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(54) Title: PROCESSES AND INTERMEDIATES FOR PREPARING A MEDICAMENT
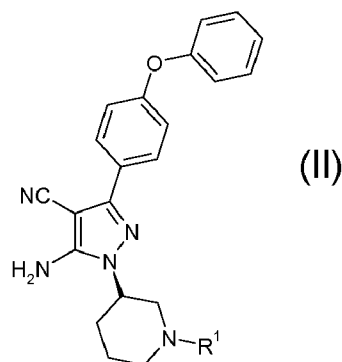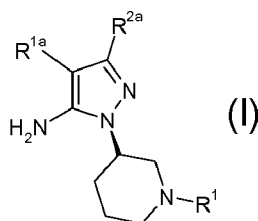
(57) Abstract: Disclosed is a process for the preparation of the following compounds: (I), (II) where R^1, R^{1a} and R^{2a} have the definitions in the description, as well as a process to prepare other intermediates that may be useful to synthesise downstream products, especially compounds that are useful as medicaments, for instance Bruton's tyrosine kinase (Btk) inhibitors such as ibrutinib. Also disclosed are other processes, other intermediates and compounds *per se*.

PROCESSES AND INTERMEDIATES FOR PREPARING A MEDICAMENT

Field of the invention

5   The present invention relates to synthesis procedures and synthesis intermediates of substituted bicyclic compounds, especially compounds that are useful as medicaments, for instance Bruton's tyrosine kinase (Btk) inhibitors such as ibrutinib.

Background of the Invention

10   Ibrutinib is an organic small molecule having IUPAC name 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. It is described in a number of published documents, including international patent application WO2008/039218 (Example 1b), and is described as an irreversible inhibitor of Btk.

15

Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor stimulation to downstream intracellular responses. Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, *Curr Op Imm*, 2000, 276-281; Schaeffer and Schwartzberg, *Curr Op Imm* 2000, 282-288). In addition, Btk

20   plays a role in a number of other hematopoetic cell signaling pathways, e.g. Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. See e.g., C. A. Jeffries, et al., (2003), *Journal of Biological Chemistry* 278:26258-

25   26264; N. J. Horwood, et al., (2003), *The Journal of Experimental Medicine* 197:1603-1611; Iwaki et al. (2005), *Journal of Biological Chemistry* 280(48):40261-40270; Vassilev et al. (1999), *Journal of Biological Chemistry* 274(3):1646-1656, and Quek *et al* (1998), *Current Biology* 8(20):1137-1140.

30   Ibrutinib is therefore being studied in Phase II and III clinical trials for various hematological malignancies such as chronic lymphocytic leukemia, mantle cell lymphoma, diffuse large B-cell lymphoma and multiple myeloma.

There are various processes for preparing functionalised bicyclic heterocycles, for

35   example as described in US patent document US 2011/0082137, which includes syntheses to fused bicycles from pyrazoles and substituted hydrazines.

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Ibrutinib may be prepared in WO2008/039218 (Example 1b) in accordance with the following scheme:
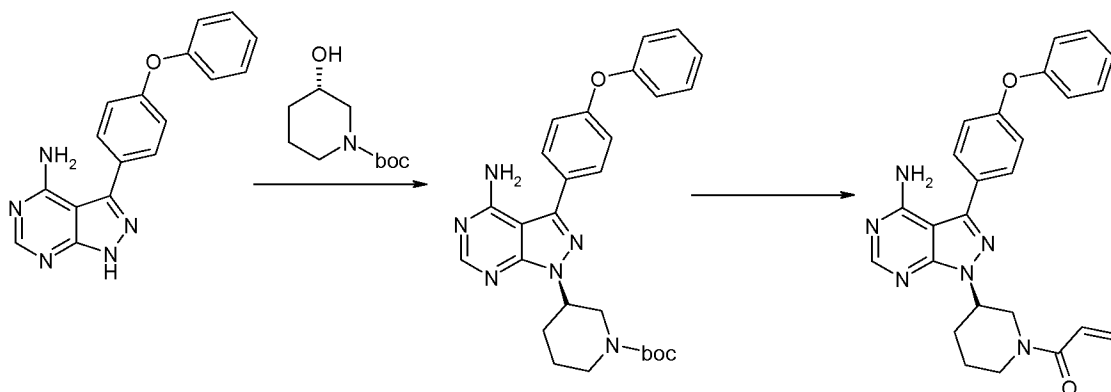
5   First, 4-amino-3-(4-phenoxyphenyl)-1H-pyrazole[3,4-d]pyrimidine may be prepared in accordance with procedures described in WO2008/039218, for instance by converting 4-phenoxybenzoic acid to the corresponding acyl chloride (by using thionyl chloride), which latter product may be reacted with malononitrile to prepare 1,1-dicyano-2-hydroxy-2-(4-phenoxyphenyl)ethene. The methoxy moiety is then methylated using

