atmosphere. Upon completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (10-100% EtOAc in PE then 0-50% MeOH in EtOAc) to afford (4R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one (80 mg, crude) as a yellow oil which was used without further purification.

m/z ES+ [M+H]⁺ 709.2

Step g. To a solution of (4R,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)oxazolidin-2-one (70 mg, 0.099 mmol) in THF (2 mL) was added TBAF (1 M, 0.49 mmol). The reaction was stirred at rt for 12 h. Upon completion, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by prep-HPLC to give the title compound (10 mg, 18%) as a brown solid.

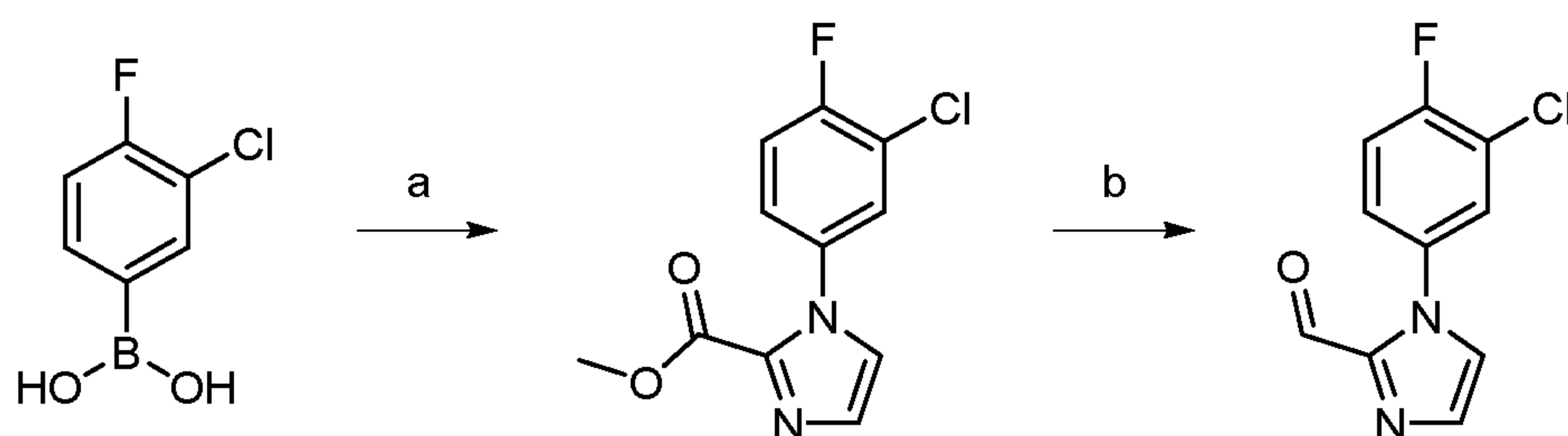
m/z ES+ [M+H]⁺ 471.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.26 (s, 1H), 7.85 – 7.81 (m, 2H), 7.75 (d, $J = 2.0$ Hz, 1H), 7.72 – 7.67 (m, 1H), 7.65 – 7.58 (m, 1H), 7.35 (s, 1H), 5.95 (d, $J = 4.4$ Hz, 1H), 5.03 (q, $J = 3.6$ Hz, 1H), 3.87 (dd, $J = 12.4, 3.6$ Hz, 1H), 3.68 (dd, $J = 12.4, 2.8$ Hz, 1H), 2.47 (s, 3H).

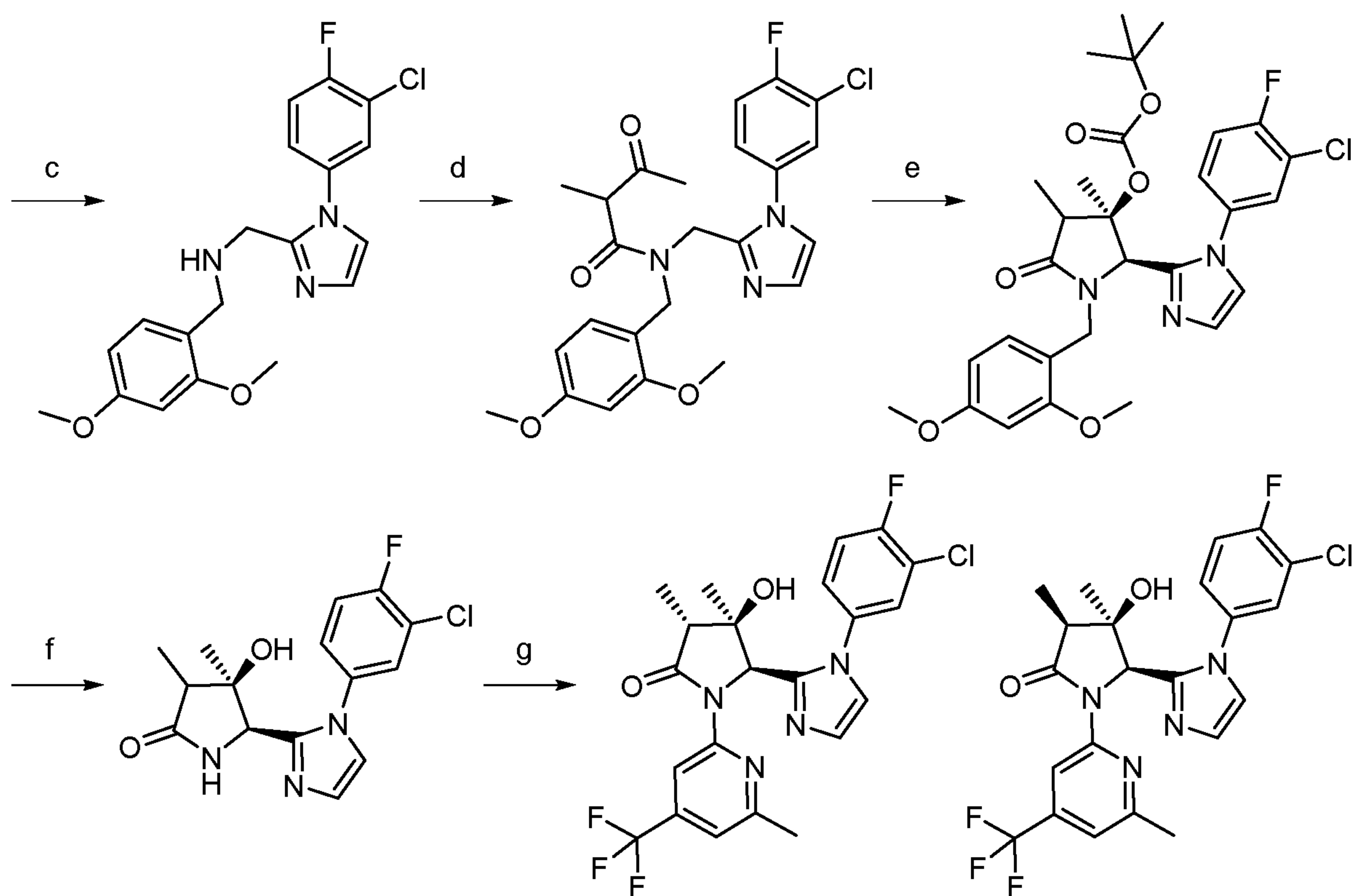
Example 47

Rel-(3R,4R,5R)-5-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-3,4-dimethyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one

Example 48

Rel-(3S,4R,5R)-5-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-3,4-dimethyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one





Step a. To a solution of methyl 1*H*-imidazole-2-carboxylate (5.00 g, 39.7 mmol) and (3-chloro-4-fluoro-phenyl)boronic acid (7.60 g, 43.6 mmol) in DCM (80 mL) and MeOH (80 mL) was added Cu(OAc)₂·H₂O (792 mg, 3.96 mmol) and pyridine (6.27 g, 79.3 mmol). The mixture was stirred at rt for 12 h under O₂ (15 psi). On completion, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was triturated with 25% EtOAc in PE (50 mL) and filtered. The collected solid was dried under vacuum to afford methyl 1-(3-chloro-4-fluoro-phenyl)imidazole-2-carboxylate (5 g, 50%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 – 7.41 (m, 1H), 7.31 (s, 1H), 7.29 – 7.23 (m, 2H), 7.19 (s, 1H), 3.88 (s, 3H).

Step b. To a solution of methyl 1-(3-chloro-4-fluoro-phenyl)imidazole-2-carboxylate (4.7 g, 18.5 mmol) in DCM (150 mL) was added DIBAL-H (1 M, 55.4 mmol) dropwise at -78°C. The mixture was stirred at -78°C for 2 h. On completion, the reaction mixture was quenched with sat. aq. NH₄Cl solution (50 mL) at -78°C, then warmed to rt and extracted with DCM (2 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was triturated with 50% EtOAc in PE (50 mL) and filtered. The collected solid was dried under vacuum to give 1-(3-chloro-4-fluoro-phenyl)imidazole-2-carbaldehyde (2.7 g, 65%) as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.69 (s, 1H), 7.94 – 7.88 (m, 1H), 7.83 (s, 1H), 7.63 – 7.57 (m, 2H), 7.45 (s, 1H).

Step c. To a solution of 1-(3-chloro-4-fluoro-phenyl)imidazole-2-carbaldehyde (1 g, 4.45 mmol) and (2,4-dimethoxyphenyl)methanamine (819 mg, 4.90 mmol) in DCM (15 mL) was

added molecular sieves (4 Å, 0.5 g) and acetic acid (267 mg, 4.45 mmol). The mixture was stirred at rt for 15 min and then cooled to 0°C. NaBH(OAc)₃ (1.89 g, 8.90 mmol) was added and the mixture was stirred at rt for 1 h. On completion, the reaction mixture was quenched with MeOH (5 mL) at 0°C, diluted with water (50 mL) and extracted with DCM (3 x 30 mL).

- 5 The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (20-100% EtOAc in PE, then 0-20% MeOH in DCM) to give 1-(1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-N-(2,4-dimethoxybenzyl)methanamine (1.3 g, 78%) as a brown oil.

m/z ES+ [M+H]⁺ 376.0

- 10 **Step d.** To a solution of 2-methyl-3-oxo-butanoic acid (1.00 g, 8.61 mmol) and 1-(1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-N-(2,4-dimethoxybenzyl)methanamine (1.29 g, 3.44 mmol) in pyridine (20 mL) was added T3P (16.4 g, 25.7 mmol, 50 wt.% in EtOAc). The mixture was stirred at rt for 12 h. On completion, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed
15 with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (20-100% EtOAc in PE) to give N-[[1-(3-chloro-4-fluorophenyl)imidazol-2-yl]methyl]-N-[(2,4-dimethoxyphenyl)methyl]-2-methyl-3-oxo-butanamide (950 mg, 23%) as a brown oil.

- ¹H NMR (400 MHz, CDCl₃) δ ppm 7.33 – 7.28 (m, 1H), 7.25 – 7.20 (m, 1H), 7.20 – 7.18 (m, 1H), 7.18 – 7.12 (m, 1H), 7.05 – 7.01 (m, 1H), 6.92 – 6.86 (m, 2H), 6.39 – 6.33 (m, 2H), 4.71 – 4.26 (m, 4H), 3.74 – 3.68 (m, 6H), 3.61 (s, 1H), 2.067 (s, 3H), 1.32 – 1.20 (m, 3H).

Step e. To a solution of N-[[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]methyl]-N-[(2,4-dimethoxyphenyl)methyl]-2-methyl-3-oxo-butanamide (900 mg, 1.90 mmol) and di-*tert*-butyl dicarbonate (829 mg, 3.80 mmol) in xylene (25 mL) was added DIPEA (736 mg, 5.70 mmol).

- 25 The mixture was stirred at 130°C for 12 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (20-100% EtOAc in PE) to give *tert*-butyl [(2R,3R)-2-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-1-[(2,4-dimethoxyphenyl)methyl]-3,4-dimethyl-5-oxo-pyrrolidin-3-yl] carbonate (530 mg, 49%) as a yellow solid.

- ¹H NMR (400 MHz, CDCl₃) δ ppm 7.25 – 7.19 (m, 1H), 7.18 – 7.08 (m, 3H), 6.84 (s, 1H), 6.54 – 6.48 (m, 1H), 6.38 (d, *J* = 4.0 Hz, 1H), 6.28 – 6.22 (m, 1H), 4.68 (s, 1H), 4.43 (d, *J* = 8.0 Hz, 1H), 3.94 – 3.81 (m, 2H), 3.78 (s, 3H), 3.70 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H), 1.30
35 (s, 9H).

Step f. To a solution of *tert*-butyl [(2R,3R)-2-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-1-[(2,4-dimethoxyphenyl)methyl]-3,4-dimethyl-5-oxo-pyrrolidin-3-yl] carbonate (350 mg, 0.61 mmol) in toluene (5 mL) was added methanesulfonic acid (3 mL). The mixture was stirred at 120°C for 2 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (20 mL) and extracted with EtOAc (2 x 15 mL). The organic layers were discarded, and the aqueous phase was adjusted to pH = 7~8 with sat. NaHCO₃ solution (20 mL), which was further extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄ and concentrated in vacuo to give compound (4R,5R)-5-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-4-hydroxy-3,4-dimethyl-pyrrolidin-2-one (200 mg, crude) as a yellow solid which was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 – 7.52 (m, 1H), 7.38 – 7.29 (m, 2H), 7.12 – 7.10 (m, 1H), 7.06 – 6.99 (m, 2H), 4.88 (s, 1H), 4.27 (d, *J* = 1.2 Hz, 1H), 3.06 – 2.93 (m, 1H), 1.29 (s, 3H), 1.14 (d, *J* = 8.0 Hz, 3H).

Step g. To a solution of (4R,5R)-5-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-4-hydroxy-3,4-dimethyl-pyrrolidin-2-one (180 mg, 0.56 mmol) and 2-bromo-6-methyl-4-(trifluoromethyl)-pyridine (200 mg, 0.83 mmol) in dioxane (8 mL) was added Pd₂(dba)₃ (50.9 mg, 0.056 mmol), XantPhos (64.3 mg, 0.11 mmol) and Cs₂CO₃ (362 mg, 1.11 mmol). The mixture was stirred at 85°C for 2 h under N₂. On completion, the reaction mixture was evaporated. The residue was diluted with water (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-HPLC to give **Example 47** (103 mg, 37% yield) as a white solid,

m/z ES+ [M+H]⁺ 483.0; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.59 (s, 1H), 8.12 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.77 (d, *J* = 4.0 Hz, 1H), 7.65 (t, *J* = 8.4 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.29 (s, 1H), 5.53 (s, 1H), 3.22 (q, *J* = 7.2 Hz, 1H), 2.44 (s, 3H), 1.32 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H)

and **Example 48** (16 mg, 6% yield) as a white solid,

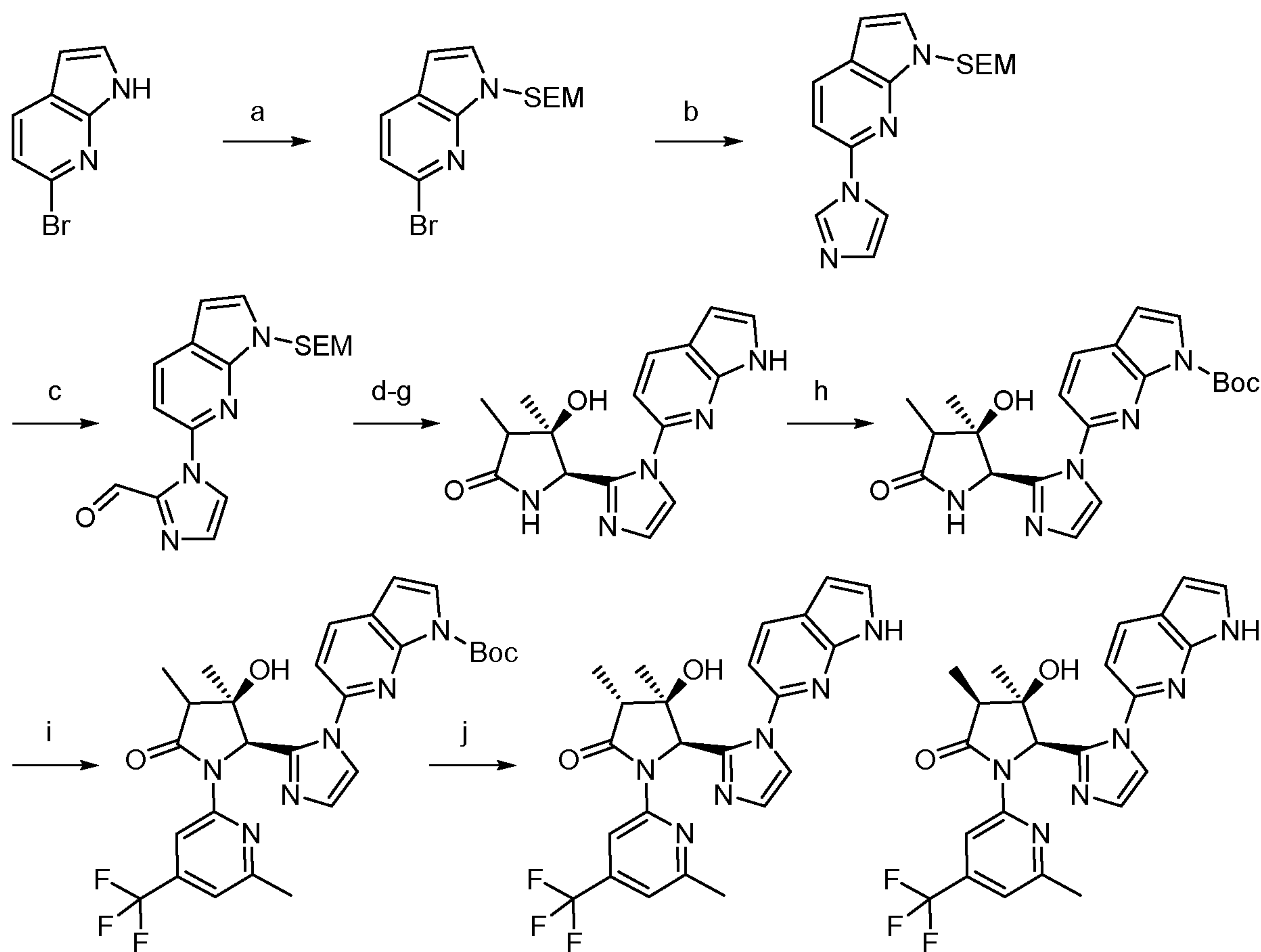
m/z ES+ [M+H]⁺ 483.0; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.43 (s, 1H), 8.22 – 8.10 (m, 1H), 7.93 – 7.85 (m, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.31 (s, 1H), 5.82 (s, 1H), 2.83 (q, *J* = 7.2 Hz, 1H), 2.42 (s, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.26 (s, 3H).

Example 49

Rel-(3R,4R,5R)-5-(1-(1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-4-hydroxy-3,4-dimethyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one

Example 50

Rel-(3S,4R,5R)-5-(1-(1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-4-hydroxy-3,4-dimethyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one



Step a. To a solution of 6-bromo-1H-pyrrolo[2,3-b]pyridine (2.7 g, 13.7 mmol) in DMF (50 mL) was added NaH (60% dispersion in mineral oil, 822 mg, 20.6 mmol) portionwise at 0°C. The mixture was stirred at 0°C for 15 min before 2-(trimethylsilyl)ethoxymethyl chloride (3.43 g, 20.6 mmol) was added slowly and stirring continued at 0°C for 30 min. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (0-3% EtOAc in PE) to give 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (4.5 g, 96%) as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.95 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 3.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 3.6 Hz, 1H), 5.57 (s, 2H), 3.54 – 3.45 (m, 2H), 0.86 – 0.79 (m, 2H), -0.12 (s, 9H).

