

PROTEIN KINASE INHIBITORS

Technical field

5

The present invention relates to therapeutically active compounds and pharmaceutically acceptable salts thereof which are useful e.g. in the treatment of cancer.

Background of the invention

10

Protein kinases are a class of proteins (enzymes) that regulate a variety of cellular functions. This is accomplished by phosphorylation of specific amino acids on protein substrates resulting in conformational alteration of the substrate protein. The conformational change modulates the activity of the substrate or its ability to interact with other binding partners. Tyrosine kinases are a subset of protein kinases that catalyze the transfer of the terminal phosphate of adenosine triphosphate (ATP) to tyrosine residues on protein substrates. The human genome contains around 90 tyrosine kinases and 43 tyrosine kinase like genes, the products of which regulate cellular proliferation, survival, differentiation, function and motility.

20

Tyrosine kinases are of two varieties, i.e. receptor and non-receptor tyrosine kinases. Receptor tyrosine kinases (e.g., FGFR) are trans-membrane proteins with a ligand-binding extracellular domain and a catalytic intracellular kinase domain, while non-receptor tyrosine kinases (e.g., c-ABL) lack trans-membrane domains and are found in the cytosol, nucleus and inner surface of cell membrane. Kinase domains of all tyrosine kinases have bilobar architecture, with an N-terminal lobe that binds ATP and magnesium, a C-terminal lobe containing an activation loop, and a cleft between the lobes to which polypeptide substrates bind.

25
30

Receptor tyrosine kinases become activated when ligand binds to the extracellular domain, resulting in receptor oligomerization and autophosphorylation of a regulatory tyrosine within the activation loop of the kinase domain. These phenomena

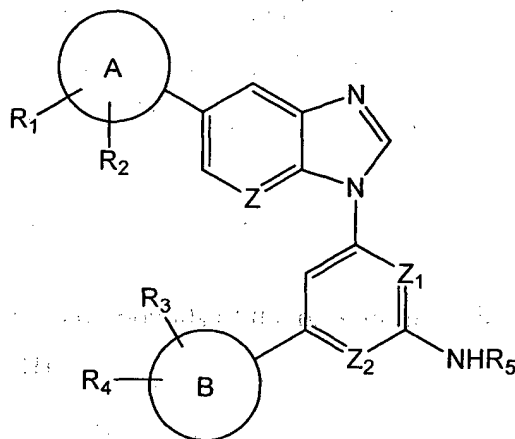
reorient important amino acid residues, thereby enhancing catalytic activity of the enzyme.

Fibroblast growth factor (FGF) has been recognized as an important mediator of many physiological processes, such as cell migration, proliferation, survival and differentiation during development and angiogenesis. There are currently over 25 known members of the FGF family. The fibroblast growth factor receptor (FGFR) family consists of four members with each composed of an extra cellular ligand binding domain, a single trans-membrane domain and an intracellular cytoplasmic protein tyrosine kinase domain. Upon stimulation with FGF, FGFRs undergo dimerisation and transphosphorylation. Upon dimerization, FGFRs activate range of downstream signaling pathways, such as MAPK and PKB/Akt pathways (Zhou, W. et. al. *Chemistry & Biology*, 2010, 17, 285). Abnormal FGFR signaling has been reported in many tumor types including multiple myeloma, gastric, endometrial, prostate and breast (Squires M. et. al. *Mol. Cancer Ther.*, September 2011, 10:1542-1552). FGFs also have role in tumor angiogenesis and mediate resistance to vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors (Casanovas, O. et. al., *Cancer Cell*, 2005, 8, 299). Consequently, FGF and FGFRs have the potential to initiate and/or promote tumorigenesis. Due to this, the FGF signaling system happens to be an attractive therapeutic target, mainly because therapies targeting FGFRs and/or FGF signaling may affect both the tumor cells and also tumor angiogenesis (Foote, K. M. et. al., WO 2009/019518 A1). Consequently, FGF and FGFRs have the potential to initiate and/or promote tumorigenesis.

Summary of the invention

It has been found that compounds of formula (I) inhibit or modulate the activity of certain protein kinases, more specifically protein tyrosine kinases. In particular, it has been found that the compounds of formula (I) are potent and selective inhibitors of FGFR kinases. The compounds of the invention have antiproliferative activity and are particularly useful in the treatment of cancer.

The compounds of the present invention have a structure represented by formula (I)



(I)

wherein

Z₁ is N and Z₂ is CH, or

Z₁ is CH and Z₂ is N, or

Z₁ and Z₂ is N;

Z is CH or N;

A is a phenyl ring or a 5-12 membered heterocyclic ring;

R₁ is H, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, C₁₋₇ alkoxy, C₁₋₇ alkyl carbonyl, amino, hydroxy, hydroxy C₁₋₇ alkyl, halo C₁₋₇ alkyl, C₁₋₇ alkylamino C₁₋₇ alkyl, -R₁₆-C(O)-R₁₇ or -E-R₆;

R₂ is H, halogen or C₁₋₇ alkyl;

B is a 5-12 membered carbocyclic or heterocyclic ring;

R₃ is H, halogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halo C₁₋₇ alkyl or halo C₁₋₇ alkoxy;

R₄ is H, halogen, C₁₋₇ alkyl or oxo;

R₅ is H, -C(O)R₇, -SO₂R₈ or an optionally substituted 5-6 membered heterocyclic ring;

R₆ is an optionally substituted 5-6 membered heterocyclic ring;

R₇ is C₁₋₇ alkyl, C₂₋₇ alkenyl, C₁₋₇ alkoxy, C₁₋₇ alkoxy C₁₋₇ alkyl, carboxy C₁₋₇ alkyl, C₁₋₇ alkoxy carbonyl C₁₋₇ alkyl, C₁₋₇ alkylamino C₁₋₇ alkyl, -NH-R₁₀ or -NH-X₁-R₁₁;

R₈ is C₁₋₇ alkyl, C₂₋₇ alkenyl, C₃₋₇ cycloalkyl, hydroxy C₁₋₇ alkyl, -NR₁₃R₁₄, -NH-X₂-R₁₅, phenyl or an optionally substituted 5-6 membered heterocyclic ring;

R₁₀ is C₁₋₇ alkyl or C₃₋₇ cycloalkyl;

R₁₁ is phenyl or an optionally substituted 5-6 membered heterocyclic ring;

R_{12} is H or C_{1-7} alkyl;

R_{13} and R_{14} are, independently, H, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{15} is phenyl or an optionally substituted 5-6 membered heterocyclic ring;

R_{16} is a bond or a C_{1-7} alkyl;

5 R_{17} is C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkylamino, amino or hydroxy;

E is a bond or a C_{1-7} alkyl;

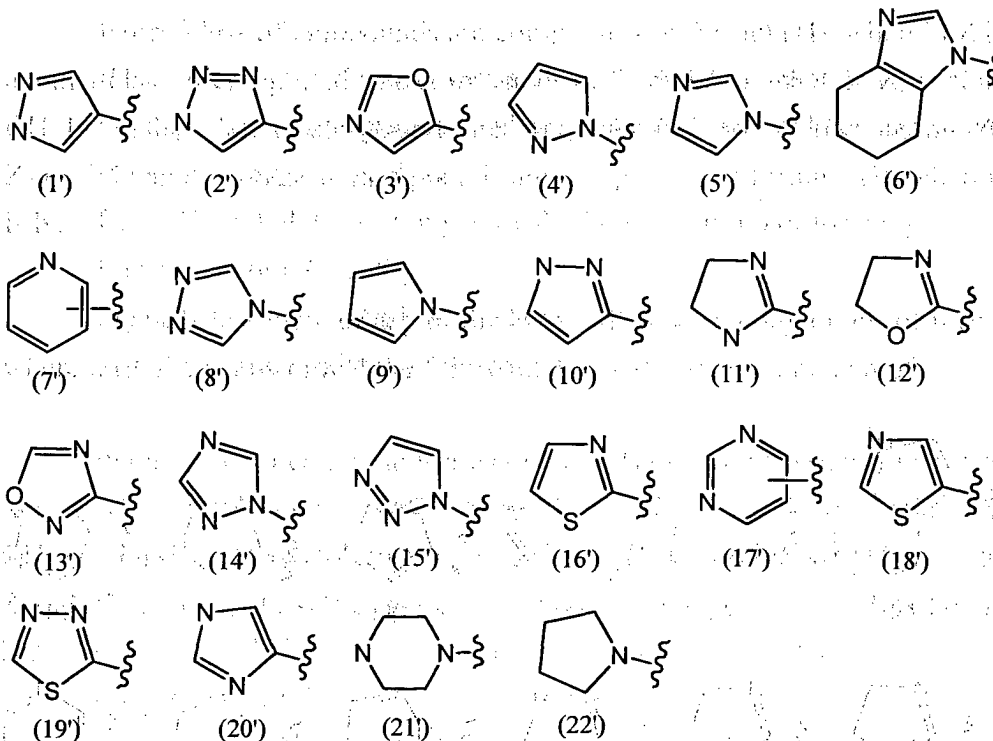
X_1 and X_2 are, independently, a bond or C_{1-7} alkyl;

and pharmaceutically acceptable salts thereof.

10 In one class of compounds are compounds of formula (I), wherein Z is CH. In another class of compounds are compounds of formula (I), wherein Z_1 is N and Z_2 is CH. In another class of compounds are compounds of formula (I), wherein Z_1 is CH and Z_2 is N. In another class of compounds are compounds of formula (I), wherein Z_1 and Z_2 is N.

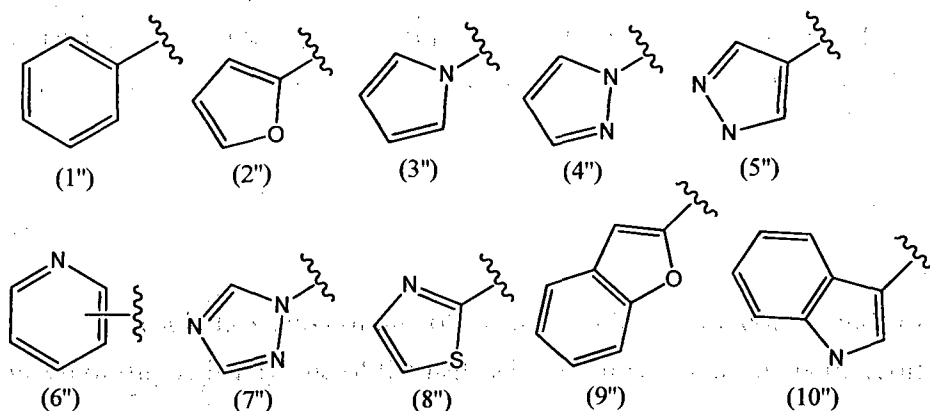
15 In a subclass class of any of the above classes are compounds of formula (I),

wherein ring A is any one of the following groups or tautomers thereof:



20 and R_1 and R_2 , as defined above, are attached to the above A-rings.

In a subclass class of any of the above classes are compounds of formula (I), wherein ring B is any one of the following groups or tautomers thereof:



5 and R_3 and R_4 , as defined above, are attached to the above B-rings.

Another subclass of the above classes are compounds wherein

A is a ring of formula (1'), (2'), (3'), (4'), (5'), (7'), (14'), (16') or (20');

R_1 is H, C_{1-7} alkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, C_{1-7} alkylamino C_{1-7} alkyl or

10 -E- R_6 ;

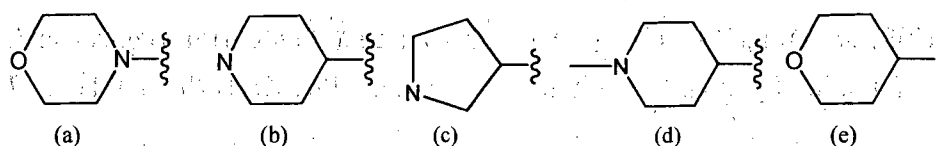
R_2 is H;

Z is CH;

B is a ring of formula (1''), (2''), (3''), (4'') or (6'');

E is a bond or C_{1-7} alkyl;

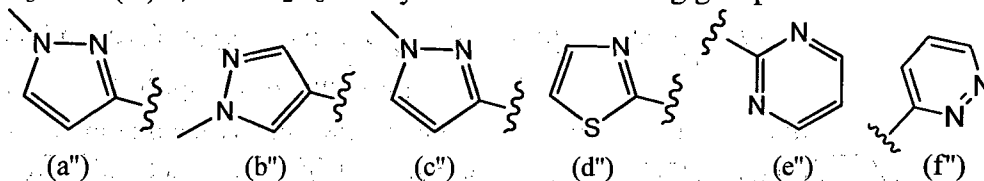
15 R_6 is any of the following groups



R_3 is H, halogen, C_{1-7} alkyl, C_{1-7} alkoxy;

R_4 is H or halogen;

20 R_5 is -C(O) R_7 or -SO₂ R_8 or any one of the following groups

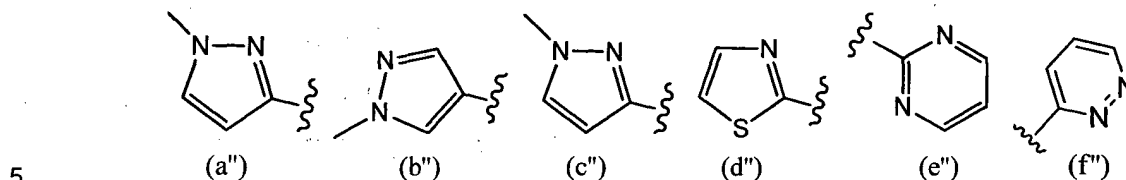


R_7 is C_{1-7} alkyl, C_{2-7} alkenyl or -NH- R_{10} ;

R_8 is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl or -NR₁₃ R_{14} ; and

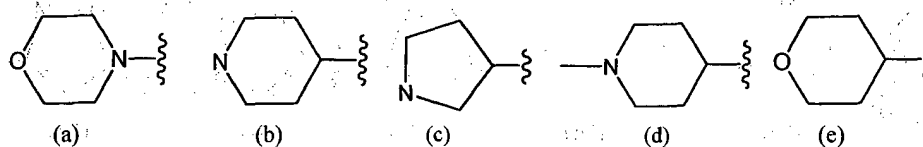
R_{10} is C_{1-7} alkyl or C_{3-7} cycloalkyl.

In one class of compounds are compounds of formula (I), wherein R_5 is $-C(O)R_7$ or $-SO_2R_8$ or any one of the following groups



In one class of compounds are compounds of formula (I), wherein R_5 is $-SO_2R_8$.

10 In one class of compounds are compounds of formula (I), wherein R_6 is any of the following groups



15 The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

20 The present invention provides further a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition, where FGFR kinase inhibition is desired.

25 The present invention provides further a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.

30 The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a condition, where FGFR kinase inhibition is desired.

35 The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer.

The present invention provides further a method for the treatment of a condition, where FGFR kinase inhibition is desired comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

5 The present invention provides further a method for the treatment of cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

10 Detailed description of the invention

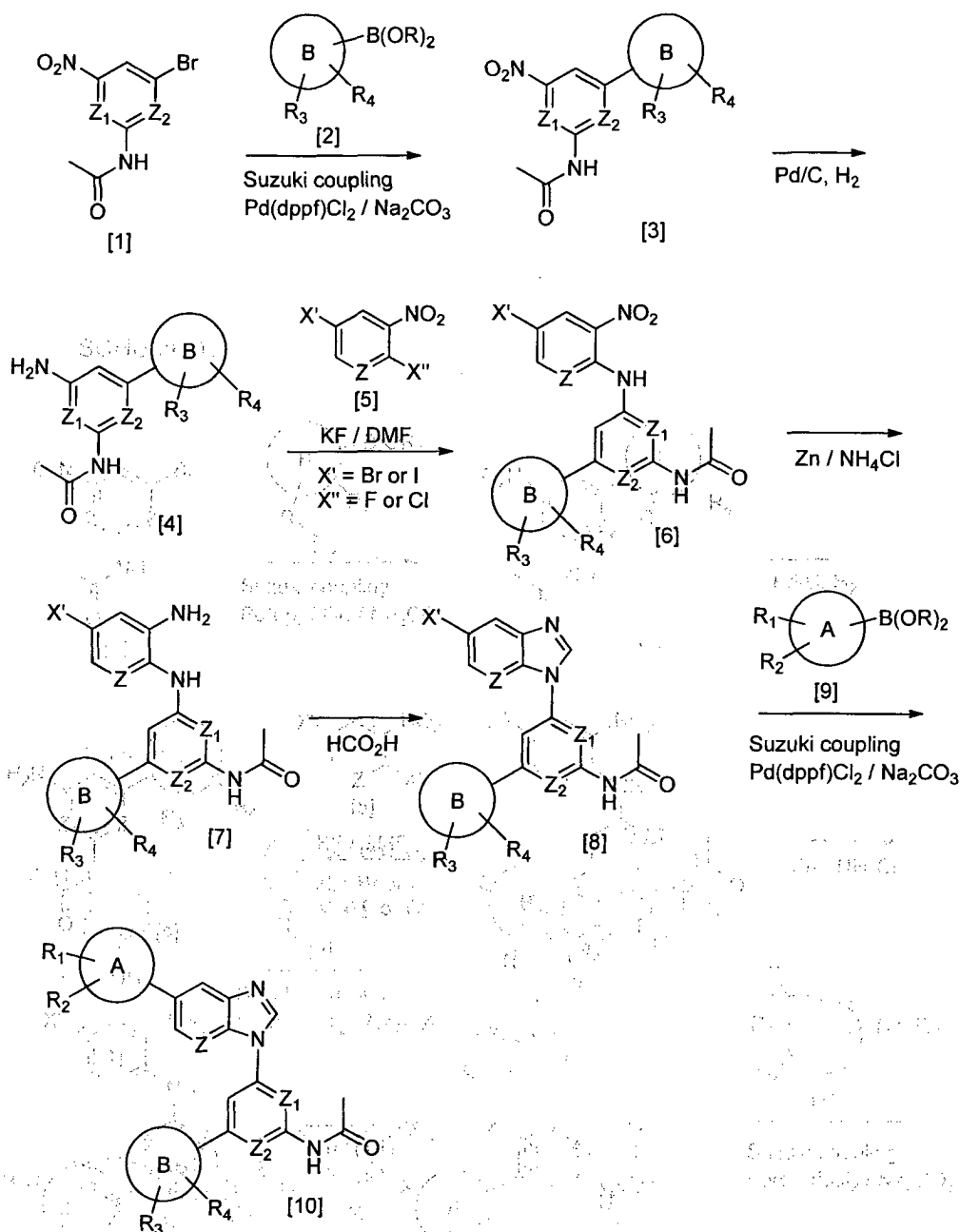
The compounds of the invention can be prepared by a variety of synthetic routes analogously to the methods known in the literature using suitable starting materials. The compounds according to formula (I) can be prepared e.g. analogously or according to 15 the following reaction Schemes. Some compounds included in the formula (I) can be obtained by converting the functional groups of the other compounds of formula (I) obtained in accordance with the following Schemes, by well known reaction steps such as oxidation, reduction, hydrolysis, acylation, alkylation, amidation, amination, sulfonation and others. It should be noted that any appropriate leaving groups, e.g. N- 20 protecting groups, such as a t-butoxycarbonyl (t-BOC) group or a phenylsulfonyl group, can be used in well known manner during the syntheses in order to improve the selectivity of the reaction steps

Compounds of formula (I), wherein R_5 is $-C(O)CH_3$ can be prepared, for 25 example, according to Scheme 1, wherein R_1 , R_2 , R_3 , R_4 , ring A, ring B and Z, Z_1 and Z_2 are as defined above, and R is hydrogen or alkyl. In the method of Scheme 1, the N-(3-bromo-5-nitrophenyl)acetamide [1] is coupled in a suitable solvent such as 1,2-dimethoxyethane with a boronic acid derivative [2] or a suitable ester thereof in the presence of $Pd(dppf)Cl_2$ and aqueous sodium carbonate at elevated temperature. The 30 nitro group of the obtained compound [3] is reduced, e.g. with hydrogen and Pd/C catalyst, iron powder and aqueous calcium chloride or zinc and aqueous ammonium chloride, and the resulting amine [4] is reacted with compound [5] in a suitable solvent such as DMF in the presence of potassium fluoride at elevated temperature to obtain

compound [6]. In case Z is CH in the compound [5], X'' is suitably fluoro, and when Z is N, X'' is suitably chloro. The nitro group in compound [6] is reduced, e.g. by using zinc and aqueous ammonium chloride or iron powder and aqueous calcium chloride, and the resulting amine [7] is heated with formic acid to produce compound [8] in a ring closure reaction. Finally, compound [10] is obtained by the Suzuki coupling between compound [8] and a boronic acid derivative [9] or a suitable ester thereof in a suitable solvent such as 1,2-dimethoxyethane in the presence of Pd(dppf)Cl₂ and aqueous sodium carbonate at elevated temperature.

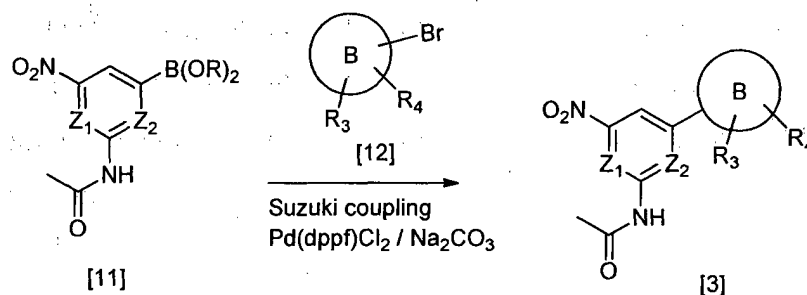
10

SCHEME 1.



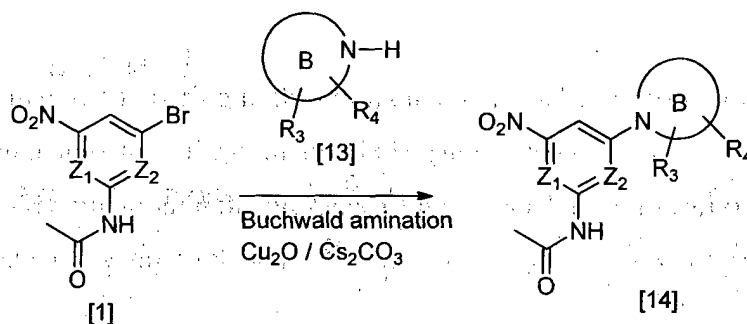
Alternatively, the compound of formula [3] can be prepared according to Scheme 2, wherein R₃, R₄, Z₁ and Z₂; ring B and R are as defined above, using the boronic acid derivative [11] or a suitable ester thereof in the presence of Pd(dppf)Cl_2 and aqueous sodium carbonate. Compound [11] can be prepared, e.g. by treating *N*-(3-bromo-5-nitrophenyl)acetamide with bis(pinacolato)diboron in the presence of Pd(dppf)Cl_2 and potassium acetate.

SCHEME 2.



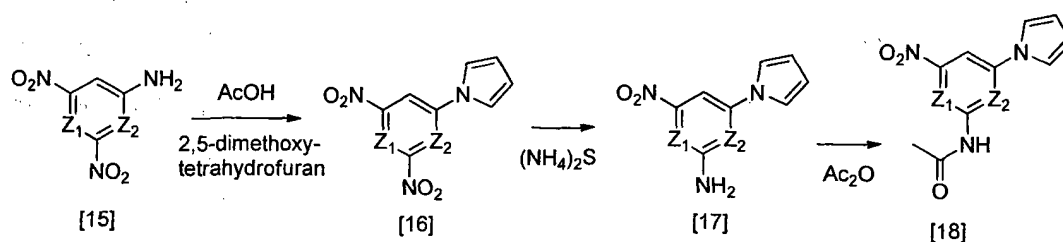
In case the B-ring in the compound [3] is a heterocycle linked to phenyl via a nitrogen heteroatom, the compound [3] can be also prepared using a copper-catalyzed Buchwald amination in the presence of a base such cesium carbonate or potassium carbonate according to Scheme 3, wherein Z_1 , Z_2 , R_3 and R_4 are as defined above.