10   trimethylsilyldiazomethane, and that methylated product is the treated with hydrazine hydrate to provide 3-amino-4-cyano-5-(4-phenoxyphenyl)pyrazole, which is reacted with formamide to provide 4-amino-3-(4-phenoxyphenyl)-1H-pyrazole[3,4-d]-pyrimidine, as illustrated in the following scheme:

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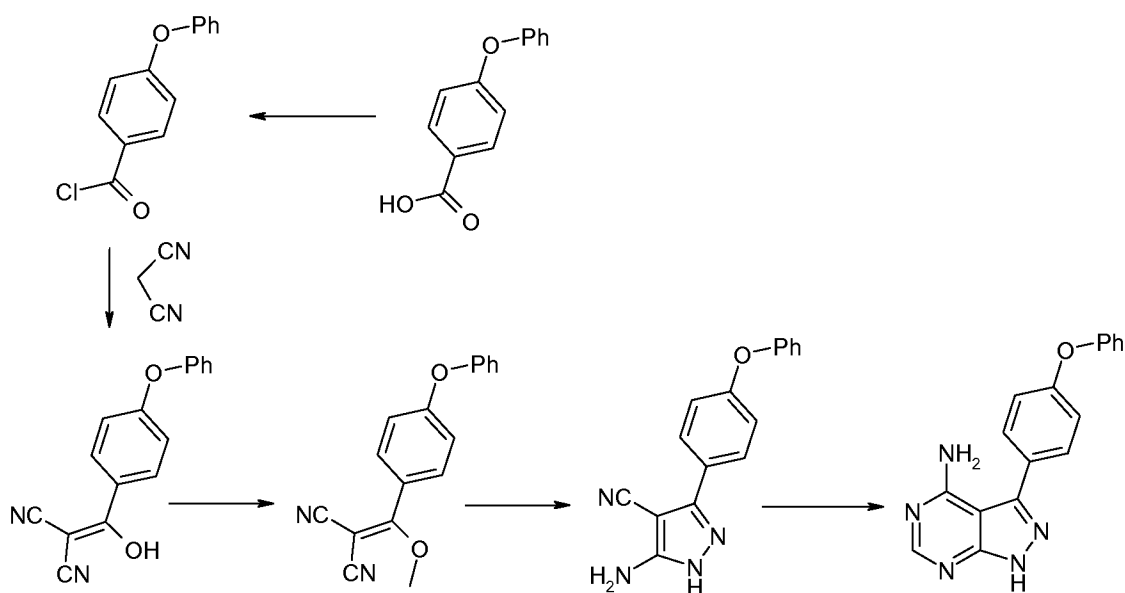
Thereafter, the 4-amino-3-(4-phenoxyphenyl)-1H-pyrazole[3,4-d]pyrimidine may have the requisite piperidinyl moiety introduced at the 1H-position (i.e. on the -NH of the

pyrazole moiety). As indicated in the above scheme, this is done by means of a Mitsunobu reaction – more specifically by converting the hydroxy moiety of the Boc-protected 3-hydroxypiperidine-1-carboxylate to a better leaving group, thereby allowing a substitution reaction with the -NH moiety of the pyrazole (with inversion).

5   Hence, the chirality of the hydroxypiperidine is translated into the product, which is then converted to the single enantiomer ibrutinib by Boc-deprotection and acylation with acryl chloride.

This process has a number of disadvantages, such as those associated with cost,
10   efficiency and environmental disadvantages. For instance the Mitsunobu step may be wasteful, costly and cumbersome. It is therefore desired to find a new process that overcomes these disadvantages.