Step b. A mixture of 6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (4.60 g, 13.4 mmol), imidazole (1.83 g, 26.9 mmol), CuI (1.28 g, 6.72 mmol), L-proline (1.55 g, 13.4 mmol) and Cs₂CO₃ (13.1 g, 40.3 mmol) in DMSO (50 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 120°C for 12 h under N₂. Upon completion, the

reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by reverse-phase column to give 6-(1*H*-imidazol-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (3.3 g, 76%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.59 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 1H), 6.60 (d, *J* = 3.6 Hz, 1H), 5.66 (s, 2H), 3.54 (t, *J* = 8.00 Hz, 2H), 0.91 – 0.80 (m, 2H), -0.15 (s, 9H).

Step c. To a solution of 6-(1*H*-imidazol-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-

pyrrolo[2,3-*b*]pyridine (3.3 g, 10.5 mmol) in THF (50 mL) was added a solution of *n*-butyllithium (2.5 M in hexane, 6.30 mL) dropwise at 0°C. The mixture was stirred at 0°C for 30 min under N₂. DMF (1.15 g, 15.7 mmol) was added, and the mixture was stirred at 0°C for 2 h. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl solution (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na₂SO₄ and evaporated to give 1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazole-2-carbaldehyde (3.8 g, crude) as a brown oil which was used in the next step without further purification.
m/z ES⁺ [M+H]⁺ 343.0

Steps d-g. Conducted in a similar manner to **Examples 47/48**, steps c-f.

Step h. A solution of (4*R*,5*R*)-5-(1-(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)-4-hydroxy-3,4-dimethylpyrrolidin-2-one (120 mg, 0.39 mmol), di-*tert*-butyl dicarbonate (168 mg, 0.77 mmol) and TEA (117 mg, 1.16 mmol) in DCM (2 mL) was stirred at rt for 2 h. Upon completion, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (10% EtOH in EtOAc) to give *tert*-butyl 6-(2-((2*R*,3*R*)-3-hydroxy-3,4-dimethyl-5-oxopyrrolidin-2-yl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (50 mg, 17%) as a yellow oil.
m/z ES⁺ [M+H]⁺ 412.2

Step i. A solution of *tert*-butyl 6-(2-((2*R*,3*R*)-3-hydroxy-3,4-dimethyl-5-oxopyrrolidin-2-yl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (45 mg, 0.11 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (39.5 mg, 0.16 mmol), Pd₂(dba)₃ (10 mg, 0.011 mmol), XantPhos (13 mg, 0.022 mmol) and K₂CO₃ (30 mg, 0.22 mmol) in dioxane (2 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 80°C for 2 h under N₂. Upon completion, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (100% EtOAc) to give *tert*-

butyl 6-(2-((2R,3R)-3-hydroxy-3,4-dimethyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-oxopyrrolidin-2-yl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (25 mg, 40%) as a yellow oil.

m/z ES+ $[M+H]^+$ 571.2

- 5 **Step j.** A solution of *tert*-butyl 6-(2-((2R,3R)-3-hydroxy-3,4-dimethyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-oxopyrrolidin-2-yl)-1*H*-imidazol-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (20 mg, 0.018 mmol) in DCM (2 mL) and TFA (0.04 mL) was stirred at rt for 30 min. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC to give **Example 49** (4 mg, 24%) as a brown oil,

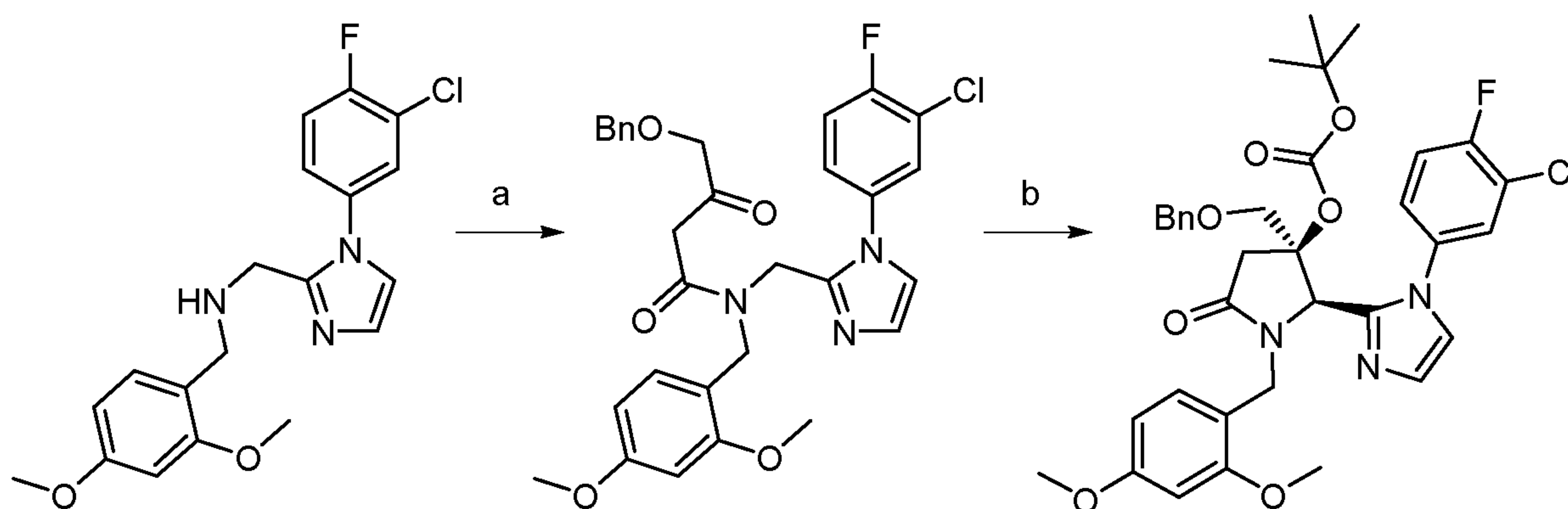
- 10 m/z ES+ $[M+H]^+$ 471.1; ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.14 (s, 1H), 8.44 (s, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 7.71 (t, J = 3.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.32 (s, 1H), 6.66 (q, J = 1.6 Hz, 1H), 5.88 (s, 1H), 3.29 (q, J = 7.5 Hz, 1H), 2.21 (s, 3H), 1.41 (s, 3H), 1.15 (d, J = 7.5 Hz, 3H).

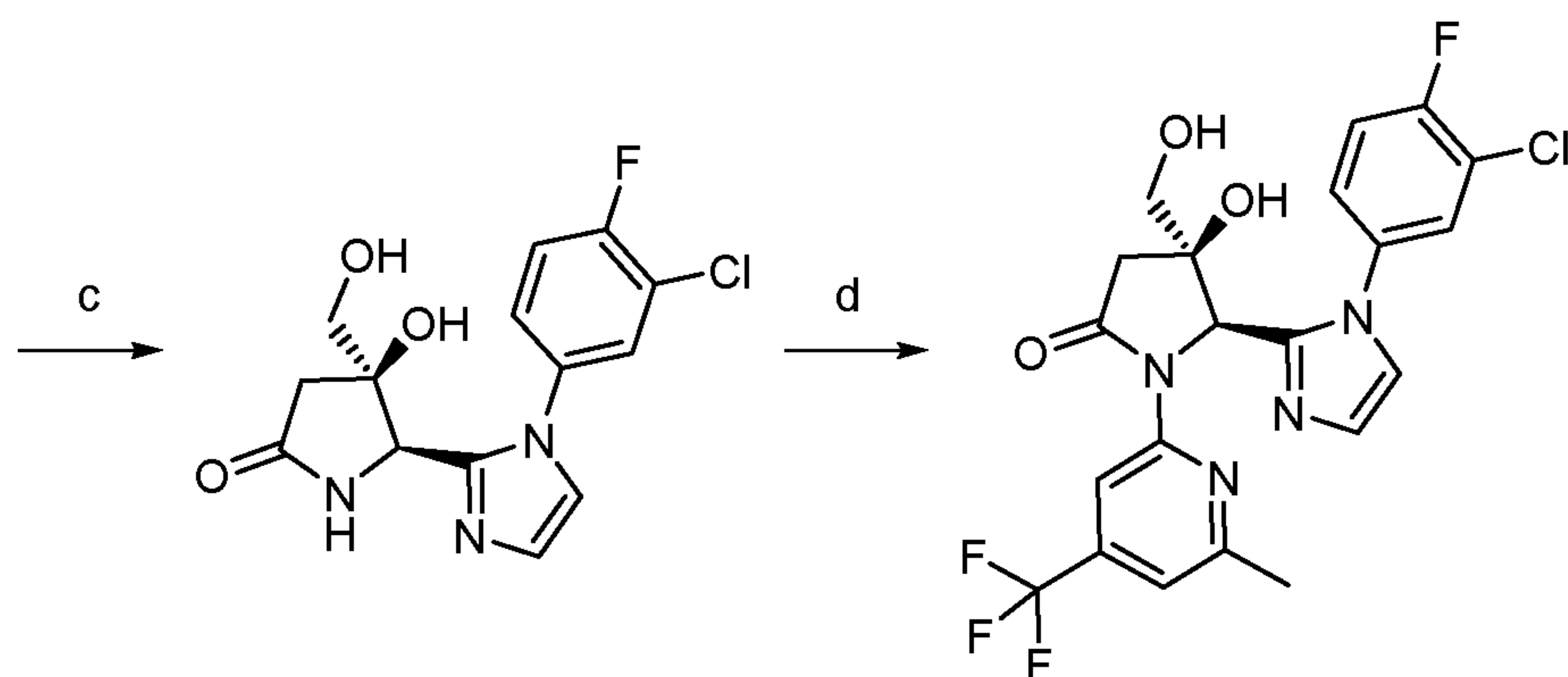
and **Example 50** (0.5 mg, 3%) as a white solid.

- 15 m/z ES+ $[M+H]^+$ 471.1; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.40 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.70 – 7.64 (m, 1H), 7.64 (d, J = 3.6 Hz, 1H), 7.56 (s, 1H), 7.22 (s, 1H), 6.70 (d, J = 3.6 Hz, 1H), 6.26 (s, 1H), 2.89 (q, J = 6.8 Hz, 1H), 2.31 (s, 3H), 1.58 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H).

20 **Example 51**

Rel-(4R,5R)-5-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-4-(hydroxymethyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one





Step a. To a solution of 1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-N-(2,4-dimethoxybenzyl)methanamine (described in **Example 47/48**, steps a-c; 1.00 g, 2.66 mmol) and 4-(benzyloxy)-3-oxobutanoic acid (CAS Number 67354-37-4; 831 mg, 3.99 mmol) in pyridine (5 mL) and DMF (5 mL) was added T3P (5.08 g, 7.98 mmol, 50 wt.% in EtOAc). The reaction mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (50 mL), dried over Na₂SO₄ and evaporated to give 4-(benzyloxy)-N-((1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)methyl)-N-(2,4-dimethoxybenzyl)-3-oxobutanamide (1.4 g, crude) as a brown oil, which was used without further purification.

m/z ES+ [M+H]⁺ 566.2

Step b. To a solution of 4-(benzyloxy)-N-((1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)methyl)-N-(2,4-dimethoxybenzyl)-3-oxobutanamide (0.70 g, 1.24 mmol) in xylene (30 mL) was added di-*tert*-butyl dicarbonate (1.35 g, 6.18 mmol). The mixture was stirred at 130°C for 12 h. Upon completion, the reaction mixture was concentrated in vacuo. The residue was purified by prep-HPLC to give (2*R*,3*R*)-3-((benzyloxy)methyl)-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-1-(2,4-dimethoxybenzyl)-5-oxopyrrolidin-3-yl *tert*-butyl carbonate (80 mg, 9%) as a brown oil.

m/z ES+ [M+H]⁺ 666.3

Step c. A solution of (2*R*,3*R*)-3-((benzyloxy)methyl)-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-1-(2,4-dimethoxybenzyl)-5-oxopyrrolidin-3-yl *tert*-butyl carbonate (80 mg, 0.12 mmol) in toluene (0.5 mL) and methanesulfonic acid (0.3 mL) was stirred at 120°C for 30 min. Upon completion, the reaction mixture was diluted with water (3 mL) and extracted with EtOAc (3 x 5 mL). The aqueous layer was quenched with 1 M NaOH solution to pH 9, and then extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by reverse-phase column chromatography to give (4*R*,5*R*)-5-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-4-(hydroxymethyl)pyrrolidin-2-one (21 mg, 51%) as a white solid.

m/z ES+ [M+H]⁺ 326.0; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.16 (s, 1H), 7.87 – 7.80 (m, 1H), 7.78 (s, 1H), 7.60 – 7.55 (m, 1H), 7.39 (s, 1H), 7.08 (s, 1H), 5.58 (s, 1H), 5.04 (br s, 1H), 4.53 (s, 1H), 2.39 (d, *J* = 16.4 Hz, 1H), 2.22 (d, *J* = 16.4 Hz, 1H).

Step d. A mixture of (4R,5R)-5-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-4-

(hydroxymethyl)pyrrolidin-2-one (20.0 mg, 0.061 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (29.5 mg, 0.12 mmol), Pd₂(dba)₃ (5.6 mg, 0.006 mmol), XantPhos (7.1 mg, 0.012 mmol) and K₂CO₃ (25.5 mg, 0.18 mmol) in 1,4-dioxane (1 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 100°C for 1 h under N₂. Upon completion, the reaction mixture was evaporated, purified by column chromatography (10-100% EtOAc in PE then 0-50% MeOH in EtOAc) and further purified by prep-HPLC to give the title compound (4 mg, 12%, HCl) as a yellow solid.

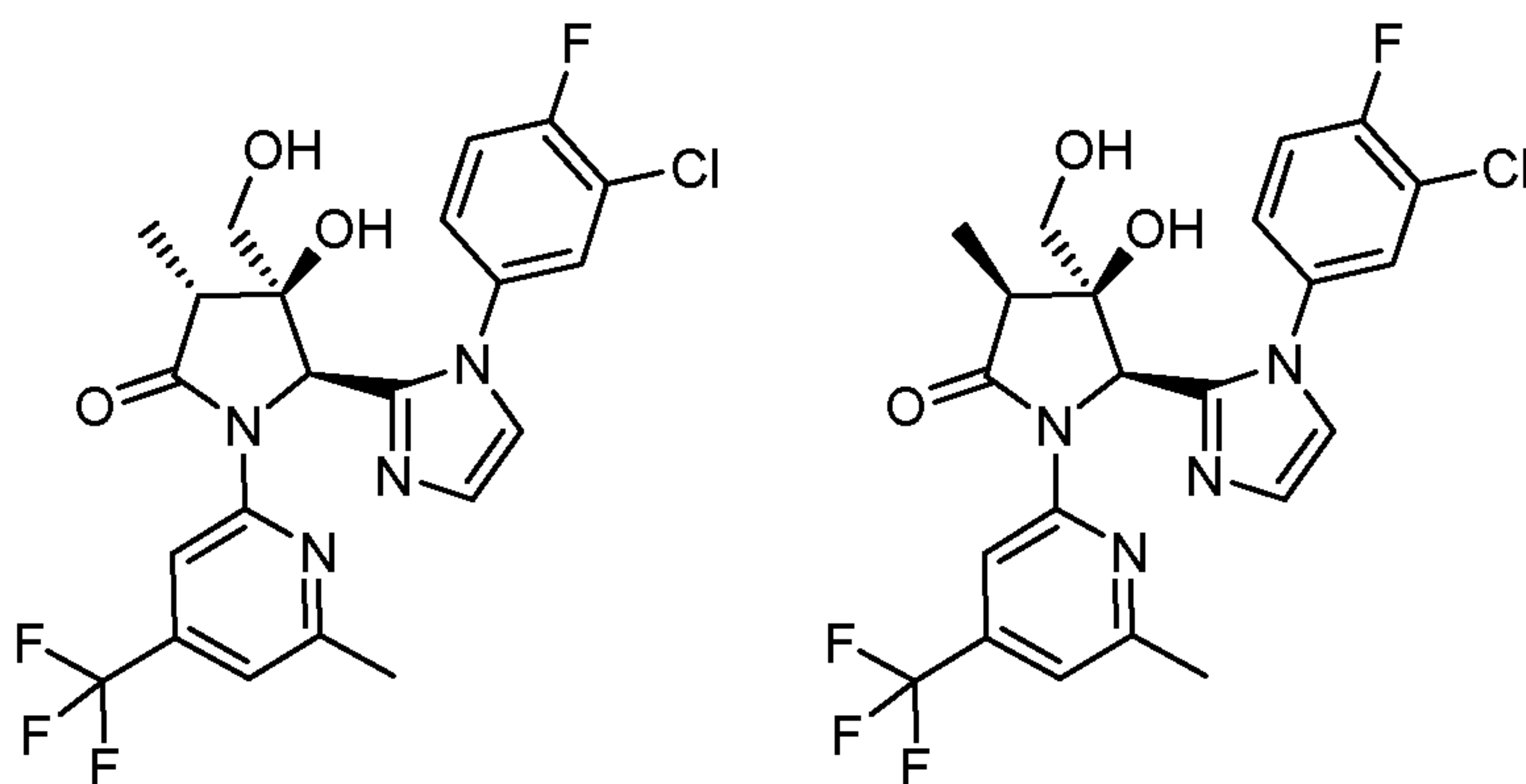
m/z ES+ [M+H]⁺ 485.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.54 (s, 1H), 8.09 – 8.05 (m, 1H), 7.89 – 7.84 (m, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.61 (t, *J* = 8.8 Hz, 1H), 7.33 (s, 1H), 5.90 (s, 1H), 3.58 – 3.53 (m, 1H), 3.51 – 3.47 (m, 1H), 2.98 (s, 2H), 2.45 (s, 3H).

Example 52

Rel-(3R,4R,5R)-5-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-4-(hydroxymethyl)-3-methyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one

Example 53

Rel-(3S,4R,5R)-5-(1-(3-Chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-4-hydroxy-4-(hydroxymethyl)-3-methyl-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one



The title compounds were prepared in a similar manner to **Example 51**, using 4-(benzyloxy)-2-methyl-3-oxobutanoic acid (CAS Number 1035815-57-6, prepared as described in *Org. Biomol. Chem.* **2012**, *10*, 3472-3485) in **step a** and separated by prep-HPLC.