SCHEME 3.



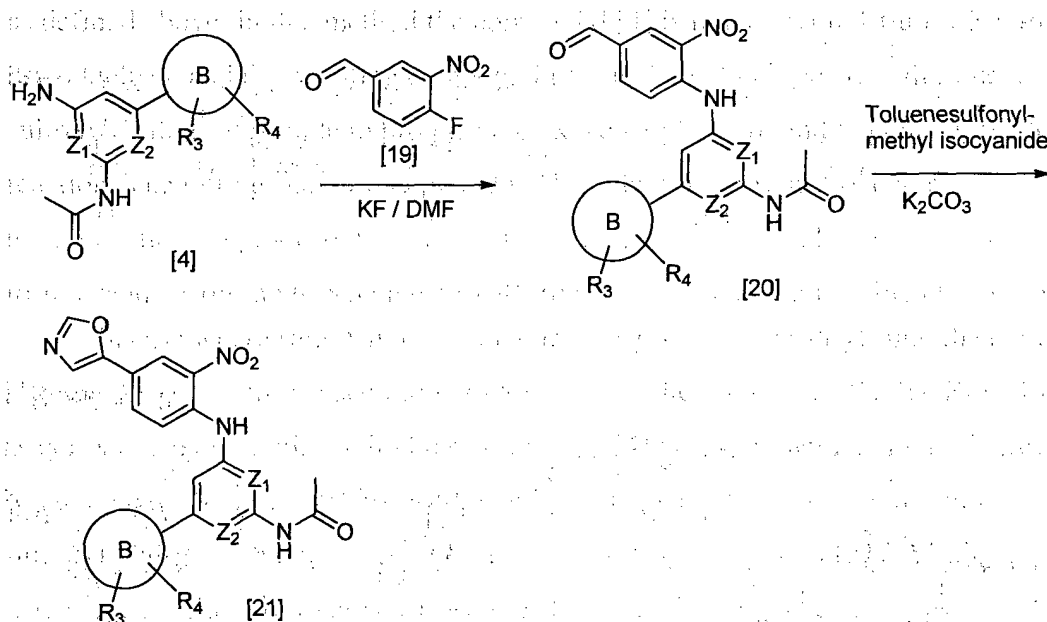
In case the B-ring in the compound [3] is pyrrole ring linked to phenyl via a nitrogen atom, the compound [3] can be also prepared from 3,5-dinitroaniline [15] and 2,5-dimethoxytetrahydrofuran according to Scheme 4, wherein Z_1 and Z_2 are as defined above. The pyrrole derivative [16] formed is reduced using ammonium sulphide to obtain compound [17], which is subsequently reacted with acetic anhydride to afford compound [18].

SCHEME 4.



In case where ring A in the compound [10] is an oxazol-5-yl ring, the compound [10] can be also prepared according to Scheme 5, wherein ring B, R_3 , R_4 , Z_1 and Z_2 are as defined above. In this method the compound [4] is treated with 4-fluoro-3-nitro-benzaldehyde and the resulting compound [20] is thereafter reacted with toluene-sulfonylmethyl isocyanide to produce the oxazol-5-yl compound [21] in a ring closure reaction. The nitro group of compound [21] can be further reduced, e.g. by hydrogenation, to produce the corresponding amine, which can be then treated with formic acid according to Scheme 1 to afford the end product in the ring closure reaction.

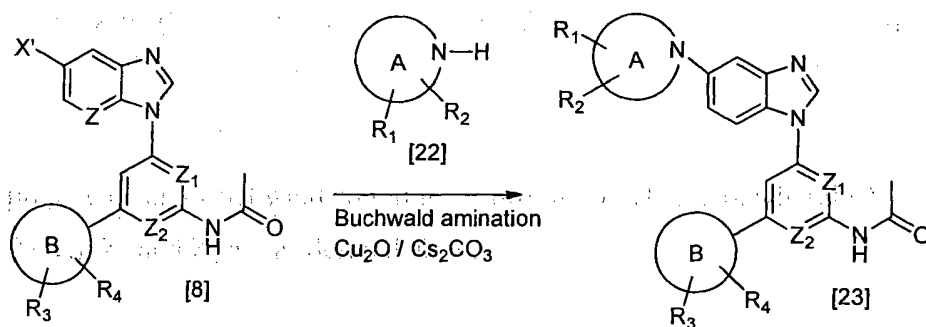
SCHEME 5.



In case where ring A in the compound [10] is a heterocycle linked to the carbon atom of the bicyclic ring via a nitrogen heteroatom, the compound [10] can be also

prepared using Buchwald coupling according to Scheme 6, wherein X', ring B, R₁, R₂, R₃, R₄, Z₁ and Z₂ are as defined above.

SCHEME 6.

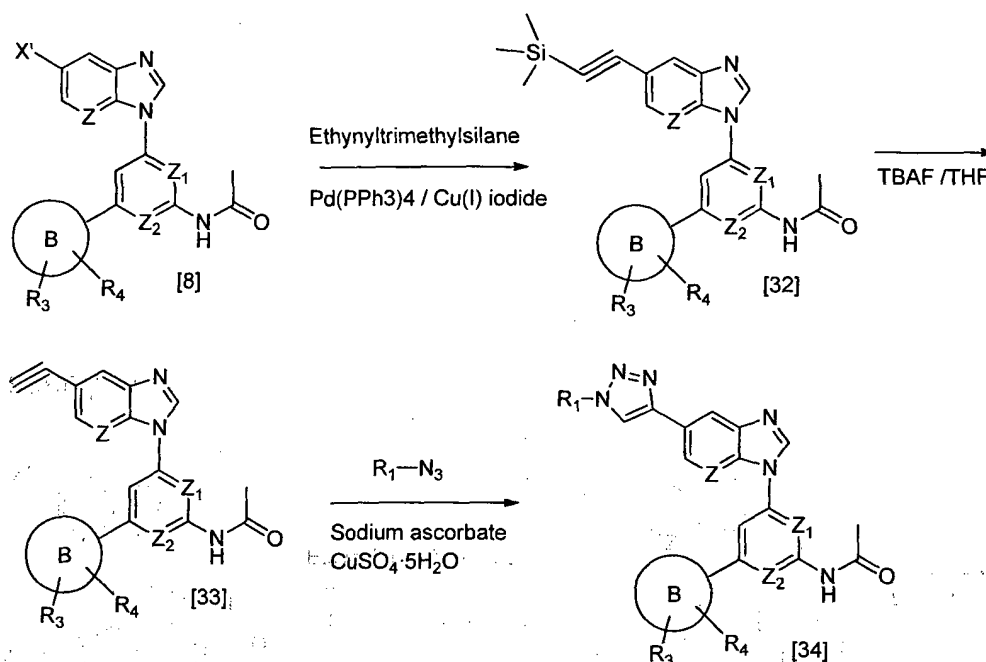


5

In case where ring A in the compound [10] is an 1H-1,2,3-triazol-4-yl ring and R₂ is hydrogen, the compound [10] can be also prepared according to Scheme 7, wherein X', Z, R₁, R₃, R₄, Z₁, Z₂ and ring B, are as defined above. The starting compound [8] is silylated by reacting with ethynyltrimethylsilane in the presence of tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) and Cu(I)iodide to produce compound [32]. Treatment with TBAF affords the ethynyl compound [33] which can be reacted with azido compound R₁-N₃ in a suitable solvent, such as DMSO:THF:water (1:1:1) or DMSO:DCM:water (1:1:1) to afford compound [34].

10

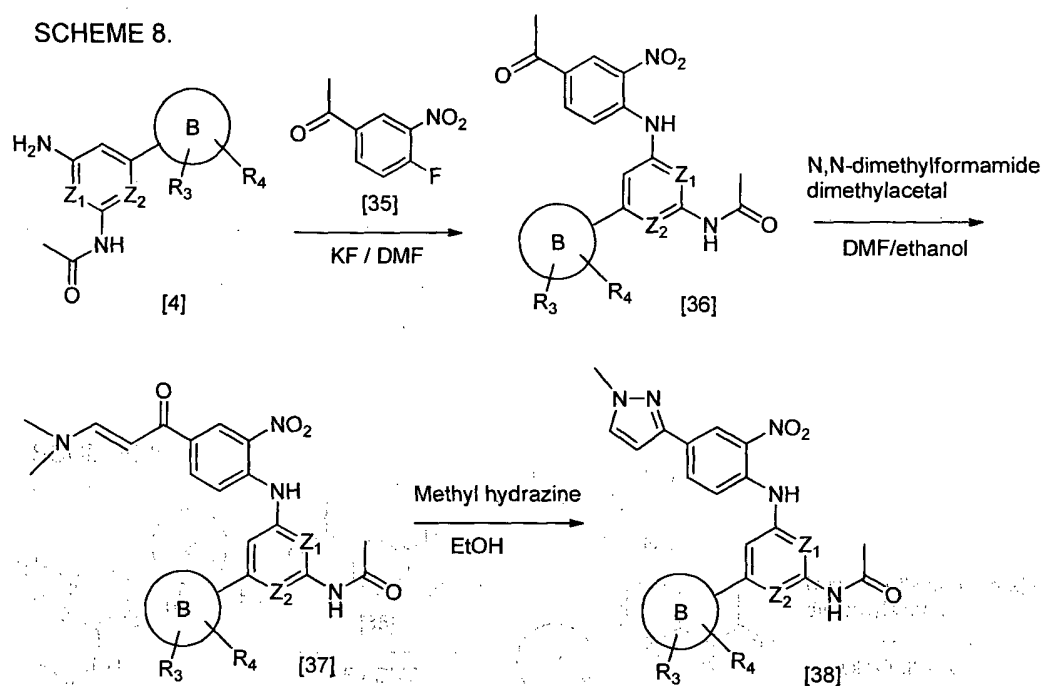
SCHEME 7.



In case where ring A in the compound [10] is a 1-methyl-1H-pyrazol-3-yl ring, the compound [10] can be also prepared according to Scheme 8, wherein R_3 , R_4 , Z_1 , Z_2 and ring B, are as defined above. In this method the compound [4] is treated with 1-(4-fluoro-3-nitrophenyl)ethanone and the resulting compound [36] is thereafter reacted with DMF dimethylacetal to produce the oxazol-5-yl compound [37]. Subsequent treatment with methyl hydrazine produces compound [38] in a ring closure reaction. The nitro group of compound [38] can be further reduced, e.g. by aqueous ammonium and zinc, to produce the corresponding amine, which can be then treated with formic acid according to Scheme 1 to afford the end product in the ring closure reaction.

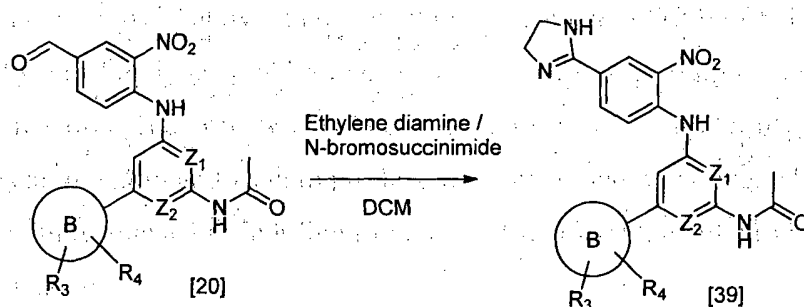
14

SCHEME 8.



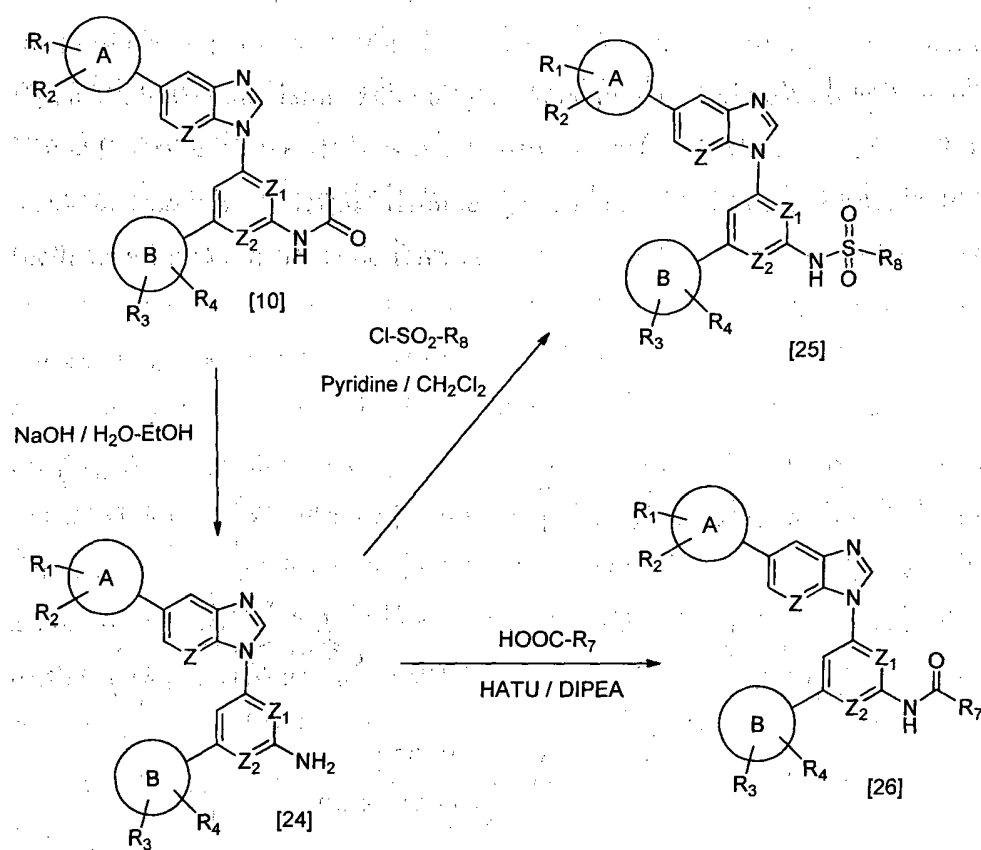
In case where ring A in the compound [10] is a 1H-imidazol-2-yl ring, the compound [10] can be also prepared according to Scheme 9, wherein R_3 , R_4 , Z_1 , Z_2 and ring B, are as defined above. In this method the compound [20] of Scheme 5 is treated with ethylene diamine and *N*-bromosuccinimide affording compound [39] in a ring closure reaction. The nitro group of compound [39] can be further reduced, e.g. by aqueous ammonium and zinc, to produce the corresponding amine, which can be then treated with formic acid according to Scheme 1 to afford the end product in the ring closure reaction.

SCHEME 9.



Various compounds of formula (I), wherein R_5 is other than $-C(O)CH_3$, can be prepared, for example, according to Scheme 10, wherein R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , Z , Z_1 , Z_2 , ring A and ring B are as defined above. The acetamide compound [10] can be converted to its corresponding amine [24], for example, by heating in ethanol in the presence of a base, such as aqueous sodium hydroxide or potassium hydroxide, or an acid such as aqueous HCl. The obtained amine [24] can be used as a starting material for subsequent reaction steps. The compounds of formula (I), wherein R_5 is $-SO_2R_8$ can be prepared, for example, by treating the amine [24] with $Cl-SO_2R_8$ in suitable solvent such as DCM in the presence of pyridine. Compounds of formula (I), wherein R_5 is $-C(O)R_7$ and R_7 is C_{1-7} alkyl or C_{1-7} alkylamino C_{1-7} alkyl, can be prepared, for example, by reacting the amine [24] with $HOOC-R_7$ in suitable solvent such as DMF in the presence of 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU) and DIPEA.

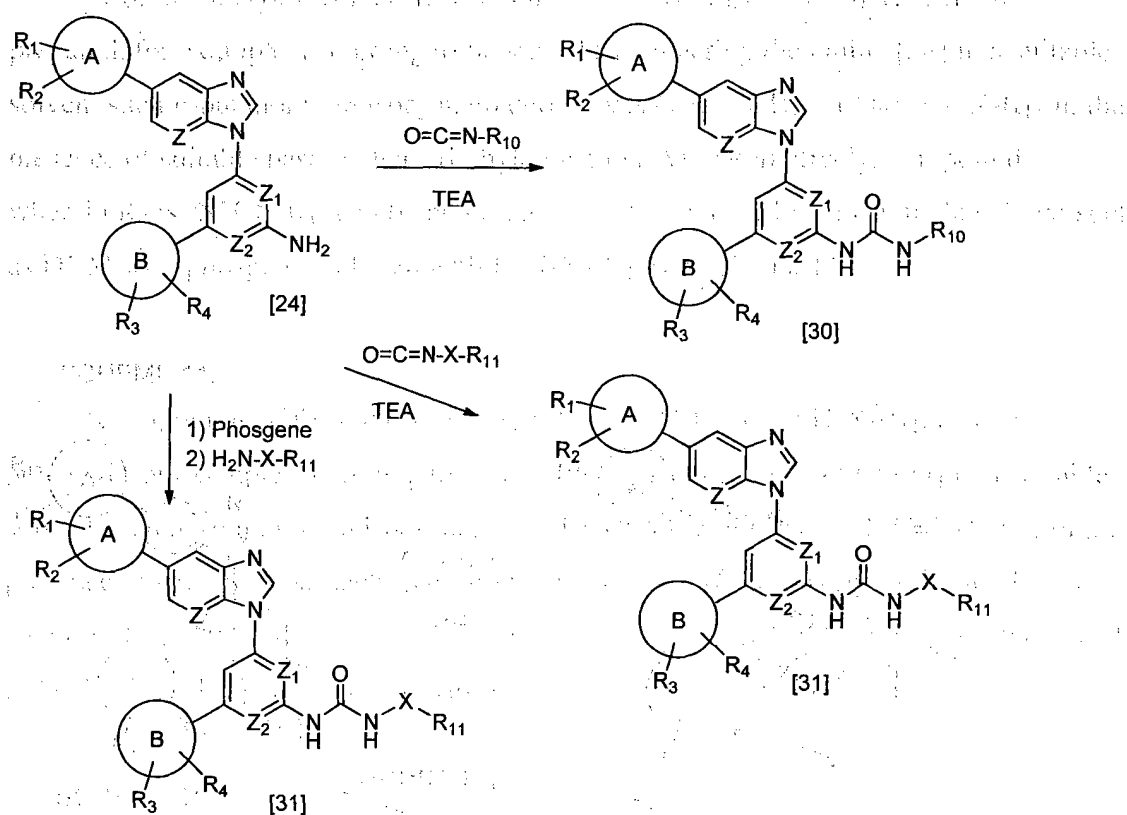
SCHEME 10.



Compounds of formula (I), wherein R_7 is $-NH-R_{10}$ or $-NH-X-R_{11}$, can be prepared, for example, according to Scheme 11 by reacting the amine [24] in a suitable solvent such n-butanol with isocyanato derivatives $O=C=N-R_{10}$ or $O=C=N-X-R_{11}$ in the presence of suitable base such as triethylamine (TEA). Alternatively, compounds

5 wherein R_7 is $-NH-X-R_{11}$ can be prepared by treating amine [24] in suitable solvent such as DCM with phosgene and then with H_2N-X-R_{11} , see Scheme 11.

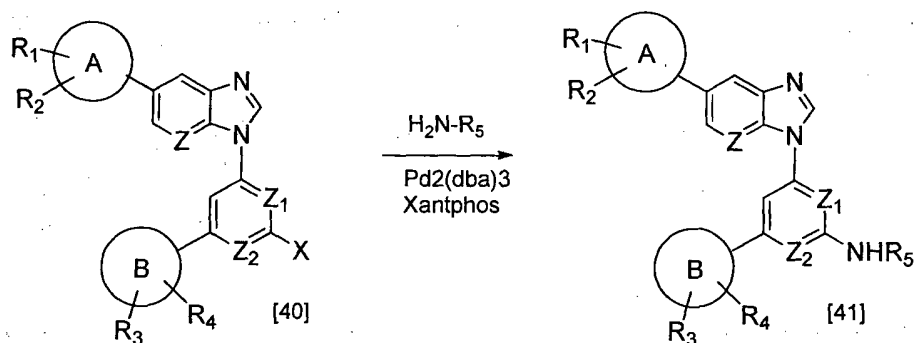
SCHEME 11.



Compounds wherein R_5 is $-C(O)R_7$, $-SO_2R_8$ or an optionally substituted 5-6 membered heterocyclic ring can also be prepared according to Scheme 12 starting from compound [40] wherein X is a halogen such as Br or Cl, and R_1 , R_2 , R_3 , R_4 , Z, Z_1 , Z_2 and ring B are as defined above, using palladium (e.g. $Pd_2(dba)_3$) catalyzed C-N coupling in the presence of a metal chelating ligand such as Xantphos.

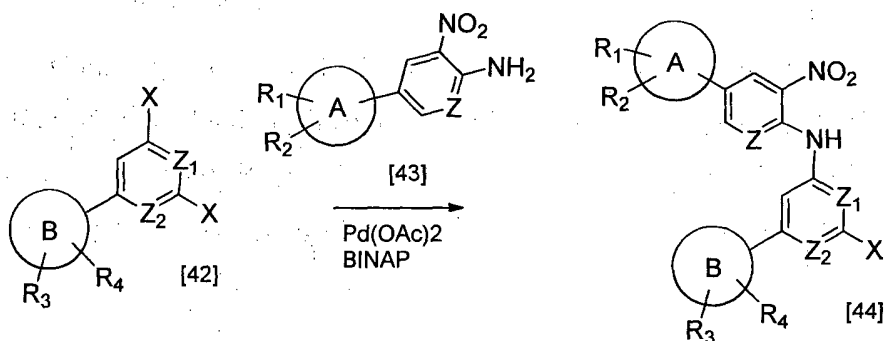
17

SCHEME 12.



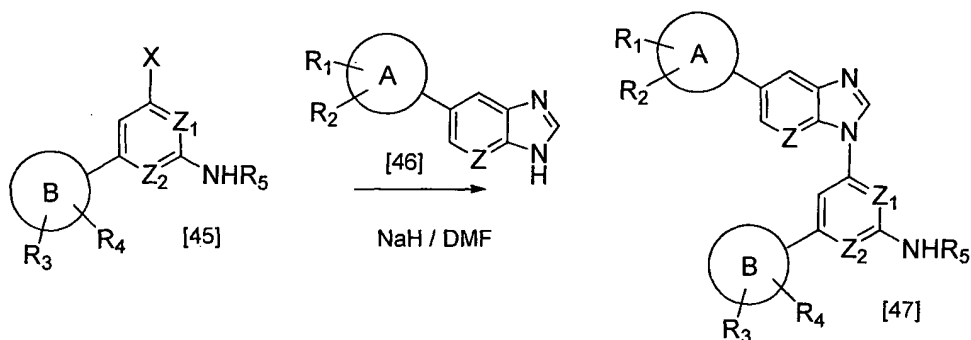
Compounds of formula (I) can be also prepared according to Scheme 13 by reacting compound [42] with compound [43] to produce compound [44] wherein X is a halogen such as Cl or Br, and R_1 , R_2 , R_3 , R_4 , Z , Z_1 , Z_2 and ring B are as defined above, followed by the bicyclic ring closure as in Scheme 1 and addition of the $-\text{NHR}_5$ group according to Scheme 12.

SCHEME 13.