There is now provided a process for the preparation of a compound of formula I,
15

(I)
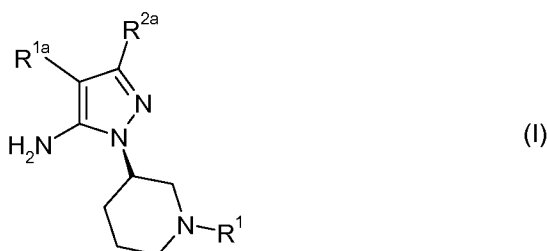
or a derivative thereof, wherein
R^1 represents hydrogen or, more preferably, a nitrogen protecting group;
R^{1a} represents -CN, -C(O)OR^{1b} or -C(O)N(R^{1c})(R^{1d});
20   R^{1b}, R^{1c} and R^{1d} each independently represent C_{1-6} alkyl, aryl or heteroaryl;
R^{2a} represents:
    (i) phenyl substituted at the 4-position with halo or -O-R^{2b}; or
    (ii) hydrogen;
R^{2b} represents hydrogen or phenyl;
25

which process comprises reaction of a compound of formula II,

(II)

30   or a derivative thereof, wherein
R^{1a} and R^{2a} are as defined above;

X^1 represents a suitable leaving group,

with a compound of formula III,

(III)

5   or a derivative thereof, wherein R^1 is as defined above,

which process is hereinafter referred to as a "process of the invention".

In the embodiment of the invention described above, it is indicated that R^1 may
10   represent hydrogen or a nitrogen-protecting group. The invention itself represents the
process, i.e. the formation of the pyrazole as specified above. However, this inventive
concept may be further divided into two: i.e. there may be two sub-embodiments of the
invention in which:
    (i) R^1 represents hydrogen; and
15   (ii) R^1 represents a nitrogen-protecting group,
and the invention may be directed to either one of these two aspects (or sub-
embodiments). For instance, in aspect (ii), R^1 is a nitrogen-protecting group, and the
process of the invention may be performed on a compound of formula (III) in which R^1
is a protecting group to provide a compound of formula (I) also containing that R^1
20   protecting group. That R^1 protecting group may be removed at any convenient stage
(e.g. in downstream steps) as described herein. This aspect (ii) is discussed herein, and
is also described in the examples (see Example 1). In the other aspect (i), R^1 is
hydrogen, and hence the compound of formula (III) represents a piperidine
unsubstituted at the nitrogen atom, and this has the advantage that the compound of
25   formula (III) need not be protected, i.e. in which R^1 is hydrogen, in order to form a
compound of formula (I) which is also not protected at the piperidine nitrogen atom.
This may therefore have the advantage that this aspect avoids the need for additional
protection and de-protection steps. This aspect (i) is also discussed herein, and is also
described in the examples (see Example 2).
30

In the processes of the invention described herein, it is indicated that "derivatives" may
be employed, which includes salts and solvates. Hence, for instance the compound of
formula (III), i.e. the hydrazine, may be in the form of the free base or in the form of a
salt (e.g. a di-hydrogen chloride salt, although the hydrazine may be in another salt

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form). Where appropriate, "derivative" may also encompass a relevant protecting group (which may be removed later in the synthesis scheme). It should also be noted that compounds mentioned herein may exhibit isomerism, e.g. tautomerism.

It is further indicated above that R^1 is a nitrogen protecting group. Such groups include those that result in the formation of:

- an amide (e.g. *N*-acetyl)
- optionally substituted *N*-alkyl (e.g. *N*-allyl or optionally substituted *N*-benzyl)
- *N*-sulfonyl (e.g. optionally substituted *N*-benzenesulfonyl)
- a carbamate
- a urea
- trityl (triphenylmethyl), diphenylmethyl, or the like

Hence, R^1 may, amongst other groups, represent:

$-C(O)R^{t1}$ (in which R^{t1} may represent hydrogen, so forming $-C(O)H$, but preferably represents C_{1-6} alkyl or optionally substituted aryl);

C_{1-6} alkyl, which alkyl group is optionally substituted by one or more substituents selected from optionally substituted aryl (e.g. preferably forming a benzyl moiety);

$-S(O)_2R^{t2}$ (in which R^{t2} preferably represents optionally substituted aryl); or, preferably, $-C(O)OR^{t3}$ (in which R^{t3} preferably represents optionally substituted aryl or, more preferably, optionally substituted C_{1-6} (e.g. C_{1-4}) alkyl, e.g. *tert*-butyl (so forming, for example, a *tert*-butoxycarbonyl protecting group, i.e. when taken together with the amino moiety, a *tert*-butylcarbamate group) or a $-CH_2$phenyl group (so forming a carboxybenzyl protecting group);

$-C(O)N(R^{t4})R^{t5}$ (in which, preferably, R^{t4} and R^{t5} independently represent hydrogen, C_{1-6} alkyl, optionally substituted aryl or $-C(O)R^{t6}$, and R^{t6} represents C_{1-6} alkyl or optionally substituted aryl).

Unless otherwise specified, alkyl groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of three) of carbon atoms be branched-chain, and/or cyclic. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such alkyl groups may also be part cyclic/acyclic. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated.