Example 52

m/z ES+ [M+H]⁺ 499.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.60 (s, 1H), 8.03 (dd, *J* = 2.8, 6.4 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.51 (t, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.15 (s,

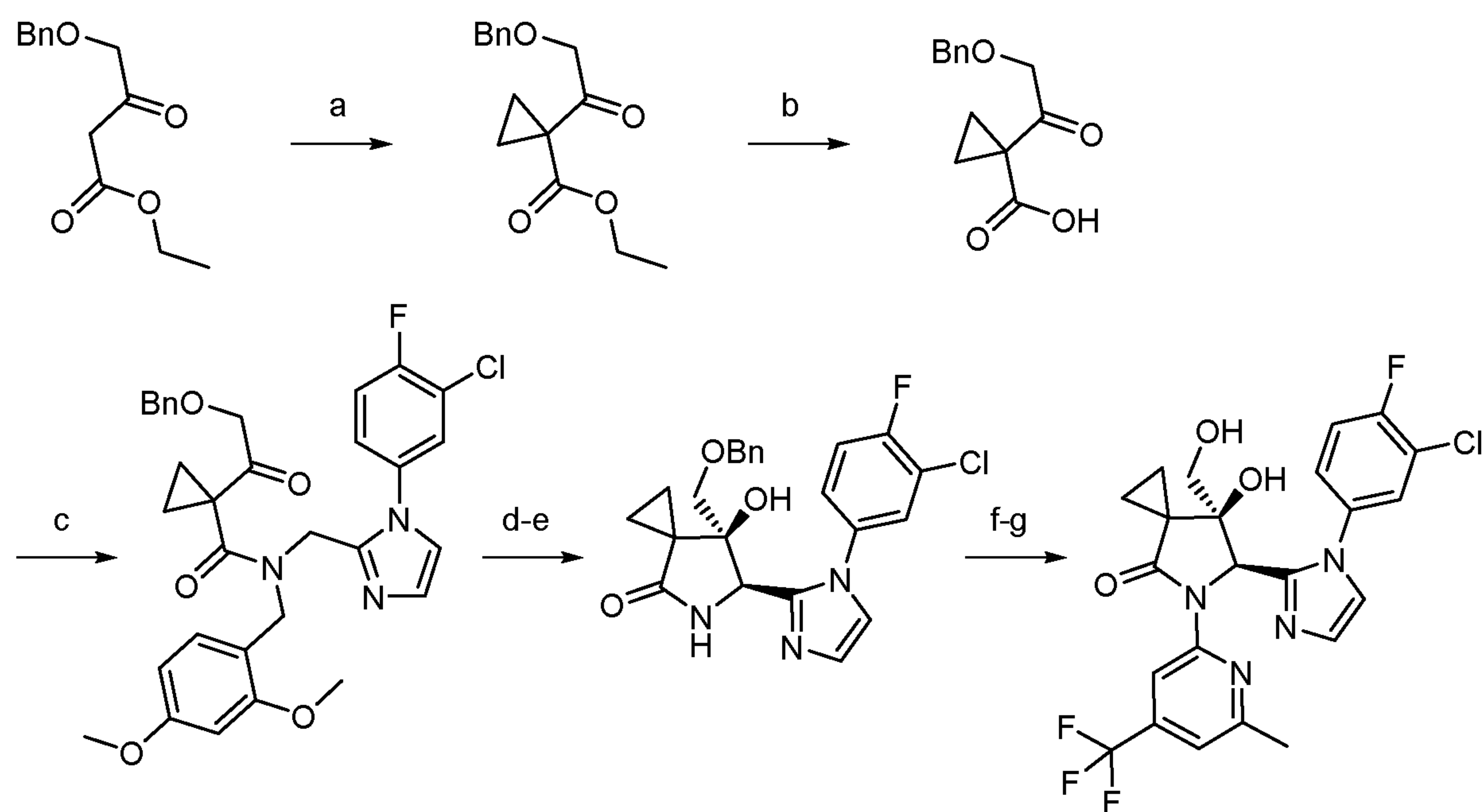
1H), 7.00 (d, $J = 1.2$ Hz, 1H), 5.76 (s, 1H), 3.65 – 3.55 (m, 2H), 3.50 (q, $J = 7.2$ Hz, 1H), 2.38 (s, 3H), 1.26 (d, $J = 7.2$ Hz, 3H).

Example 53

m/z ES+ $[M+H]^+$ 499.1; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.27 (s, 1H), 7.93 (dd, $J = 2.4$, 6.8 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.22 – 7.14 (m, 2H), 7.00 (d, $J = 1.2$ Hz, 1H), 5.84 (s, 1H), 3.48 (s, 2H), 2.89 (q, $J = 7.2$ Hz, 1H), 2.38 (s, 3H), 1.38 (d, $J = 7.6$ Hz, 3H).

Example 54

10 **Rel-(6R,7R)-6-(1-(3-Chloro-4-fluorophenyl)-1H-imidazol-2-yl)-7-hydroxy-7-(hydroxymethyl)-5-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-5-azaspiro[2.4]heptan-4-one**



15 **Step a.** To a solution of ethyl 4-benzyloxy-3-oxobutanoate (5 g, 21.2 mmol) and 1,2-dibromoethane (5.17 g, 27.5 mmol) in DMF (50 mL) was added K_2CO_3 (7.31 g, 52.9 mmol) and TBAB (34 mg, 0.11 mmol). The mixture was stirred at 80°C for 12 h. On completion, the reaction mixture was filtered and evaporated. The residue was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over Na_2SO_4 and evaporated. The residue was partially purified by column chromatography (10-25% EtOAc in PE) to afford ethyl 1-(2-benzyloxyacetyl)-cyclopropanecarboxylate (3.5 g) as a brown oil which was used without further purification. m/z ES+ $[M+H]^+$ 263.1

25 **Step b.** To a solution of ethyl 1-(2-benzyloxyacetyl)cyclopropanecarboxylate (3.2 g, 12.2 mmol) in water (40 mL) was added aq. NaOH solution (1 M, 36.6 mL). The mixture was

stirred at rt for 2 h. On completion, the reaction mixture was adjusted to pH = 3~4 with 2 M HCl solution. The aqueous layer was then extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄ and evaporated to give 1-(2-benzyloxyacetyl)cyclopropanecarboxylic acid (1.5 g, 52%) as a white solid.

5 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.84 (br s, 1H), 7.41 – 7.27 (m, 5H), 4.56 (s, 2H), 4.50 (s, 2H), 1.40 – 1.34 (m, 4H).

Step c. To a solution of 1-(2-benzyloxyacetyl)cyclopropanecarboxylic acid (1.2 g, 5.12 mmol) and N-[[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]methyl]-1-(2,4-dimethoxyphenyl)-methanamine (1.60 g, 2.56 mmol) in DCM (50 mL) was added TEA (1.04 g, 10.3 mmol) and
10 HATU (2.92 g, 7.68 mmol). The mixture was stirred at rt for 2 h. On completion, the reaction mixture was diluted with water (100 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (20-100% EtOAc in PE) to afford 1-(2-benzyloxyacetyl)-N-[[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]methyl]-N-[(2,4-
15 dimethoxyphenyl)methyl]cyclopropanecarboxamide (2.1 g, 69%) as a brown oil.
m/z ES+ [M+H]⁺ 592.3

Step d. To a solution of 1-(2-benzyloxyacetyl)-N-[[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]methyl]-N-[(2,4-dimethoxyphenyl)methyl]cyclopropanecarboxamide (2.2 g, 3.7 mmol) and di-*tert*-butyl dicarbonate (1.62 g, 7.4 mmol) in xylene (40 mL) was added DIPEA (1.44 g,
20 11.1 mmol). The mixture was stirred at 130°C for 12 h. On completion, the reaction mixture was evaporated. The residue was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by prep-HPLC to give [(6R,7R)-7-(benzyloxymethyl)-6-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-5-[(2,4-dimethoxyphenyl)-
25 methyl]-4-oxo-5-azaspiro[2.4]heptan-7-yl] *tert*-butyl carbonate (1.03 g, 40%) as a brown oil.
¹H NMR (400 MHz, CDCl₃) δ ppm 7.32 – 7.27 (m, 3H), 7.23 – 7.16 (m, 2H), 6.97 – 6.89 (m, 4H), 6.83 – 6.78 (m, 1H), 6.76 – 6.69 (m, 1H), 6.41 – 6.38 (m, 1H), 6.36 – 6.31 (m, 1H), 4.95 (d, *J* = 14.4 Hz, 1H), 4.73 (s, 1H), 4.24 – 4.03 (m, 4H), 3.82 (s, 3H), 3.59 (s, 3H), 3.42 – 3.33 (m, 1H), 1.38 (s, 9H), 1.36 – 1.27 (m, 2H), 1.23 – 1.13 (m, 2H).

30 **Step e.** To a solution of [(6R,7R)-7-(benzyloxymethyl)-6-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-5-[(2,4-dimethoxyphenyl)methyl]-4-oxo-5-azaspiro[2.4]heptan-7-yl] *tert*-butyl carbonate (500 mg, 0.72 mmol) in MeCN (15 mL) and water (1.5 mL) was added CAN (1.19 g, 2.17 mmol). The mixture was stirred at rt for 2 h. On completion, the reaction mixture was quenched with sat. aq. NaHCO₃ (15 mL), and then extracted with EtOAc (3 x 10
35 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (100% EtOAc) to give [(6R,7R)-7-

(benzyloxymethyl)-6-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-4-oxo-5-azaspiro[2.4]heptan-7-yl] *tert*-butyl carbonate (50 mg, 13%) as a brown solid.

Step f. To a solution of [(6R,7R)-7-(benzyloxymethyl)-6-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-4-oxo-5-azaspiro[2.4]heptan-7-yl] *tert*-butyl carbonate (90 mg, 0.17 mmol) and 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (48 mg, 0.20 mmol) in dioxane (3 mL) was added Pd₂(dba)₃ (15 mg, 0.017 mmol), XantPhos (19 mg, 0.033 mmol) and K₂CO₃ (69 mg, 0.50 mmol) under N₂ atmosphere. The mixture was stirred at 100°C for 1.5 h under N₂ atmosphere. On completion, the reaction mixture was diluted with water (8 mL) and extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and evaporated. The residue was partially purified by prep-TLC (50% EtOAc in PE) to give [(6R,7R)-7-(benzyloxymethyl)-6-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-5-[6-methyl-4-(trifluoromethyl)-2-pyridyl]-4-oxo-5-azaspiro[2.4]heptan-7-yl] *tert*-butyl carbonate (100 mg) as a yellow oil which was used without further purification.

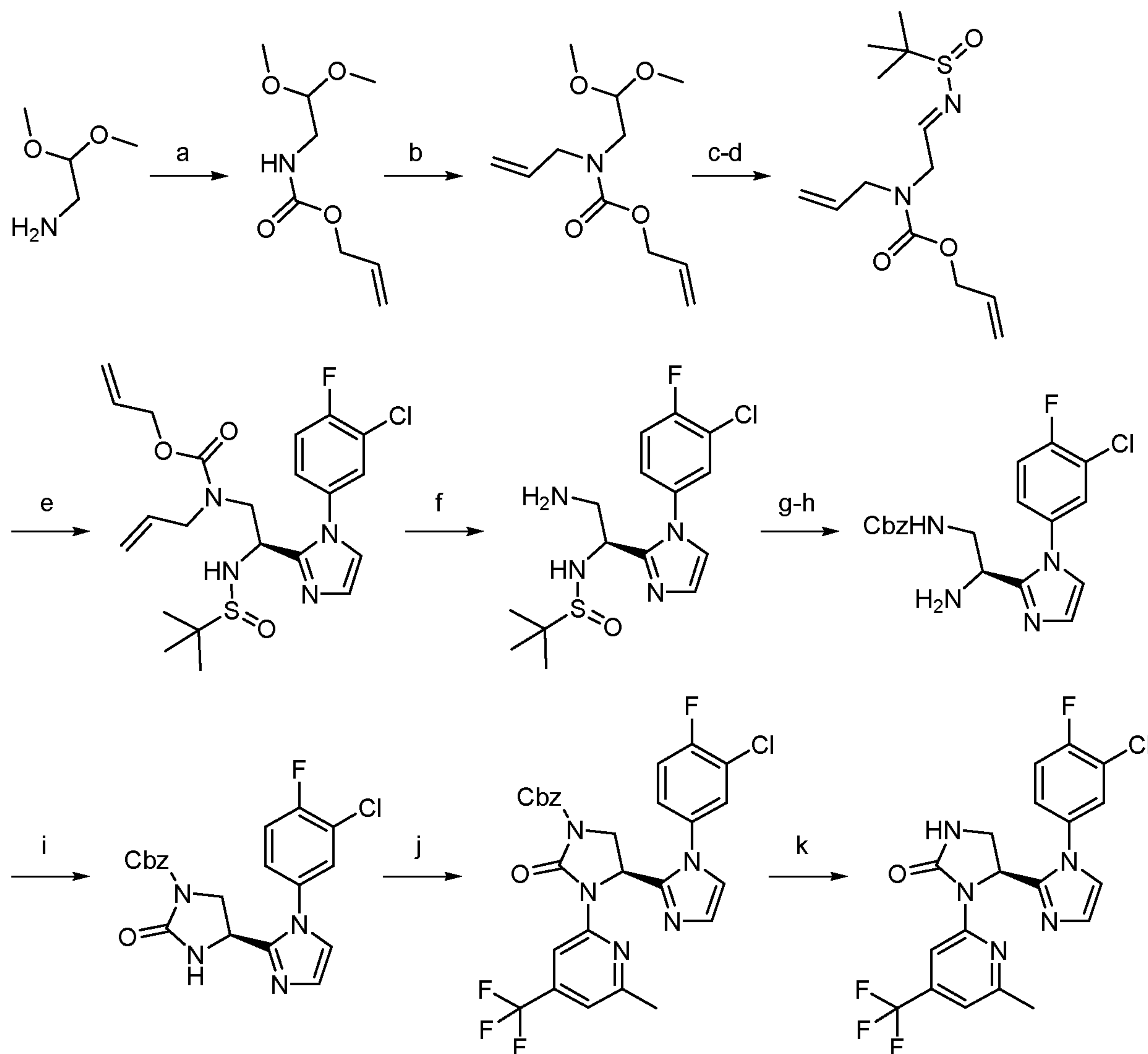
m/z ES+ [M+H]⁺ 701.4

Step g. To a solution of [(6R,7R)-7-(benzyloxymethyl)-6-[1-(3-chloro-4-fluoro-phenyl)imidazol-2-yl]-5-[6-methyl-4-(trifluoromethyl)-2-pyridyl]-4-oxo-5-azaspiro[2.4]heptan-7-yl] *tert*-butyl carbonate (100 mg, 0.14 mmol) in DCM (2 mL) was added a solution of BCl₃ (1 M in toluene, 1.43 mL) dropwise at 0°C. The mixture was stirred at rt for 1 h. On completion, the reaction mixture was quenched by sat. aq. NH₄Cl (5 mL) at 0°C, and then extracted with DCM (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (50% EtOAc in PE) and then further purified by prep-HPLC to give the title compound (11 mg, 14%) as a yellow solid.

m/z ES+ [M+H]⁺ 511.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.56 (s, 1H), 7.99 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.48 (t, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 1.6 Hz, 1H), 7.15 (s, 1H), 6.99 (d, *J* = 1.2 Hz, 1H), 5.99 (s, 1H), 3.51 (s, 2H), 2.41 (s, 3H), 1.32 – 1.19 (m, 3H), 1.07 – 0.99 (m, 1H).

Example 55

(S)-5-(1-(3-Chloro-4-fluorophenyl)-1H-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one



Step a. To a solution of 2,2-dimethoxyethanamine (10.0 g, 95.1 mmol) and TEA (8.75 g, 86.5 mmol) in DCM (100 mL) was added allyl carbonochloridate (10.4 g, 86.5 mmol) dropwise at 0°C. The mixture was then stirred at 0°C for 1 h. On completion, the reaction mixture was diluted with water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic layers were washed with saturated NH₄Cl solution (400 mL x 3), dried over Na₂SO₄ and evaporated to afford allyl (2,2-dimethoxyethyl)carbamate (17.0 g, crude) as a colorless liquid which was used in the next step without further purification.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.29 (t, *J* = 5.6 Hz, 1H), 5.93 - 5.86 (m, 1H), 5.25 (dd, *J* = 15.6, 14.0 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.56 (d, *J* = 5.2 Hz, 2H), 4.34 (t, *J* = 5.6 Hz, 1H), 3.25 (s, 6H), 3.07 (t, *J* = 6.0 Hz, 2H).

Step b. To a solution of allyl (2,2-dimethoxyethyl)carbamate (17.0 g, 89.9 mmol) in DMF (200 mL) was added NaH (4.31 g, 108 mmol, 60% dispersion in mineral oil) portionwise at 0°C under N₂ atmosphere. The mixture was then stirred at 0°C for 30 min. Then 3-bromoprop-1-ene (12.0 g, 98.8 mmol) was added dropwise, and the mixture was stirred at 0°C for 1 h. On completion, the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (4 x 600 mL), dried and evaporated to afford allyl allyl(2,2-dimethoxyethyl)carbamate (20.0 g, crude) as a yellow oil which was used in the next step without further purification.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 5.93 - 5.88 (m, 2H), 5.29 - 5.10 (m, 4H), 5.53 (d, *J* = 4.0, 2H), 4.47 (t, *J* = 5.6 Hz, 1H), 3.88 (d, *J* = 4.4 Hz, 2H), 3.28 - 3.25 (m, 8H).

Step c. A solution of allyl allyl(2,2-dimethoxyethyl)carbamate (20.0 g, 87.2 mmol) in formic acid (200 mL) and water (40 mL) was stirred at 15°C for 1 h. On completion, the reaction mixture was concentrated in vacuo. The mixture was diluted with water (60 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2 x 300 mL), dried over Na₂SO₄ and evaporated to give allyl allyl(2-oxoethyl)carbamate (14.7 g, crude) as a yellow liquid which was used in the next step without further purification.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.49 (d, *J* = 10.4 Hz, 1H), 5.91 - 5.78 (m, 2H), 5.27 - 5.12 (m, 4H), 4.54 (t, *J* = 4.4 Hz, 2H), 4.09 - 3.88 (m, 4H).

Step d. To a solution of allyl allyl(2-oxoethyl)carbamate (14.7 g, 80.2 mmol) and (S)-2-methylpropane-2-sulfinamide (11.9 g, 98.3 mmol) in THF (300 mL) was added Ti(OEt)₄ (56.0 g, 245.6 mmol) under N₂ atmosphere. The mixture was then stirred at 10°C for 12 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (60 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 x 300 mL) and brine (2 x 300 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (10-15% EtOAc in PE) to give (S)-allyl allyl(2-((tert-butylsulfinyl)imino)ethyl)carbamate (14.6 g, 64%) as a yellow oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.85 (s, 1H), 5.90 - 5.81 (m, 2H), 5.28 - 5.11 (m, 4H), 4.54 - 4.25 (m, 4H), 3.94 - 3.85 (m, 2H), 1.09 (s, 9H).

Step e. To a solution of 1-(3-chloro-4-fluoro-phenyl)imidazole (2.00 g, 10.2 mmol) in THF (26 mL) was added a solution of LDA (2 M in THF, 7.63 mL) dropwise at -78°C under N₂ atmosphere. The mixture was stirred at -78°C for 0.5 h. Then a solution of (S,E)-allyl allyl(2-((tert-butylsulfinyl)imino)ethyl)carbamate (3.50 g, 12.2 mmol) in THF (26 mL) was added. The mixture was stirred at -78°C for 2 h. On completion, the reaction mixture was slowly quenched with sat. aq. NH₄Cl (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 90 mL), dried over Na₂SO₄ and evaporated. The

residue was purified by prep HPLC to give allyl allyl((2S)-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-(1,1-dimethylethylsulfinamido)ethyl)carbamate (1.50 g, 31%) as a yellow oil.
m/z ES+ [M+H]⁺ 483.1

Step f. A solution of allyl allyl((2S)-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-(1,1-dimethylethylsulfinamido)ethyl)carbamate (1.50 g, 3.11 mmol), 1,3-dimethylbarbituric acid (3.15 g, 20.20 mmol) in MeOH (15 mL) was added Pd(PPh₃)₄ (359 mg, 0.31 mmol) under N₂ atmosphere. Then the mixture was stirred at 70°C for 6 h under N₂ atmosphere. On completion, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (100% EtOAc, then 0-10% MeOH in DCM) and further purified by prep HPLC to give (S)-N-((S)-2-amino-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (800 mg, 72%) as a yellow solid.

m/z ES+ [M+H]⁺ 359.2; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.80 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.38 (s, 1H), 7.04 (s, 1H), 5.46 (d, *J* = 8.4 Hz, 1H), 4.43 - 4.38 (m, 1H), 3.44 (d, *J* = 6.4 Hz, 1H), 3.20 - 3.10 (m, 1H), 0.93 (s, 9H).