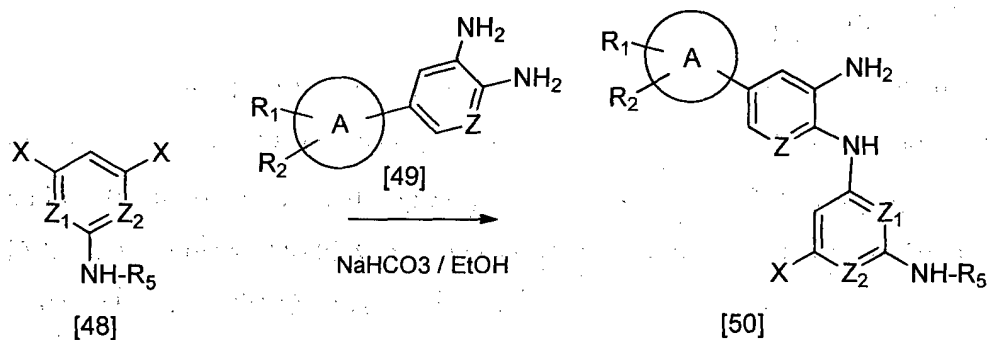
Compounds of formula (I) can be also prepared according to Scheme 14 by reacting compound [45] with compound [46] wherein X is a halogen such as Cl or Br, and R_1 , R_2 , R_3 , R_4 , R_5 , Z , Z_1 , Z_2 and rings A and B are as defined above.

SCHEME 14.



Compounds of formula (I) can be also prepared according to Scheme 15 by reacting compound [48] with compound [49] wherein X is a halogen such as Cl or Br, and R₁, R₂, R₅, Z, Z₁, Z₂ and rings A and B are as defined above. The formed compound [50] can be subjected to bicyclic ring closure and addition of B-ring by Suzuki coupling as described in Scheme 1 to obtaining compounds of formula (I).

SCHEME 15.



Pharmaceutically acceptable salts are well known in the field of pharmaceuticals. Non-limiting examples of suitable salts include metal salts, ammonium salt, salts with organic base, salts with inorganic acid, salts with organic acid, and salts with basic or acidic amino acid. Non-limiting examples of metal salts include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt, and magnesium salt. Non-limiting examples of salts with inorganic or organic acids include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the

pharmacological properties of the free form. Non-limiting examples of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl esters. Phosphate esters and carbonate esters, are also within the scope of the invention.

5

The terms employed herein have the following meanings:

The term "halo" or "halogen", as employed herein as such or as part of another group, refers to chlorine, bromine, fluorine or iodine.

10

The term " C_{1-7} alkyl", as employed herein as such or as part of another group, refers to a straight or branched chain saturated hydrocarbon group having 1, 2, 3, 4, 5, 6 or 7 carbon atom(s). Representative examples of C_{1-7} alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl and *n*-hexyl. The term " C_{1-3} alkyl" refers to an preferred embodiment of " C_{1-7} alkyl" having 1, 2 or 3 carbon atoms.

15

The term " C_{3-7} cycloalkyl", as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group containing 3, 4, 5, 6 or 7 carbon atoms. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

20

The term " C_{3-7} cycloalkyl C_{1-7} alkyl", as employed herein refers to a C_{3-7} cycloalkyl group, as defined herein, appended to the parent molecular moiety through a C_{1-7} alkyl group, as defined herein.

25

The term " C_{2-7} alkenyl", as employed herein as such or as part of another group, refers to an aliphatic hydrocarbon group having 2 to 7 carbon atoms and containing one or several double bonds. Representative examples include, but are not limited to, ethenyl, propenyl and cyclohexenyl.

30

The term "hydroxy", as employed herein as such or as part of another group, refers to an -OH group. The term "cyano", as employed herein as such or as part of another group, refers to a -CN group. The term "carboxy", as employed herein as such or as part of another group, refers to -COOH group. The term "carbonyl", as employed
5 herein as such or as part of another group, refers to a carbon atom double-bonded to an oxygen atom (C=O). The term "oxo", as employed herein as such or as part of another group, refers to oxygen atom linked to another atom by a double bond (=O).

The term "C₁₋₇ alkoxy", as employed herein as such or as part of another group,
10 refers to C₁₋₇ alkyl, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of C₁₋₇ alkoxy include, but are not limited to methoxy, ethoxy, propoxy, butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy.

The term "hydroxyl C₁₋₇ alkyl", as employed herein, refers to at least one
15 hydroxy group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of hydroxyl C₁₋₇ alkyl include, but are not limited to, hydroxymethyl, 2,2-dihydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl and 1-methyl-1-hydroxy-propyl.

The term "halo C₁₋₇ alkyl", as employed herein, refers to at least one halogen, as
20 defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of halo C₁₋₇ alkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl and 3-bromopropyl.

The term "cyano C₁₋₇ alkyl", as employed herein, refers to a cyano group, as
25 defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of cyano C₁₋₇ alkyl include, but are not limited to, cyanomethyl, 1-cyanoethyl, 1-cyanopropyl and 2-cyanopropyl.

The term "carboxy C₁₋₇ alkyl", as employed herein as such or as part of another group, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein.

5 The term "halo C₁₋₇ alkoxy", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkoxy group, as defined herein.

10 The term "phenyl C₁₋₇ alkoxy", as employed herein, refers to at least one phenyl group appended to the parent molecular moiety through a C₁₋₇ alkoxy group, as defined herein.

15 The term "C₁₋₇ alkylcarbonyl", as employed herein as such or as part of another group, refers to a C₁₋₇ alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

20 The term "C₁₋₇ alkoxy carbonyl", as employed herein as such or as part of another group, refers to a C₁₋₇ alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

25 The term "C₁₋₇ alkoxy carbonyl C₁₋₇ alkyl", as employed herein as such or as part of another group, refers to a C₁₋₇ alkoxy carbonyl group, as defined herein, appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein.

30 The term "aminocarbonyl", as employed herein as such or as part of another group, refers to an amino group appended to the parent molecular moiety through a carbonyl group, as defined herein.

35 The term "amino C₁₋₇ alkyl", as employed herein, refers to at least one amino group appended to the parent molecular moiety through a C₁₋₇ alkyl group, as defined herein. Representative examples of amino C₁₋₇ alkyl include, but are not limited to,

aminomethyl, 2-aminoethyl, 1-aminoethyl, 2,2-diaminoethyl, 3-aminopropyl, 2-aminopropyl, 4-aminobutyl and 1-methyl-1-aminoethyl.

The term "C₁₋₇ alkylamino", as employed herein as such or as part of another group, refers to at least one C₁₋₇ alkyl group, as defined herein, appended to the parent molecular moiety through an amino group. Representative examples of C₁₋₇ alkylamino include, but are not limited to methylamino, ethylamino, propylamino, butylamino, dimethylamino, diethylamino and *N*-ethyl-*N*-methylamino.

The term "C₁₋₇ alkylamino C₁₋₇ alkyl", as employed herein as such or as part of another group, refers to at least one C₁₋₇ alkylamino group, as defined herein, appended to the parent molecular moiety through an C₁₋₇ alkyl group, as defined herein.

The term "carboxy C₁₋₇ alkylamino", as employed herein as such or as part of another group, refers to at least one carboxy group, as defined herein, appended to the parent molecular moiety through an C₁₋₇ alkylamino group, as defined herein.

The term "C₁₋₇ alkoxy C₁₋₇ alkyl", as employed herein, refers to at least one C₁₋₇ alkoxy group, as defined herein, appended to the parent molecular moiety through an C₁₋₇ alkyl group, as defined herein.

The term "C₁₋₇ alkoxy carbonyl C₁₋₇ alkyl", as employed herein, refers to at least one C₁₋₇ alkoxy carbonyl group, as defined herein, appended to the parent molecular moiety through an C₁₋₇ alkyl group, as defined herein.

The term "substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine, or C₁₋₇ alkyl, C₃₋₇ cycloalkyl, halo C₁₋₇ alkyl, hydroxy, amino, C₁₋₇ alkoxy, C₁₋₇ acyl C₁₋₇ alkylamino, amino C₁₋₇ alkyl, nitro, cyano, thiol or methylsulfonyl substituents. Preferred are halogen, C₁₋₇ alkyl, halo C₁₋₇ alkyl, hydroxy, amino, C₁₋₇ alkoxy and methylsulfonyl substituents. Particularly preferred are 1 to 3 of C₁₋₃ alkyl substituents.

The "substituted" groups may contain 1 to 3, preferably 1 or 2, of the above mentioned substituents.

The term "5 - 6 membered heterocyclic ring" as employed herein, refers to a saturated, partially saturated or aromatic ring with 5 or 6 ring atoms, of which 1-4 atoms are heteroatoms selected from a group consisting of N, O and S. Representative examples of 5-6-membered heterocyclic ring include, but are not limited to, pyrazolyl, 1,2,4-triazol-1-yl, 1,2,3-triazol-1-yl, pyrimidinyl, pyridinyl, tetrazolyl, piperazinyl, furanyl, morpholinyl, piperidinyl, pyrrolidinyl, thiazolyl, isoxazolyl, pyrazinyl tetrahydropyranyl, 1,2,4-oxadiazolyl, oxazolyl, imidazolyl, indolyl and 4,5-dihydroimidazolyl rings.

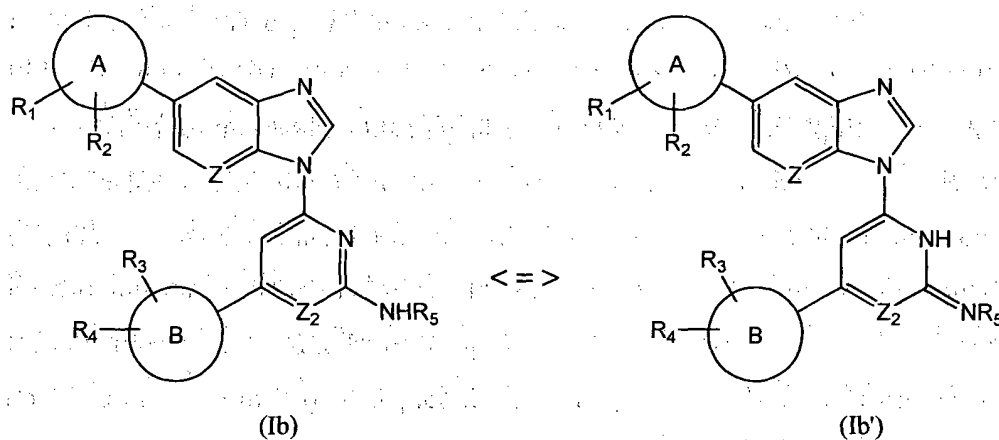
The term "5 - 12 membered heterocyclic ring" as employed herein, refers to a monocyclic or bicyclic saturated, partially saturated or aromatic ring with 5 to 12 ring atoms, of which 1-5 atoms are heteroatoms selected from a group consisting of N, O and S. Representative examples of 5 - 12 membered heterocyclic ring include the examples given above and additionally, but not limited to, indazolyl, pyrazolo[1,5-a]pyrimidinyl, benzo[d]imidazolyl, imidazo[4,5-b]pyridinyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl and benzofuranyl rings.

The term "5 - 12 membered carbocyclic ring" as employed herein, refers to a saturated, partially saturated or aromatic ring with 5 to 12 ring atoms consisting of carbon atoms only. Representative examples of 5 - 12 membered carbocyclic ring include, but are not limited to, phenyl, naphthyl and cyclohexyl rings.

The definition of formula (I) above is inclusive of all the possible isotopes and isomers, such as stereoisomers, of the compounds, including geometric isomers, for example *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, such as diastereomers and enantiomers, and prodrug esters, e.g. phosphate esters and carbonate esters.

It will be appreciated by those skilled in the art that the present compounds may contain at least one chiral center. Accordingly, the compounds may exist in optically active or racemic forms. It is to be understood that the formula (I) includes any racemic or optically active form, or mixtures thereof. In one embodiment, the compounds are the pure (R)-isomers. In another embodiment, the compounds are the pure (S)-isomers. In another embodiment, the compounds are a mixture of the (R) and the (S) isomers. In another embodiment, the compounds are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. The compounds may contain two chiral centers. In such case, according to one embodiment, the compounds of the invention are pure diastereomers. According to other embodiment, the compounds are a mixture of several diastereomers. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers or diastereomers, from the mixture thereof the conventional resolution methods, e.g. fractional crystallisation, may be used.

The present compounds may also exist as tautomers or equilibrium mixtures thereof wherein a proton of a compound shifts from one atom to another. Examples of tautomers include, but are not limited to, amido-imido, keto-enol, phenol-keto, oxime-nitroso, nitro-aci, imine-enamine and the like. Tautomeric forms of compounds of formula (I) are intended to be encompassed by compounds formula (I) even though only one tautomeric form may be depicted. For example, compounds of formula (Ib')



wherein R₁, R₂, R₃, R₄, R₅, Z, Z₂ and rings A and B are as defined above, are imido tautomers of amido compounds of formula (Ib) and are, therefore, within the scope of formula (I) as defined herein.

5 Examples of preferred compounds of formula (I) include

4-(2, 4-Difluorophenyl)-N-(1-methyl-1H-pyrazol-3-yl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl) pyridin-2-amine;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

10 Sodium salt of imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)methanesulfonamide;

15 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

Sodium salt of imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

20 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

Imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

25 Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)methanesulfonamide;

30 N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

5 N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)methanesulfonamide;

10 N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

Sodium salt of imido form of N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

15 N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

20 N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide;

N-(6-(5-(1H-pyrazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)-pyridin-2-yl)cyclopropanesulfonamide;

N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

25 N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide;

N-(4-(2-chlorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

30 N-(3-chloro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

N-(5-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

N-(6-(5-(1H-imidazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)-pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

5 N-(4-(2,4-difluorophenyl)-6-(5-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-ethyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

10 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-imidazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyrimidin-2-yl)acetamide;

15 Ethyl 1-(1-(6-(cyclopropanesulfonamido)-4-(2,4-difluorophenyl)pyridin-2-yl)-1H-benzo[d]imidazol-5-yl)-1H-1,2,3-triazole-4-carboxylate;

N-(4-(2-(difluoromethoxy)-4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

20 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide;

N-(6-(2,4-difluorophenyl)-4-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

or a pharmaceutically acceptable salt or tautomer thereof.

25 Compounds of the invention may be administered to a patient in therapeutically effective amounts which range usually from about 0.1 to about 5000 mg, preferably from about 1 to about 2000 mg, per day depending on the age, weight, ethnic group, condition of the patient, condition to be treated, administration route and the active ingredient used. The compounds of the invention can be formulated into dosage forms
30 using the principles known in the art. The compound can be given to a patient as such or in combination with suitable pharmaceutical excipients in the form of tablets, granules, capsules, suppositories, emulsions, suspensions or solutions. Choosing suitable

ingredients for the composition is a routine for those of ordinary skill in the art. Suitable carriers, solvents, gel forming ingredients, dispersion forming ingredients, antioxidants, colours, sweeteners, wetting compounds and other ingredients normally used in this field of technology may be also used. The compositions containing the active compound can be given enterally or parenterally, the oral route being the preferred way. The contents of the active compound in the composition is from about 0.5 to 100 %, preferably from about 0.5 to about 20 %, per weight of the total composition.

The compounds of the invention can be given to the subject as the sole active ingredient or in combination with one of more other active ingredients for treatment of a particular disease, for example cancer.

The present invention will be explained in more detail by the following experiments and examples. The experiments and examples are meant only for illustrating purposes and do not limit the scope of the invention defined in claims.

EXPERIMENTS

1. Inhibition of FGFR1 kinase

FGFR1 assay

Compounds were screened in the TR-FRET assay with FGFR1 kinase. 5 ng of FGFR1 [Upstate, USA] kinase was used for assay. The compound was incubated with the kinase for 30 minutes at room temperature. After the incubation, substrate mix [40 nM Ultra light poly GT (Perkin Elmer, USA) and 13 μ M ATP (Sigma)] was added. The above reaction was stopped by the addition of 40mM EDTA after the 30 min kinase reaction. The Eu-labelled antiphospho-tyrosine antibody [Perkin Elmer, USA] was added at 0.5 nM and the fluorescence emission at 615 nm/665 nm [excitation at 340 nm] was measured. The compounds were initially screened at 100 nM and 1 μ M concentrations. The compounds with >50 % inhibition at 100 nM of FGFR1 were taken

for the full dose response studies. The final DMSO concentration in the assay was 1 %. For IC₅₀ determination, 1/3rd serial dilution was made from the 20 mM DMSO stock solution. 2 µl of these were transferred to the test wells containing 20 µl of the reaction mixture [total reaction volume 20 µl]. The fluorescence was measured in Perkin Elmer
 5 Wallac 1420 Multilabel Counter Victor 3. The IC₅₀ was determined by fitting the dose response data to sigmoidal curve fitting equation using GraphPad Prism software V5.

Results

10 Enzymatic activity and selectivity of selected compounds of the invention on different kinases is presented in Table 1. The compounds of the invention were found to be potent and selective FGFR kinase inhibitors.

TABLE 1. Inhibition of FGFR1 kinase

Compound	Inhibition (%) of FGFR1 at 1000 nM	IC ₅₀ of FGFR1 inhibition (nM)
Example 1	97	16.5
Example 2	99	3.9
Example 2 (imido)	97	3.3
Example 4	98	4.3
Example 5	99	1.1
Example 5 (imido)	98	4.4
Example 6	99	1.7
Example 6 (imido)	98	1.7
Example 8	99	5.42
Example 8 (imido)	97	3.3
Example 10	97	5.8
Example 11	98	2.8
Example 11 (imido)	98	3.2
Example 12	97	1.5
Example 12 (imido)	99	5.2
Example 14	98	14.4
Example 16	97	3.4
Example 17	96	4.6
Example 17 (imido)	97	5.2

Example 18	97	5
Example 19	96	28.5
Example 21	99	3.7
Example 22	97	9.2
Example 23	97	10
Example 25	97	3.1
Example 26	94	21.9
Example 28	97	7.2
Example 29	97	9.7
Example 30	96	24
Example 32	99	21.7
Example 33	99	2
Example 34	99	1.6
Example 35	99	2
Example 36	99	4.7
Example 37	99	1.3
Example 38	87	12
Example 39	81	294.2
Example 40	76	293.5
Example 41	93	32.7
Example 43	94	43.4

The preparation of the compounds of the invention is illustrated by the following Examples.

5

EXAMPLES.

LCMS data has been recorded in +ve mode unless otherwise mentioned.

Intermediate Example 1.

10

4-(1-Methyl-1H-pyrazol-4-yl)-2-nitroaniline

15

A solution of 4-bromo-2-nitroaniline (6 g, 27.6 mmol) in 1, 2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.90 g, 33.1 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (2.25 g, 27.6 mmol, 0.1 eq) and aqueous sodium carbonate (8.79 g, 82.9 mmol, 3.0 eq) were added sequentially and the

mixture was further degassed for 5 min and then heated at 90 °C for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off under reduced pressure to afford the crude residue which was purified by column chromatography (60-120 silica gel, 40 % ethyl acetate in hexane) to afford the title product in 75 % yield (4.5 g). LC-MS (ESI): Calculated mass: 218.21; Observed mass: 218.9 [M+H]⁺ (rt: 0.390 min).

Intermediate Example 2.

tert-Butyl 3-(4-(1H-benzo[d]imidazol-5-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate

a) *tert*-Butyl 3-(methanesulfonyl) pyrrolidine-1-carboxylate

To a solution of *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (0.5 g, 2.67 mmol, 1.0 eq) in DCM (10 ml) was added TEA (0.8 ml, 5.35 mmol, 2.0 eq). The mixture was stirred at RT for 15 min. Then methanesulfonyl chloride (0.23 ml, 2.94 mmol 1.1 eq) was added and the mixture was stirred for 3 h. The mixture was then quenched with water and extracted with CH₂Cl₂ (3 × 50 ml). The solvent was distilled off to afford the title product in 86 % yield (0.6 g).

b) *tert*-butyl 3-(4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-pyrazol-1-yl) pyrrolidine-1-carboxylate

To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.6 g, 2.26 mmol) in DMF were added sodium hydride at 0 °C (0.108 g, 4.53 mmol, 2 eq) and the compound of Intermediate Example 2(a) (0.44 g, 2.26 mmol, 1.0 eq.). The mixture was stirred at RT for 1 h and heated at 90 °C for 4 h and quenched with ice and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue in 50 % yield (0.4 g).

c) *tert*-Butyl 3-(4-(1H-benzo[d]imidazol-5-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate

To a degassed (N₂ bubbling) solution of 5-bromo-1H-benzo[d]imidazole (0.050 g, 0.15 mmol) in 1,4-dioxane (10 ml) were added the compound of Intermediate Example 2(b) (0.052 g, 0.15 mmol, 1 eq), Pd(PPh₃)₄ (16 mg, 0.015 mmol, 0.1 eq) and cesium carbonate (0.118 g, 0.36 mmol, 2.5 eq) using the procedure of Intermediate Example 1. The mixture was heated at 90 °C for 16 h. The reaction mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the product in 40 % yield (20 mg). LC-MS (ESI): Calculated mass: 353.2; Observed mass: 354.4 [M+H]⁺ (rt: 0.11 min).

Intermediate Example 3.

4-(1-(2-(Dimethylamino)ethyl)-1H-pyrazol-4-yl)-2-nitroaniline

a) 2-(4-iodo-1H-pyrazol-1-yl)-N,N-dimethylethanamine

To a solution of 4-iodo-1H-pyrazole (2.8 g; 10 mmol) in acetonitrile (50 ml) were added cesium carbonate (5.04 g, 15 mmol, 1.5 eq) and 2-chloro-N,N-dimethylethanamine hydrochloride (2.96 g, 20 mmol, 2 eq) and the mixture was stirred at RT for 8 h. The mixture was quenched with water and extracted with EtOAc (3 × 150 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude product in 38 % yield (1 g).

b) 4-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-2-nitroaniline

A solution of the compound of Example 3(a) (0.5 g, 1.9 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 2-Nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.74 g, 2.8 mmol, 1.5 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.16 g, 0.2 mmol, 0.1 eq) and aqueous sodium carbonate (0.5 g, 4.7 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was heated at 90 °C for 16 h. The reaction mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 70 % ethyl acetate in hexane) to afford the title

product in 65 % yield (0.3 g). LC-MS (ESI): Calculated mass: 275.14; Observed mass: 276.15 $[M+H]^+$ (rt: 0.18 min).

Intermediate Example 4.

5 5-(1H-Pyrazol-1-yl)-1H-benzo[d]imidazole

a) 2-nitro-4-(1H-pyrazol-1-yl)aniline

To a solution of 4-bromo-2-nitroaniline (3 g, 13.8 mmol) in DMF (12 ml) were
10 added pyrazole (1.12 g, 16.4 mmol, 1.2 eq.), copper(I) oxide (0.1 g, 0.69 mmol, 0.05 eq.) and cesium carbonate (8 g, 24.6 mmol, 1.8 eq.) and the mixture was heated at 100 °C overnight. The mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off and the crude residue was purified by column chromatography (60-120 silica gel, 20 % ethyl acetate in hexane) to afford the title
15 product in 53.5 % yield (1.5 g).

b) 5-(1H-pyrazol-1-yl)-1H-benzo[d]imidazole

A mixture of the compound of Example 4(a) (0.5 g, 2.5 mmol) and iron powder
20 (1.39 g, 25 mmol, 10 eq) were refluxed in formic acid (20 ml) overnight. The formic acid was distilled off and the crude product was dissolved in ethyl acetate and filtered. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 87 % yield (0.4 g). LC-MS (ESI): Calculated mass: 184.07; Observed mass: 185.3 $[M+H]^+$ (rt: 0.097 min).

Intermediate Example 5.