The term "aryl", when used herein, includes C_{6-10} groups. Such groups may be monocyclic, bicyclic or tricyclic and, when polycyclic, be either wholly or partly aromatic. C_{6-10} aryl groups that may be mentioned include phenyl, naphthyl, and the

like. For the avoidance of doubt, the point of attachment of substituents on aryl groups may be *via* any carbon atom of the ring system.

The term "heteroaryl", when used herein, includes 5- to 14-membered heteroaryl
5   groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur. Such heteroaryl group may comprise one, two or three rings, of which at least one is aromatic. Preferably, such groups are 5- to 12-membered, e.g. 5- to 10-membered.

10   Where mentioned herein, C_{1-6} alkyl, aryl and heteroaryl may be optionally substituted. Such substitution is possible if it does not affect the concept of the invention, i.e. the process(es) defined herein (which may be performed on certain compounds irrespective of the substitution pattern thereon). Such substituents include aryl (e.g. phenyl, itself optionally substituted by substituents selected from halo, alkyl and the like), alkyl,
15   halo, -CN and the like.

It is indicated that X^1 represents a suitable leaving group, and in particular may represent chloro, bromo, iodo, $-OR^{3a}$ (in which R^{3a} represents optionally substituted alkyl, e.g. in which the optional substituent(s) include aryl such as phenyl, so forming
20   e.g. $-OCH_3$, $-OCH_2$-phenyl or the like) or a sulfonate group (e.g. $-O-S(O)_2R^{4a}$, in which R^{4a} represents optionally substituted alkyl or aryl, so forming e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$ or $-S(O)_2PhMe$ or the like, i.e. tosyl, mesyl or the like).
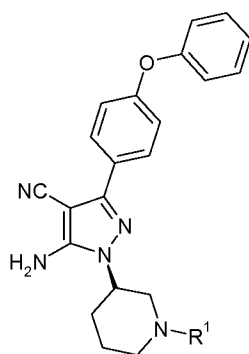
Preferred compounds of formula (I) that may be prepared by a process of the invention
25   described herein include those in which:
R^{1a} represents $-CN$;
R^{2a} represents phenyl substituted at the 4-position by $-O-R^{2b}$; and/or
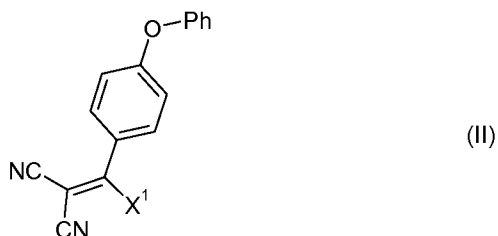R^{2b} represents phenyl;
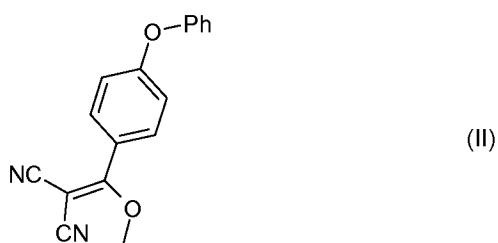hence the compound of formula (I) is preferably:

(I)

30

the compound of formula (II) is preferably:

(II)

wherein, preferably, X^1 represents $-OR^{3a}$, in which R^{3a} is preferably alkyl, more preferably unsubstituted alkyl and, most preferably, methyl, so forming a $-OCH_3$ group; and hence, most preferably, the compound of formula (II) represents:

(II)

.

For the avoidance of doubt, the compound of formula (III) is a single enantiomer containing a chiral centre that has an (R)-configuration. By single enantiomer, we mean that the compound is present in some enantiomeric excess (in this case, that there is more (R)-enantiomer present than the (S)-enantiomer), for instance in greater than 50% ee, e.g. greater than 60%ee. The chirality is retained in the process of the reaction, i.e. the reaction is stereospecific, and the compound of formula (I) thereby produced is also a single enantiomer with the same configuration at the relevant chiral centre. Downstream synthetic steps will also proceed with retention of the stereochemistry (unless specified otherwise).

Particularly preferred protecting groups that R^1 may represent include those forming carbamates (especially the *tert*-butoxycarbonyl or t-Boc group and the carboxybenzyl or Cbz group) and substituted alkyl moieties (especially the benzyl group). Such protecting groups may be more easily introduced onto the compound of formula (III) and/or ultimately more easily removed from the relevant nitrogen atom in a downstream step.