Step g. To a solution of (S)-N-((S)-2-amino-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (750 mg, 2.09 mmol) and NaHCO₃ (351 mg, 4.18 mmol) in 1,4-dioxane (8 mL) and water (0.8 mL) was added benzyl chloroformate (357 mg, 2.09 mmol). The mixture was stirred at rt for 1 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na₂SO₄ and evaporated. The crude product was purified by prep HPLC to give benzyl ((S)-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-((S)-1,1-dimethylethylsulfinamido)ethyl)carbamate (700 mg, 68%) as a yellow oil.

m/z ES+ [M+H]⁺ 493.1

Step h. A solution of benzyl ((S)-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-((S)-1,1-dimethylethylsulfinamido)ethyl)carbamate (650 mg, 1.32 mmol) in HCl/dioxane (4 M, 7 mL) was stirred at rt for 1 h. On completion, the reaction mixture was concentrated in vacuo. The residue was diluted with water (15 mL), then adjusted to pH = 8~9 with sat. aq. NaHCO₃ solution, and further extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over Na₂SO₄ and evaporated to give (S)-benzyl (2-amino-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethyl)carbamate (550 mg, crude) as a yellow oil which was used in the next step without further purification.

m/z ES+ [M+H]⁺ 389.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.86 (d, *J* = 6.0 Hz, 1H), 7.58 - 7.56 (m, 2H), 7.34 - 7.29 (m, 6H), 7.00 (s, 1H), 4.94 (s, 2H), 3.81 (t, *J* = 6.8 Hz, 1H), 3.31 - 3.26 (m, 2H).

Step i. To a solution of (S)-benzyl (2-amino-2-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)ethyl)carbamate (550 mg, 1.41 mmol) in DCM (9 mL) was added CDI (275 mg, 1.70 mmol). The mixture was stirred at rt for 1 h. On completion, the reaction mixture was diluted with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (2 x 60 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (100% EtOAc, then 0-2% MeOH in DCM), further purified by prep HPLC, and finally by prep-TLC (10% MeOH in DCM) to give (S)-benzyl 4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 37%) as a yellow oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.99 (s, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.34 - 7.29 (m, 6H), 7.00 (s, 1H), 4.94 (s, 2H), 3.81 (t, *J* = 6.8 Hz, 1H), 3.31 - 3.26 (m, 2H).

Step j. To a solution of (S)-benzyl 4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 0.31 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (105 mg, 0.44 mmol), K₂CO₃ (87 mg, 0.63 mmol) and XantPhos (36 mg, 0.063 mmol) in 1,4-dioxane (2 mL) was added Pd₂(dba)₃ (29 mg, 0.031 mmol) under N₂. The mixture was stirred at 80°C for 1 h under N₂ atmosphere. On completion, the reaction mixture was evaporated, diluted with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (25-35% EtOAc in PE) and then further purified by prep HPLC to give (S)-benzyl 4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 72%) as a yellow oil.

¹H NMR (400 MHz, CD₃OD) δ ppm 8.32 (s, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 7.47 - 7.35 (m, 7H), 7.23 (s, 1H), 7.16 (s, 1H), 6.99 (s, 1H), 5.80 - 5.76 (m, 1H), 5.30 (d, *J* = 2.8 Hz, 1H), 4.27 (t, *J* = 10.0 Hz, 1H), 3.98 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.49 - 3.10 (m, 1H), 2.37 (s, 3H).

Step k. To a solution of (S)-benzyl 4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 0.23 mmol) in DCM (5 mL) was added TFA (7.70 g, 67.5 mmol). The mixture was stirred at 40°C for 4 h. On completion, the reaction mixture was diluted with water (8 mL), adjusted to pH = 8-9 with sat. aq. NaHCO₃ and extracted with DCM (3 x 8 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over Na₂SO₄ and evaporated. A 40 mg sample of crude product was purified by prep-HPLC to give the title compound (27 mg, 67%) as an off-white solid.

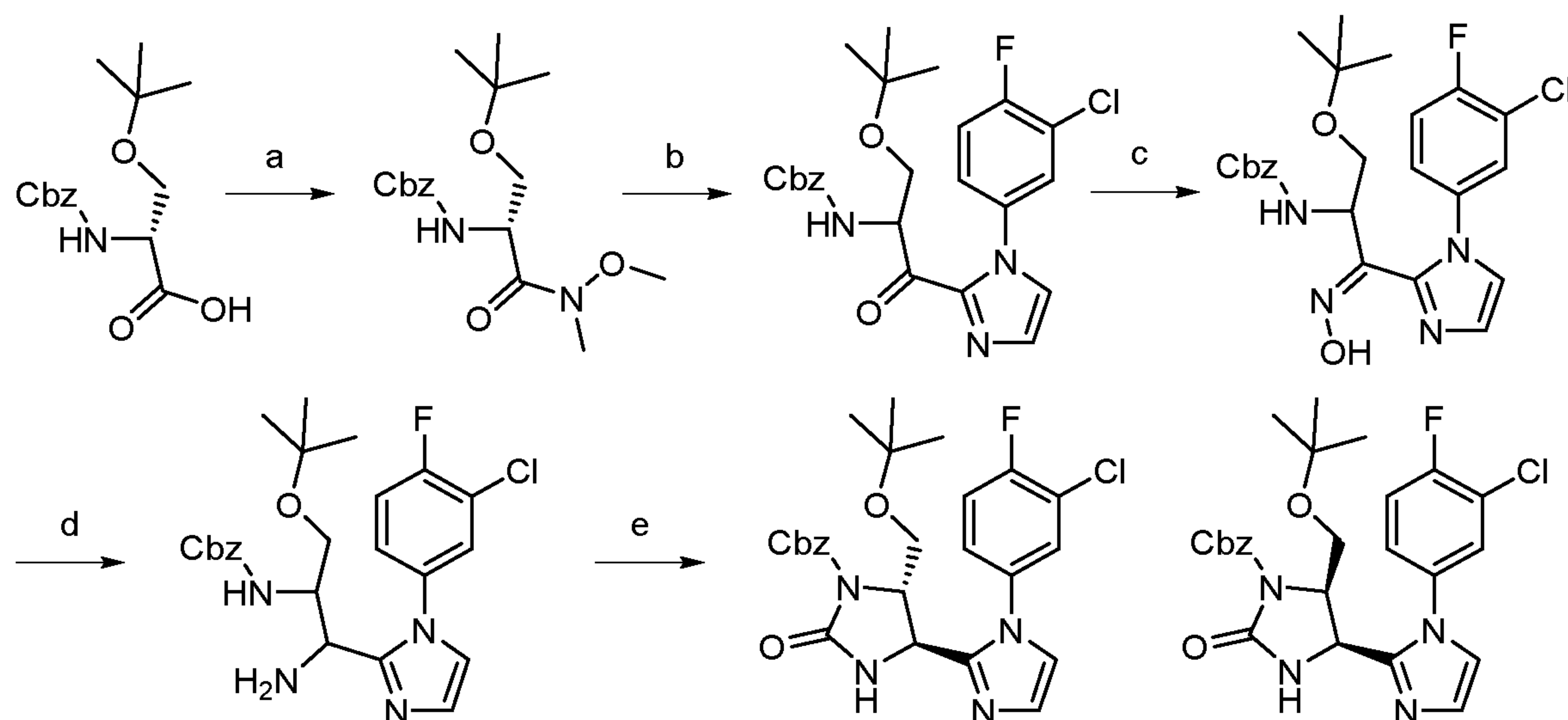
m/z ES+ [M+H]⁺ 440.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.28 (s, 1H), 7.92 – 7.89 (m, 1H), 7.83 (s, 1H), 7.77 – 7.72 (m, 2H), 7.68 – 7.63 (m, 1H), 7.50 (br s, 1H), 7.19 (s, 1H), 5.70 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.81 (t, *J* = 10.0 Hz, 1H), 3.71 – 3.56 (m, 1H), 2.29 (s, 3H).

5 Intermediate 1

Rel-Benzyl (4S,5S)-5-(tert-butoxymethyl)-4-(1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-2-oxoimidazolidine-1-carboxylate

Intermediate 2

10 **Rel-Benzyl (4S,5R)-5-(tert-butoxymethyl)-4-(1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-2-oxoimidazolidine-1-carboxylate**



Step a. A mixture of (R)-2-(((benzyloxy)carbonyl)amino)-3-(tert-butoxy)propanoic acid (7.0 g, 23.7 mmol), N,O-dimethylhydroxylamine hydrochloride (2.5 g, 26.1 mmol), HATU (10.8 g, 28.4 mmol), DIPEA (9.2 g, 71.0 mmol) in DCM (150 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at rt for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was diluted with DCM/water (150/150 mL) and then separated. The organic layers were washed with brine (100 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (10-20% EtOAc in PE) to give (R)-benzyl (3-(tert-butoxy)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (7.2 g, 90%) as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.41 – 7.26 (m, 5H), 5.08 – 4.95 (m, 2H), 4.64 (s, 1H), 3.73 (s, 3H), 3.52 – 3.45 (m, 1H), 3.40 (d, *J* = 7.2 Hz, 1H), 3.36 – 3.35 (m, 1H), 3.12 (s, 3H), 1.10 (s, 9H).

25 **Step b.** To a solution of 1-(3-chloro-4-fluoro-phenyl)imidazole (2.0 g, 10.20 mmol) in THF (20 mL) was added a solution of LDA (2 M in THF, 13.2 mmol) at -70°C under N₂ atmosphere. The mixture was stirred at -70°C for 30 min. Then (R)-benzyl (3-(tert-butoxy)-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (3.61 g, 10.7 mmol) in THF (10 mL)

was added dropwise into the reaction. The mixture was stirred at -70°C for 2 h. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl solution (20 mL) at -70°C, then diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and evaporated. The residue was purified by reverse-phase column chromatography to give benzyl (3-(*tert*-butoxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-1-oxopropan-2-yl)carbamate (1.3 g, 26%) as a colourless oil.

m/z ES+ [M+H]⁺ 474.1

Step c. A mixture of benzyl (3-(*tert*-butoxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-1-oxopropan-2-yl)carbamate (1.2 g, 2.50 mmol), hydroxylamine hydrochloride (1.2 g, 17.70 mmol) in pyridine (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 60°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC to give benzyl (3-(*tert*-butoxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-1-(hydroxyimino)propan-2-yl)carbamate (1.0 g, 80%) as an off-white solid.

m/z ES+ [M+H]⁺ 489.2

Step d. A mixture of benzyl (3-(*tert*-butoxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-1-(hydroxyimino)propan-2-yl)carbamate (2.0 g, 4.10 mmol), NaBH₄ (1.6 g, 40.90 mmol), NiCl₂·6H₂O (972 mg, 4.1 mmol) in MeOH (20 mL) and EtOH (20 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 16°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was diluted with EtOAc (300 mL) and water (10 mL), then filtered and evaporated. The residue was purified by prep-HPLC to give benzyl (1-amino-3-(*tert*-butoxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (750 mg, 39%) as a yellow oil.

m/z ES+ [M+H]⁺ 475.2

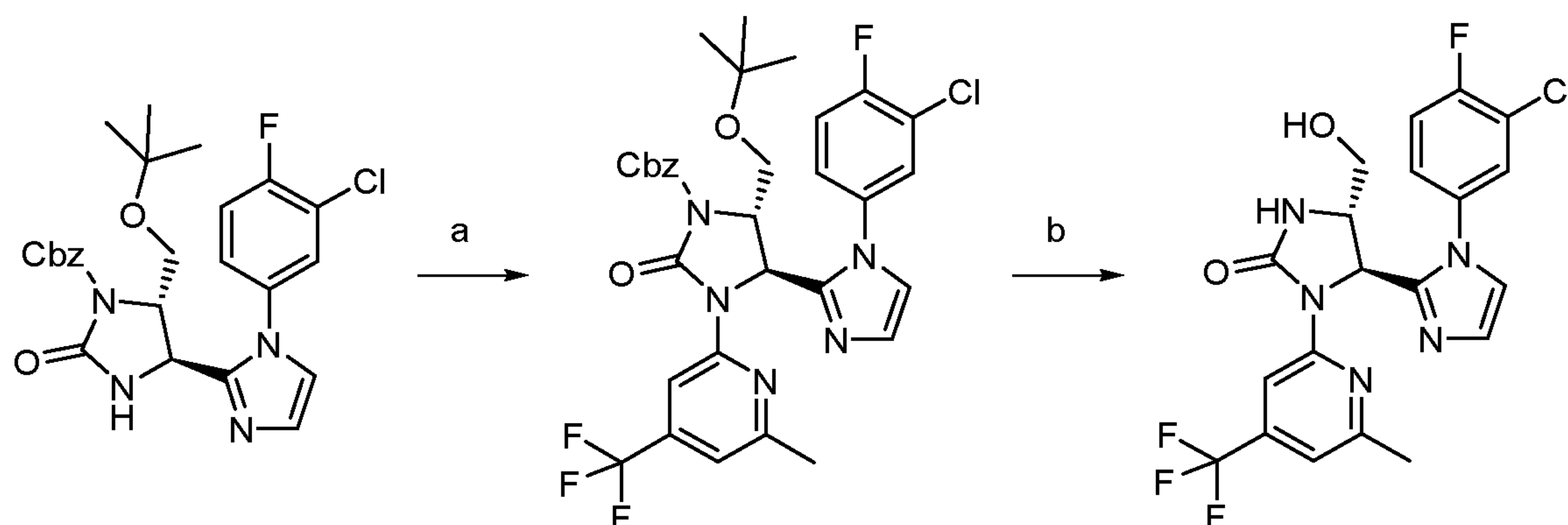
Step e. A mixture of benzyl (1-amino-3-(*tert*-butoxy)-1-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)propan-2-yl)carbamate (300 mg, 0.63 mmol), CDI (123 mg, 0.76 mmol) in DCM (5 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at rt for 4 h under N₂ atmosphere. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC to give **Intermediate 1** (130 mg, 41%) as a white solid, m/z ES+ [M+H]⁺ 501.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.00 (s, 1H), 7.83 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.55 – 7.50 (m, 1H), 7.44 – 7.33 (m, 6H), 7.08 (s, 1H), 5.28 – 5.11 (m, 2H), 4.38 (s, 1H), 4.32 – 4.24 (m, 1H), 3.47 – 3.40 (m, 1H), 3.37 (d, *J* = 7.6 Hz, 1H), 0.92 (s, 9H).

and **Intermediate 2** (60 mg, 18% yield) as a white solid.

m/z ES+ [M+H]⁺ 501.1; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.83 (d, *J* = 4.0 Hz, 2H), 7.72 – 7.60 (m, 1H), 7.58 – 7.48 (m, 1H), 7.47 – 7.28 (m, 6H), 7.10 (s, 1H), 5.21 (dd, *J* = 8.0, 12.4 Hz, 2H), 4.85 (d, *J* = 8.4 Hz, 1H), 4.43 – 4.28 (m, 1H), 3.67 – 3.46 (m, 2H), 0.83 (s, 9H).

5 Example 56

(4S,5S)-5-(1-(3-Chloro-4-fluorophenyl)-1H-imidazol-2-yl)-4-(hydroxymethyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one



Step a. A mixture of **Intermediate 1** (110 mg, 0.22 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (79 mg, 0.33 mmol), Pd₂(dba)₃ (20 mg, 0.02 mmol), XantPhos (25 mg, 0.044 mmol) and K₂CO₃ (60 mg, 0.44 mmol) in dioxane (1 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100°C for 2 h under N₂ atmosphere. Upon completion, the reaction mixture was filtered and evaporated and the residue was purified by prep-TLC (33% EtOAc in PE) to give *trans*-benzyl 5-(*tert*-butoxymethyl)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (110 mg, 76 %) as an off-white solid.

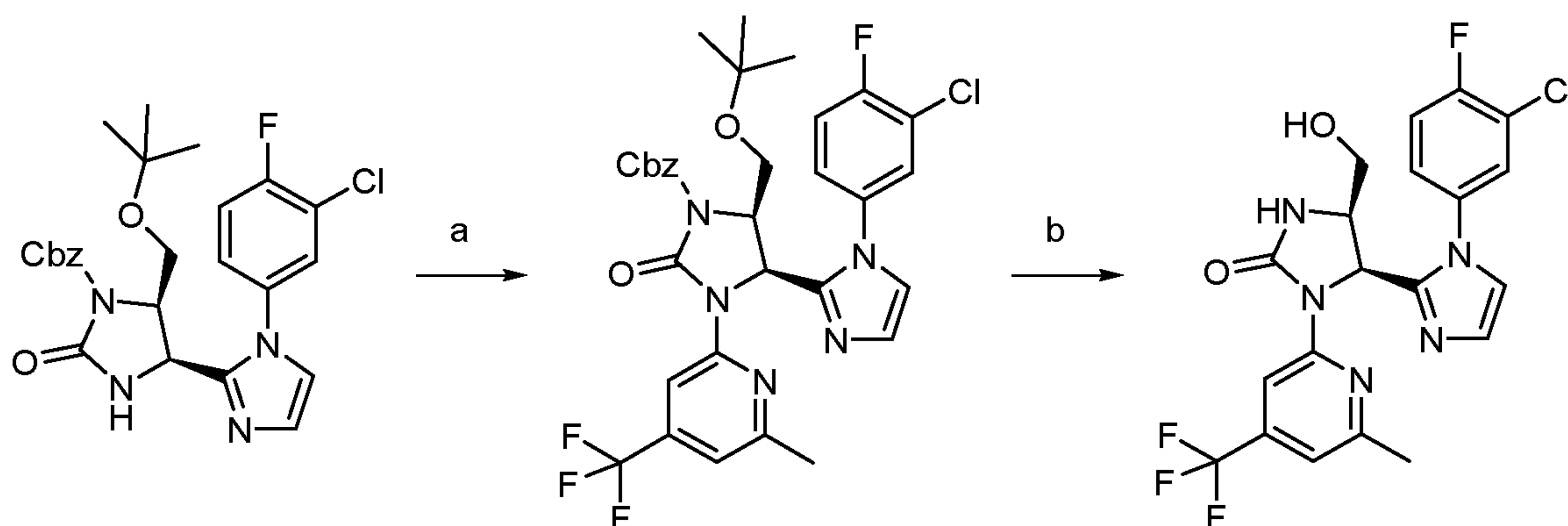
m/z ES+ [M+H]⁺ 660.3

Step b. A suspension of *trans*-benzyl 5-(*tert*-butoxymethyl)-4-(1-(3-chloro-4-fluorophenyl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (110 mg, 0.17 mmol) in DCM (5 mL) and TFA (5 mL) was stirred at 40°C for 6 h. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC. The desired enantiomer was isolated by further purification using prep chiral SFC to give the title compound (28 mg, 47%) as a yellow solid.

m/z ES+ [M+H]⁺ 470.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.32 (s, 1H), 7.83 (dd, *J* = 2.8, 6.4 Hz, 1H), 7.62 (td, *J* = 3.6, 8.0 Hz, 1H), 7.52 – 7.42 (m, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 6.0 Hz, 2H), 5.70 (d, *J* = 3.6 Hz, 1H), 3.76 (dd, *J* = 4.4, 8.4 Hz, 1H), 3.52 (d, *J* = 4.8 Hz, 2H), 2.39 (s, 3H).