N-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)cyclopropanesulfonamide

a) 2,6-dichloro-4-(2,4-difluorophenyl)pyridine

30

A solution of 2,6-dichloro-4-iodopyridine (1.5 g, 5.49 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N_2 bubbling for 5 min. 2,4-Difluorophenylboronic acid (0.86 g, 5.49 mmol, 1 eq) was added and the mixture was degassed for another 5 min.

Pd(dppf)Cl₂ (0.358 g, 0.43 mmol, 0.08 eq) and aqueous sodium carbonate (1.45 g, 13.7 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was heated at 90 °C for 16 h. The reaction mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 3 % ethyl acetate in hexane) to yield the title product in 98.5 % yield (1.4 g).

b) N-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Intermediate Example 5(a) (0.9 g, 3.46 mmol) in dioxane (20 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (0.36 g, 2.94 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (39 mg, 0.173 mmol, 0.05 eq) and xantphos (200 mg, 0.35 mmol, 0.1 eq) and Cs₂CO₃ (3.37 g, 10.4 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 16 h. The mixture was filtered through celite and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) to afford the title product in 50 % yield (0.6 g). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.05 (s, 1H), 7.76-7.68 (m, 1H), 7.51-7.43 (m, 1H), 7.35 (s, 1H), 7.30-7.24 (m, 1H), 7.16 (s, 1H), 3.09-3.01 (m, 1H), 1.22-1.09 (m, 2H), 1.08-1.03 (m, 2H).

Intermediate Example 6.

5-(1-Methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

A mixture of the compound of Intermediate Example 1 (3 g, 13.7 mmol) and iron powder (7.68 g, 137 mmol, 10 eq) were refluxed in formic acid (50 ml) overnight. The formic acid was distilled off and the crude product was dissolved in ethyl acetate and filtered. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 55.5 % yield (1.5 g). LC-MS (ESI): Calculated mass: 198.09; Observed mass: 199.2 [M+H]⁺ (rt: 0.097 min).

Intermediate Example 7.

5-(1-Methyl-1H-pyrazol-4-yl)-3-nitropyridin-2-amine

A solution of 5-bromo-3-nitropyridin-2-amine (5 g, 23 mmol) in 1, 2-dimethoxyethane (50 ml) was degassed by N₂ bubbling for 5 min. 1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (7.2 g, 37 mmol, 1.5 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (1.88 g, 2.3 mmol, 0.1 eq) and aqueous sodium carbonate (6.1 g, 52 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was heated at 90 °C for 16 h. The reaction mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 70 % ethyl acetate in hexane) to afford the title product in 50 % yield (2.5 g). LC-MS (ESI): Calculated mass: 219.08; Observed mass: 220.1 [M+H]⁺ (rt: 0.22 min).

Intermediate Example 8.**4-(1-(2-Morpholinoethyl)-1H-pyrazol-4-yl)-2-nitroaniline****a) 4-(2-(4-bromo-1H-pyrazol-1-yl)ethyl)morpholine**

To a solution of 4-(2-chloroethyl)morpholine (2.55 g, 13.6 mmol) and 4-bromo-1H-pyrazole (2 g, 13.6 mmol, 1 eq) in DMF (50 ml) was added K₂CO₃ (0.16 g, 6.72 mmol, 1.5 eq) and the mixture was stirred at RT for 24 h. The mixture was then quenched with water and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude product in 57 % yield (2 g).

b) 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine

A solution of the compound of Intermediate Example 8(a) (1 g, 3.8 mmol) in DME (15 ml) was degassed by N₂ bubbling for 5 min. Bispinacolato diborane (1.46 g, 5.7 mmol, 1.5 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.313 g, 0.38 mmol, 0.1 eq) and potassium acetate (1.32 g, 13.4 mmol, 3.5

eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was then heated at 100 °C for 4 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 87 % yield (1 g). LC-MS (ESI):
5 Calculated mass: 307.2; Observed mass: 308.5 [M+H]⁺ (rt: 0.10 min).

c) 4-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-2-nitroaniline

10 A solution of the compound of Intermediate Example 8(b) (1 g, 4.6 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 4-Bromo-2-nitroaniline (1.41 g, 4.6 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.38 g, 0.46 mmol, 0.1 eq) and aqueous sodium carbonate (1.41 g, 13.8 mmol, 3 eq) were added sequentially using the procedure of Intermediate
15 Example 1 and the mixture was then heated at 100 °C for 4 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 42 % yield (0.6 g). LC-MS (ESI): Calculated mass: 317.15; Observed mass: 318.05 [M+H]⁺ (rt: 0.20 min).

20 **Intermediate Example 9.**

4-(1H-Imidazol-1-yl)-2-nitroaniline

To a solution of 4-bromo-2-nitroaniline (3 g, 13.8 mmol) in DMF (12 ml) were
25 added imidazole (2.71 g, 27.6 mmol, 2 eq), copper(I) oxide (0.1 g, 0.69 mmol, 0.05 eq) and cesium carbonate (13.4 g, 41.4 mmol, 3 eq) and the mixture was heated at 100 °C overnight. The mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off and the crude residue was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 40 % yield
30 (1.1 g). ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.17 (br s, 1H), 8.12 (d, 1H), 7.73-7.68 (m, 2H), 7.59 (s, 2H), 7.15 (d, 1H), 7.08 (s, 1H).

35 **Intermediate Example 10.**

5-(1-Ethyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazole**a) 2-Nitro-4-((trimethylsilyl)ethynyl)aniline**

5 A solution of the compound of 4-iodo-2-nitroaniline (1 g, 3.8 mmol) in DMF-Et₃N (1:1; 20 ml) was degassed by N₂ bubbling for 15 min. Pd(PPh₃)₄ (0.22 g, 0.19 mmol, 0.05 eq.), copper(I) iodide (0.073 g, 0.386 mmol, 0.1 eq.) and ethynyltrimethylsilane (0.45 ml, 4.63 mmol, 1.2 eq.) were added sequentially and the mixture was stirred for 12 h at RT. The mixture was quenched and extracted as in Intermediate Example 1.
10 The solvent was distilled off and the crude residue was purified by column chromatography (60-120 silica gel, 10 % ethyl acetate in hexane) to afford the title product in 67 % yield (0.6 g).

b) 4-Ethynyl-2-nitroaniline

15 To a solution of the compound of Intermediate Example 10(a) (0.5 g, 2.15 mmol) in THF (10 ml) at 0 °C was added TBAF (0.5 g, 2.17 mmol, 1.2 eq.) and the mixture was stirred for 0.5 h. The mixture was filtered over a pad of silica and distilled to afford the title product in 86 % yield (0.3 g).

c) 4-(1-Ethyl-1H-1,2,3-triazol-4-yl)-2-nitroaniline

20 A mixture of the compound of Intermediate Example 10(b) (0.3 g, 1.85 mmol), sodium azide (0.24 g, 3.7 mmol, 1.0 eq.), methyl iodide (0.23 g, 1.85 mmol, 1.0 eq.), sodium ascorbate (0.36 g, 1.85 mmol, 1.0 eq.) and copper sulfate pentahydrate (0.23 g, 0.92 mmol, 0.5 eq.) in DMSO, THF and water (1:1:0.5, 5 ml) was stirred for 12 h at RT. The mixture was quenched with water and the precipitate formed was filtered and dried. The crude product was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) to afford the title product in 25 % yield (100 mg).

d) 5-(1-Ethyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazole

A solution of the compound of Intermediate Example 10(c) (0.1 g, 0.42 mmol) in formic acid (2 ml), iron (0.23 g, 4.2 mmol) was added and heated at 100 °C for 16 h. The formic acid was distilled off under reduced pressure and the crude product was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 33 % yield (30 mg). LC-MS (ESI): Calculated mass: 213.1; Observed mass: 214.1 [M+H]⁺ (rt: 0.14 min).

Intermediate Example 11.

10 5-(1-Methyl-1H-imidazol-4-yl)-1H-benzo[d]imidazole

a) 4-(1-Methyl-1H-imidazol-4-yl)-2-nitroaniline

A solution of 2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.45 g, 5.55 mmol, 1.1 eq) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 4-Bromo-1-methyl-1H-imidazole (0.81 g, 5 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.4 g, 0.5 mmol, 0.1 eq) and aqueous sodium carbonate (1.59 g, 15 mmol, 3 eq) were added sequentially using the procedure of Intermediate Example 1 and then heated at 100 °C for 4 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 60 % yield (0.6 g). LC-MS (ESI): Calculated mass: 218.08; Observed mass: 219.2 [M+H]⁺ (rt: 0.09 min).

25 b) 5-(1-methyl-1H-imidazol-4-yl)-1H-benzo[d]imidazole

To a solution of the compound of Intermediate Example 11(a) (0.3 g, 1.376 mmol) in formic acid (5 ml), iron (0.77 g, 13.76 mmol) was added and the mixture was heated at 90 °C for 12 h. The formic acid was distilled off and the crude product was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 26

% yield (0.07 g). LC-MS (ESI): Calculated mass: 198.09; Observed mass: 199.2
[M+H]⁺ (rt: 0.10 min).

Intermediate Example 12.

5 5-((Trimethylsilyl)ethynyl)-1H-benzo[d]imidazole

a) 5-Iodo-1H-benzo[d]imidazole

To a solution 4-iodo-2-nitroaniline (1 g, 3.7 mmol) in formic acid (10 ml), iron
10 (2.1 g, 37 mmol) was added and heated at 90 °C for 12 h. The formic acid was distilled
off and the crude was dissolved in ethyl acetate. The ethyl acetate layer was washed with
water, brine and dried over sodium sulphate. The solvent was distilled off to afford the
title product in 68 % yield (0.85 g). LC-MS (ESI): Calculated mass: 243.95; Observed
mass: 244.8 [M+H]⁺ (rt: 0.173 min).

15 b) 5-((Trimethylsilyl)ethynyl)-1H-benzo[d]imidazole

A solution of of the compound of Intermediate Example 12(a) (0.7 g, 2.56 mmol)
in DMF-Et₃N (1:1; 10 ml) was degassed by N₂ bubbling for 15 min. Pd(dppf)Cl₂ (0.11
20 g, 0.14 mmol, 0.05 eq), copper(I) iodide (0.054g, 0.25 mmol, 0.1 eq) and ethynyltri-
methylsilane (0.3 g, 3.15 mmol, 1.1 eq) were added sequentially and the mixture was
stirred for 12 h at RT. The mixture was quenched and extracted as in Intermediate
Example 1. The solvent was distilled off and the crude residue was recrystallized from
hexane to afford the title product in 57 % yield (0.35 g). LC-MS (ESI): Calculated mass:
25 214.09; Observed mass: 215.5 [M+H]⁺ (rt: 0.22 min).

Intermediate Example 13.

30 4-(1-Methyl-1H-pyrazol-4-yl) benzene-1, 2-diamine

To a solution of the compound Intermediate Example 1 (1 g, 4.58 mmol) in THF
(10 ml) were added a solution of ammonium chloride (1.486 g, 27.5 mmol, 6 eq) in
water (5 ml) and zinc (1.78 g, 27.5 mmol, 6 eq). The reaction mixture was stirred at RT
for 6 h and filtered. The filtrate was diluted with water and extracted with ethyl acetate

(3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 3 % methanol in DCM) to afford the title product in 58 % yield (0.5 g). LC-MS (ESI): Calculated mass: 188.11; Observed mass: 189.0 [M+H]⁺ (rt: 0.113 min).

Intermediate Example 14.

Ethyl 1-(1H-benzo[d]imidazol-5-yl)-1H-1,2,3-triazole-4-carboxylate

10 a) 1H-benzo[d]imidazol-5-amine

To a solution of 5-nitro-1H-benzo[d]imidazole (5 g, 44.2 mmol) in methanol (100 ml) was added Pd/C and the reaction mixture was stirred at RT for 16 h and filtered. The filtrate was diluted with water and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by washing with diethyl ether to afford the title product in 85 % yield (2.5 g). LC-MS (ESI): Calculated mass: 133.06; Observed mass: 134.2 [M+H]⁺ (rt: 0.175 min).

20 b) 5-Azido-1H-benzo[d]imidazole

To a solution of the compound of Intermediate Example 14(a) (2 g, 15 mmol) in concentrated HCl (8 ml) at 0 °C was added aqueous solution of NaNO₂ (1.3 g, 18.7 mmol, 1.25 eq) dropwise and the mixture was stirred at 0 °C for 30 min. Then NaN₃ (1.13 g, 18.7 mmol, 1.25 eq) was added at 0 °C and the mixture was stirred for 15 min. The mixture was quenched and extracted as in Intermediate Example 1(a). The solvent was distilled off to afford the product in 75 % yield (1.8 g). LC-MS (ESI): Calculated mass: 159.05; Observed mass: 160.0 [M+H]⁺ (rt: 0.136 min).

30 c) Ethyl 1-(1H-benzo[d]imidazol-5-yl)-1H-1,2,3-triazole-4-carboxylate

A mixture of the compound of Intermediate Example 14(b) (1.75 g, 10.99 mmol), ethyl propiolate (1.08 g, 10.99 mmol, 1.0 eq), sodium ascorbate (0.22 g, 1.09 mmol, 0.1 eq) and copper sulfate pentahydrate (30 mg, 0.1 mmol, 0.01 eq) in *t*-butanol and water (1:0.5, 20 ml) was stirred for 48 h at RT. The volatiles were evaporated and the reaction mixture was extracted with 10 % methanol in CH₂Cl₂ (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate and concentrated. The light brown solid obtained (1.6 g, 56.6 % yield) was directly taken for the next step without further purification. LC-MS (ESI): Calculated mass: 257.09; Observed mass: 258.05 [M+H]⁺ (rt: 0.193 min).

Intermediate Example 15.

N-(6-chloro-4-(2-(difluoromethoxy)-4-fluorophenyl)pyridin-2-yl)cyclopropane-sulfonamide

a) 1-Bromo-2-(difluoromethoxy)-4-fluorobenzene

To a solution of 2-bromo-5-fluorophenol (3 g, 15.7 mmol) in DMF (5 ml) was added cesium carbonate (7.7 g, 23.56 mmol, 1.5 eq) and sodium chlorodifluoroacetate (6 g, 39.26 mmol, 2.5 eq) and the reaction mixture was heated at 100 °C for 15 h. The reaction mixture was then extracted with water and ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % ethyl acetate in hexane) in 58 % yield (2.2 g).

b) 2,6-Dichloro-4-(2-(difluoromethoxy)-4-fluorophenyl)pyridine

A solution of the compound of Intermediate Example 15(a) (2.2 g, 9.13 mmol) in 1,2-dimethoxyethane (50 ml) was degassed by N₂ bubbling for 5 min. 2,6-Dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.75 g, 10.04 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.74 g, 0.9 mmol, 0.1 eq) and aqueous sodium carbonate (2.9 g, 27.3 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and then heated at 110 °C

for 4 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % ethyl acetate in hexane) to afford the title product in 43 % yield (1.2 g). LC-MS (ESI): Calculated mass: 306.98; Observed mass: 307.85 $[M+H]^+$ (rt: 2.0 min).

c) N-(6-chloro-4-(2-(difluoromethoxy)-4-fluorophenyl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Intermediate Example 15(b) (0.5 g, 1.62 mmol) in dioxane (10 ml) was degassed by N_2 bubbling for 5 min. Cyclopropane sulfonamide (0.19 g, 1.62 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (18 mg, 0.08 mmol, 0.05 eq) and xantphos (46 mg, 0.08 mmol, 0.05 eq) and cesium carbonate (1.56 g, 4.8 mmol, 3.0 eq) were added sequentially and the reaction mixture was further degassed for 5 min and then heated at 100 °C for 5 h. The reaction mixture was filtered through celite pad and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) in 47 % yield (0.3 g). LC-MS (ESI): Calculated mass: 392.02; Observed mass: 392.85 $[M+H]^+$ (rt: 1.82 min).

Intermediate Example 16.

N-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)acetamide

A solution of the compound of Intermediate Example 5(a) (0.5 g, 1.92 mmol) in dioxane (20 ml) was degassed by N_2 bubbling for 5 min. Acetamide (0.11 g, 1.92 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (43 mg, 0.19 mmol, 0.1 eq) and xantphos (222 mg, 0.38 mmol, 0.2 eq) and Cs_2CO_3 (1.88 g, 5.76 mmol, 3.0 eq) were added and the reaction mixture was further degassed for 5 min and then heated at 100 °C for 16 h. The reaction mixture was filtered through celite and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the

crude residue which was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) to afford the title product in 64.5 % yield (0.35 g). LC-MS (ESI): Calculated mass: 282.04; Observed mass: 283.0 [M+H]⁺ (rt: 1.60 min).

5 **Example 1.**

4-(2, 4-Difluorophenyl)-N-(1-methyl-1H-pyrazol-3-yl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl) pyridin-2-amine

10 a) 6-Chloro-4-(2, 4-difluorophenyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitro-phenyl) pyridin-2-amine
(rt: 1.60 min) Calculated mass: 282.04; Observed mass: 283.0 [M+H]⁺ (rt: 1.60 min)

A solution of the compound of Intermediate Example 5(a) (0.8 g, 3.07 mmol) in toluene (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate
15 Example 1 (0.8 g, 3.69 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (0.027 g, 0.123 mmol, 0.04 eq) and BINAP (0.076 g, 0.123 mmol, 0.04 eq) and potassium *tert*-butoxide (0.69 g, 6.15 mmol, 2.0 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 100 °C for 5 h. The mixture was filtered through celite pad and extracted with ethyl
20 acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) in 29.5 % yield (0.4 g). LC-MS (ESI): Calculated mass: 441.2; Observed mass: 442.0 [M+H]⁺ (rt: 1.84 min).

25 b) 1-(6-Chloro-4-(2, 4-difluorophenyl) pyridin-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

To a solution of the compound of Example 1(a) (0.4 g, 0.907 mmol) in formic
30 acid (5 ml), iron (0.5 g, 9.07 mmol) was added and the mixture was heated at 100 °C for 16 h. The formic acid was distilled off and the crude product was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium

sulphate. The solvent was distilled off to afford the title product in 47 % yield (0.18 g).
LC-MS (ESI): Calculated mass: 421.2; Observed mass: 422.5 [M+H]⁺ (rt: 1.83 min).

c) 4-(2, 4-Difluorophenyl)-N-(1-methyl-1H-pyrazol-3-yl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl) pyridin-2-amine

A solution of the compound of Example 1(b) (0.07 g, 0.166 mmol) in toluene (5 ml) was degassed by N₂ bubbling for 5 min. 1-Methyl-1H-pyrazol-3-amine (0.024 g, 0.199 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd₂(dba)₃ (0.007 g, 0.0083 mmol, 0.05 eq) and xantphos (0.005g, 0.0083 mmol, 0.05 eq) and Cs₂CO₃ (0.162 g, 0.4988 mmol, 3.0 eq) were added sequentially using the procedure of Example 1(a) and the mixture was heated at 100 °C for 16 h. The mixture was filtered and extracted using the procedure of Example 1(a). The solvent was distilled off to afford the crude residue which was purified by preparative HPLC to afford the title product in 15 % yield (12 mg). ¹H NMR (400 MHz, CD₃OD): δ 8.83 (s, 1H), 8.24-8.22 (d, 1H), 8.03 (s, 1H), 7.90-7.89 (d, 2H), 7.77-7.71 (m, 1H), 7.62-7.60 (m, 1H), 7.51 (d, 1H), 7.30-7.25 (d, 2H), 7.20-7.13 (m, 2H), 6.43-6.42 (d, 1H), 3.97 (s, 3H), 3.86 (s, 3H); LC-MS (ESI): Calculated mass: 482.18; Observed mass: 483.55 [M+H]⁺ (rt: 1.57 min).

Example 2.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 1(b) (42 mg, 0.1 mmol) in dioxane (1 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (0.11 g, 0.1 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (2 mg, 0.008 mmol, 0.08 eq) and xantphos (5 mg, 0.008 mmol, 0.08 eq) and Cs₂CO₃ (100 mg, 0.3 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 16 h. The mixture was filtered through celite and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by preparative HPLC to yield the title product in 20 %

yield (10 mg). ^1H NMR (300 MHz, CD_3OD): δ 9.33 (s, 1H), 8.68 (d, 1H), 8.08 (s, 1H), 7.94-7.92 (m, 2H), 7.81-7.73 (m, 2H), 7.70 (s, 1H), 7.24-7.16 (m, 3H), 3.96 (s, 3H), 3.16-3.09 (m, 1H), 1.28-1.24 (m, 2H), 1.05-1.01 (m, 2H); LC-MS (ESI): Calculated mass: 506.1; Observed mass: 507.1 $[\text{M}+\text{H}]^+$ (rt: 1.52 min).

5 **Example 2 (imido).**

Sodium salt of imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

The compound (34 mg) was prepared using the procedure described in Example 17 (imido) starting from the title compound of Example 2. The desired compound was
10 crystallized from ethanol. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 8.83 (s, 1H), 8.81-8.78 (d, 1H), 8.19 (s, 1H), 7.93 (s, 1H), 7.88 (d, 1H), 7.76-7.68 (m, 1H), 7.53-7.5 (d, 1H), 7.45-7.37 (dt, 1H), 7.27-7.20 (dt, 1H), 6.93 (s, 1H), 6.5 (s, 1H), 3.87 (s, 3H), 2.9 (m, 1H), 0.81-0.8 (m, 2H), 0.6-0.58 (m, 2H); LC-MS (ESI): Calculated mass: 506.1; Observed
15 mass: 506.8 $[\text{M}+\text{H}]^+$ (rt: 1.54 min).

Example 3.

10 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)acetamide

20 The compound was prepared from the compound of Example 1(b) using the procedure of Example 2. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.81 (s, 1H), 9.07 (s, 1H), 8.58 (d, 1H), 8.32-8.22 (m, 2H), 7.96-7.95 (m, 2H), 7.85-7.81 (m, 2H), 7.59 (d, 1H), 7.61-7.49 (m, 1H), 7.36-7.31 (m, 1H), 3.89 (s, 3H), 2.21 (s, 3H); LC-MS (ESI):
25 Calculated mass: 444.15; Observed mass: 445.3 $[\text{M}+\text{H}]^+$ (rt: 1.43 min).

30 **Example 4.**

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)methanesulfonamide

30 The compound was prepared from the compound of Example 1(b) using the procedure of Example 2. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.2 (s, 1H), 9.03 (s, 1H), 8.60 (d, 1H), 8.21 (s, 1H), 7.95 (s, 2H), 7.89-7.82 (m, 1H), 7.74 (s, 1H), 7.59-7.48 (m,

2H), 7.34-7.31 (m, 1H), 7.05 (s, 1H), 3.87 (s, 3H), 3.38 (s, 3H); LC-MS (ESI):

Calculated mass: 480.12; Observed mass: 481.05 $[M+H]^+$ (rt: 1.39 min).

Example 5.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
5 imidazol-1-yl)pyridin-2-yl)ethanesulfonamide

The compound was prepared from the compound of Example 1(b) using the
procedure of Example 2. ^1H NMR (400 MHz, DMSO- d_6): δ 11.1 (s, 1H), 9.02 (s, 1H),
8.61 (d, 1H), 8.22 (s, 1H), 7.95-7.94 (m, 2H), 7.89-7.83 (m, 1H), 7.74 (s, 1H), 7.60-7.56
10 (m, 1H), 7.54-7.48 (m, 1H), 7.36-7.31 (m, 1H), 7.06 (s, 1H), 3.87 (s, 3H), 3.54 (quartet,
2H), 1.26 (t, 3H); LC-MS (ESI): Calculated mass: 494.13; Observed mass: 494.8
 $[M+H]^+$ (rt: 1.5 min).

Example 5 (imido).