Such a process of the invention may be conducted using the free base of a compound of formula (III) or salt thereof, e.g. a di-hydrogen chloride salt of the compound of formula (III). Further the protecting group R^1 is preferably a non acid-labile protecting group (e.g. a group labile to base or removable though hydrogenation or the like) such

as a carboxybenzyl (Cbz) protecting group. However, the choice of this protecting group is influenced by the choice of the protecting group R^2 (e.g. the two are preferably mutually compatible) as indicated hereinafter.

5   In this aspect of the process of the invention, the compound of formula (III) (or derivative thereof, e.g. di-HCl salt) may be added to the compounds of formula (II). Preferably less than two equivalents of the compound of formula (III) is employed compared to the compound of formula (II), more preferably less than 1.5 equivalents. However, the equivalents ratio of compound of formula (III) to compound of formula
10   (II) may be between 1.5 : 1 to 1: 1.5, preferably between 1.2 : 1 to 1 : 1.2 and in particular, the ratio is about 1 : 1.

       Preferably, this aspect of the process of the invention may be performed in a suitable solvent, such as in the presence of a polar solvent, such as an alcoholic solvent (e.g.
15   ethanol) and/or water, or mixtures thereof. It is preferred that a mixture of an alcohol (e.g. ethanol) and water is employed. Compared to the weight of the compound of formula (II) employed, at least one (e.g. at least five, but preferably less than 20) volume equivalent(s) of the solvent/alcohol and at least one (e.g. at least five, but preferably less than 20) volume equivalents of water are employed. Preferably about
20   13 volume equivalents of the alcohol and about 10 volume equivalents of water are employed.

       Preferably, the compound of formula (II) in the presence of a suitable solvent (as described above) is cooled to below room temperature, for example to below 10°C, e.g.
25   to about 5°C. The compound of formula (III) (or derivative thereof) is then added to the mixture of compound of formula (II) and solvent. Preferably this is done so as to maintain the temperature of the reaction mixture below room temperature (e.g. at below about 10°C, preferably between 5 and 10°C). For instance, this addition may be drop-wise.
30
       This process aspect of the invention is preferably conducted in the presence of a base, such as an organic base, preferably an amine base such as a tertiary amine base (e.g. triethylamine). Preferably between one and four molar equivalents of base are employed in the process of the invention (compared to the molar equivalents of the
35   compound of formula (II) or (III)), and more preferably between 1.5 and 2.5 equivalents are employed (e.g. about two equivalents). Preferably the base is added dropwise, and preferably the temperature is maintained at below room temperature (e.g. at below about 10°C, preferably between 5 and 10°C).

After the addition of the base, the reaction mixture is the preferably allowed to warm to about room temperature, after which it is allowed to stir at that temperature for a period of time (during which the conversion to desired product compound (I) may be

5   monitored), which may depend on the conversion rate to product. Typically, the reaction mixture is allowed to stir for at least 20 minutes, for example for about one hour, after which further water may be added (e.g. between about 10 and 20 volume equivalents), the reaction mixture may be cooled (again) to below room temperature (e.g. to below about 10°C, preferably about 5°C or below, e.g. about 0°C). The desired

10   product may then solidify, and may therefore be separated/isolated by filtration. It may be further purified if required.

Such an aspect of the process of the invention has several advantages. For instance, the fact that the substituted hydrazine of formula (III) (that may be employed in e.g. the

15   free base form, or in the salt form which may be formed *in situ*) is employed in the reaction has at least the following advantages:

(i)   the use of hydrazine hydrate is avoided, which is a hazardous reagent to handle, especially at high temperatures (for instance hydrazine is combustible even in the absence of oxygen);

20   (ii)   the reaction leads to a 1N-substituted pyrazole and hence downstream substitution at the 1N-position is circumvented (when substitution is required at that position), for instance a downstream Mitsunobu reaction to introduce a substituent is circumvented, the latter reaction generating enormous amounts of waste (e.g. the Mitsunobu reaction may require two equivalents of the

25   3-hydroxy-N-Boc piperidine, due to a competing elimination reaction);

(iii) the use of the expensive chiral 3-hydroxy-N-Boc piperidine is circumvented;

(iv)   the reaction of compound (II) with a non-symmetrical hydrazine may be expected to result in a variety of products (as opposed to reaction with the symmetrical hydrazine itself) but however, advantageously and unexpectedly,

30   the reaction proceeds in a regioselective manner. That is the process of the invention predominantly results in the formation of a pyrazole with a substitution pattern as depicted by the compound of formula (I), i.e. in the 1(N)-position the piperidine, R^{2a} group (e.g. 4-phenoxy-phenyl) in the 3-position, etc, as opposed to a pyrazole with the piperidine at the 2-position

35   adjacent the R^{2a} group. Advantageously, the desired regioisomer is present in higher quantity than the undesired regioisomer, and for instance is present in a ratio of greater than 75:25 compared to the undesired regioisomer, more

particularly, this ratio is greater than 90:10, and most advantageously there may be a negligible or undetectable amount of the undesired regioisomer.