Example 57

(4R,5S)-5-(1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-4-(hydroxymethyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one

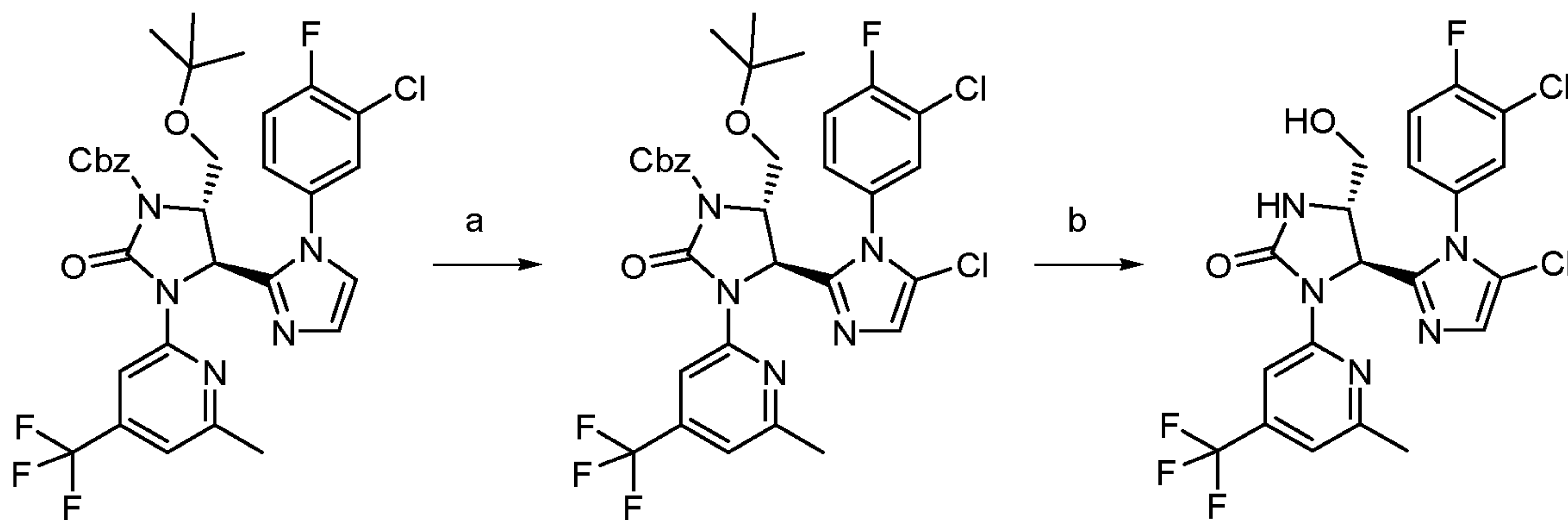


- 5 The title compound was prepared in a similar manner to **Example 56**, using **Intermediate 2** in step a.

m/z ES⁺ [M+H]⁺ 470.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.37 (s, 1H), 8.04 (d, *J* = 5.6 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.8 Hz, 1H), 7.28 (s, 1H), 7.05 (d, *J* = 6.4 Hz, 2H), 5.93 (d, *J* = 9.6 Hz, 1H), 4.18 – 4.07 (m, 1H), 3.55 – 3.47 (m, 1H), 3.46 – 3.38 (m, 1H), 2.38 (s, 3H).

Example 58

Rel-(4S,5S)-5-(5-Chloro-1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-4-(hydroxymethyl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one



Step a. A mixture of *trans*-benzyl 5-(tert-butoxymethyl)-4-(1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (45 mg, 0.068 mmol), N-chlorosuccinimide (9.1 mg, 0.068 mmol), acetic acid (4 mg, 0.067 mmol) in DMF (1 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 60°C for 12 h under N₂. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC to give *trans*-benzyl 5-(tert-butoxymethyl)-4-(5-chloro-1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (40 mg, 77%) as a yellow solid.

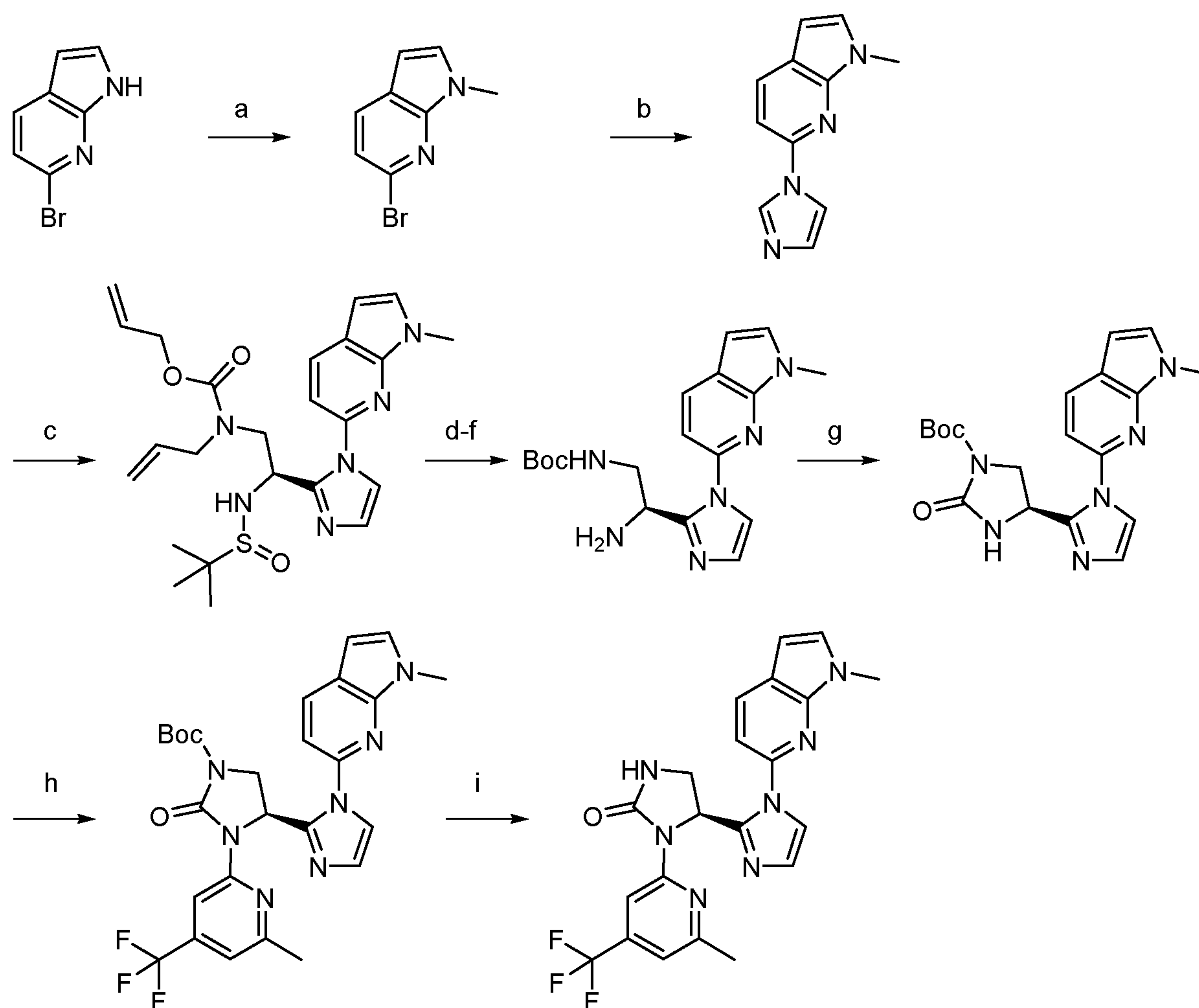
m/z ES+ [M+H]⁺ 694.2

Step b. A solution of *trans*-benzyl 5-(tert-butoxymethyl)-4-(5-chloro-1-(3-chloro-4-fluorophenyl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (34 mg, 0.049 mmol) in TFA (0.5 mL) and DCM (0.5 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 40°C for 4 h under N₂. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC to give the title compound (5 mg, 17%) as a pink solid.

m/z ES+ [M+H]⁺ 504.1; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.36 – 8.24 (m, 1H), 8.05 – 7.65 (m, 1H), 7.60 – 7.41 (m, 1H), 7.35 – 7.25 (m, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 5.53 (d, *J* = 9.2 Hz, 1H), 3.81 – 3.69 (m, 1H), 3.56 – 3.43 (m, 2H), 2.51 – 2.40 (m, 3H).

Example 59

(S)-5-(1-(1-Methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one



Step a. To a solution of 6-bromo-1H-pyrrolo[2,3-b]pyridine (2.40 g, 12.2 mmol) in THF (30 mL) was added NaH (585 mg, 14.6 mmol, 60% dispersion in mineral oil) portionwise at 0°C.

The mixture was stirred at 0°C for 30 min. Iodomethane (2.07 g, 14.6 mmol) was added slowly to the reaction and the mixture was stirred at 0°C for 2 h. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (6-10% EtOAc in PE) to give 6-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.47 g, 96%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 211.0

Step b. A mixture of 6-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2.40 g, 11.4 mmol), imidazole (1.70 g, 25.0 mmol), CuI (1.08 g, 5.7 mmol), Cs₂CO₃ (11.1 g, 34.1 mmol) and L-proline (1.31 g, 11.4 mmol) in DMSO (30 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 120°C for 12 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched by aq. ammonium hydroxide solution (5 mL), then diluted with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over Na₂SO₄ and evaporated. The residue was purified by reverse-phase column chromatography to give 6-(1*H*-imidazol-1-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.87 g, 83%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 199.7; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.59 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 7.53 (d, *J* = 3.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.14 (s, 1H), 6.52 (d, *J* = 3.6 Hz, 1H), 3.84 (s, 3H).

Step c. To a solution of 6-(1*H*-imidazol-1-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.84 g, 4.24 mmol) in THF (10 mL) was added a solution of LDA (2 M in THF, 5.08 mmol) dropwise at -78°C and the mixture was stirred at -78°C for 30 min. Then (R)-allyl allyl(2-((*tert*-butylsulfinyl)imino)ethyl)carbamate (prepared in a similar manner to **Example 55**, steps a-d; 1.82 g, 6.36 mmol) in THF (3 mL) was added slowly into the reaction and the mixture was stirred at -78°C for 11.5 h. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and evaporated. The residue was purified by reverse-phase column chromatography to give allyl allyl((2*S*)-2-(1,1-dimethylethylsulfinamido)-2-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (1.1 g, 54%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 485.3

Step d. A mixture of allyl allyl((2*S*)-2-(1,1-dimethylethylsulfinamido)-2-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (1.1 g, 2.27 mmol), 1,3-dimethylbarbituric acid (2.3 g, 14.76 mmol), Pd(PPh₃)₄ (262 mg, 0.23 mmol) in MeOH (20 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 70°C for 5 h under N₂. Upon completion, the reaction mixture was filtered and evaporated and the

residue was purified by column chromatography (0-50% EtOAc in PE) to give (R)-N-((S)-2-amino-1-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfonamide (0.7 g, 86%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 361.2

- 5 **Step e.** To a solution of (R)-N-((S)-2-amino-1-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfonamide (0.7 g, 1.94 mmol) in MeCN (20 mL) was added di-*tert*-butyl dicarbonate (1.27 g, 5.83 mmol) and TEA (590 mg, 5.83 mmol). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was evaporated and the residue was purified by reverse-phase column chromatography to give *tert*-butyl ((S)-2-
10 ((R)-1,1-dimethylethylsulfonamido)-2-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (800 mg, 89%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 461.2

- Step f.** To a solution of *tert*-butyl ((S)-2-((R)-1,1-dimethylethylsulfonamido)-2-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (0.8 g, 1.74 mmol) in MeOH
15 (20 mL) was added HCl/dioxane (4 M, 3.48 mmol). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was quenched with aq. NaOH solution (4 M, 1 mL), and evaporated to give (S)-*tert*-butyl (2-amino-2-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (0.5 g, 81%) as a yellow solid which was used without further purification.

- 20 *m/z* ES⁺ [M+H]⁺ 357.1

- Step g.** To a solution of (S)-*tert*-butyl (2-amino-2-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (0.5 g, 1.40 mmol) in DCM (20 mL) was added CDI (273 mg, 1.68 mmol). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was evaporated and the residue was purified by prep-HPLC to give (S)-*tert*-butyl 4-(1-(1-
25 methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 24%) as a yellow solid.

- m/z* ES⁺ [M+H]⁺ 383.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.18 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 1.2 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 1.2 Hz, 1H), 6.57 (d, *J* = 3.6 Hz, 1H), 5.18 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.85 (s, 3H),
30 3.30 – 3.25 (m, 2H), 1.43 (s, 9H).

- Step h.** A mixture of (S)-*tert*-butyl 4-(1-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 0.34 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (122 mg, 0.51 mmol), Pd₂(dba)₃ (31 mg, 0.034 mmol), XantPhos (39 mg, 0.07 mmol) and K₂CO₃ (141 mg, 1.02 mmol) in 1,4-dioxane (3 mL) was degassed and
35 purged with N₂ 3 times, and then the mixture was stirred at 100°C for 2 h under N₂. Upon completion, the reaction mixture was filtered and evaporated and the residue was purified by column chromatography (20-50% EtOAc in PE) to give (S)-*tert*-butyl 4-(1-(1-methyl-1*H*-

pyrrolo[2,3-b]pyridin-6-yl)-1*H*-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 71%) as a yellow solid.

m/z ES+ $[M+H]^+$ 542.3

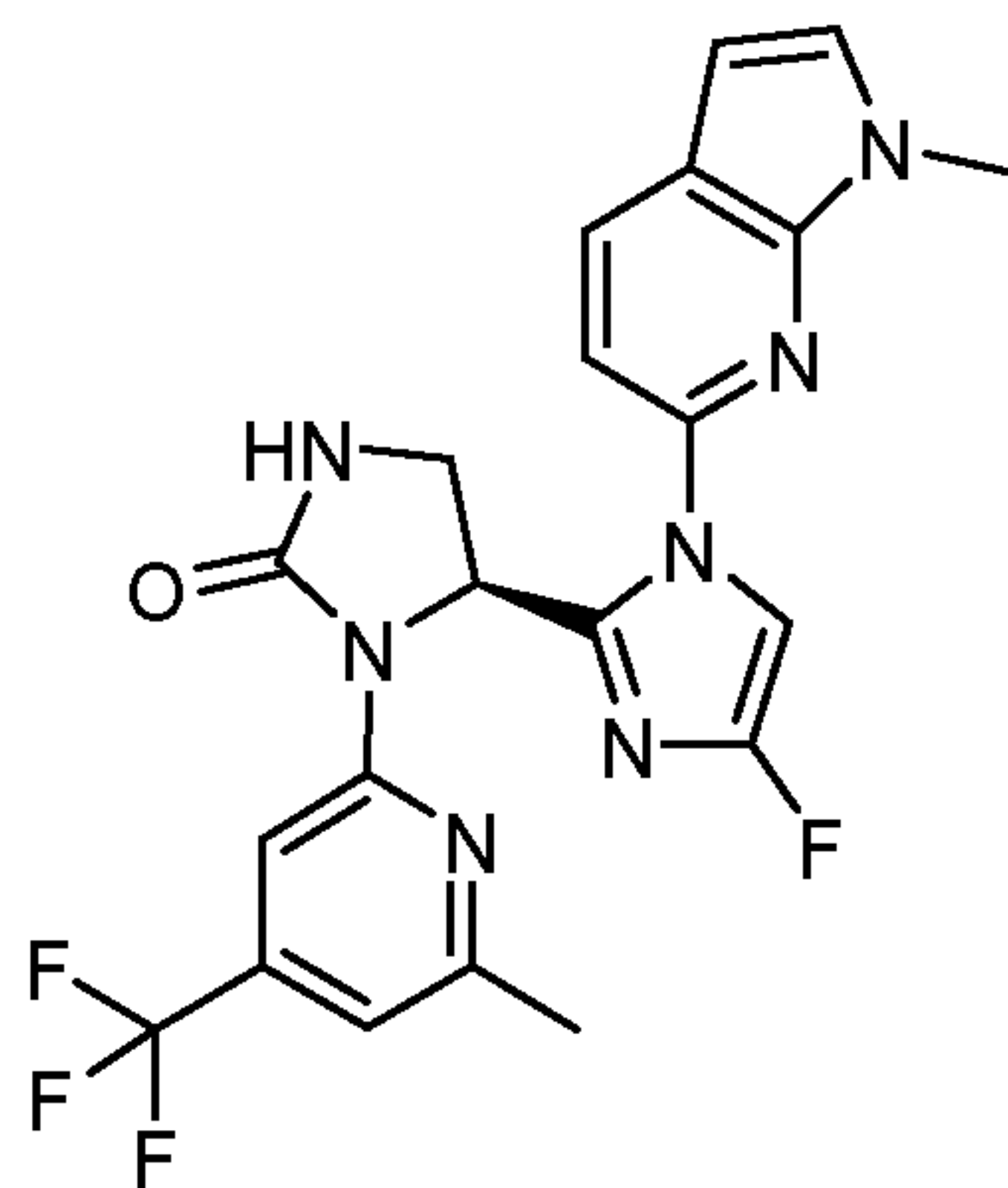
Step i. To a solution of (S)-*tert*-butyl 4-(1-(1-methyl-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1*H*-

imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxoimidazolidine-1-carboxylate (130 mg, 0.24 mmol) in DCM (5 mL) was added TFA (2.74 g, 24.0 mmol) and the mixture was stirred at rt for 30 min. Upon completion, the reaction mixture was quenched with sat. aq. NaHCO₃ (20 mL), diluted with water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and concentrated in vacuo. The obtained residue was purified by prep-HPLC to give the title compound (100 mg, 94%) as a white solid.

m/z ES+ $[M+H]^+$ 442.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.32 – 8.23 (m, 2H), 7.95 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 3.2 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.45 (dd, J = 8.4, 2.4 Hz, 1H), 7.03 (s, 1H), 6.67 (dd, J = 3.2, 2.0 Hz, 1H), 6.34 – 6.22 (m, 1H), 4.34 (t, J = 10.0 Hz, 1H), 4.01 (dd, J = 10.0, 5.6 Hz, 1H), 3.94 (s, 3H), 2.19 (s, 3H).

Example 60

(S)-5-(4-Fluoro-1-(1-methyl-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1*H*-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one



The title compound was prepared in a similar manner to **Example 59**, using 5-fluoro-1*H*-imidazole (CAS Number 30086-17-0) in **step b**.