Sodium salt of imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-
15 pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide

The compound (30 mg) was prepared using the procedure described in Example 17
(imido) starting from the title compound of Example 5. The desired compound was
washed with diethylether and dried. ^1H NMR (300 MHz, DMSO- d_6): δ 8.83 (s, 1H),
20 8.8-8.7 (d, 1H), 8.19 (s, 1H), 7.93 (s, 1H), 7.88 (s, 1H), 7.73-7.69 (m, 1H), 7.52-7.49
(dd, 1H), 7.27-7.21 (t, 1H), 6.94 (s, 1H), 6.48 (s, 1H), 3.87 (s, 3H), 3.11-3.04 (q, 2H),
1.14-1.07 (t, 3H); LC-MS (ESI): Calculated mass: 494.13; Observed mass: 495.1
 $[M+H]^+$ (rt: 1.42 min).

Example 6.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide

The compound was prepared from the compound of Example 1(b) using the
30 procedure of Example 2. ^1H NMR (400 MHz, DMSO- d_6): δ 11.1 (s, 1H), 9.04 (s, 1H),
8.67 (d, 1H), 8.22 (s, 1H), 7.96-7.94 (m, 2H), 7.87-7.85 (m, 1H), 7.73 (s, 1H), 7.61-7.52
(m, 2H), 7.34 (m, 1H), 7.06 (s, 1H), 3.95 (m, 1H), 3.87 (s, 3H), 1.33 (d, 6H); LC-MS
(ESI): Calculated mass: 508.15; Observed mass: 509.05 $[M+H]^+$ (rt: 1.65 min).

Example 6 (imido).

Imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide

5 A slurry of the crude residue of the compound of Example 6 (12 g) was stirred at 65 °C with THF (166 ml) and filtered in hot condition. The solid material was dried under vacuum to afford 3.5 g of the title compound. ¹H NMR(400MHz, DMSO-d₆) δ 8.83-8.81 (m, 2H), 8.18 (s, 1H), 7.92 (s, 1H), 7.87 (s, 1H), 7.73-7.69 (m, 1H), 7.5-7.48 (d, 1H), 7.43-7.37 (dt, 1H), 7.25-7.21(dt, 1H), 6.93 (s, 1H), 6.49 (s, 1H), 3.87 (s, 3H), 3.75-10 3.65 (sep, 1H), 1.16-1.14 (d, 6H); LC-MS (ESI): Calculated mass: 508.15 (free base); Observed mass: 508.8 [M+H]⁺ (free base) (rt: 1.51 min).

Example 7.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-15 imidazol-1-yl)pyridin-2-yl)pyridazin-3-amine

The compound was prepared from the compound of Example 1(b) using the procedure of Example 2. ¹H NMR (400 MHz, DMSO-d₆): δ 10.29 (s, 1H), 8.93 (s, 1H), 8.90-8.87 (m, 1H), 8.43-8.42 (m, 1H), 8.24-8.18 (m, 2H), 8.15-8.10 (m, 2H), 7.99 (s, 20 1H), 7.96 (s, 1H), 7.65-7.62 (m, 2H), 7.5-7.44 (m, 1H), 7.36-7.28 (m, 2H), 3.87 (s, 3H); LC-MS (ESI): Calculated mass: 480.16; Observed mass: 481.1 [M+H]⁺ (rt: 1.39 min).

Example 8.

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

25

a) 2,6-Dichloro-4-(2-fluorophenyl)pyridine

A solution of 2,6-dichloro-4-iodopyridine (1.09 g, 4 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 2-Fluorophenylboronic acid (0.67 g, 4.8 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.33 g, 0.4 mmol, 0.1 eq) and aqueous sodium carbonate (1.27 g, 12 mmol, 3 eq) were added sequentially using the procedure of Intermediate Example 1 and 30

the mixture was then heated at 90 °C for 2 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 1 % ethyl acetate in hexane) to yield the title product in 100 % yield (0.97 g).

5

b) 6-Chloro-4-(2-fluorophenyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)pyridin-2-amine

10 A solution of the compound of Example 8(a) (0.97 g, 4 mmol) in toluene (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (0.96 g, 4.4 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (36 mg, 0.16 mmol, 0.04 eq) and BINAP (99 mg, 0.16 mmol, 0.04 eq) and potassium *tert*-butoxide (0.67 g, 6 mmol, 1.5 eq) were added sequentially
15 following the procedure of Example 1(a). The crude residue of the product was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) in 36 % yield (0.6 g). LC-MS (ESI): Calculated mass: 423.09; Observed mass: 424.05 [M+H]⁺ (rt: 2.04 min).

20 c) 1-(6-chloro-4-(2-fluorophenyl)pyridin-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

To a solution the compound of Example 8(b) (0.59 g, 1.4 mmol) in formic acid (5 ml), iron (0.78 g, 14 mmol) was added and heated at 100 °C for 16 h. The formic
25 acid was distilled off and the crude product was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 53 % yield (0.3 g). LC-MS (ESI):
Calculated mass: 403.1; Observed mass: 404.1 [M+H]⁺ (rt: 1.66 min).

30 d) N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 8(c) (0.1 g, 0.25 mmol) in dioxane (1 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (30 mg, 0.25

mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (5 mg, 0.02 mmol, 0.08 eq) and xantphos (12 mg, 0.02 mmol, 0.08 eq) and Cs₂CO₃ (0.24 g, 0.75 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 16 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by preparative HPLC to afford the title product in 8 % yield (10 mg).
¹H NMR (400 MHz, CD₃OD): δ 8.91 (s, 1H), 8.62 (d, 1H), 8.05 (s, 1H), 7.91 (m, 2H), 7.73-7.67 (m, 3H), 7.58-7.52 (m, 1H), 7.41-7.33 (m, 2H), 7.21 (s, 1H), 3.97 (s, 3H), 3.17-3.15 (m, 1H), 1.30-1.26 (m, 2H), 1.06-1.04 (m, 2H); LC-MS (ESI): Calculated mass: 488.14; Observed mass: 489.2 [M+H]⁺ (rt: 1.46 min).

Example 8 (imido).

Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

The compound (45 mg) was prepared using the procedure described in Example 17 (imido) starting from the title compound of Example 8. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.82 (s, 1H), 8.79-8.76 (d, 1H), 8.18 (s, 1H), 7.91 (s, 1H), 7.87 (d, 1H), 7.67-7.62 (m, 1H), 7.52-7.42 (m, 2H), 7.37-7.31 (m, 2H), 6.93 (s, 1H), 6.53 (s, 1H), 3.86 (s, 3H), 2.89 (m, 1H), 0.82-0.79 (m, 2H), 0.61-0.57 (m, 2H); LC-MS (ESI): Calculated mass: 488.14; Observed mass: 489.4 [M+H]⁺ (rt: 1.49 min).

Example 9.

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)acetamide

The compound was prepared from the compound of Example 8(c) using the procedure of Example 8. ¹H NMR (300 MHz, CD₃OD): δ 8.88 (s, 1H), 8.37-8.35 (m, 2H), 8.01 (s, 1H), 7.87 (m, 2H), 7.69-7.61 (m, 3H), 7.59-7.49 (m, 1H), 7.36-7.34 (m, 2H), 3.95 (s, 3H), 2.26 (m, 3H); LC-MS (ESI): Calculated mass: 426.16; Observed mass: 427.25 [M+H]⁺ (rt: 1.4 min).

Example 10.

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)methanesulfonamide

The compound was prepared from the compound of Example 8(c) using the procedure of Example 8. ^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 11.2 (s, 1H), 9.02 (s, 1H), 8.60 (d, 1H), 8.20 (s, 1H), 7.94 (s, 2H), 7.74 (m, 2H), 7.56 (m, 2H), 7.41 (m, 2H), 7.07 (s, 1H), 3.86 (s, 3H), 3.38 (s, 3H); LC-MS (ESI): Calculated mass: 462.13; Observed mass: 463.1 $[\text{M}+\text{H}]^+$ (rt: 1.31 min).

Example 11.

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide

The compound was prepared from the compound of Example 8(c) using the procedure of Example 8(d). ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 11.1 (s, 1H), 9.03 (s, 1H), 8.61 (d, 1H), 8.22 (s, 1H), 7.95-7.94 (m, 2H), 7.79-7.76 (m, 2H), 7.60-7.57 (m, 2H), 7.46-7.40 (m, 2H), 7.09 (s, 1H), 3.87 (s, 3H), 3.55 (quartet, 2H), 1.26 (t, 3H); LC-MS (ESI): Calculated mass: 476.14; Observed mass: 477.0 $[\text{M}+\text{H}]^+$ (rt: 1.41 min).

Example 11 (imido).

Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide

The compound (34 mg) was prepared using the procedure described in Example 17 (imido) starting from the title compound of Example 11. The desired compound was washed with diethyl ether and dried. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 8.83 (s, 1H), 8.8-8.78 (d, 1H), 8.2 (s, 1H), 7.93 (s, 1H), 7.89-7.88 (d, 1H), 7.68-7.65 (dt, 1H), 7.52-7.46 (m, 1H), 7.38-7.33 (m, 2H), 6.96 (s, 1H), 6.51 (s, 1H), 3.22 (s, 3H), 3.11-3.06 (q, 2H), 1.14-1.08 (t, 3H); LC-MS (ESI): Calculated mass: 476.14; Observed mass: 477.0 $[\text{M}+\text{H}]^+$ (rt: 1.41 min). Observed mass: 476.8 $[\text{M}+\text{H}]^+$ (rt: 1.37 min).

Example 12.

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide

The compound was prepared from the compound of Example 8(c) using the procedure of Example 8. ^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 11.03 (s, 1H), 9.03 (s, 1H),

8.67 (d, 1H), 8.22 (s, 1H), 7.96-7.94 (m, 2H), 7.79-7.73 (m, 2H), 7.61-7.55 (m, 2H), 7.42-7.39 (m, 2H), 7.08 (s, 1H), 3.96-3.93 (m, 1H), 3.87 (s, 3H), 1.33 (d, 6H); LC-MS (ESI): Calculated mass: 490.16; Observed mass: 491.1 [M+H]⁺ (rt: 1.48 min).

Example 12 (imido).

5 Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide

The title compound (24 mg) was prepared using the procedure described in Example 17 (imido) starting from the title compound of Example 12. ¹H NMR (400 MHz, DMSO-
10 d₆): δ 8.83-8.81 (m, 2H), 8.19 (s, 1H), 7.92 (s, 1H), 7.87 (d, 1H), 7.67-7.63 (dt, 1H), 7.51-7.46 (m, 2H), 7.37-7.32 (m, 2H), 6.94 (s, 1H), 6.51 (s, 1H), 3.87 (s, 3H), 3.75-3.65 (m, 1H), 1.16-1.14 (d, 6H); LC-MS (ESI): Calculated mass: 490.16; Observed mass: 491.4 [M+H]⁺ (rt: 1.5 min).

15 **Example 13.**

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)pyridazin-3-amine

The compound was prepared from the compound of Example 8(c) using the
20 procedure of Example 8. ¹H NMR (400 MHz, DMSO-d₆): δ 10.49 (s, 1H), 9.01 (s, 1H), 8.85-8.83 (m, 1H), 8.32-8.29 (m, 1H), 8.20 (s, 1H), 8.05 (s, 1H), 7.99-7.94 (m, 3H), 7.79-7.78 (m, 1H), 7.63-7.58 (m, 4H), 7.47-7.41 (m, 2H), 3.87 (s, 3H); LC-MS (ESI): Calculated mass: 462.17; Observed mass: 463.2 [M+H]⁺ (rt: 0.95 min).

Example 14.

25 N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

a) 2,6-Dichloro-4-(4-fluorophenyl)pyridine

30 A solution of 2,6-dichloro-4-iodopyridine (2.18 g, 8 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 4-Fluorophenylboronic acid (1.34 g, 9.6 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (1.3 g, 1.6 mmol, 0.2 eq) and aqueous sodium carbonate (2.54 g, 24 mmol,

3 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was then heated at 90 °C for 2 h. The reaction mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 1 % ethyl acetate in hexane) to yield the title product in 77 % yield (1.5 g). LC-MS (ESI):
5 Calculated mass: 240.99; Observed mass: 242.0 [M+H]⁺ (rt: 1.95 min).

b) 6-Chloro-4-(4-fluorophenyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)pyridin-2-amine

10 A solution of the compound of Example 14(a) (0.97 g, 4 mmol) in toluene (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (0.96 g, 4.4 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min.
15 Palladium acetate (36 mg, 0.16 mmol, 0.04 eq) and BINAP (99 mg, 0.16 mmol, 0.04 eq) and potassium *tert*-butoxide (0.67 g, 6 mmol, 1.5 eq) were added sequentially following the procedure of Example 1(a). The crude residue of the product was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) in 15 %
20 yield (0.25 g).

c) N1-(6-chloro-4-(4-fluorophenyl)pyridin-2-yl)-4-(1-methyl-1H-pyrazol-4-yl)-benzene-1,2-diamine

To a solution of the compound of Example 14(b) (0.25 g, 0.6 mmol) in THF (10
25 ml) were added a solution of ammonium chloride (0.26 g, 4.8 mmol, 8 eq) in water (2 ml) and zinc (0.31 g, 4.8 mmol, 8 eq). The mixture was stirred at RT for 6 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The
30 solvent was distilled off to afford the title product in 100 % yield (0.24 g). LC-MS (ESI): Calculated mass: 393.12; Observed mass: 394.5 [M+H]⁺ (rt: 1.59 min).

d) 1-(6-chloro-4-(4-fluorophenyl)pyridin-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

A solution of the compound of Example 14(c) (0.24 g, 0.6 mmol) and formic acid (5 ml) was heated at 100 °C for 16 h. The formic acid was distilled off and the crude product was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 38 % yield (90 mg). LC-MS (ESI): Calculated mass: 403.1;

5 Observed mass: 404.2 [M+H]⁺ (rt: 1.68 min).

e) N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

10 A solution the compound of Example 14(d) (40 mg, 01 mmol) in dioxane (1 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (12 mg, 0.1 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (2 mg, 0.008 mmol, 0.08 eq) and xantphos (5 mg, 0.008 mmol, 0.08 eq) and Cs₂CO₃ (0.1 g, 0.3 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then
15 heated at 100 °C for 16 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by preparative HPLC to afford the title product in 20 % yield (10 mg). ¹H NMR (400 MHz, CD₃OD): δ 8.97 (s, 1H), 8.68 (d, 1H), 8.06 (s, 1H), 7.92-7.89 (m, 4H), 7.73 (m, 1H), 7.69-7.67 (m, 1H), 7.34-7.29 (m, 2H), 7.21 (m, 1H), 3.97 (s, 3H), 3.16-3.09 (m,
20 1H), 1.30-1.26 (m, 2H), 1.05-1.03 (m, 2H); LC-MS (ESI): Calculated mass: 488.14; Observed mass: 489.1 [M+H]⁺ (rt: 1.5 min).

Example 15.

N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)acetamide

25

The compound was prepared from the compound of Example 14(d) using the procedure of Example 14. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.75 (s, 1H), 9.13 (s, 1H), 8.59 (d, 1H), 8.29 (d, 1H), 7.93-7.89 (m, 5H), 7.56 (d, 2H), 7.43-7.4 (m, 2H), 3.86 (s, 3H), 2.19 (m, 3H); LC-MS (ESI): Calculated mass: 426.16; Observed mass: 427.5
30 [M+H]⁺ (rt: 1.47 min).

Example 16.

N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)methanesulfonamide

The compound was prepared from the compound of Example 14(d) using the procedure of Example 14. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.2 (s, 1H), 9.12 (s, 1H), 8.63 (d, 1H), 8.22 (s, 1H), 7.96-7.92 (m, 4H), 7.86 (s, 1H), 7.59-7.57 (m, 1H), 7.46-7.42 (m, 2H), 7.11 (s, 1H), 3.88 (s, 3H), 3.38 (s, 3H); LC-MS (ESI): Calculated mass: 462.13; Observed mass: 462.8 [M+H]⁺ (rt: 1.43 min).

Example 17.

N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide

The compound was prepared from the compound of Example 14(d) using the procedure of Example 14(e). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.0 (s, 1H), 9.13 (s, 1H), 8.68 (d, 1H), 8.22 (s, 1H), 7.96-7.87 (m, 5H), 7.62-7.58 (m, 1H), 7.47-7.41 (m, 2H), 7.12 (s, 1H), 3.99-3.93 (m, 1H), 3.87 (s, 3H), 1.34 (d, 6H); LC-MS (ESI): Calculated mass: 490.16; Observed mass: 491.05 [M+H]⁺ (rt: 1.58 min).

Example 17 (imido).

Sodium salt of imido form of N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide

To the compound of Example 17 (37 mg) isopropyl alcohol (1 ml) and sodium *tert*-butoxide (7 mg) were added and after refluxing overnight the mixture was evaporated to yield 32 mg of the title compound. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.9 (s, 1H), 8.87-8.84 (d, 1H), 7.9 (s, 1H), 7.85-7.8 (m, 3H), 7.49-7.46 (d, 1H), 7.35-7.29 (t, 2H), 7.08 (s, 1H), 6.6 (s, 1H), 3.86 (s, 3H), 3.73-3.69 (m, 1H), 1.15-1.31 (d, 6H); Calculated mass: 490.16; Observed mass: 491.45 [M+H]⁺ (rt: 1.52min).

Example 18.

N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

a) 2,6-Dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

A solution of 2,6-dichloro-4-iodopyridine (15 g, 54.9 mmol) in DMF (150 ml) was degassed by N₂ bubbling for 5 min. Bispinacolato diborane (17.63 g, 82.4 mmol, 1.5 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (2.24 g, 2.7 mmol, 0.05 eq) and potassium acetate (8.07 g, 82.4 mmol, 1.5 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was then heated at 90 °C for 3 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 67 % yield (10 g). ¹H NMR (300 MHz, CDCl₃): δ 7.59 (s, 2H), 1.35 (s, 6H), 1.26 (s, 6H).

b) 2',6'-Dichloro-3-fluoro-2,4'-bipyridine

A solution of 2-bromo-3-fluoropyridine (3 g, 17 mmol) in 1,2-dimethoxyethane (30 mL) was degassed by N₂ bubbling for 5 min. The compound of Example 18(a) (9.3 g, 34 mmol, 2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (1.39 g, 1.7 mmol, 0.1 eq) and aqueous sodium carbonate (4.5 g, 42 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was then heated at 110 °C for 4 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % ethyl acetate in hexane) to afford the title product in 30 % yield (1.2 g). ¹H NMR (300 MHz, CDCl₃): δ 7.61-7.55 (m, 2H), 7.42-7.31 (m, 3H).

c) 6'-chloro-3-fluoro-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)-[2,4'-bipyridin]-2'-amine

A solution of the compound of Example 18(b) (1.2 g, 5 mmol) in dioxane (12 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (1.29 g, 6 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (110 mg, 0.5 mmol, 0.1 eq) and BINAP (610 mg, 1 mmol, 0.2 eq) and cesium carbonate (4.07 g, 12.4 mmol, 2.5 eq) were added sequentially following the

procedure of Example 1(a). The crude residue of the product was purified by column chromatography (60-120 silica gel, 70 % ethyl acetate in hexane) to yield the title product in 38 % yield (0.8 g).

- 5 d) N1-(6'-chloro-3-fluoro-[2,4'-bipyridin]-2'-yl)-4-(1-methyl-1H-pyrazol-4-yl)-benzene-1,2-diamine

To a solution of the compound of Example 18(c) (0.8 g, 1.9 mmol) in THF (15 ml) were added a solution of ammonium chloride (0.8 g, 15.1 mmol, 8 eq) in water (5
10 ml) and zinc (0.97 g, 15.1 mmol, 8 eq). The mixture was stirred at RT for 6 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the title product in 100 % yield (0.8 g). LC-MS (ESI): Calculated mass: 394.11; Observed mass: 395.0 [M+H]⁺ (rt: 1.34 min).

- 15 e) 1-(6'-chloro-3-fluoro-[2,4'-bipyridin]-2'-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

A solution of the compound of Example 18(d) (0.4 g, 1 mmol) and formic acid (5 ml) was heated at 110 °C for 12 h. The formic acid was distilled off and the crude was
20 extracted as in Example 8(c). The solvent was distilled off to afford the title product in 100 % yield (0.4 g). ¹H NMR (300 MHz, CD₃OD): δ 8.95 (s, 1H), 8.64 (m, 1H), 8.38 (s, 1H), 8.29-8.27 (m, 2H), 8.03-8.02 (m, 2H), 7.92-7.81 (m, 2H), 7.69-7.64 (m, 2H), 3.95 (s, 3H).

- 25 f) N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

A solution of the compound of Example 18(e) (40 mg, 0.1 mmol) in dioxane (1 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (12 mg, 0.1
30 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd₂(dba)₃ (9 mg, 0.01 mmol, 0.1 eq) and xantphos (6 mg, 0.01 mmol, 0.1 eq) and Cs₂CO₃ (80 mg, 0.25 mmol, 2.5 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 16 h. The mixture was filtered through celite and extracted as in

Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % methanol in CHCl_3) to afford the title product in 50 % yield (15 mg). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 11.22 (s, 1H), 9.0 (s, 1H), 8.69-8.63 (m, 2H), 8.24 (s, 1H), 8.04-7.98 (m, 4H), 7.71-7.6 (m, 2H), 7.49 (s, 1H), 3.88 (s, 3H), 3.17-3.15 (m, 1H), 1.13-1.12 (m, 2H), 1.05-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 489.14; Observed mass: 490.01 $[\text{M}+\text{H}]^+$ (rt: 0.57 min).

Example 19.

N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide

The compound was prepared from the compound of Example 18(e) using the procedure of Example 18. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 11.1 (s, 1H), 9.34 (s, 1H), 8.84 (s, 1H), 8.62 (d, 1H), 8.45 (d, 1H), 8.12 (s, 1H), 8.07 (s, 1H), 7.94-7.92 (m, 2H), 7.86-7.74 (m, 2H), 7.63-7.57 (m, 1H), 3.89 (s, 3H), 2.22 (m, 3H); LC-MS (ESI): Calculated mass: 427.16; Observed mass: 428.3 $[\text{M}+\text{H}]^+$ (rt: 0.7 min).

Example 20.

N-(3-fluoro-6'-(6-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

a) 6'-Chloro-3-fluoro-N-(5-(1-methyl-1H-pyrazol-4-yl)-3-nitropyridin-2-yl)-[2,4'-bipyridin]-2'-amine

A solution of 2',6'-dichloro-3-fluoro-2,4'-bipyridine (0.5 g, 2.1 mmol) in dioxane (12 ml) was degassed by N_2 bubbling for 5 min. The compound of Intermediate Example 7 (0.55 g, 2.5 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. $\text{Pd}_2(\text{dba})_3$ (0.19 g, 0.21 mmol, 0.1 eq) and xantphos (0.24 g, 0.42 mmol, 0.2 eq) and cesium carbonate (1.68 g, 5.2 mmol, 2.5 eq) were added sequentially following the procedure of Example 1(a). The crude residue of the product was purified by column chromatography (60-120 silica gel, 70 % ethyl acetate in hexane) to yield the title product in 32 % yield (0.28 g). LC-MS (ESI): Calculated mass: 425.08; Observed mass: 426.3 $[\text{M}+\text{H}]^+$ (rt: 1.72 min).

b) N2-(6'-chloro-3-fluoro-[2,4'-bipyridin]-2'-yl)-5-(1-methyl-1H-pyrazol-4-yl)pyridine-2,3-diamine

To a solution of the compound of Example 20(a) (0.28 g, 0.7 mmol) in THF (10 ml) were added a solution of ammonium chloride (0.28 g, 5.6 mmol, 8 eq) in water (5 ml) and zinc (0.33 g, 5.6 mmol, 8 eq). The mixture was stirred at RT for 2 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the title product in 72 % yield (0.2 g).

c) 3-(6'-Chloro-3-fluoro-[2,4'-bipyridin]-2'-yl)-6-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridine

A solution the compound of Example 20(b) (0.2 g, 0.5 mmol) and formic acid (5 ml) was heated at 100 °C for 16 h. The formic acid was distilled off and the crude was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 75 % yield (0.15 g).

d) N-(3-fluoro-6'-(6-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

A solution of the compound of Example 20(c) (40 mg, 0.1 mmol) in dioxane (1 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (14 mg, 0.12 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd₂(dba)₃ (9 mg, 0.01 mmol, 0.1 eq) and xantphos (6 mg, 0.01 mmol, 0.1 eq) and Cs₂CO₃ (80 mg, 0.25 mmol, 2.5 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 16 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % methanol in CHCl₃) to afford the title product in 8 % yield (5 mg). ¹H NMR (300 MHz, CDCl₃): δ 9.24 (s, 1H), 9.16 (s, 1H), 8.69 (s, 1H), 8.64 (m, 1H), 8.3 (s, 1H), 7.98 (s, 1H), 7.85 (s, 1H), 7.73 (s, 1H), 7.61-7.58 (m, 2H), 7.48-7.44 (m, 1H), 4.0 (s, 3H), 2.88 (m, 1H), 1.40-1.31 (m, 2H), 1.08-1.1 (m, 2H); LC-MS (ESI): Calculated mass: 490.13; Observed mass: 491.0 [M+H]⁺ (rt: 1.16 min).