Hence, this aspect of the process of the invention may be advantageous in terms of economy (e.g. cost of goods), efficiency and environmental considerations (e.g. less waste).

After the first process of the invention, the compound of formula (I) that is prepared may be converted to a compound of formula (IV),

(IV)
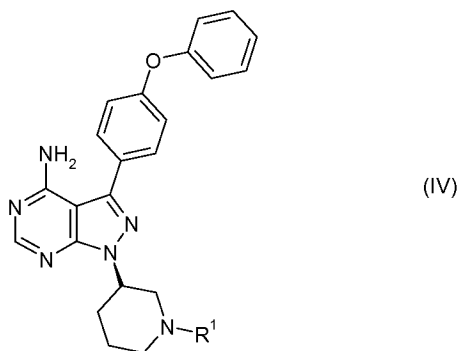
or a derivative (including isomer) thereof, wherein R^1 is as hereinbefore defined. In particular, the preparation routes are particularly suitable for corresponding compounds in which R^1 represents a protecting group (as defined herein) or may also be suitable for corresponding compounds in which R^1 represents hydrogen (such embodiments may be specifically referred to below).

In the conversion to the compound of formula (IV), the compound of formula (I) may first be converted to a compound of formula (IVA),

(IVA)
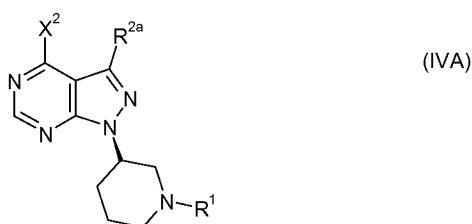
or a derivative (including isomer), wherein X^2 represent -OH or $-NH_2$, and R^1 and R^{2a} are as hereinbefore defined.

For instance, for compounds of formula (I) in which R^{1a} represents -CN, a corresponding product of formula (IVA) in which X^2 represents $-NH_2$ may be produced by reaction with either:

(i) formamide (HCONH$_2$);

(ii) formamidine or a formamidine salt H-C(=NH)-NH$_3$$^+X^-$, wherein X$^-$ represents a suitable counterion, such as a halide (e.g. Cl$^-$) or an oxy anion (e.g. acyl-O$^-$), so forming for example formamidine HCl or formamidine acetate or the like;

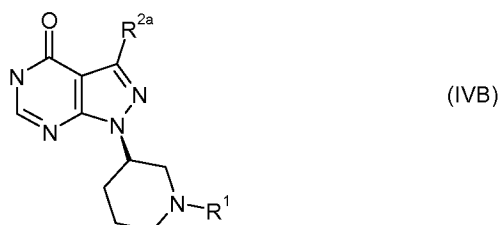(iii) alkyl (e.g. ethyl) formimidate, or a salt thereof, such as ethyl formimidate HCl;

(iv) ethylorthoformate followed by ammonium acetate.

For the aspect of the invention where compounds of formula (I) in which R^1 represents hydrogen are concerned, such compounds may also be converted to a compound of formula (IV) or a compound of formula (IVA), and in this instance, such a reaction may result in the replacement of the hydrogen at R^1, for example by reaction with formamide (HCONH$_2$), this may result in concurrent substitution (along with the desired cyclisation) at the R^1 position to a compound of formula (IV) or (IVA) in which R^1 represents -C(O)H. In such an instance, an additional step of deprotection (or removal of the -C(O)H moiety) may be required at an appropriate stage in the sequence (for example as described in Example 2 hereinafter). Such an intermediate may also be used to ultimately prepare Ibrutinib as defined hereinafter.