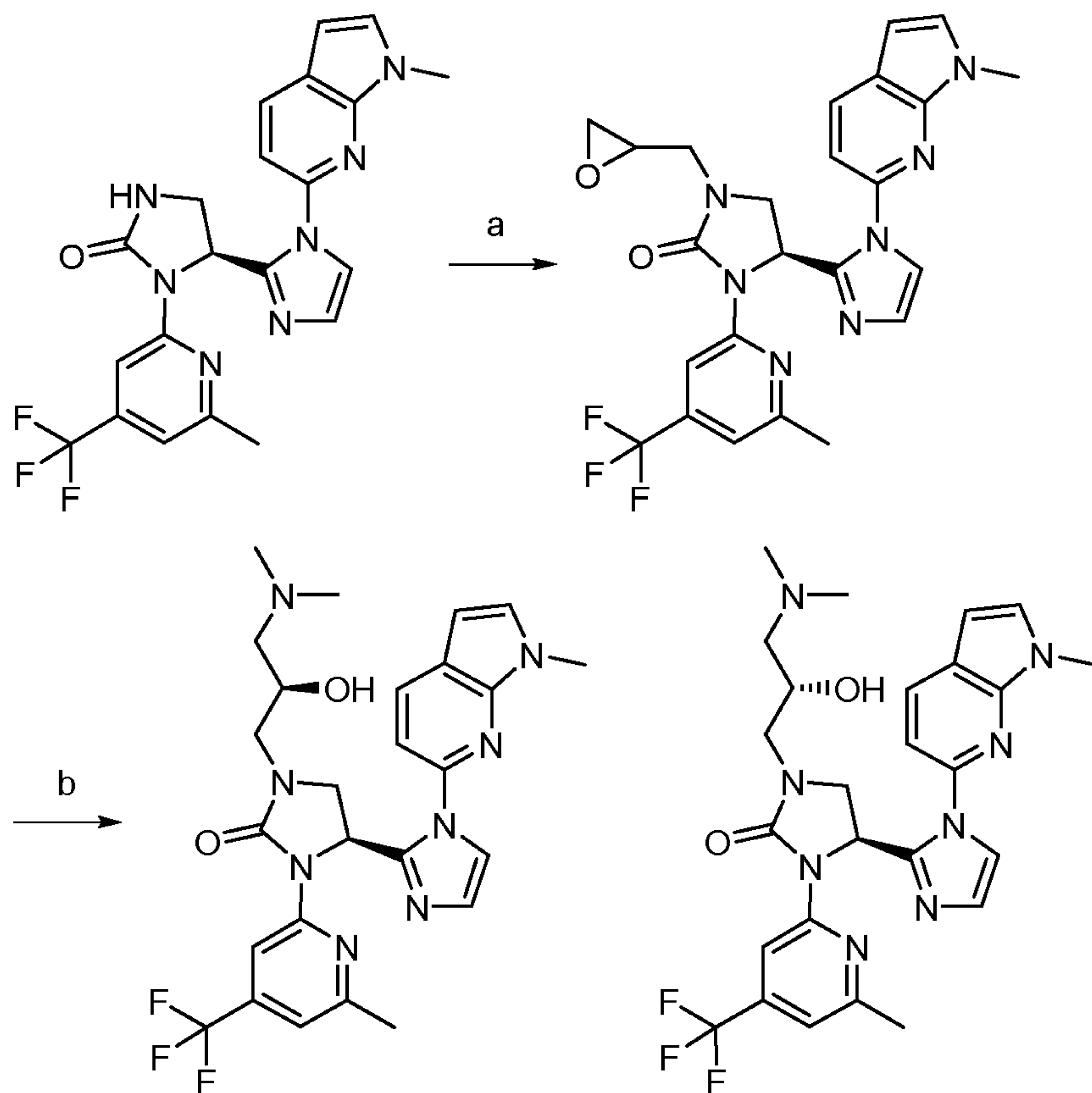
m/z ES+ $[M+H]^+$ 460.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.20 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.60 (d, J = 3.6 Hz, 1H), 6.19 (dt, J = 5.6, 4.8 Hz, 1H), 4.21 (t, J = 9.6 Hz, 1H), 3.92 (s, 3H), 3.83 (dd, J = 9.2, 5.2 Hz, 1H), 2.16 (s, 3H).

Example 61

(S)-1-((R)-3-(Dimethylamino)-2-hydroxypropyl)-4-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one

Example 62

- 5 **(S)-1-((S)-3-(Dimethylamino)-2-hydroxypropyl)-4-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one**



- Step a.** To a solution of (S)-5-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one (200 mg, 0.45 mmol), 2-(bromomethyl)oxirane (93 mg, 0.68 mmol) in DMF (3 mL) was added Cs₂CO₃ (443 mg, 1.36 mmol). The mixture was stirred at 80°C for 1 h. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl solution (30 mL), and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (25-50% EtOAc in PE) to give (4S)-4-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1-(oxiran-2-ylmethyl)imidazolidin-2-one (140 mg, 62%) as a yellow solid.

m/z ES+ [M+H]⁺ 498.1

- 20 **Step b.** To a solution of (4S)-4-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1-(oxiran-2-ylmethyl)imidazolidin-2-one (140 mg, 0.28 mmol) in MeOH (3 mL) was added a solution of dimethylamine (2 M in THF, 16.9

mmol). The mixture was stirred at rt for 12 h. Upon completion, the reaction mixture was filtered and evaporated and the residue was purified by prep-HPLC and the stereoisomers were isolated by further purification using prep chiral SFC to give **Example 61** (22 mg, 27%) as a yellow solid,

5 m/z ES+ [M+H]⁺ 543.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.29 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.48 (d, *J* = 3.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 1.2 Hz, 1H), 6.93 (s, 1H), 6.61 (d, *J* = 3.6 Hz, 1H), 6.20 (dd, *J* = 9.6, 4.8 Hz, 1H), 4.37 (t, *J* = 9.6 Hz, 1H), 4.19 (s, 1H), 3.96 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.93 (s, 3H), 3.56 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.34 (d, *J* = 6.8 Hz, 1H), 2.91 – 2.73 (m, 2H), 2.61 (s, 3H), 2.59 (s, 3H), 2.11 (s, 3H).

and **Example 62** (46 mg, 57%) as a yellow oil.

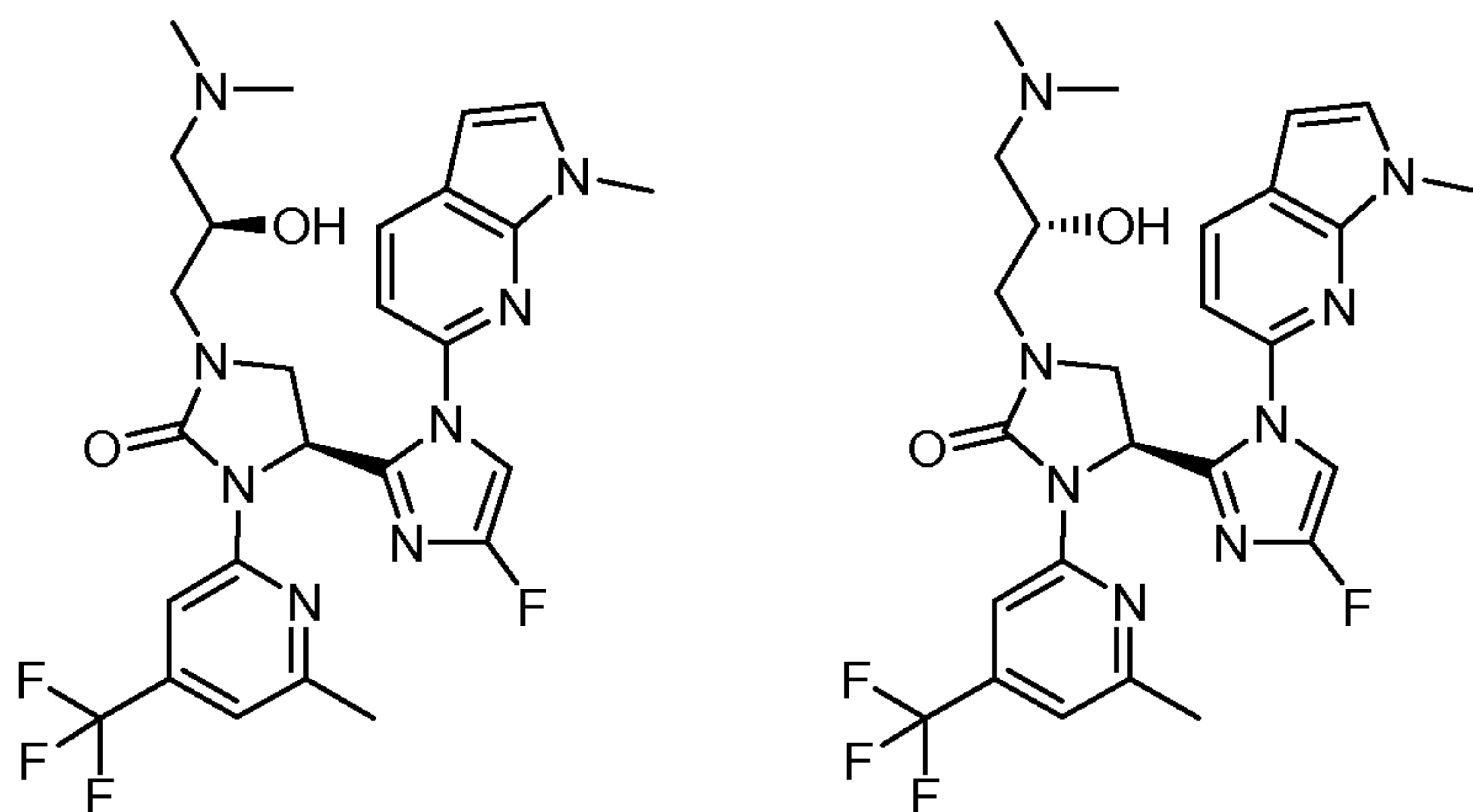
m/z ES+ [M+H]⁺ 543.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.33 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.52 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.19 (s, 1H), 6.97 (s, 1H), 6.63 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.24 (dd, *J* = 10.0, 4.4 Hz, 1H), 4.41 – 4.25 (m, 2H), 4.12 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.93 (s, 3H), 3.72 – 3.56 (m, 1H), 3.40 – 3.25 (m, 3H), 2.95 (s, 6H), 2.12 (s, 3H).

Example 63

20 **(S)-1-((R)-3-(Dimethylamino)-2-hydroxypropyl)-4-(4-fluoro-1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one**

Example 64

25 **(S)-1-((S)-3-(Dimethylamino)-2-hydroxypropyl)-4-(4-fluoro-1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one**



The title compounds were prepared in a similar manner to **Examples 61/62**, using **Example 60** in step a.

Example 63

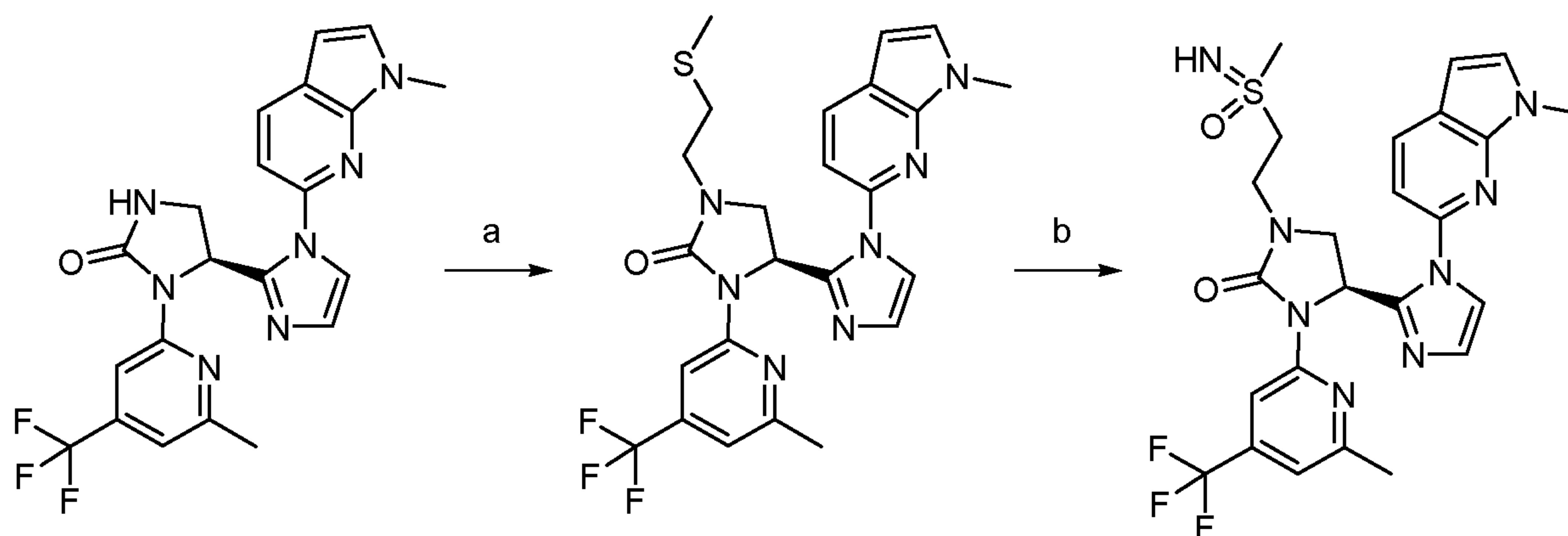
m/z ES+ [M+H]⁺ 561.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.29 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 6.22 – 6.17 (m, 1H), 4.28 – 4.40 (m, 2H), 3.98 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.93 (s, 3H), 3.62 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.46 – 3.35 (m, 2H), 3.29 – 3.21 (m, 1H),
 5 2.98 (s, 3H), 2.93 (s, 3H), 2.13 (s, 3H).

Example 64

m/z ES+ [M+H]⁺ 561.2; ¹H NMR (400 MHz, CD₃OD) δ ppm 8.31 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 6.23 – 6.17 (m, 1H), 4.35 – 4.30 (m, 1H), 4.27 (t, *J* = 9.6 Hz, 1H),
 10 4.14 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.92 (s, 3H), 3.77 (dd, *J* = 14.8, 4.8 Hz, 1H), 3.49 (dd, *J* = 12.8, 11.2 Hz, 1H), 3.29 – 3.23 (m, 2H), 2.98 (s, 3H), 2.92 (s, 3H), 2.12 (s, 3H).

Example 65

(4S)-4-(1-(1-Methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1-(2-(S-methylsulfonimidoyl)ethyl)imidazolidin-2-one
 15



Step a. To a solution of (S)-5-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one (130 mg, 0.30 mmol), KI (147 mg, 0.88 mmol) in DMF (3 mL) was added (2-chloroethyl)(methyl)sulfane (163 mg, 1.47 mmol) and Cs₂CO₃ (288 mg, 0.88 mmol). The mixture was stirred at 60°C for 12 h. Upon
 20 completion, the reaction mixture was quenched by sat. aq. NH₄Cl solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and evaporated. The residue was purified by prep-TLC (50% EtOAc in PE) to give (S)-4-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1-(2-(methylthio)ethyl)imidazolidin-2-one (30 mg, 20%)
 25 as a yellow solid.

m/z ES+ [M+H]⁺ 516.3

Step b. To a solution of (S)-4-(1-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)-3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1-(2-(methylthio)ethyl)imidazolidin-2-one (30 mg,

0.06 mmol) in MeOH (3 mL) was added $\text{NH}_2\text{COONH}_4$ (11 mg, 0.15 mmol) and $\text{PhI}(\text{OAc})_2$ (47 mg, 0.15 mmol). The mixture was stirred at -10°C for 1 h. Upon completion, the reaction mixture was filtered and evaporated. The crude residue was purified by prep-HPLC to give the title compound (1 mg, 4%) as a brown gum.

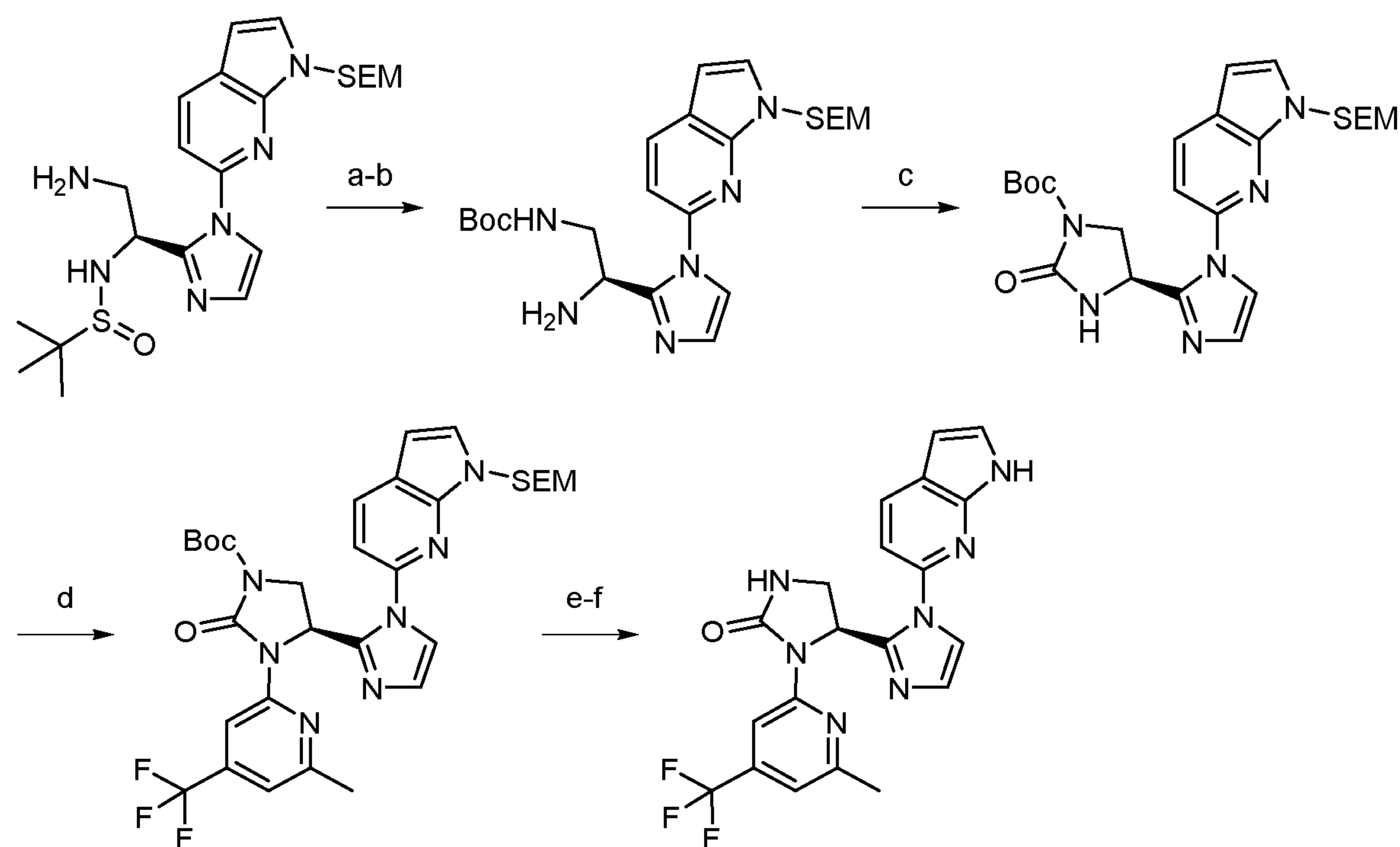
- 5 m/z ES+ $[\text{M}+\text{H}]^+$ 547.2; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.38 (s, 1H), 8.34 (d, $J = 8.4$ Hz, 1H), 8.03 (d, $J = 7.2$ Hz, 1H), 7.61 (dd, $J = 3.6, 1.2$ Hz, 1H), 7.60 – 7.53 (m, 2H), 7.09 (d, $J = 4.0$ Hz, 1H), 6.70 (d, $J = 2.8$ Hz, 1H), 6.29 (td, $J = 10.0, 4.8$ Hz, 1H), 4.80 – 4.75 (m, 1H), 4.51 – 4.37 (m, 1H), 4.17 – 4.04 (m, 2H), 4.04 – 3.99 (m, 2H), 3.97 (s, 3H), 3.53 (t, $J = 4.4$ Hz, 3H), 2.19 (d, $J = 6.4$ Hz, 3H).

10

Example 66

(S)-5-(1-(3-Chloro-4-fluorophenyl)-1H-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one

15



20

Step a. To a solution of N-((S)-2-amino-1-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-yl)-1H-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (prepared in a similar manner to **Example 55**, steps a-f, using 6-(1H-imidazol-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (**Example 50**, steps a-b) in step e; 800 mg, 1.68 mmol) in MeCN (10 mL) was added di-*tert*-butyl dicarbonate (1.10 g, 5.03 mmol) and TEA (510 mg, 5.03 mmol). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by reverse-phase flash column to give *tert*-butyl ((2S)-2-(1,1-dimethylethylsulfinamido)-2-(1-(1-((2-

(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (950 mg, 98%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 577.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.19 – 8.14 (m, 1H), 7.76 – 7.71 (m, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.08 – 6.99 (m, 1H), 6.71 – 6.56 (m, 2H), 5.72 – 5.59 (m, 2H), 5.39 – 5.21 (m, 2H), 3.76 – 3.67 (m, 1H), 3.64 – 3.48 (m, 3H), 1.36 (s, 9H), 1.00 (s, 1H), 0.92 – 0.83 (m, 1H), 0.72 (s, 9H), -0.12 (s, 9H).