Example 21.

N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

- 5 a) 6-Chloro-4-(2,4-difluorophenyl)-N-(4-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-2-nitrophenyl)pyridin-2-amine

A solution of the compound of Intermediate Example 5(a) (0.2 g, 0.8 mmol) in
10 dioxane (15 ml) was degassed by N₂ bubbling for 5 min. The compound Intermediate
Example 3 (0.23 g, 0.9 mmol, 1.1 eq) was added and the mixture was degassed for
another 5 min. Palladium acetate (0.017 g, 0.08 mmol, 0.1 eq) and BINAP (0.1 g, 0.16
mmol, 0.2 eq) and cesium carbonate (0.65 g, 2 mmol, 2.0 eq) were added sequentially
and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The
15 mixture was filtered through celite and extracted as in Example 1. The solvent was
distilled off to afford the crude residue which was purified by column chromatography
(60-120 silica gel, 10 % methanol in CH₂Cl₂) to afford the title product in 55 % yield
(0.1 g). LC-MS (ESI): Calculated mass: 498.14; Observed mass: 499.7 [M+H]⁺ (rt: 1.41
min).

- 20 b) N1-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-4-(1-(2-(dimethylamino)-ethyl)-1H-pyrazol-4-yl)benzene-1,2-diamine

To a solution of the compound of Example 21(a) (0.1 g, 0.2 mmol) in THF (10
25 ml) were added a solution of ammonium chloride (85 mg, 1.6 mmol, 8 eq) in water (2
ml) and zinc (0.1 g, 1.6 mmol, 8 eq). The mixture was stirred at RT for 12 h and filtered.
The filtrate was diluted with water and extracted as in Intermediate Example 1. The
solvent was distilled off to afford the title product in 100 % yield (93 mg).

- 30 c) 2-(4-(1-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-1-yl)-N,N-dimethylethanamine

A solution the compound of Example 21(b) (93 mg, 0.2 mmol) and formic acid
(5 ml) was heated at 100 °C for 12 h. The formic acid was distilled off and the crude was

extracted as in Example 8(c). The solvent was distilled off to afford desired title product in 83 % yield (80 mg). LC-MS (ESI): Calculated mass: 478.15; Observed mass: 479.45 $[M+H]^+$ (rt: 1.36 min).

5 d) N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 21(c) (80 mg, 0.2 mmol) in dioxane (5 ml) was degassed by N_2 bubbling for 5 min. Cyclopropane sulfonamide (29 mg, 0.24 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(OAc) $_2$ (5 mg, 0.02 mmol, 0.1 eq) and xantphos (23 mg, 0.04 mmol, 0.2 eq) and Cs $_2$ CO $_3$ (162 mg, 0.5 mmol, 2.5 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % methanol in CH $_2$ Cl $_2$) to afford the desired title product in 35 % yield (20 mg). ^1H NMR (400 MHz, CDCl $_3$): δ 8.7 (s, 1H), 8.04 (m, 2H), 7.82 (d, 2H), 7.56 (m, 2H), 7.41 (m, 2H), 7.07-7.02 (m, 2H), 4.29 (m, 2H), 2.89-2.84 (m, 3H), 2.33 (s, 6H), 1.39 (m, 2H), 1.08 (m, 2H); LC-MS (ESI): Calculated mass: 563.19; Observed mass: 564.25 $[M+H]^+$ (rt: 0.59 min).

20 **Example 22.**

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide

a) 4-Chloro-6-(2-fluorophenyl)pyrimidin-2-amine

25 A solution of 4,6-dichloropyrimidin-2-amine (5 g, 30.6 mmol) in 1,2-dimethoxyethane (50 ml) was degassed by N_2 bubbling for 5 min. 2-Fluorophenylboronic acid (4.27 g, 30.6 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl $_2$ (1.25 g, 1.53 mmol, 0.05 eq) and aqueous sodium carbonate (8.12 g, 76.6 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and then heated at 90 °C for 3 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 30 %

ethyl acetate in hexane) to afford the title product in 15 % yield (1 g). LC-MS (ESI): Calculated mass: 223.03; Observed mass: 224.0 $[M+H]^+$ (rt: 1.53 min).

b) N-(4-chloro-6-(2-fluorophenyl)pyrimidin-2-yl)cyclopropanesulfonamide

To an icecold solution of the compound of Example 22(a) (1 g, 4.48 mmol) in DMF (50 ml) was added NaH (0.16 g, 6.72 mmol, 1.5 eq). The mixture was stirred for 10 min and cyclopropylsulfonyl chloride (0.76 g, 5.38 mmol, 1.2 eq) was added and the mixture was stirred at RT for 24 h. The mixture was then quenched with water and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude product which was purified by column chromatography (60-120 silica gel, 5 % ethyl acetate in hexane) to afford the title product in 34 % yield (0.5 g). LC-MS (ESI): Calculated mass: 327.02; Observed mass: 327.8 $[M+H]^+$ (rt: 1.61 min).

c) N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide

To an icecold solution of the compound of Example 22(b) (0.2 g, 0.61 mmol) in DMF (50 ml) in a sealed tube was added NaH (22 mg, 0.9 mmol, 1.5 eq). The mixture was stirred for 10 min and the compound of Intermediate Example 6 (0.12 g, 0.61 mmol, 1 eq) was added. The mixture was stirred at RT for 24 h and then quenched and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford a crude product mixture from which the title compound was isolated by preparative TLC in 0.01% yield (3 mg). ^1H NMR (400 MHz, CDCl_3): δ 8.75 (s, 1H), 8.36 (d, 1H), 8.24-8.21 (m, 2H), 7.99 (s, 1H), 7.85-7.81 (m, 2H), 7.69 (s, 1H), 7.63-7.55 (m, 3H), 7.39-7.37 (m, 1H), 3.99 (s, 3H), 3.3 (m, 1H), 1.12-1.10 (m, 2H), 0.88-0.84 (m, 2H); LC-MS (ESI): Calculated mass: 489.14; Observed mass: 490.4 $[M+H]^+$ (rt: 1.43 min).

Example 23.

N-(6-(5-(1H-pyrazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)-pyrimidin-2-yl)cyclopropanesulfonamide

A solution of the title compound of Intermediate Example 5 (50 mg, 0.144 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 4 (26 mg, 0.144 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (1.3 mg, 0.0072 mmol, 0.05 eq), N,N-dimethyl glycine
5 (1.4 mg, 0.0144 mmol, 0.1 eq) and Cs₂CO₃ (141 mg, 0.434 mmol, 3.0 eq) were added and the reaction mixture was further degassed for 5 min and then heated at 100 °C for 24 h. The reaction mixture was filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford a crude product mixture from which the title compound was isolated by preparative HPLC to afford the title compound in 14 % yield
10 (10 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.2 (s, 1H), 9.18 (d, 1H), 8.86 (d, 1H), 8.66 (d, 1H), 8.23 (d, 1H), 7.96-7.86 (m, 2H), 7.83-7.78 (m, 2H), 7.59-7.51 (m, 1H), 7.39-7.34 (m, 1H), 7.16 (s, 1H), 6.59 (s, 1H), 3.19-3.14 (m, 1H), 1.24-1.12 (m, 2H), 1.06-1.03 (m, 2H); LC-MS (ESI): Calculated mass: 492.12; Observed mass: 493.4 [M+H]⁺ (rt: 1.71 min).

15 **Example 24.**

N-(4-(2,4-difluorophenyl)-6-(6-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)pyridin-2-yl)cyclopropanesulfonamide

20 a) 6-Chloro-4-(2,4-difluorophenyl)-N-(5-(1-methyl-1H-pyrazol-4-yl)-3-nitropyridin-2-yl)pyridin-2-amine

A solution of the compound of Intermediate Example 5(a) (0.5 g, 1.92 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example
25 7 (0.42 g, 1.92 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd₂(dba)₃ (0.087 g, 0.09 mmol, 0.05 eq) and xantphos (0.11 g, 0.192 mmol, 0.1 eq) and cesium carbonate (1.56 g, 4.8 mmol, 2.5 eq) were added sequentially following the procedure of Example 1(a) and the mixture was then heated at 110 °C for 16 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was
30 distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 20 % ethyl acetate in hexane) to afford the title product in 46 % yield (0.4 g).

b) N2-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)pyridine-2,3-diamine

To a solution of the compound of Example 24(a) (0.39 g, 0.88 mmol) in THF (10 ml) were added a solution of ammonium chloride (0.37 g, 7 mmol, 8 eq) in water (2 ml) and zinc (0.46 g, 7 mmol, 8 eq). The mixture was stirred at RT for 6 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the title product in 88 % yield (0.32 g).

c) 3-(6-Chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridine

A solution the compound of Example 24(b) (0.32 g, 0.77 mmol) and formic acid (10 ml) was heated at 100 °C for 16 h. The formic acid was distilled off and the crude was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 70 % yield (0.23 g). LC-MS (ESI): Calculated mass: 422.09; Observed mass: 423.2 [M+H]⁺ (rt: 1.74 min).

d) N-(4-(2,4-difluorophenyl)-6-(6-(1-methyl-1H-pyrazol-4-yl)-3H-imidazo[4,5-b]pyridin-3-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 24(c) (150 mg, 0.35 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (55 mg, 0.46 mmol, 1.3 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (4 mg, 0.017 mmol, 0.05 eq) and xantphos (20 mg, 0.03 mmol, 0.1 eq) and Cs₂CO₃ (288 mg, 0.88 mmol, 2.5 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 3 % methanol in CH₂Cl₂) to afford the title product in 27 % yield (48 mg). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.07 (s, 1H), 9.09 (s, 1H), 8.80 (d, 1H), 8.49-8.45 (m, 2H), 8.30 (s, 1H), 8.05 (d, 1H), 7.81-7.73 (m, 1H), 7.57-7.49 (m, 1H), 7.38-7.32 (m, 1H), 7.11 (s, 1H), 3.89 (s, 3H), 3.41-3.37

(m, 1H), 1.13-1.10 (m, 4H); LC-MS (ESI): Calculated mass: 507.13; Observed mass: 508.1 [M+H]⁺ (rt: 1.54 min).

Example 25.

N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-
5 [2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

a) 2',6'-Dichloro-3,5-difluoro-2,4'-bipyridine

A solution of 2-bromo-3,5-difluoropyridine (1.6 g, 5.84 mmol) in 1,2-di-
10 methoxyethane (30 ml) was degassed by N₂ bubbling for 5 min. The compound of
Example 18(a) (1.36 g, 7 mmol, 2 eq) was added and the mixture was degassed for
another 5 min. Pd(dppf)Cl₂ (0.47 g, 0.58 mmol, 0.1 eq) and aqueous sodium carbonate
(1.85 g, 17.5 mmol, 3 eq) were added sequentially using the procedure of Intermediate
Example 1 and the mixture was then heated at 90 °C for 2 h. The reaction mixture was
15 quenched and extracted as in Intermediate Example 1. The solvent was distilled off to
afford the crude residue which was purified by column chromatography (60-120 silica
gel, 5 % ethyl acetate in hexane) to afford the title product in 72 % yield (1.1 g).

**b) 6'-Chloro-3,5-difluoro-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)-[2,4'-
20 bipyridin]-2'-amine**

A solution of the compound of Example 25(a) (0.4 g, 1.5 mmol) in dioxane (12
ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1
25 (0.4 g, 1.84 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min.
Palladium acetate (17 mg, 0.08 mmol, 0.05 eq) and BINAP (47 mg, 0.08 mmol, 0.05
eq) and potassium *tert*-butoxide (0.26 g, 2.29 mmol, 1.5 eq) were added sequentially
following the procedure of Example 1(a) and the mixture was then heated at 110 °C for
72 h. The crude residue of the product was purified by column chromatography (60-120
30 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 18 % yield (0.12 g).
LC-MS (ESI): Calculated mass: 442.08; Observed mass: 443.05 [M+H]⁺ (rt: 1.98 min).

c) N1-(6'-chloro-3,5-difluoro-[2,4'-bipyridin]-2'-yl)-4-(1-methyl-1H-pyrazol-4-yl)benzene-1,2-diamine

To a solution of the compound of Example 25(b) (0.12 g, 0.27 mmol) in THF (15 ml) were added a solution of ammonium chloride (0.15 g, 2.7 mmol, 8 eq) in water (2 ml) and zinc (0.18 g, 2.7 mmol, 8 eq). The mixture was stirred at RT for 6 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the title product in 90 % yield (0.1 g).

d) 1-(6'-Chloro-3,5-difluoro-[2,4'-bipyridin]-2'-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

A solution the compound of Example 25(c) (0.1 g, 0.242 mmol) and formic acid (10 ml) was heated at 100 °C for 16 h. The formic acid was distilled off and the crude product was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 78 % yield (80 mg). LC-MS (ESI): Calculated mass: 422.09; Observed mass: 422.8 [M+H]⁺ (rt: 1.69 min).

e) N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

A solution of the compound of Example 25(d) (80 mg, 0.19 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (28 mg, 0.23 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (4.2 mg, 0.019 mmol, 0.1 eq) and xantphos (22 mg, 0.04 mmol, 0.2 eq) and Cs₂CO₃ (185 mg, 0.57 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by preparative TLC to afford the title product in 5 % yield (5 mg). ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.98 (s, 1H), 8.76 (d, 1H), 8.61 (d, 1H), 8.25-8.18 (m, 2H), 7.96 (m, 3H), 7.62-7.59 (m, 1H), 7.47 (s, 1H), 3.88 (s, 3H), 3.12 (m, 1H), 1.14-1.12 (m, 2H), 1.04-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 507.13; Observed mass: 508.1 [M+H]⁺ (rt: 1.27 min).

Example 26.

N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide

5 The compound was prepared from the compound of Example 25(d) using the procedure of Example 28. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.85 (s, 1H), 9.0 (s, 1H), 8.76 (d, 1H), 8.58 (s, 1H), 8.50 (d, 1H), 8.23-8.21 (m, 2H), 8.0 (s, 1H), 7.95 (m, 2H), 7.62-7.59 (m, 1H), 3.88 (s, 3H), 2.21 (s, 3H); LC-MS (ESI): Calculated mass: 445.15; Observed mass: 446.1 [M+H]⁺ (rt: 1.08 min).

Example 27.

10 N-(6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-4-(1H-pyrrol-1-yl)pyridin-2-yl)acetamide

a) 2,6-Dichloro-4-(1H-pyrrol-1-yl)pyridine

15 A solution 2,6-dichloropyridin-4-amine (2 g, 12.3 mmol) and 2,5-dimethoxyfuran (1.94 g, 14.7 mmol, 1.2 eq) in acetic acid (10 ml) was heated at 90 °C for 2 h. The mixture was quenched with water and extracted with EtOAc (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent
20 was distilled off to afford the title product in 80 % yield (2.1 g).

b) 6-Chloro-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)-4-(1H-pyrrol-1-yl)pyridin-2-amine

25 To an icecold solution of the compound of Example 27(a) (1 g, 4.58 mmol) in DMSO (20 ml) was added NaH (0.13 g, 5.5 mmol, 1.2 eq). The mixture was stirred for 10 min and the compound of Intermediate Example 1 (1.1 g, 5.5 mmol, 1.2 eq) was added. The mixture was stirred at RT for 16 h and then quenched with water and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with
30 water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude product which was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 25 % yield (0.45 g). LC-MS (ESI): Calculated mass: 394.09; Observed mass: 394.8 [M+H]⁺ (rt: 1.87 min).

c) N1-(6-chloro-4-(1H-pyrrol-1-yl)pyridin-2-yl)-4-(1-methyl-1H-pyrazol-4-yl)benzene-1,2-diamine

5 To a solution of the compound of Example 27(b) (0.43 g, 1.1 mmol) in THF (30 ml) were added a solution of ammonium chloride (0.58 g, 10.9 mmol, 10 eq) in water (5 ml) and zinc (0.71 g, 10.9 mmol, 10 eq). The mixture was stirred at RT for 6 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the product in 90 % yield (0.36 g). LC-MS (ESI):
10 Calculated mass: 364.12; Observed mass: 365.0 [M+H]⁺ (rt: 1.47 min).

d) 1-(6-Chloro-4-(1H-pyrrol-1-yl)pyridin-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

15 A solution of the compound of Example 27(c) (0.35 g, 0.96 mmol) and formic acid (10 ml) was heated at 100 °C for 16 h. The formic acid was distilled off and the crude was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 97 % yield (350 mg). LC-MS (ESI): Calculated mass: 374.10; Observed mass: 375.1 [M+H]⁺ (rt: 1.59 min).

20 e) N-(6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-4-(1H-pyrrol-1-yl)pyridin-2-yl)acetamide

A solution of the compound of Example 27(d) (100 mg, 0.27 mmol) in dioxane
25 (5 ml) was degassed by N₂ bubbling for 5 min. Acetamide (19 mg, 0.32 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (3 mg, 0.013 mmol, 0.05 eq) and xantphos (15 mg, 0.026 mmol, 0.1 eq) and Cs₂CO₃ (261 mg, 0.8 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The mixture was filtered through celite and extracted as in Example
30 1. The solvent was distilled off to afford the crude residue which was purified by preparative HPLC to afford the title product in 75 % yield (80 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.79 (s, 1H), 9.13 (s, 1H), 8.63 (d, 1H), 8.21 (s, 2H), 7.95-7.93 (m, 2H),

7.84 (d, 1H), 7.60-7.57 (m, 3H), 6.41-6.40 (m, 2H), 3.88 (s, 3H), 2.21 (s, 3H); LC-MS (ESI): Calculated mass: 397.17; Observed mass: 398.1 [M+H]⁺ (rt: 1.24 min).

Example 28.

N-(4-(2-chlorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

a) 2,6-Dichloro-4-(2-chlorophenyl)pyridine

A solution of 2,6-dichloro-4-iodopyridine (1 g, 3.65 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 2-Chlorophenylboronic acid (0.68 g, 4.38 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.3 g, 0.37 mmol, 0.1 eq) and aqueous sodium carbonate (1.16 g, 10.9 mmol, 3 eq) were added sequentially using the procedure of Intermediate Example 1 and the mixture was heated at 90 °C for 2 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 5 % ethyl acetate in hexane) to afford the title product in 74 % yield (0.7 g). ¹H NMR (300 MHz, CDCl₃): δ 7.53-7.49 (m, 1H), 7.41-7.35 (m, 3H), 7.32-7.29 (m, 1H), 7.26 (m, 1H).

b) 6-Chloro-4-(2-chlorophenyl)-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)pyridin-2-amine

A solution of the compound of Example 28(a) (0.7 g, 2.7 mmol) in toluene (10 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (0.6 g, 2.7 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (24 mg, 0.11 mmol, 0.04 eq) and BINAP (67 mg, 0.11 mmol, 0.04 eq) and potassium *tert*-butoxide (0.3 g, 2.7 mmol, 1 eq) were added sequentially following the procedure of Example 1(a) and the mixture was heated at 100 °C overnight. The crude residue of the product was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) to afford the title product in 71 % yield (0.5 g). LC-MS (ESI): Calculated mass: 439.06; Observed mass: 439.95 [M+H]⁺ (rt: 2.02 min).

c) 1-(6-Chloro-4-(2-chlorophenyl)pyridin-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

A solution of the compound of Example 28(b) (0.5 g, 1.13 mmol) in formic acid (10 ml), iron (0.63 g, 11.4 mmol) was added and heated at 100 °C for 16 h. The formic acid was distilled off and the crude was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 63 % yield (0.3 g). LC-MS (ESI): Calculated mass: 419.07; Observed mass: 421.8 [M+H]⁺ (rt: 1.84 min).

d) N-(4-(2-chlorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 28(c) (200 mg, 0.47 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropanesulfonamide (63 mg, 0.52 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (5 mg, 0.023 mmol, 0.05 eq) and xantphos (15 mg, 0.023 mmol, 0.05 eq) and Cs₂CO₃ (450 mg, 1.41 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (2 % methanol in CHCl₃) to afford the title product in 15 % yield (30 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.17 (s, 1H), 9.0 (s, 1H), 8.71 (d, 1H), 8.23 (s, 1H), 7.96-7.94 (m, 2H), 7.67-7.65 (m, 2H), 7.62-7.59 (m, 2H), 7.54-7.52 (m, 2H), 6.98 (s, 1H), 3.87 (s, 3H), 3.16 (m, 1H), 1.12-1.11 (m, 2H), 1.04-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 504.11; Observed mass: 504.7 [M+H]⁺ (rt: 1.59 min).

Example 29.

N-(3-chloro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

a) 2',3,6'-Trichloro-2,4'-bipyridine

A solution of (2,6-dichloropyridin-4-yl)boronic acid (0.76 g, 4 mmol) in 1,2-dimethoxyethane (15 ml) was degassed by N₂ bubbling for 5 min. 2-Bromo-3-chloropyridine (0.7 g, 3.63 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (0.3 g, 0.36 mmol, 0.1 eq) and aqueous sodium carbonate (1.15 g, 10.9 mmol, 3 eq) were added sequentially using the procedure of Intermediate Example 1 and then heated at 90 °C for 2 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 10 % ethyl acetate in hexane) to afford the title product in 74 % yield (0.7 g). ¹H NMR (300 MHz, CDCl₃): δ 8.63 (dd, 1H), 7.86 (m, 1H), 7.68 (s, 2H), 7.37 (dd, 1H).

b) 3,6'-Dichloro-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)-[2,4'-bipyridin]-2'-amine

A solution of the compound of Example 29(a) (0.69 g, 3.17 mmol) in toluene (10 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (0.69 g, 3.17 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (25 mg, 0.115 mmol, 0.04 eq) and BINAP (71 mg, 0.115 mmol, 0.04 eq) and potassium *tert*-butoxide (0.38 g, 3.46 mmol, 1.2 eq) were added sequentially following the procedure of Example 1(a) and the mixture was heated at 100 °C overnight. The crude residue of the product was purified by column chromatography (60-120 silica gel, 30 % ethyl acetate in hexane) to afford the title product in 43 % yield (0.3 g). ¹H NMR (300 MHz, CDCl₃): δ 10.25 (s, 1H), 8.77 (d, 1H), 8.65-8.63 (m, 1H), 8.30 (d, 1H), 7.88-7.85 (m, 1H), 7.79-7.73 (m, 2H), 7.67 (s, 1H), 7.37-7.33 (m, 2H), 7.22 (m, 1H), 3.97 (s, 3H).

c) 1-(3,6'-Dichloro-[2,4'-bipyridin]-2'-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

A solution of the compound of Example 29(b) (0.3 g, 0.68 mmol) in formic acid (10 ml), iron (0.38 g, 6.8 mmol) was added and heated at 100 °C for 16 h. The formic acid was distilled off and the crude was dissolved in ethyl acetate. The ethyl acetate

layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 64 % yield (0.18 g). LC-MS (ESI): Calculated mass: 420.07; Observed mass: 421.2 $[M+H]^+$ (rt: 1.56 min).