For compounds of formula (I) in which R^{1a} represents -C(O)OR^{1b} or -C(O)N(R^{1c})(R^{1d}), a corresponding product of formula (IVA) in which X^2 represents -OH (or a tautomer thereof, as depicted by formula (IVB) below) may be produced by reaction with for example, CH(OEt)$_3$ optionally in the presence of a catalyst (e.g. ZnCl$_2$, 0.1 equiv), followed by the addition of e.g. NH$_4$OAc, which reaction may be performed in the presence of a suitable solvent (e.g. an aromatic solvent such as toluene):

(IVB)

Thereafter, compounds of formula (IVA) in which X^2 represents -OH (or the tautomer, i.e. compound (IVB) depicted above) may be converted to corresponding compounds of formula (IVA) in which X^2 represents -NH$_2$, by first converting to the corresponding chlorinated derivative (which need not be isolated) followed by a nucelophilic aromatic substitution to provide the desired compound, conditions including the use of POCl$_3$ (or another suitable chlorinating reagent) followed by reaction with NH$_4$OAc (or another suitable source of ammonia).

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For compounds of formula (IVA) in which R^{2a} represents hydrogen, such a compound may be converted to a compound of formula (IVC):

(IVC)

5

wherein X^2 is as hereinbefore defined, and X^3 is a suitable group such as halo (e.g. bromo, chloro or preferably, iodo), which reaction may take place in the presence of a source of halide, for instance an electrophile that provides a source of iodine includes

10   iodine, diiodoethane, or preferably, N-iodosuccinimide, and sources of bromide and chloride include N-bromosuccinimide and N-chlorosuccinimide, and which reaction may be performed in the presence of a suitable solvent such as an alcohol (e.g. methanol) or preferably a halogenated solvent (e.g. chloroform) or a polar aprotic solvent (such as DMF).

15

Compounds of formula (IVC), in particular those in which X^2 represents -NH$_2$, may be converted to compounds of formula (IVA) in which R^{2a} represents phenyl substituted at the 4-position with halo or -OR^{2b}, by reaction of the compound of formula (IVC) with a compound of formula (IVD):

20

$$X^4\text{-}R^{2aa} \qquad \text{(IVD)}$$

wherein R^{2aa} represents phenyl substituted at the 4-position with halo or -OR^{2b} (with R^{2b} as hereinbefore defined), and wherein X^4 represents a suitable group such as

25   -B(OH)$_2$, -B(OR^w)$_2$ or -Sn(R^w)$_3$, in which each R^w independently represents a C$_{1-6}$ alkyl group, or, in the case of -B(OR^w)$_2$, the respective R^w groups may be linked together to form a 4- to 6-membered cyclic group (such as a 4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl group, thereby forming e.g. a pinacolato boronate group), and wherein the coupling reaction may be performed in the presence of a suitable catalyst system, e.g. a

30   metal (or a salt or complex thereof) such as Pd, CuI, Pd/C, Pd(OAc)$_2$, Pd(Ph$_3$P)$_2$Cl$_2$, Pd(Ph$_3$P)$_4$, Pd$_2$(dba)$_3$ and/or NiCl$_2$ (preferred catalysts include palladium) and a ligand such as PdCl$_2$(dppf).DCM, t-Bu$_3$P or the like, optionally in the presence of a suitable base (e.g. a carbonate base, hydroxide base, etc) and a suitable solvent.

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Where, e.g. for compounds of formula (IVA) as defined above in which X^2 represents -NH₂ (or a protected derivative thereof) and R^{2a} represents phenyl substituted at the 4-positon by halo or -OH, then conversion to the compound of formula (IV) may be possible by a coupling reaction with X^4-phenyl-O-phenyl or X^4-phenyl, for instance using similar catalytic coupling reactions to those mentioned above.

Hence, ultimately compounds of formula (IV) may be prepared according to the processes mentioned above.

The processes discussed above (including those to prepare compounds of formula (IV) and (IVA)) are also embraced by the concept of the invention, and are also processes that may be referred to herein as a "process of the invention".

There is therefore provided a process for the preparation of a compound of formula (IV) which process comprises a process for the preparation of a compound of formula (I) as hereinbefore defined followed by a process for the conversion of (I) to (IV) as hereinbefore described.

There is also provided a process for the preparation of a compound (IV) or (IVA), which process comprises reaction of a compound of formula (I) (as hereinbefore defined) with a formamidine salt defined at (ii) above. Such a process is also an aspect of the invention and has associated advantages compared with reaction with formamide. For instance, the use of the formamidine salt may be advantageous as it circumvents the use of formamide, the latter being using in prior processes at high temperatures (e.g. at about 165°C, which represents a thermal hazard), whereas the use of the formamidine salt allows lower temperatures to be employed.

This aspect of the invention (conversion of compound (I) to compound (IV) or (IVA)) is preferably performed by reaction of the compound (I) with a formamidine salt (as defined hereinbefore). The formamidine salt is preferably an acetate salt and is preferably employed in excess compared with the molar equivalents of compound of formula (I) employed (e.g. in greater than two equivalents compared to compound of formula (I), e.g. greater than five equivalents, such as greater than 10 equivalents and preferably about fifteen equivalents).