Step b. To a solution of *tert*-butyl ((2*S*)-2-(1,1-dimethylethylsulfonamido)-2-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (920 mg, 1.59 mmol) in MeOH (15 mL) was added HCl/dioxane (4 M, 1.0 mL). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was quenched by aq. NaOH solution (20 wt%, 1 mL), and then dried over Na₂SO₄, filtered and evaporated to give (S)-*tert*-butyl (2-amino-2-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (750 mg, crude) as a yellow solid, which was used without further purification.

m/z ES⁺ [M+H]⁺ 473.2

Step c. To a solution of (S)-*tert*-butyl (2-amino-2-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)ethyl)carbamate (730 mg, 1.54 mmol) in DCM (15 mL) was added CDI (301 mg, 1.85 mmol). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by reverse-phase flash column to give (S)-*tert*-butyl 2-oxo-4-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)imidazolidine-1-carboxylate (440 mg, 57%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 499.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.23 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 7.76 – 7.72 (m, 1H), 7.68 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 1.2 Hz, 1H), 6.67 – 6.61 (m, 1H), 5.76 – 5.66 (m, 1H), 5.61 – 5.56 (m, 1H), 5.20 (dd, *J* = 9.2, 4.4 Hz, 1H), 4.19 (t, *J* = 10.0 Hz, 1H), 4.04 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.52 (t, *J* = 8.0 Hz, 2H), 1.44 (s, 9H), 0.86 – 0.76 (m, 2H), -0.12 (s, 9H).

Step d. A mixture of (S)-*tert*-butyl 2-oxo-4-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1*H*-imidazol-2-yl)imidazolidine-1-carboxylate (430 mg, 0.86 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (290 mg, 1.21 mmol), K₂CO₃ (358 mg, 2.59 mmol), XantPhos (100 mg, 0.17 mmol) and Pd₂(dba)₃ (79 mg, 0.086 mmol) in 1,4-dioxane (6 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100°C for 2 h under N₂ atmosphere. Upon completion, the reaction mixture was quenched with sat. aq. NH₄Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (15-20% EtOAc in PE) to give (S)-*tert*-butyl 3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxo-4-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-

pyrrolo[2,3-b]pyridin-6-yl)-1*H*-imidazol-2-yl)imidazolidine-1-carboxylate (500 mg, 88%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 658.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.29 (d, *J* = 8.0 Hz, 1H), 8.25 (s, 1H), 7.76 (d, *J* = 3.6 Hz, 1H), 7.66 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.18 (s, 1H), 6.91 (s, 1H), 6.67 (d, *J* = 3.6 Hz, 1H), 6.19 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.72 – 5.60 (m, 2H), 4.06 – 3.98 (m, 2H), 3.58 – 3.44 (m, 2H), 2.03 (s, 3H), 1.51 (s, 9H), 0.91 – 0.69 (m, 2H), -0.21 (s, 9H).

Step e. To a solution of (S)-*tert*-butyl 3-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-2-oxo-4-(1-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1*H*-imidazol-2-yl)imidazolidine-1-carboxylate (540 mg, 0.82 mmol) in DCM (10 mL) was added TFA (9.36 g, 82.1 mmol). The mixture was stirred at 45°C for 12 h. Upon completion, the reaction mixture was evaporated and the residue was purified by reverse-phase flash column to give (S)-5-(1-(1-(hydroxymethyl)-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1*H*-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one (360 mg, 96%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 458.3

Step f. To a solution of (S)-5-(1-(1-(hydroxymethyl)-1*H*-pyrrolo[2,3-b]pyridin-6-yl)-1*H*-imidazol-2-yl)-1-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)imidazolidin-2-one (360 mg, 0.79 mmol) in MeOH (10 mL) was added NaOH (126 mg, 3.15 mmol). The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was filtered and evaporated. The residue was purified by prep-HPLC to give the title compound (55 mg, 16%) as a yellow solid.

m/z ES⁺ [M+H]⁺ 428.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.88 (s, 1H), 8.29 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.01 (s, 1H), 6.86 (s, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 6.10 (dd, *J* = 9.6, 3.6 Hz, 1H), 4.10 (t, *J* = 9.6 Hz, 1H), 3.50 (dd, *J* = 9.2, 3.6 Hz, 1H), 2.06 (s, 3H).

BIOLOGICAL DATA

PolΘ Full Length Enzyme Potency Assay

PicoGreen assay was used to measure the ability of compounds to inhibit the activity of PolΘ in vitro. N-His, C-term FLAG tagged PolΘ protein (amino acids 2-2590) expressed in baculovirus was purified and stored at -80°C in aliquots. Assay measurements were performed with 1X buffer comprising 25 mM Tris HCl pH 7.5, 12.5 mM NaCl, 0.5 mM MgCl₂, 5% glycerol, 0.01% Triton X-100, 0.01% BGG and 1 mM DTT. Test compounds were prepared by dilution in 100% DMSO to give the correct dose range for 12 point concentration response and appropriate volume (60 nL) dispensed into 384 well micro assay plates (Perkin Elmer low volume black ProxiPlates product code 6008269) using a Labcyte Echo 550 acoustic dispenser. DMSO concentration was maintained at 1% by back filling with DMSO

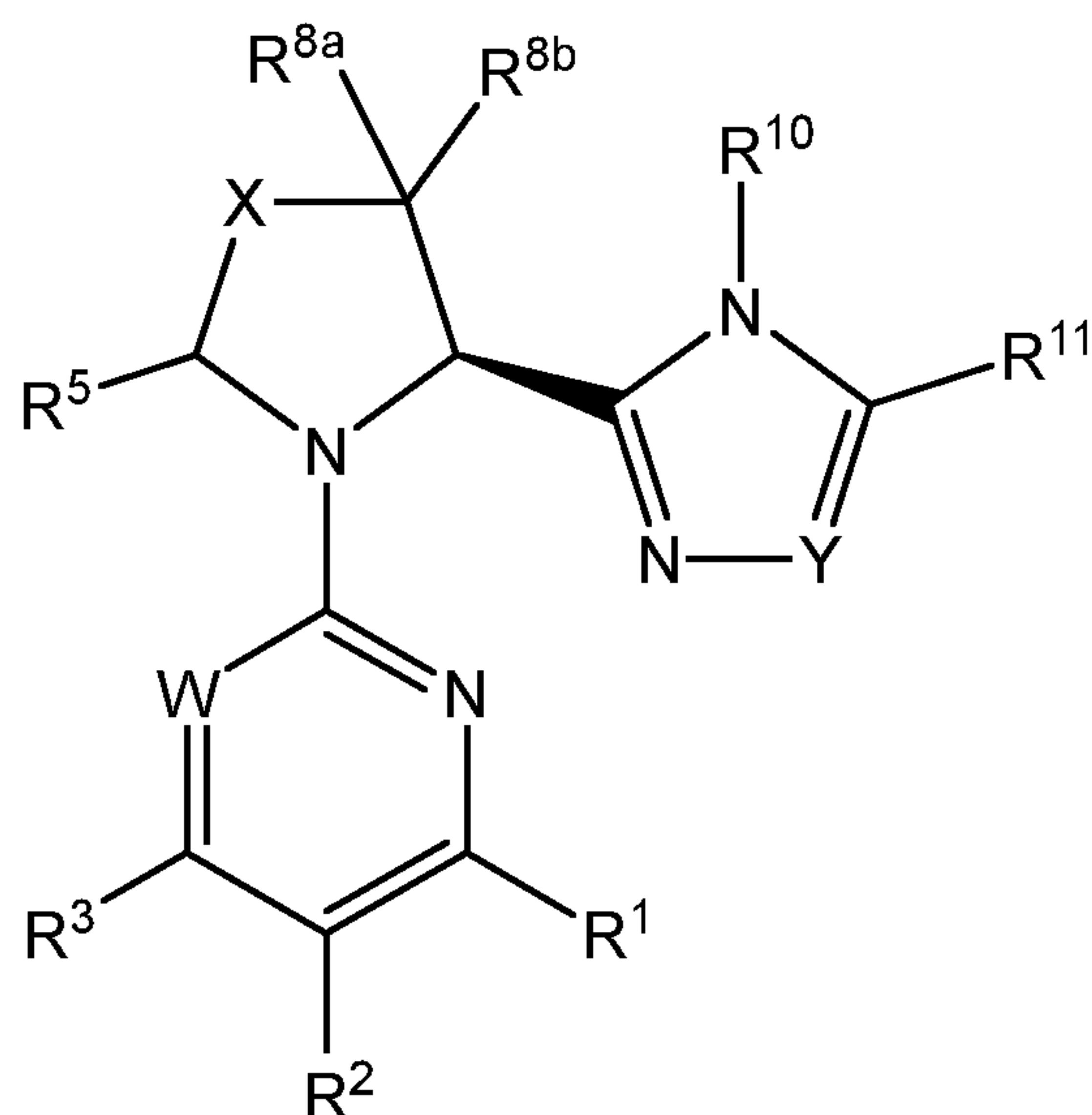
solution. 3 μ L purified recombinant Pol Θ and primer (5' - GCG GCT GTC ATA AG – 3' (SEQ ID NO: 1)): template (5' – GCT ACA TTG ACA ATG GCA TCA AAT CTC AGA TTG CGT CTT ATG ACA GCC GCG – 3' (SEQ ID NO: 2)) duplex (1:1.1) was diluted in assay buffer to a 2X working concentration (4 nM Pol Θ and 100 nM PTD). This was dispensed into each well of the compound plate using a VIAFLO 16 channel manual pipette (Integra) and pre-incubated at rt for 30 min. 3 μ L of 2X working solution of dNTPs (40 μ M) (dATP, dCTP, dGTP, dTTP; Sigma D6500, D4635, D4010, T0251) diluted in assay buffer was then added and the reaction incubated for 60 min at rt. The reaction was stopped by addition of 10 mM EDTA, 25 mM Tris pH 7.5 and 1:200 dilution of PicoGreen dye (Invitrogen P7581). After 90 minutes at rt in the dark, fluorescence was read on a BMG Pherastar FS plate reader using 485/520nm module and raw data analysed using IDBS Activity Base to generate IC₅₀ values.

The compounds of **Examples 1 to 66** were tested in the above mentioned enzyme potency assay and the results are shown in the following table:

Example Number	PolΘ IC ₅₀ (nM)	Example Number	PolΘ IC ₅₀ (nM)	Example Number	PolΘ IC ₅₀ (nM)
1	64	23	1247	45	15
2	116	24	3114	46	6
3	125	25	3073	47	11
4	480	26	556	48	7
5	2634	27	19	49	37
6	2995	28	459	50	32
7	1056	29	1175	51	316
8	1511	30	71	52	23
9	9	31	95	53	23
10	481	32	92	54	43
11	43	33	1183	55	33
12	8	34	3221	56	48
13	176	35	362	57	4
14	1390	36	81	58	3
15	1120	37	641	59	45
16	1811	38	27	60	9
17	1556	39	54	61	3
18	2390	40	3	62	4
19	111	41	158	63	10
20	216	42	10	64	4
21	709	43	5	65	3
22	64	44	8	66	18

CLAIMS

1. A compound of formula (I):



5

(I)

or a tautomeric or a stereochemically isomeric form, a pharmaceutically acceptable salt or a solvate thereof, wherein:

W represents =C(R⁴)- or =N-;

10 R¹, R², R³ and R⁴ independently represent hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, haloC₁₋₆ alkyl, C₃₋₈ cycloalkyl, cyano or -NR^xR^y;

X represents -C(R^{6a})(R^{6b})-, -N(R⁷)- or -O-;

R⁵ represents hydrogen, -CH₂-R^z or oxo, or together with R^{6b} may join to form a bridged group, such that when X represents -N(R⁷)- or -O-, R⁵ represents oxo and such that when R⁴ represents cyano, R⁵ represents a group other than oxo;

15 R^{6a} represents hydrogen, hydroxy, C₁₋₆ alkyl, haloC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanol, C₃₋₈ cycloalkyl, halogen, -NR^vR^w or heterocyclyl;

R^{6b} represents hydrogen, or together with R⁵ may join to form a bridged group, or together with R^{6a} may join to form a C₃₋₈ cycloalkyl group;

20 R⁷ represents hydrogen, C₁₋₆ alkyl, haloC₁₋₆ alkyl, C₃₋₈ cycloalkyl, heterocyclyl, C₁₋₆ alkylsulfonimidoyl or C₁₋₆ alkylamino optionally substituted by one or more (e.g. 1 or 2) hydroxyl groups;

R^{8a} represents hydrogen, -CH₂-R^z or hydroxy;

R^{8b} represents hydrogen or hydroxy, such that when X represents -N(R⁷)- or -O-, R^{8b} represents hydrogen;

25 Y represents -C(R⁹)= or -N=;

R⁹ represents hydrogen, halogen or C₁₋₆ alkyl;

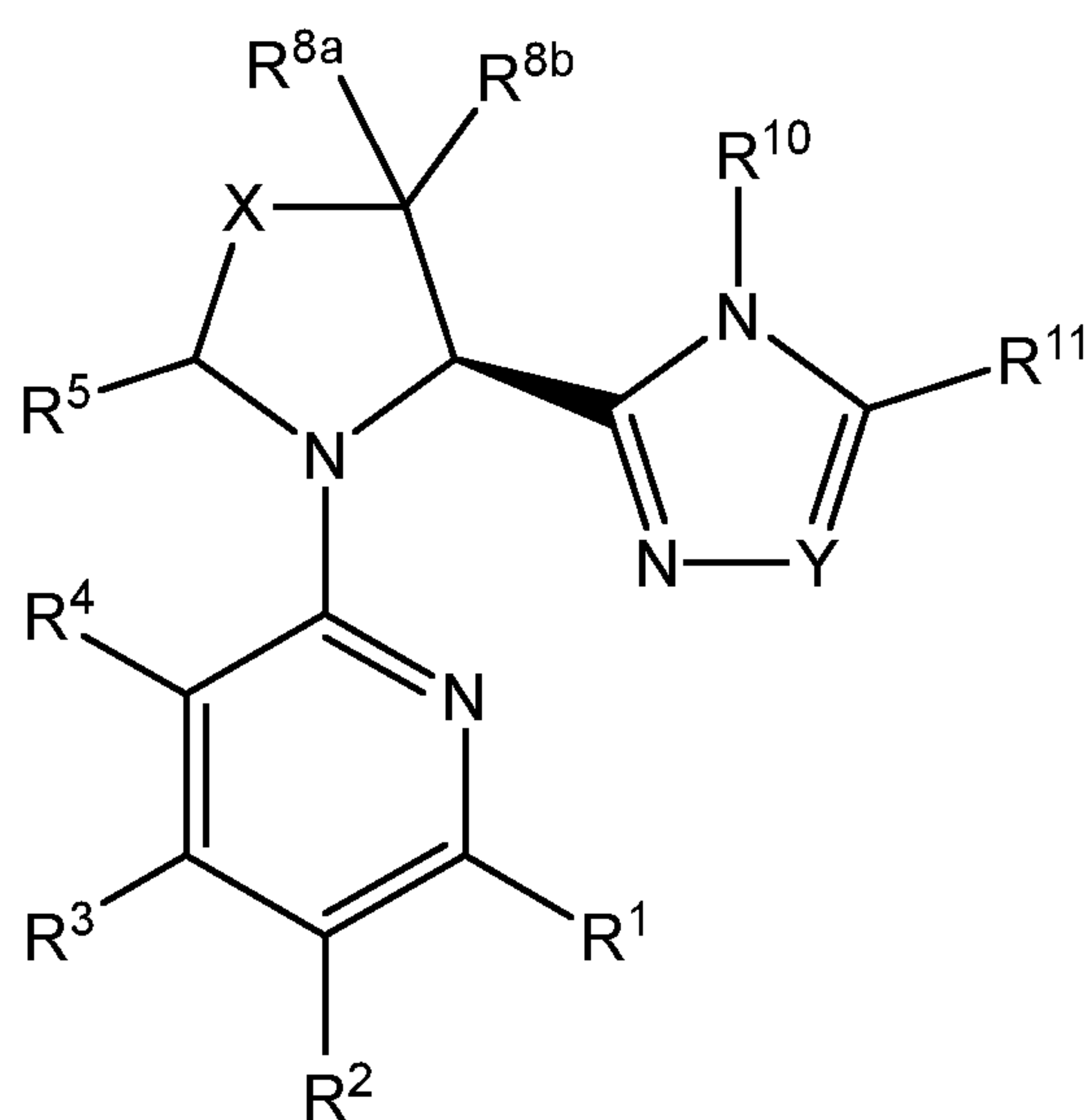
R^{10} represents phenyl or a 5 or 6 membered heteroaryl ring optionally fused to a 5 membered heteroaryl ring, wherein said phenyl or heteroaryl rings may optionally each be substituted by one or more (e.g. 1, 2 or 3) C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkanol, $-CONR^tR^u$, $-CH_2-NR^tR^u$, C_{3-8} cycloalkyl, halogen, cyano or $haloC_{1-6}$ alkyl groups;

5 R^{11} represents hydrogen, halogen or C_{1-6} alkyl;

R^t , R^u , R^v , R^w , R^x and R^y independently represent hydrogen, C_{1-6} alkyl, $haloC_{1-6}$ alkyl, C_{3-8} cycloalkyl, $-COC_{1-6}$ alkyl or heterocyclyl, wherein said alkyl groups may be optionally substituted with or more hydroxy, amino or sulfone groups and said heterocyclyl ring may be optionally substituted by one or more oxo or $-COC_{1-6}$ alkyl groups; and

10 R^z represents hydrogen, C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy or C_{1-6} alkanol.

2. The compound as defined in claim 1, which is a compound of formula (I)^a:



(I)^a

15 wherein R^1 , R^2 , R^3 , R^4 , R^5 , X, R^{8a} , R^{8b} , Y, R^{10} and R^{11} are as defined in claim 1.

3. The compound as defined in claim 1 or claim 2, wherein R^1 represents hydrogen or C_{1-6} alkyl (such as methyl).

20 4. The compound as defined in any one of claims 1 to 3, wherein R^2 represents hydrogen or C_{1-6} alkyl (such as methyl).

5. The compound as defined in any one of claims 1 to 4, wherein R^3 represents C_{1-6} alkyl (such as methyl or ethyl) or $haloC_{1-6}$ alkyl (such as trifluoromethyl).

25

6. The compound as defined in any one of claims 1 to 5, wherein R⁴ represents hydrogen or cyano.

7. The compound as defined in claim 1, wherein W represents C(R⁴)- and:

5 R¹ represents C₁₋₆ alkyl (such as methyl), R² represents hydrogen, R³ represents haloC₁₋₆ alkyl (such as trifluoromethyl) and R⁴ represents cyano; or

R¹ represents C₁₋₆ alkyl (such as methyl), R² represents hydrogen, R³ represents C₁₋₆ alkyl (such as methyl) and R⁴ represents cyano; or

10 R¹ represents hydrogen, R² represents C₁₋₆ alkyl (such as methyl), R³ represents C₁₋₆ alkyl (such as ethyl) and R⁴ represents cyano; or

R¹ represents C₁₋₆ alkyl (such as methyl), R² represents hydrogen, R³ represents haloC₁₋₆ alkyl (such as trifluoromethyl) and R⁴ represents hydrogen.

15 8. The compound as defined in any one of claims 1 to 7, wherein R⁵ represents hydrogen, oxo, or R⁵ together with R^{6b} joins to form a bridged group.

9. The compound as defined in any one of claims 1 to 8, wherein X represents -C(R^{6a})(R^{6b})- and: R^{6a} represents hydrogen, C₁₋₆ alkyl (such as methyl), hydroxy, C₁₋₆ alkanol (such as CH₂OH) or -NR^vR^w (such as -NHCOMe); R^{6b} represents hydrogen; or R^{6b} together with R⁵ joins to form a bridged group; or R^{6b} together with R^{6a} joins to form a C₃₋₈ cycloalkyl group (such as a cyclopropyl group).