- 5 d) N-(3-chloro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

A solution of the compound of Example 29(c) (100 mg, 0.24 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropanesulfonamide (34 mg, 0.28 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (3 mg, 0.011 mmol, 0.05 eq) and xantphos (6 mg, 0.011 mmol, 0.05 eq) and Cs₂CO₃ (230 mg, 0.71 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was
15 purified by column chromatography (2 % methanol in CHCl₃) to afford the title product in 15 % yield (17 mg). ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.22 (s, 1H), 8.98 (s, 1H), 8.74-8.67 (m, 2H), 8.23 (s, 1H), 8.19-8.16 (m, 1H), 7.97-7.95 (m, 2H), 7.85 (m, 1H), 7.62-7.58 (m, 2H), 7.19 (s, 1H), 3.87 (s, 3H), 3.16 (m, 1H), 1.13-1.12 (m, 2H), 1.06-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 505.11; Observed mass: 506.00 $[M+H]^+$
20 (rt: 1.52 min).

Example 30.

N-(5-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

- 25 a) 2',6'-Dichloro-5-fluoro-2,4'-bipyridine

A solution of 2-bromo-5-fluoropyridine (2 g, 11 mmol) in 1,2-dimethoxyethane (30 ml) was degassed by N₂ bubbling for 5 min. The compound of Example 18(a) (3.11 g, 11 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd(PPh₃)₄ (1.31 g, 0.011 mmol, 0.1 eq) and aqueous sodium carbonate (9.28 g, 28.5 mmol, 2.5 eq) were added sequentially using the procedure of Intermediate Example 1 and then heated at 90 °C for 2 h. The reaction mixture was then quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which

was purified by column chromatography (60-120 silica gel, 5 % ethyl acetate in hexane) to afford the title product in 39 % yield (1 g).

b) 6'-Chloro-5-fluoro-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)-[2,4'-
5 bipyridin]-2'-amine

A solution of the compound of Example 30(a) (0.2 g, 0.82 mmol) in toluene (12 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (0.2 g, 0.9 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min.
10 Palladium acetate (14.7 mg, .065 mmol, 0.08 eq) and BINAP (40 mg, 0.065 mmol, 0.08 eq) and potassium *tert*-butoxide (0.23 g, 2.06 mmol, 2.5 eq) were added sequentially following the procedure of Example 1(a) and then heated at 110 °C for 16 h. The crude residue of the product was purified by column chromatography (60-120 silica gel, 50 %
15 ethyl acetate in hexane) to afford the title product in 29 % yield (0.1 g).

c) N1-(6'-chloro-5-fluoro-[2,4'-bipyridin]-2'-yl)-4-(1-methyl-1H-pyrazol-4-
10 yl)benzene-1,2-diamine

20 To a solution of the compound of Example 30(b) (0.28 g, 0.66 mmol) in THF (10 ml) were added a solution of ammonium chloride (0.29 g, 5.28 mmol, 8 eq) in water (2 ml) and zinc (0.34 g, 5.28 mmol, 8 eq). The mixture was stirred at RT for 1 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the title product in 96 % yield (0.25 g). LC-MS
25 (ESI): Calculated mass: 394.11; Observed mass: 395.1 [M+H]⁺ (rt: 1.42 min).

d) 1-(6'-Chloro-5-fluoro-[2,4'-bipyridin]-2'-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole

30 A solution of the compound of Example 30(c) (0.25 g, 0.63 mmol) and formic acid (10 ml) was heated at 100 °C for 4 h. The formic acid was distilled off and the crude was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 55 % yield (150 mg). LC-MS (ESI): Calculated mass: 404.1; Observed mass: 404.8 [M+H]⁺ (rt: 1.7 min).

e) N-(5-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide

5 A solution of the compound of Example 30(d) (50 mg, 0.123 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropanesulfonamide (15 mg, 0.123 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (2 mg, 0.009 mmol, 0.08 eq) and xantphos (5.7 mg, 0.008 mmol, 0.08 eq) and Cs₂CO₃ (120 mg, 0.37 mmol, 3 eq) were added and the mixture was further degassed for 5 min
10 and then heated at 100 °C for 24 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by preparative TLC to afford the title product in 25 % yield (15 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.16 (s, 1H), 9.14 (s, 1H), 8.81 (d, 1H), 8.73 (d, 1H), 8.40-8.37 (m, 1H), 8.23 (s, 1H), 8.15 (s, 1H), 8.05-8.0 (m, 1H), 7.97-7.95 (m, 2H), 7.66 (s, 1H), 7.62-7.59 (m, 1H), 3.89 (s, 3H), 3.16-3.12 (m, 1H), 1.13-1.10 (m, 2H), 1.03-1.0 (m, 2H); LC-MS (ESI): Calculated mass: 489.14; Observed mass: 490.4 [M+H]⁺ (rt: 1.23 min).

Example 31.

N-(5-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide

The compound was prepared from the compound of Example 30(d). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.78 (s, 1H), 9.16 (s, 1H), 8.82-8.78 (m, 2H), 8.62 (d, 1H), 8.39-8.37 (m, 1H), 8.22-8.20 (m, 2H), 8.04-7.99 (m, 1H), 7.96 (s, 2H), 7.62-7.59 (m, 1H), 3.89 (s, 3H), 2.23 (m, 3H); LC-MS (ESI): Calculated mass: 427.16; Observed mass: 428.3 [M+H]⁺ (rt: 1.91 min).

Example 32.

N-(6-(5-(1H-imidazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)-pyridin-2-yl)cyclopropanesulfonamide

30

a) N-(4-(1H-imidazol-1-yl)-2-nitrophenyl)-6-chloro-4-(2,4-difluorophenyl)-pyridin-2-amine

A solution of the compound of Intermediate Example 5(a) (0.6 g, 2.94 mmol) in toluene (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 9 (0.76 g, 2.94 mmol, 1 eq) was added and the mixture was degassed for
5 another 5 min. Palladium acetate (32 mg, 0.147 mmol, 0.05 eq) and BINAP (182 mg, 0.294 mmol, 0.1 eq) and potassium *tert*-butoxide (0.9 g, 7.35 mmol, 2.5 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 100 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by column
10 chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 12 % yield (150 mg).

b) N1-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-4-(1H-imidazol-1-yl)-benzene-1,2-diamine

15 To a solution of the compound of Example 32(a) (0.15 g, 0.35 mmol) in THF (10 ml) were added a solution of ammonium chloride (0.15 g, 2.81 mmol, 8 eq) in water (2 ml) and zinc (0.18 g, 2.81 mmol, 8 eq). The mixture was stirred at RT for 1 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1.
20 The solvent was distilled off to afford the title product in 72 % yield (0.1 g).

c) 1-(6-Chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-5-(1H-imidazol-1-yl)-1H-benzo[d]imidazole

25 A solution of the compound of Example 32(b) (0.1 g, 0.25 mmol) and formic acid (2 ml) was heated at 90 °C for 4 h. The formic acid was distilled off and the crude was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 50 % yield (50 mg).

30 d) N-(6-(5-(1H-imidazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 32(c) (50 mg, 0.122 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropanesulfonamide (15 mg, 0.122

mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (2 mg, 0.009 mmol, 0.08 eq) and xantphos (5.7 mg, 0.008 mmol, 0.08 eq) and Cs₂CO₃ (120 mg, 0.37 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 12 h. The mixture was filtered through celite and extracted
5 as in Example 1. The solvent was distilled off to afford the crude residue which was purified by preparative TLC to afford the title product in 33 % yield (20 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.22 (s, 1H), 9.12 (s, 1H), 8.67 (d, 1H), 8.38 (s, 1H), 8.08 (d, 1H), 7.91-7.85 (m, 2H), 7.79 (s, 1H), 7.71-7.69 (m, 1H), 7.56-7.51 (m, 1H), 7.38-7.33 (m, 1H), 7.13 (s, 2H), 3.16-3.11 (m, 1H), 1.12-1.08 (m, 2H), 1.03-1.01 (m, 2H); LC-MS
10 (ESI): Calculated mass: 492.12; Observed mass: 493.1 [M+H]⁺ (rt: 0.30 min).

Example 33.

N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

15 a) 6-Chloro-4-(2,4-difluorophenyl)-N-(4-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-2-nitrophenyl)pyridin-2-amine

A solution of the compound of Intermediate Example 5(a) (0.49 g, 1.89 mmol) in
20 dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 8 (0.6 g, 1.89 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (34 mg, 0.15 mmol, 0.08 eq) and BINAP (94 mg, 0.15 mmol, 0.08 eq) and potassium *tert*-butoxide (0.53 g, 4.73 mmol, 2.5 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 100 °C
25 for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 50 % ethyl acetate in hexane) to afford the title product in 20 % yield (200 mg).

30 b) N1-(6-chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-4-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)benzene-1,2-diamine

To a solution of the compound of Example 33(a) (0.2 g, 0.37 mmol) in THF (10 ml) were added a solution of ammonium chloride (0.16 g, 2.96 mmol, 8 eq) in water (2

ml) and zinc (0.19 g, 2.96 mmol, 8 eq). The mixture was stirred at RT for 1 h and filtered. The filtrate was diluted with water and extracted as in Intermediate Example 1. The solvent was distilled off to afford the title product in 79 % yield (0.15 g). LC-MS (ESI): Calculated mass: 510.17; Observed mass: 511.1 [M+H]⁺ (rt: 0.66 min).

5

c) 4-(2-(4-(1-(6-Chloro-4-(2,4-difluorophenyl)pyridin-2-yl)-1H-benzo[d]-imidazol-5-yl)-1H-pyrazol-1-yl)ethyl)morpholine

A solution the compound of Example 33(b) (0.15 g, 0.29 mmol) and formic acid
10 (2 ml) was heated at 90 °C for 12 h. The formic acid was distilled off and the crude was extracted as in Example 8(c). The solvent was distilled off to afford the title product in 50 % yield (75 mg). LC-MS (ESI): Calculated mass: 520.16; Observed mass: 521.2 [M+H]⁺ (rt: 1.03 min).

15 d) N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Example 33(c) (75 mg, 0.144 mmol) in dioxane
(5 ml) was degassed by N₂ bubbling for 5 min. Cyclopropanesulfonamide (17 mg, 0.144
20 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Pd(OAc)₂ (2.5 mg, 0.011 mmol, 0.08 eq) and xantphos (8.3 mg, 0.0144 mmol, 0.1 eq) and Cs₂CO₃ (117 mg, 0.36 mmol, 2.5 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 12 h. The mixture was filtered through celite and extracted as in Example 1. The solvent was distilled off to afford the crude residue which was
25 purified by preparative TLC to afford the title product in 29 % yield (25 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.16 (s, 1H), 9.05 (s, 1H), 8.69 (d, 1H), 8.29 (s, 1H), 7.98-7.96 (m, 2H), 7.88-7.85 (m, 1H), 7.75 (s, 1H), 7.62-7.59 (m, 1H), 7.56-7.49 (m, 1H), 7.37-7.32 (m, 1H), 7.09 (s, 1H), 4.27-4.24 (m, 2H), 3.58-3.55 (m, 4H), 3.18-3.13 (m, 1H), 2.78-2.74 (m, 2H), 2.53-2.49 (m, 4H), 1.15-1.07 (m, 2H), 1.05-1.01 (m, 2H); LC-
30 MS (ESI): Calculated mass: 605.2; Observed mass: 605.8 [M+H]⁺ (rt: 0.44 min).

Example 34.

N-(4-(2,4-difluorophenyl)-6-(5-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

a) *tert*-Butyl 3-(4-(1-(6-(cyclopropanesulfonamido)-4-(2,4-difluorophenyl)-pyridin-2-yl)-1H-benzo[d]imidazol-5-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate

5 A solution of the compound of Intermediate Example 5 (113mg, 0.347 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 2 (120 mg, 0.347 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (3.3 mg, 0.0174 mmol, 0.05 eq), N,N-dimethyl glycine (1.7 mg, 0.0174 mmol, 0.05 eq) and Cs₂CO₃ (282 mg, 0.87 mmol, 2.5 eq) were added and the
10 mixture was further degassed for 5 min and then heated at 100 °C for 24 h. The mixture was filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford the crude product mixture which was purified by preparative TLC to afford the
5 title product in 10 % yield (20 mg). LC-MS (ESI): Calculated mass: 661.23; Observed mass: 662.6 [M+H]⁺ (rt: 1.71 min).

15 b) N-(4-(2,4-difluorophenyl)-6-(5-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

20 To a solution of the compound of Example 34(a) (15 mg, 0.028 mmol) in 1,4-dioxane (5 ml) at 0 °C was added HCl in dioxane and stirred at RT for 1 h. The solvent was distilled off and the residue was washed several times with diethyl ether to give the
5 title product in 78 % yield (10 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.23 (s, 1H), 9.38 (s, 1H), 9.28 (s, 1H), 9.22 (s, 1H), 8.76 (d, 1H), 8.49 (s, 1H), 8.16 (s, 1H), 8.03 (s, 1H), 7.91-7.85 (m, 1H), 7.79 (s, 1H), 7.71-7.69 (m, 1H), 7.57-7.52 (m, 1H), 7.37-7.34
10 (m, 1H), 7.14 (s, 1H), 5.20-5.18 (m, 1H), 3.62-3.37 (m, 3H), 3.19-3.15 (m, 2H), 2.43-
25 2.33 (m, 2H), 1.19-1.12 (m, 2H), 1.05-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 561.18; Observed mass: 562.6 [M+H]⁺ (RT: 0.40 min).

Example 35.

30 N-(4-(2,4-difluorophenyl)-6-(5-(1-ethyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Intermediate Example 5 (48 mg, 0.14 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate

Example 10 (30 mg, 0.14 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (2 mg, 0.014 mmol, 0.1 eq), N,N-dimethyl glycine (1 mg, 0.014 mmol, 0.1 eq) and Cs₂CO₃ (130 mg, 0.42 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 24 h. The mixture was
5 filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford the crude product mixture which was purified by preparative TLC to afford the title product in 33 % yield (24 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.18 (s, 1H), 9.11 (s, 1H), 8.79 (d, 1H), 8.71 (s, 1H), 8.22 (s, 1H), 7.92-7.85 (m, 2H), 7.79 (s, 1H), 7.56-7.50 (m, 1H), 7.38-7.33 (m, 1H), 7.13 (s, 1H), 4.44 (quartet, 2H), 3.18-3.13 (m,
10 1H), 1.51 (t, 3H), 1.14-1.09 (m, 2H), 1.07-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 521.14; Observed mass: 522.1 [M+H]⁺ (rt: 1.52 min).

Example 36.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

15

a) N-(4-(2,4-difluorophenyl)-6-(5-ethynyl-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

20

A solution of the compound of Intermediate Example 5 (0.17 g, 0.51 mmol, 1.1 eq) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 12 (100 mg, 0.46 mmol) was added and the mixture was degassed for another 5 min. CuI (8 mg, 0.04 mmol, 0.1 eq), N,N-dimethyl glycine (4 mg, 0.04 mmol, 0.1 eq) and Cs₂CO₃ (450 mg, 1.4 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 24 h. The mixture
25 was filtered through celite and washed with 3 % methanol/chloroform to afford crude product mixture which was recrystallized from diethyl ether to afford the product mixture in 40 % yield (80 mg) which was directly taken for the next step. LC-MS (ESI): Calculated mass: 450.1; Observed mass: 451.3 [M+H]⁺ (rt: 1.65 min).

25

30

b) N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A mixture of Example 36(a) (0.1 g, 0.22 mmol), sodium azide (28 mg, 0.44 mmol, 2.0 eq), methyl iodide (31 mg, 0.22 mmol, 1.0 eq), sodium ascorbate (43 mg, 0.022 mmol, 0.1 eq) and copper sulfate pentahydrate (5 mg, 0.022 mmol, 0.1 eq) in DMSO and water (1:0.5, 3 ml) was stirred for 12 h at RT. The mixture was quenched with water and the precipitate formed was filtered and dried. The crude product mixture was purified by column chromatography (60-120 silica gel, 2 % methanol in CHCl₃) to give the title product in 6.3 % yield (7 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.18 (s, 1H), 9.11 (s, 1H), 8.79 (d, 1H), 8.62 (s, 1H), 8.21 (d, 1H), 7.90-7.85 (m, 2H), 7.79 (s, 1H), 7.56-7.50 (m, 1H), 7.38-7.33 (m, 1H), 7.13 (s, 1H), 4.12 (s, 3H), 3.34-3.13 (m, 1H), 1.16-1.12 (m, 2H), 1.06-0.94 (m, 2H); LC-MS (ESI): Calculated mass: 507.13; Observed mass: 508.1 [M+H]⁺ (rt: 1.52 min).

Example 37.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-imidazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Intermediate Example 5 (34 mg, 0.1 mmol) in DMF (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 11 (20 mg, 0.1 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (2 mg, 0.01 mmol, 0.1 eq), N,N-dimethyl glycine (0.52 mg, 0.005 mmol, 0.05 eq) and Cs₂CO₃ (82 mg, 0.25 mmol, 2.5 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 24 h. The mixture was filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford the crude product mixture which was purified by preparative TLC to yield the title compound in 10 % yield (5 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.11 (s, 1H), 9.02 (s, 1H), 8.66 (d, 1H), 8.09 (d, 1H), 7.89-7.84 (m, 1H), 7.81-7.75 (m, 2H), 7.68-7.64 (m, 2H), 7.54-7.48 (m, 1H), 7.37-7.32 (m, 1H), 7.13 (s, 1H), 3.71 (s, 3H), 3.18-3.14 (m, 1H), 1.15-1.12 (m, 2H), 1.06-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 506.13; Observed mass: 507.35 [M+H]⁺ (rt: 0.18 min).

Example 38.

N-(4-(2, 4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl) pyrimidin-2-yl) acetamide

a) N-(4, 6-dichloropyrimidin-2-yl) acetamide

To a solution of 4, 6-dichloropyrimidin-2-amine (5 g, 30.48 mmol) in toluene (50 ml) was added acetic anhydride (15 ml, 152.43 mmol) and the mixture was heated at 120 °C for 16 h. The solvent was evaporated and the crude product was taken in hexane (50 ml) and dichloromethane (6 ml) and filtered to afford the title product in 80 % yield (5 g). LC-MS (ESI): Calculated mass: 206.0; Observed mass: 208.0 [M+H]⁺ (rt: 0.245 min).

b) N-(4-((2-amino-4-(1-methyl-1H-pyrazol-4-yl) phenyl) amino)-6-chloro-pyrimidin-2-yl) acetamide

A solution of the compound of Intermediate Example 13 (1.4 g, 7.44 mmol), the compound of Example 38(a) (1.53 g, 7.44 mmol,) and sodium bicarbonate (1.56 g, 18.6 mmol, 2.5 eq) in ethanol was heated at 80 °C for 16 h. The mixture was quenched with water and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 3 % methanol in DCM) to afford the the title product in 19.2 % yield (0.5 g). LC-MS (ESI): Calculated mass: 357.11; Observed mass: 358.1 [M+H]⁺ (rt: 0.123 min).

c) N-(4-chloro-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl) pyrimidin-2-yl) acetamide

A mixture of the compound of Example 38(b) (0.15 g, 0.42 mmol) and formic acid (2 ml) was heated at 80 °C for 2 h. The formic acid was distilled off and the crude was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 97 % yield (0.15 g). LC-MS (ESI): Calculated mass: 367.07; Observed mass: 368.1 [M+H]⁺ (rt: 0.318 min).

d) N-(4-(2, 4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl) pyrimidin-2-yl) acetamide

A solution of the compound of Example 38(c) (0.08 g, 0.217 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. 2,4-Difluorophenylboronic acid (0.04 g, 0.261 mmol, 1.2 eq) was added and the mixture was degassed for another 5 min. Pd(PPh₃)₄ (0.025 g, 0.021 mmol, 0.1 eq) and aqueous cesium carbonate (0.106 g, 0.326 mmol, 1.5 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 100 °C for 2 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 30 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by preparative HPLC to afford the title product in 10.4 % yield (10 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.1 (s, 1H), 9.25 (s, 1H), 9.12 (d, 1H), 8.23 (s, 1H), 8.11-8.07 (m, 1H), 8.03 (s, 1H), 7.96 (d, 2H), 7.63 (d, 1H), 7.54 (t, 1H), 7.36 (t, 1H), 3.88 (s, 3H), 2.27 (s, 3H); LC-MS (ESI): Calculated mass: 445.15; Observed mass: 445.9 [M+H]⁺ (rt: 1.33 min).

Example 39.

Ethyl 1-(1-(6-(cyclopropanesulfonamido)-4-(2,4-difluorophenyl)pyridin-2-yl)-1H-benzo[d]imidazol-5-yl)-1H-1,2,3-triazole-4-carboxylate

A solution of the compound of Intermediate Example 5 (200 mg, 0.58 mmol) in DMF (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 14 (149 mg, 0.58 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (11 mg, 0.05 mmol, 0.1 eq), N,N-dimethyl glycine (8 mg, 0.05 mmol, 0.1 eq) and Cs₂CO₃ (570 mg, 1.74 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 24 h. The mixture was filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford the crude product mixture which was purified by preparative HPLC to afford the title product in 5 % yield (18 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.11 (s, 1H), 9.59 (d, 1H), 9.26 (s, 1H), 8.95 (d, 1H), 8.38 (s, 1H), 8.02-8.00 (m, 1H), 7.92-7.83 (m, 2H), 7.56-7.51 (m, 1H), 7.51-7.34 (m, 1H), 7.17 (s, 1H), 4.38 (quartet, 2H), 3.17-3.13 (m, 1H), 1.36 (t, 3H), 1.13-1.12 (m, 2H), 1.04-1.02 (m, 2H); LC-MS (ESI): Calculated mass: 565.13; Observed mass: 566.2 [M+H]⁺ (rt: 1.63 min).

Example 40.

N-(4-(2-(difluoromethoxy)-4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide

A solution of the compound of Intermediate Example 15 (300 mg, 0.75 mmol) in DMF (10 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 6 (149 mg, 0.75 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (14 mg, 0.075 mmol, 0.1 eq), N,N-dimethyl glycine (8 mg, 0.075 mmol, 0.1 eq) and Cs₂CO₃ (730 mg, 2.25 mmol, 3 eq) were added and the reaction mixture was further degassed for 5 min and then heated at 100 °C for 2 days. The reaction mixture was filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford the crude product mixture which was purified by column chromatography (60-120 silica gel, 2 % methanol in chloroform) to afford the title product in 2 % yield (8 mg). ¹H NMR (400 MHz, CD₃OD): δ 8.83 (s, 1H), 8.56 (d, 1H), 8.02 (s, 1H), 7.89-7.87 (m, 2H), 7.69-7.63 (m, 2H), 7.57 (s, 1H), 7.22-7.15 (m, 2H), 7.15 (s, 1H), 6.97 (s, 0.5 H), 6.79 (s, 0.5 H), 3.94 (s, 3H), 3.15-3.05 (m, 1H), 1.28-1.15 (m, 2H), 1.00-0.87 (m, 2H); LC-MS (ESI): Calculated mass: 554.13; Observed mass: 555.5 [M+H]⁺ (rt: 1.66 min).

Example 41.