10. The compound as defined in any one of claims 1 to 8, wherein X represents -N(R⁷)- and R⁷ represents hydrogen, C₁₋₆ alkylsulfonimidoyl (such as -(CH₂)₂-S(=O)(=NH)(Me)) or
25 C₁₋₆ alkylamino optionally substituted by one or more (e.g. 1 or 2) hydroxyl groups (such as -CH₂-CH₂OH-CH₂-N(Me)₂).

11. The compound as defined in any one of claims 1 to 10, wherein R^{8a} and R^{8b} both represent hydrogen, or R^{8a} represents hydroxy and R^{8b} represents hydrogen, or R^{8a}
30 represents -CH₂-R^z (such as methyl) and R^{8b} represents hydroxy, or R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydrogen or hydroxy.

12. The compound as defined in any one of claims 1 to 11, wherein X represents -C(R^{6a})(R^{6b})- and:

35 R⁵ represents hydrogen, R^{6a} represents hydrogen, R^{6b} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents hydrogen, R^{6a} represents hydroxy, R^{6b} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents hydrogen, R^{6a} represents hydroxy, R^{6b} represents hydrogen, R^{8a} represents hydroxy and R^{8b} represents hydrogen; or

5 R⁵ together with R^{6b} joins to form a bridged group, R^{6a} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ together with R^{6b} joins to form a bridged group, R^{6a} represents C₁₋₆ alkanol (such as CH₂OH) and R^{8a} and R^{8b} both represent hydrogen; or

10 R⁵ represents hydrogen, R^{6a} represents NR^vR^w (such as -NHCOMe), R^{6b} represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents oxo, R^{6a} represents C₁₋₆ alkyl (such as methyl), R^{6b} represents hydrogen, R^{8a} represents -CH₂-R^z (such as methyl) and R^{8b} represents hydroxy; or

R⁵ represents oxo, R^{6a} and R^{6b} both represent hydrogen, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydroxy; or

15 R⁵ represents oxo, R^{6a} represents C₁₋₆ alkyl (such as methyl), R^{6b} represents hydrogen, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydroxy; or

R⁵ represents oxo, R^{6a} and R^{6b} join to form a C₃₋₈ cycloalkyl group (such as a cyclopropyl group), R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydroxy.

20 13. The compound as defined in any one of claims 1 to 11, wherein X represents -O- and:

R⁵ represents oxo and R^{8a} and R^{8b} both represent hydrogen; or

R⁵ represents oxo, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydrogen.

25

14. The compound as defined in any one of claims 1 to 11, wherein X represents -N(R⁷)- and:

R⁵ represents oxo, R⁷ represents hydrogen and R^{8a} and R^{8b} both represent hydrogen; or

30 R⁵ represents oxo, R⁷ represents hydrogen, R^{8a} represents -CH₂-R^z (such as -CH₂-OH) and R^{8b} represents hydrogen; or

R⁵ represents oxo, R⁷ represents C₁₋₆ alkylamino optionally substituted by one or more (e.g. 1 or 2) hydroxyl groups (such as -CH₂-CH₂OH-CH₂-N(Me)₂) and R^{8a} and R^{8b} both represent hydrogen; or

35 R⁵ represents oxo, R⁷ represents C₁₋₆ alkylsulfonimidoyl (such as -(CH₂)₂-S(=O)(=NH)(Me)) and R^{8a} and R^{8b} both represent hydrogen.

15. The compound as defined in any one of claims 1 to 14, wherein R⁹ represents hydrogen, halogen (such as fluorine or chlorine) or C₁₋₆ alkyl (such as methyl).

16. The compound as defined in any one of claims 1 to 15, wherein R¹⁰ represents phenyl or a 5 or 6 membered heteroaryl ring (such as pyridyl or pyrazolyl) optionally fused to a 5 membered heteroaryl ring (such as pyrrolopyridinyl) wherein said phenyl or heteroaryl rings may optionally each be substituted by one or more (e.g. 1, 2 or 3) C₁₋₆ alkyl (such as methyl or isopropyl), C₁₋₆ alkoxy (such as methoxy), C₁₋₆ alkanol (such as CH₂OH), -CONR^tR^u (such as -CONH₂), -CH₂-NR^tR^u (such as -CH₂-NH₂), halogen (such as fluorine or chlorine), cyano or haloC₁₋₆ alkyl (such as trifluoromethyl).

17. The compound as defined in any one of claims 1 to 16, wherein R¹¹ represents hydrogen, halogen (such as chlorine) or C₁₋₆ alkyl (such as methyl).

18. The compound as defined in claim 1, wherein the compound is the free base of a compound of Examples 1-66 or a pharmaceutically acceptable salt or solvate thereof.

19. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 18.

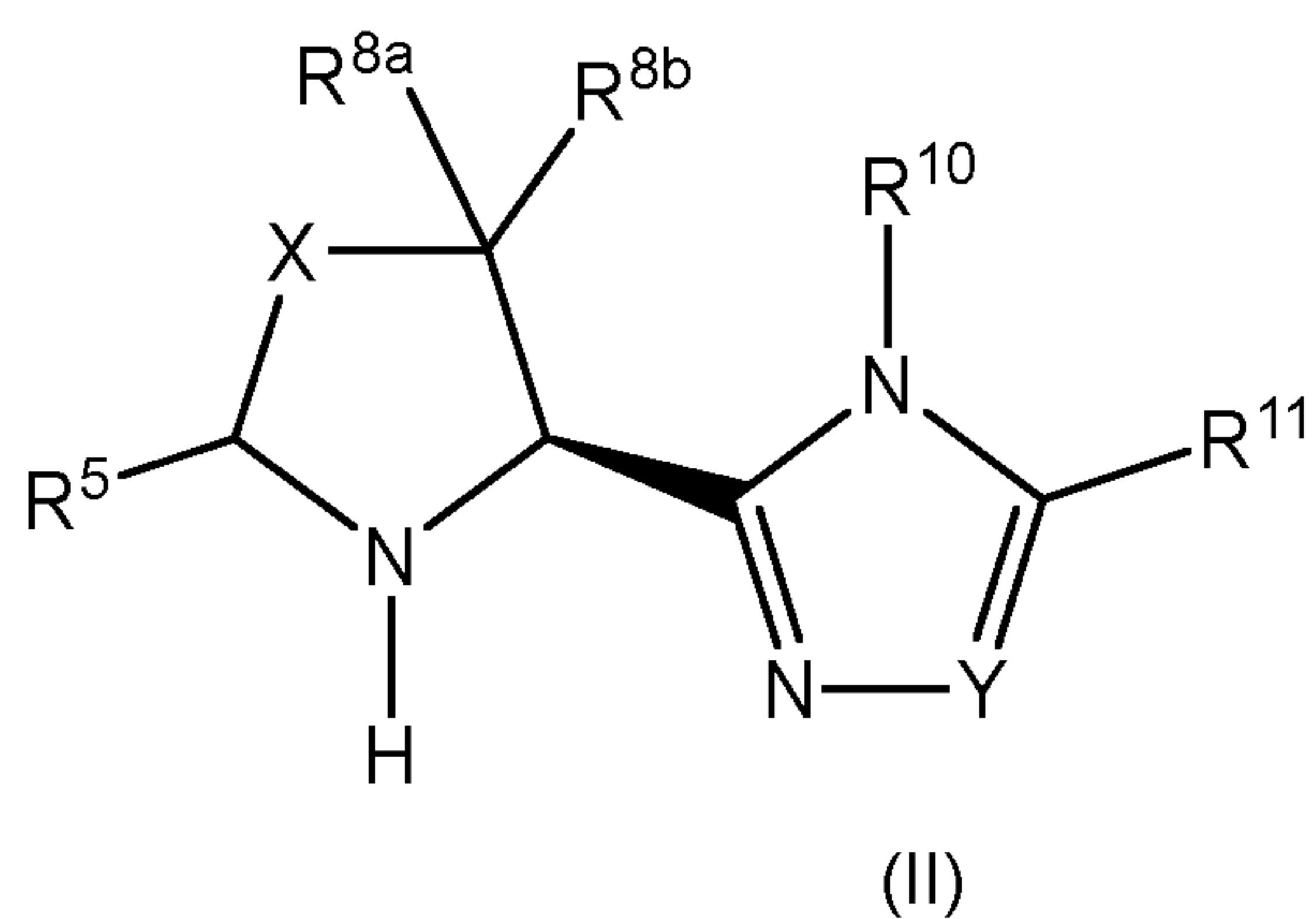
20. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 18, in combination with one or more therapeutic agents.

21. A compound as defined in any of claims 1 to 18 for use in therapy.

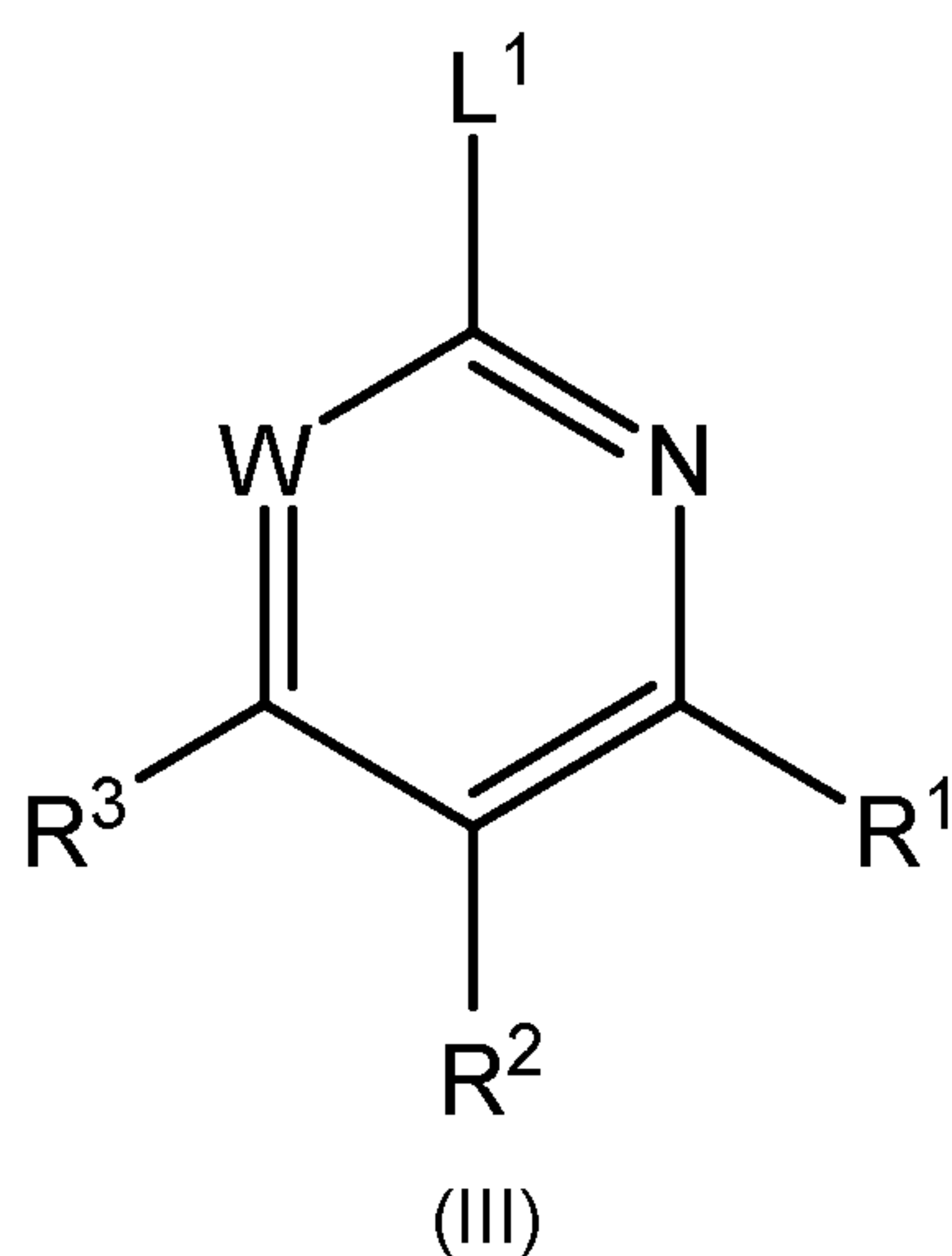
22. A compound as defined in any of claims 1 to 18 for use in the prophylaxis or treatment of cancer.

23. A process for preparing a compound of formula (I) as herein defined in claim 1 which comprises:

(a) reacting a compound of formula (II):

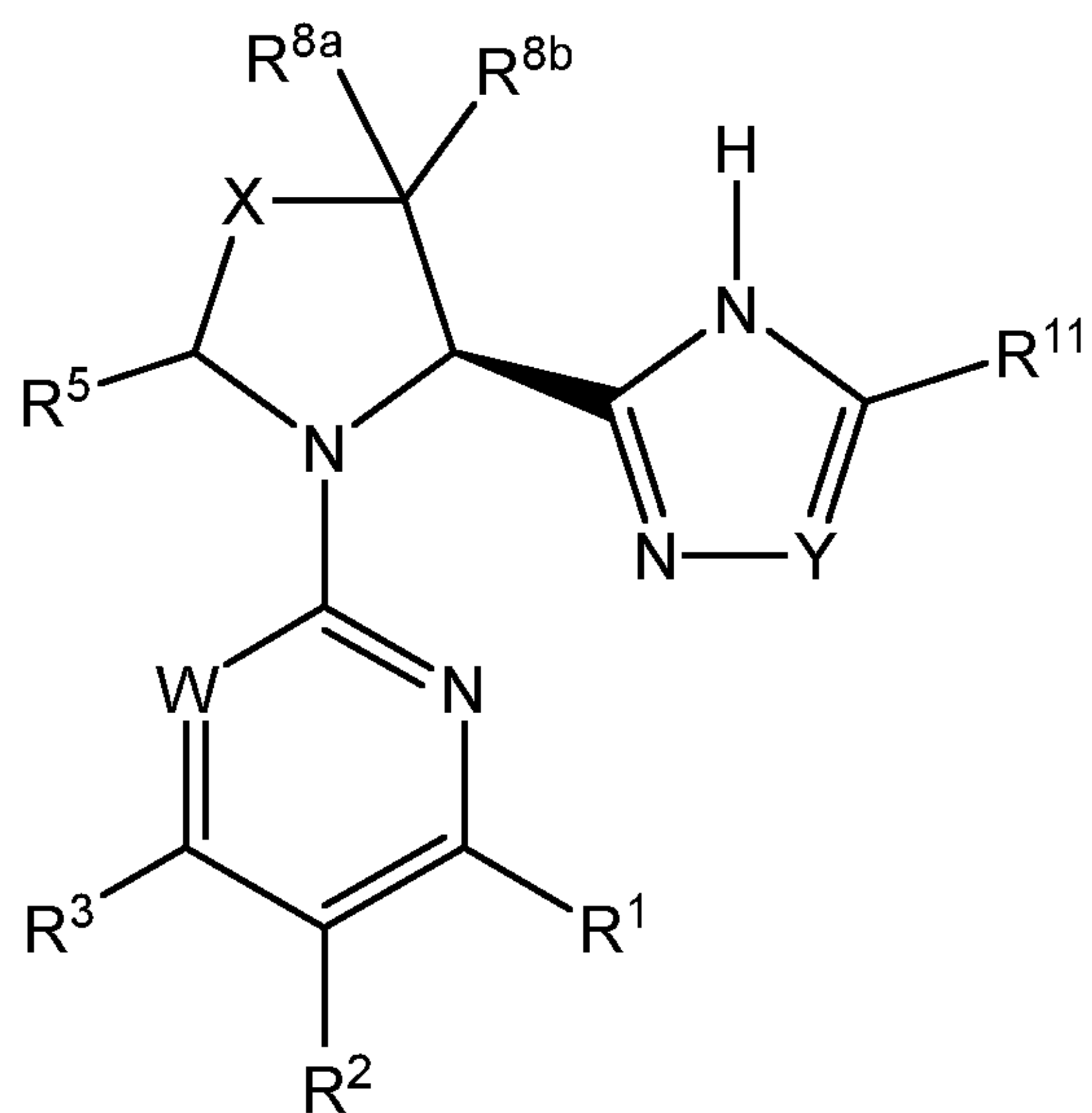


wherein R^5 , X , R^{8a} , R^{8b} , Y , R^{10} and R^{11} are as defined in claim 1, with a compound of formula (III):



wherein R^1 , R^2 , R^3 and W are as defined in claim 1 and L^1 represents a suitable leaving group, such as a halogen atom (e.g. chlorine);

(b) reacting a compound of formula (IV):



(IV)

wherein R^1 , R^2 , R^3 , W , R^5 , X , R^{8a} , R^{8b} , Y and R^{11} are as defined in claim 1, with a compound of formula $R^{10}-L^2$, wherein R^{10} is as defined in claim 1 and L^2 represents a suitable leaving group, such as boronic acid or a halogen atom (e.g. fluorine);

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(c) deprotection of a protected derivative of a compound of formula (I);

(d) interconversion of a compound of formula (I) or protected derivative thereof to a further compound of formula (I) or protected derivative thereof; and

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(e) optional formation of a pharmaceutically acceptable salt of a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2020/053257

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D401/14 C07D413/14 C07D471/04 A61P35/00 A61K31/437 A61K31/4439 ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/035410 A1 (UNIV TEMPLE [US]; UNIV LELAND STANFORD JUNIOR) 22 February 2018 (2018-02-22) claim 1 page 5, line 11 - line 13 -----	1-23
A	WU JING ET AL: "Optimization of 2-(3-(arylalkyl amino carbonyl) phenyl)-3-(2-methoxyphenyl)-4-thiazolidino ne derivatives as potent antitumor growth and metastasis agents", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 80, June 2014 (2014-06), pages 340-351, XP055781860, ISSN: 0223-5234, DOI: 10.1016/j.ejmech.2014.04.068 table 1; compound 14 ----- - / - -	1-23
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 4 May 2021		Date of mailing of the international search report 12/05/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Miniejew, Catherine

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2020/053257

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/177524 A1 (HOFFMANN LA ROCHE [CH]; GENENTECH INC [US]) 6 November 2014 (2014-11-06) page 224; claims 1, 18; compounds 5-aa -----	1-23
A	WO 2016/016316 A1 (NUEVOLUTION AS [DK]) 4 February 2016 (2016-02-04) page 412; compound S161 claims 1, 40-41 -----	1-23

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB2020/053257

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2020/053257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018035410	A1	22-02-2018	NONE

WO 2014177524	A1	06-11-2014	BR 112015027381 A2
		CA 2907912	A1 25-07-2017
		CN 105164114	A 06-11-2014
		EP 2991977	A1 16-12-2015
		HK 1213560	A1 09-03-2016
		JP 6523251	B2 08-07-2016
		JP 2016517873	A 29-05-2019
		JP 2019142954	A 20-06-2016
		KR 20160002850	A 29-08-2019
		RU 2015147601	A 08-01-2016
		US 2016046608	A1 05-06-2017
		WO 2014177524	A1 18-02-2016
			06-11-2014

WO 2016016316	A1	04-02-2016	AU 2015295405 A1
		BR 112017002053	A2 09-03-2017
		CA 2956871	A1 30-01-2018
		CL 2017000240	A1 04-02-2016
		CN 106573915	A 06-10-2017
		EP 3174868	A1 19-04-2017
		JP 6759514	B2 07-06-2017
		JP 2017522346	A 23-09-2020
		KR 20170038877	A 10-08-2017
		RU 2017104510	A 07-04-2017
		SG 10201900631T	A 03-09-2018
		SG 11201700776X	A 27-02-2019
		US 2017349607	A1 27-02-2017
		WO 2016016316	A1 07-12-2017
		ZA 201700670	B 04-02-2016
			29-07-2020