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide

a) 4-Chloro-6-(2,4-difluorophenyl)pyrimidin-2-amine

A solution of 4,6-dichloropyrimidin-2-amine (5 g, 30 mmol) in 1,2-dimethoxyethane (50 ml) was degassed by N₂ bubbling for 5 min. 2,4-Difluorophenylboronic acid (4.38 g, 27 mmol, 0.9 eq) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (1.38 g, 1.5 mmol, 0.05 eq) and aqueous sodium carbonate (4.9 g, 46 mmol, 1.5 eq) were added sequentially using the procedure of Intermediate Example 1 and heated at 90 °C for 6 h. The reaction mixture was quenched and extracted as in Intermediate Example 1. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 70 % ethyl acetate in hexane) to afford the title product in 70 % yield (4 g). LC-MS (ESI): Calculated mass: 241.02; Observed mass: 242.05 [M+H]⁺ (rt: 1.58 min).

b) 6-(2,4-Difluorophenyl)-N4-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl)-pyrimidine-2,4-diamine

5

A solution of the compound of Example 41(a) (0.5 g, 2.1 mmol) in dioxane (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate Example 1 (0.5 g, 2.3 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min. Pd₂dba₃ (0.19 g, 0.2 mmol, 0.1 eq) and xantphos (0.24 g, 0.4 mmol, 0.2 eq) and cesium carbonate (1.68 g, 5.2 mmol, 2.5 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 110 °C for 16 h. The mixture was filtered through celite pad and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude residue which was purified by column chromatography (60-120 silica gel, 70 % ethyl acetate in hexane) in 22.5 % yield (0.2 g). LC-MS (ESI): Calculated mass: 423.13; Observed mass: 423.9 [M+H]⁺ (rt: 0.26 min).

15

c) N4-(2-amino-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-(2,4-difluorophenyl)-pyrimidine-2,4-diamine

20

To a solution of the compound of Example 41(b) (0.12 g, 0.3 mmol) in THF (15 ml) were added a solution of ammonium chloride (0.12 g, 2.3 mmol, 8 eq) in water (5 ml) and zinc (0.145 g, 2.3 mmol, 8 eq). The mixture was stirred at RT for 2 h and filtered. The filtrate was diluted with water and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude product in 83 % yield (0.1 g). LC-MS (ESI): Calculated mass: 393.15; Observed mass: 394.3 [M+H]⁺ (rt: 0.14 min).

25

d) 4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl)pyrimidin-2-amine

30

A solution of the compound of Example 41(c) (0.1 g, 0.2 mmol) in formic acid (5 ml) was heated at 100 °C for 16 h. The formic acid was distilled off and the crude product was dissolved in ethyl acetate. The ethyl acetate layer was washed with water,

brine and dried over sodium sulphate. The solvent was distilled off to afford the title product in 24 % yield (20 mg).

e) N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
5 imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide

To an icecold solution of the compound of Example 41(d) (50 mg, 0.1 mmol) in DMF (50 ml) was added NaH (4 mg, 0.2 mmol, 2 eq). The mixture was stirred for 10 min and cyclopropylsulfonyl chloride (26 mg, 0.2 mmol, 2 eq) was added and the
10 mixture was stirred at RT for 12 h. The mixture was then quenched with water and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off to afford the crude product which was purified by preparative HPLC to afford the title product in 6 % yield (3 mg). ¹H NMR (400 MHz, CDCl₃): δ 8.73 (s, 1H), 8.39 (d, 1H), 8.36-8.27 (m,
15 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.93 (d, 1H), 7.87 (d, 1H), 7.74 (d, 1H), 7.67-7.64 (m, 1H), 7.20-7.01 (m, 2H), 3.83 (s, 3H), 3.30-3.26 (m, 1H), 1.51-1.42 (m, 2H), 1.16-1.12 (m, 2H); LC-MS (ESI): Calculated mass: 507.13; Observed mass: 508.2 [M+H]⁺ (rt: 1.48 min).

Example 42.

20 Ethyl 1-(1-(6-acetamido-4-(2,4-difluorophenyl)pyridin-2-yl)-1H-benzo[d]-imidazol-5-yl)-1H-1,2,3-triazole-4-carboxylate

A solution of the compound of Intermediate Example 16 (150 mg, 0.53 mmol) in DMF (5 ml) was degassed by N₂ bubbling for 5 min. The compound of Intermediate
25 Example 6 (137 mg, 0.53 mmol, 1 eq) was added and the mixture was degassed for another 5 min. CuI (10 mg, 0.05 mmol, 0.1 eq), N,N-dimethyl glycine (7 mg, 0.05 mmol, 0.1 eq) and Cs₂CO₃ (0.52 g, 1.59 mmol, 3 eq) were added and the mixture was further degassed for 5 min and then heated at 110 °C for 16 h. The mixture was filtered through celite and washed with ethyl acetate. The solvent was distilled off to afford the
30 crude product mixture which was purified by preparative HPLC to yield the title product in 4.5 % yield (16 mg). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.95 (s, 1H), 9.58 (d, 1H), 9.22 (s, 1H), 8.98 (d, 1H), 8.39 (s, 1H), 8.03-7.96 (m, 2H), 7.89-7.83 (m, 2H), 7.55-7.49

(m, 1H), 7.47-7.33 (m, 1H), 4.39 (quartet, 2H), 2.22 (s, 1H), 1.36 (t, 3H); LC-MS (ESI): Calculated mass: 503.15; Observed mass: 504.1 [M+H]⁺ (rt: 1.63 min).

Example 43.

N-(6-(2, 4-difluorophenyl)-4-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
5 imidazol-1-yl) pyridin-2-yl) cyclopropanesulfonamide

a) 4-(1-methyl-1H-pyrazol-4-yl)-2-nitroaniline

A solution of 4-bromo-2-nitroaniline (6 g, 27.6 mmol) in 1, 2-dimethoxyethane
10 (15 ml) was degassed by N₂ bubbling for 5 min. 1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.90 g, 33.1 mmol, 1.2 eq.) was added and the mixture was degassed for another 5 min. Pd(dppf)Cl₂ (2.25 g, 27.6 mmol, 0.1 eq) and aqueous sodium carbonate (8.79 g, 82.9 mmol, 3.0 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 90 °C for 2 h. The mixture
15 was quenched with water and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off under reduced pressure to afford the crude residue which was purified by column chromatography (60-120 silica gel, 40 % ethyl acetate in hexane) to yield the title product in 75 % yield (4.5 g). LC-MS (ESI): Calculated mass: 218.21; Observed
20 mass: 218.9 [M+H]⁺ (rt: 0.390 min). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.10-8.08 (m, 2H), 7.81 (s, 1H), 7.66-7.63 (m, 1H), 7.44(s, 2H), 7.05-7.03(d, 1H), 3.84 (s, 3H).

b) 2, 6-dichloro-N-(4-(1-methyl-1H-pyrazol-4-yl)-2-nitrophenyl) pyridin-4-
amine

25

A solution of 2,6-dichloro-4-iodopyridine (1 g, 3.66 mmol) in toluene (15 ml) was degassed by N₂ bubbling for 5 min. The compound of Example 43(a) (0.958 g, 4.39 mmol, 1.2 eq.) was added and the mixture was degassed for another 5 min. Palladium acetate (0.032 g, 0.146 mmol, 0.04 eq) and BINAP (0.091 g, 0.146 mmol, 0.04 eq.) and
30 potassium tert-butoxide (0.616 g, 5.49 mmol, 1.5 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 100 °C for 5 h. The mixture was filtered through celite and extracted with ethyl acetate (3 × 100 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent

was distilled off under reduced pressure to afford the crude residue which was purified by column chromatography (60-120 silica gel, 25 % ethyl acetate in hexane) in 42.3 % yield (550 mg). LC-MS (ESI): Calculated mass: 363.04; Observed mass: 364.0 $[M+H]^+$ (rt: 1.578 min).

5

c) 1-(2, 6-dichloropyridin-4-yl)-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazole

A solution of the compound of Example 43(b) (0.55 g, 1.51 mmol) in formic acid (10 ml) and iron (0.843 g, 15.1 mmol) was heated at 100 °C for 16 h. The formic acid was distilled off under reduced pressure and the crude product was dissolved in ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off under reduced pressure to afford the title compound in 77 % yield (0.4 g). LC-MS (ESI): Calculated mass: 343.04; Observed mass: 344.05 $[M+H]^+$ (rt: 1.169 min).

15

d) N-(6-chloro-4-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl) cyclopropanesulfonamide

A solution of the compound of Example 43(c) (0.54 g, 1.56 mmol) in dioxane (15 ml) was degassed by N₂ bubbling for 5 min. Cyclopropane sulfonamide (0.189 g, 1.56 mmol, 1 eq) was added and the mixture was degassed for another 5 min. Palladium acetate (0.028 g, 0.125 mmol, 0.08 eq) and xantphos (0.072 g, 0.125 mmol, 0.08 eq) and Cs₂CO₃ (1.53 g, 4.7 mmol, 3.0 eq) were added and the mixture was further degassed for 5 min and then heated at 100 °C for 16 h. The mixture was filtered through celite and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off under reduced pressure to afford the crude residue which was purified by column chromatography (60-120 silica gel, 3 % methanol in hexane) to yield the title product in 37 % yield (250 mg). LC-MS (ESI): Calculated mass: 428.08; Observed mass: 429.2 $[M+H]^+$ (rt: 0.854 min).

30

e) N-(6-(2, 4-difluorophenyl)-4-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-imidazol-1-yl) pyridin-2-yl) cyclopropanesulfonamide

A solution of the compound of Example 43(d) (0.15 g, 0.350 mmol) in DME (4 ml) was degassed by N₂ bubbling for 5 min. 2,4-Difluorophenylboronic acid (0.06 g, 0.385 mmol, 1.1 eq) was added and the mixture was degassed for another 5 min. Pd(PPh₃)₄ (0.039 g, 0.035mmol, 0.1 eq) and aqueous cesium carbonate (0.341 g, 1.051 mmol, 3 eq) were added sequentially and the mixture was further degassed for 5 min and then heated at 100 °C for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 30 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. The solvent was distilled off under reduced pressure to afford the crude residue which was purified by preparative TLC to yield the title product in 11.2 % yield (20 mg). ¹H NMR (400 MHz, DMSO- *d*₆): δ 11.0 (s, 1H), 8.78 (s, 1H), 8.21 (s, 1H), 8.08-8.04 (m, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 7.78-7.76 (d, 2H), 7.65-7.63 (d, 1H), 7.49-7.43 (m, 1H), 7.35-7.29 (m, 2H), 3.87 (s, 3H), 3.23 (m, 1H), 1.13-1.06 (m, 4H). LC-MS (ESI): Calculated mass: 506.13; Observed mass: 507.5 [M+H]⁺ (rt: 1.583 min).

Abbreviations:

RT - Room temperature

rt - Retention time

BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

DMF - *N,N*-dimethylformamide

THF - Tetrahydrofuran

TEA - Triethyl amine

TLC – Thin layer chromatography

DCM – Dichloromethane

DME - Dimethoxyethane

DMSO - Dimethylsulfoxide

EDC - 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride

HATU - 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluoro-phosphate methanaminium

HOBt - Hydroxybenzotriazole

DIPEA - *N,N*-diisopropylethylamine

5 TBAF - tetra-*n*-butylammonium fluoride

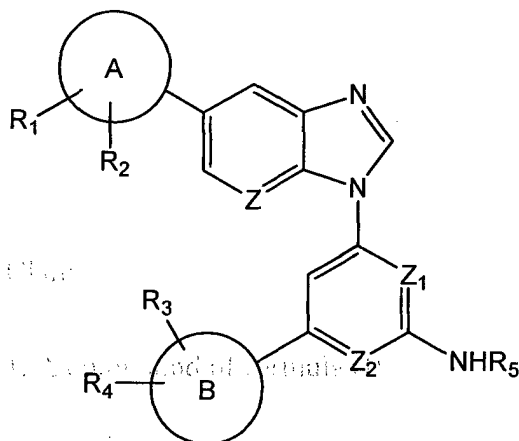
Pd(dppf)Cl₂ - 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride

Pd(PPh₃)₄ - Tetrakis(triphenylphosphine)palladium(0)

Pd₂(dba)₃ - Tris(dibenzylideneacetone)dipalladium(0)

Claims

- 5 1. A compound of formula (I)



(I)

wherein

Z₁ is N and Z₂ is CH, or

10 Z₁ is CH and Z₂ is N, or

Z₁ and Z₂ is N;

Z is CH or N;

A is a phenyl ring or a 5-12 membered heterocyclic ring;

15 R₁ is H, C₁₋₇ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl C₁₋₇ alkyl, C₁₋₇ alkoxy, C₁₋₇ alkyl carbonyl, amino, hydroxy, hydroxy C₁₋₇ alkyl, halo C₁₋₇ alkyl, C₁₋₇ alkylamino C₁₋₇ alkyl, -R₁₆-C(O)-R₁₇ or -E-R₆;

R₂ is H, halogen or C₁₋₇ alkyl;

B is a 5-12 membered carbocyclic or heterocyclic ring;

R₃ is H, halogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, halo C₁₋₇ alkyl or halo C₁₋₇ alkoxy;

20 R₄ is H, halogen, C₁₋₇ alkyl or oxo;

R₅ is H, -C(O)R₇, -SO₂R₈ or an optionally substituted 5-6 membered heterocyclic ring;

R₆ is an optionally substituted 5-6 membered heterocyclic ring;

25 R₇ is C₁₋₇ alkyl, C₂₋₇ alkenyl, C₁₋₇ alkoxy, C₁₋₇ alkoxy C₁₋₇ alkyl, carboxy C₁₋₇ alkyl, C₁₋₇ alkoxy carbonyl C₁₋₇ alkyl, C₁₋₇ alkylamino C₁₋₇ alkyl, -NH-R₁₀ or -NH-X₁-R₁₁;

R_8 is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl, $-NR_{13}R_{14}$, $-NH-$
 X_2-R_{15} , phenyl or an optionally substituted 5-6 membered heterocyclic ring;

R_{10} is C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{11} is phenyl or an optionally substituted 5-6 membered heterocyclic ring;

5 R_{12} is H or C_{1-7} alkyl;

R_{13} and R_{14} are, independently, H, C_{1-7} alkyl or C_{3-7} cycloalkyl;

R_{15} is phenyl or an optionally substituted 5-6 membered heterocyclic ring;

R_{16} is a bond or a C_{1-7} alkyl;

R_{17} is C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkylamino, amino or hydroxy;

10 E is a bond or a C_{1-7} alkyl;

X_1 and X_2 are, independently, a bond or C_{1-7} alkyl;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein Z is CH.

15

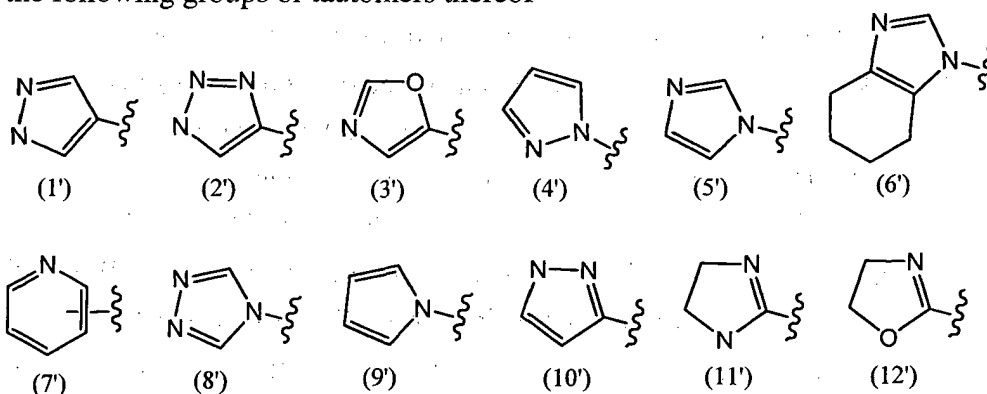
3. A compound according to claim 1 or 2, wherein Z_1 is N and Z_2 is CH.

4. A compound according to claim 1 or 2, wherein Z_1 is CH and Z_2 is N.

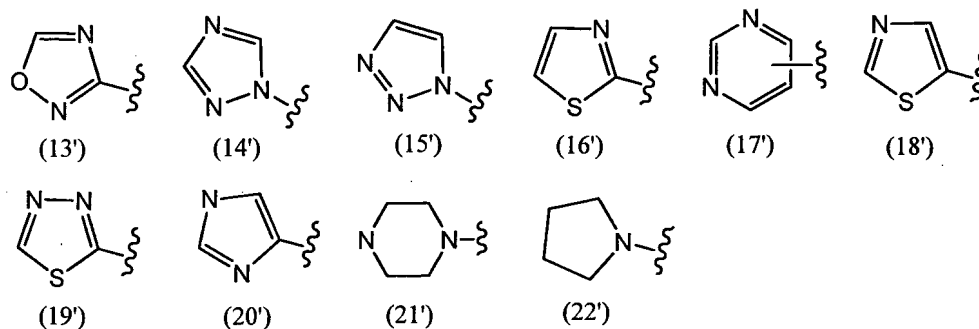
10

20 5. A compound according to claim 1 or 2, wherein Z_1 and Z_2 is N.

6. A compound according to any of claims 1 to 5, wherein ring A is any one of
the following groups or tautomers thereof

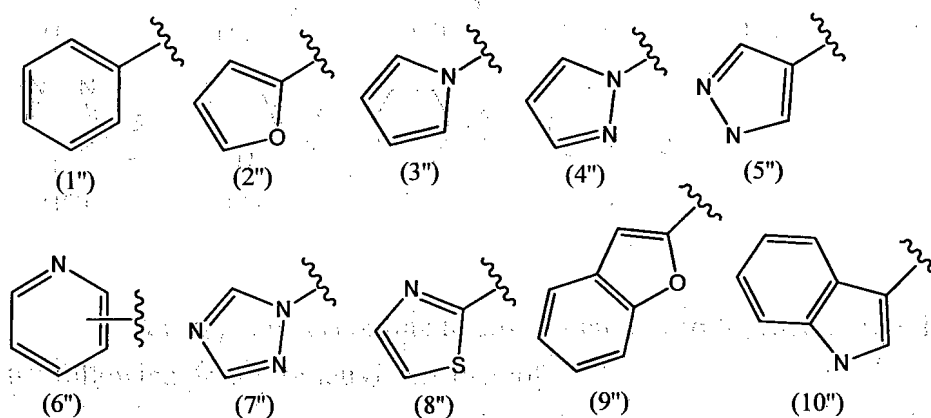


91



7. A compound according to any of claims 1 to 6, wherein ring B is any one of the following groups or tautomers thereof

5



8. A compound according to any of claims 1 to 7, wherein

A is a ring of formula (1'), (2'), (3'), (4'), (5'), (7'), (14'), (16') or (20');

10 R_1 is H, C_{1-7} alkyl, C_{1-7} alkoxy, hydroxy C_{1-7} alkyl, C_{1-7} alkylamino C_{1-7} alkyl or $-E-R_6$;

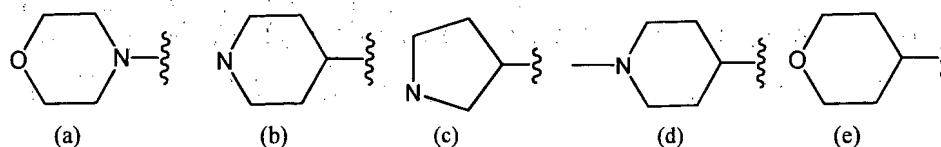
R_2 is H;

Z is CH;

B is a ring of formula (1''), (2''), (3''), (4'') or (6'');

15 E is a bond or C_{1-7} alkyl;

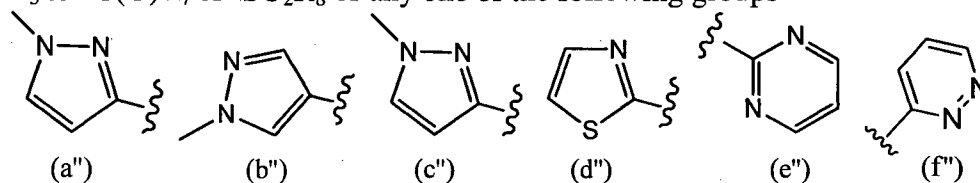
R_6 is any of the following groups



R_3 is H, halogen, C_{1-7} alkyl, C_{1-7} alkoxy;

R_4 is H or halogen;

R_5 is $-C(O)R_7$ or $-SO_2R_8$ or any one of the following groups



R_7 is C_{1-7} alkyl, C_{2-7} alkenyl or $-NH-R_{10}$;

5 R_8 is C_{1-7} alkyl, C_{2-7} alkenyl, C_{3-7} cycloalkyl, hydroxy C_{1-7} alkyl or $-NR_{13}R_{14}$; and
 R_{10} is C_{1-7} alkyl or C_{3-7} cycloalkyl.

9. A compound according to any of claims 1 to 8, wherein B is a ring of formula
 10 (1''), (3'') or (6'').

10. A compound according to any of claims 1 to 9, wherein A is a ring of
 formula (1'), (2'), (4'), (5') or (20'').

11. A compound according to any of claims 1 to 10, wherein R_5 is $-SO_2R_8$.

12. A compound according to any of claims 1 to 11, wherein Z is CH, Z_1 is N
 and Z_2 is CH, A is a ring of formula (1'), B is a ring of formula (1''), R_1 is C_{1-7} alkyl, R_2
 is H, R_3 is halogen, R_4 is H or halogen, R_5 is $-SO_2R_8$ and R_8 is C_{1-7} alkyl or
 C_{3-7} cycloalkyl.

13. A compound according to any of claims 1 to 12, which is

4-(2, 4-Difluorophenyl)-N-(1-methyl-1H-pyrazol-3-yl)-6-(5-(1-methyl-1H-
 pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl) pyridin-2-amine;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
 25 imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

Sodium salt of imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-
 pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
 imidazol-1-yl)pyridin-2-yl)methanesulfonamide;

30 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]-
 imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

Sodium salt of imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

5 Imido form of N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

10 Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)methanesulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

15 Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)ethanesulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

20 Sodium salt of imido form of N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)methanesulfonamide;

25 N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

Sodium salt of imido form of N-(4-(4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)propane-2-sulfonamide;

30 N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

N-(3-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide;

5 N-(6-(5-(1H-pyrazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)-pyridin-2-yl)cyclopropanesulfonamide;

N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

10 N-(3,5-difluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)acetamide;

N-(4-(2-chlorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(3-chloro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

15 N-(5-fluoro-6'-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)-[2,4'-bipyridin]-2'-yl)cyclopropanesulfonamide;

N-(6-(5-(1H-imidazol-1-yl)-1H-benzo[d]imidazol-1-yl)-4-(2,4-difluorophenyl)-pyridin-2-yl)cyclopropanesulfonamide;

20 N-(4-(2,4-difluorophenyl)-6-(5-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-ethyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

25 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-imidazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

30 N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)acetamide;

Ethyl 1-(1-(6-(cyclopropanesulfonamido)-4-(2,4-difluorophenyl)pyridin-2-yl)-1H-benzo[d]imidazol-5-yl)-1H-1,2,3-triazole-4-carboxylate;

N-(4-(2-(difluoromethoxy)-4-fluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-2-yl)cyclopropanesulfonamide;

N-(4-(2,4-difluorophenyl)-6-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-2-yl)cyclopropanesulfonamide;

- 5 N-(6-(2, 4-difluorophenyl)-4-(5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-1-yl) pyridin-2-yl) cyclopropanesulfonamide;
or a pharmaceutically acceptable salt or tautomer thereof.

- 10 14. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

- 15 15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition, where FGFR kinase inhibition is desired.

- 20 16. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.