This aspect of the process of the invention may be performed in the presence of a suitable solvent, which may be selected from aromatic solvents (e.g. toluene), alcohols,

ethers and N-methyl-2-pyrrolidone, or the like. Glycols ethers may be particularly
preferred (e.g. due to high boiling points), and a particularly preferred solvent is
therefore ethylene glycol monoethyl ether. The solvent is preferably de-gassed and the
reaction is preferably carried out under an inert atmosphere. More than five volume
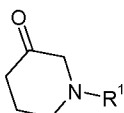5   equivalents of solvent is employed (e.g. more than ten, and preferably around 13).

The resultant reaction mixture is then preferably heated to above room temperature, e.g.
to above 40°C, e.g. above 60°C such as above 80°C. Most preferably it is heated to
above 100°C. However, the temperature of the reaction mixture is preferably below
10   160°C, for instance the preferred temperature range is between 100°C and 140°C, most
preferably between about 110°C and 130°C (e.g. about 120°C).

The reaction mixture may be monitored for progress, consequently affecting the time
period of the reaction. After adequate completion of the reaction, mixture may be
15   allowed to cool down and the reaction mixture worked up to provided the desired
compound.

There is further provided a process for the preparation of a compound of formula (III)
as hereinbefore defined, which process comprises resolution of a corresponding
20   racemic mixture (or derivative, e.g. protected derivative, thereof), which may be
performed by means of chiral chromatography (e.g. using chiral SFC), thereby
advantageously obtaining a compound of formula (III) in greater than 50%ee, for
example greater than 60%ee. Given that the process of the invention is stereoselective,
it is possible to purify downstream so as to provide an enantiomerically pure
25   downstream compound.

Advantageously, this may produce product (compound (III)) in greater than 50% ee, for
instance greater than 60% ee. Introducing the chirality at this stage allows the
processes hereinbefore described to be effected, thereby circumventing other methods
30   for introducing the chirality (e.g. using chiral 3-hydroxy-piperidine) and circumventing
the undesired Mitsunobu reaction prior disclosed in a process for preparing ibrutinib.

Compounds of formula (III), or protected derivatives thereof may be prepared by
reaction of a compound of formula (VI),
35

(VI)

-15-

or a derivative thereof, wherein R^1 is as hereinbefore defined, with a compound of formula (VII),

$$R^2\text{-N(H)-NH}_2 \qquad\qquad\qquad \text{(VII)}$$

5

wherein R^2 is hydrogen or a suitable nitrogen protecting group (which may be subsequently removed),

which may also be referred to as an aspect of the invention. This aspect of the
10   invention may be conducted under standard dehydration reaction conditions optionally in the presence of a suitable solvent.

In general, the protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.
15

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

The use of protecting groups is described in "Protective Groups in Organic Chemistry",
20   edited by J.W.F. McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

The following scheme (which may have its individual numbering, as may the experimental section) provides a non-limiting example of various processes of the
25   invention:

For instance, for compounds of formula (II) in which X^1 represents an alkoxy leaving group $-OR^{3a}$ (or sulfonate), then such a compound may be prepared by alkylation (e.g.

methylation) (or appropriate sulfonylation) of a compound corresponding to a compound of formula (II) but in which -OR^{3a} represents -OH. Conversion of the –OH to other suitable leaving groups (e.g. to halo) may also be effected.

5   Compounds corresponding to formula (II) but in which -OR^{3a} represents -OH may be prepared by reaction of a compound of formula (VIII),

$$R^{2a}\text{-}C(O)X^{1a} \qquad \text{(VIII)}$$

10   wherein X^{1a} represents a suitable leaving group (e.g. chloro) and R^{2a} is as hereinbefore defined, with a compound of formula (IX),

$$NC\text{-}CH_2\text{-}R^{1a} \qquad \text{(IX)}$$
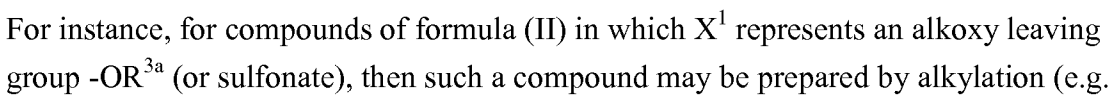
15   wherein R^{1a} is as hereinbefore defined, under suitable reaction conditions.

Some compounds described herein may be novel themselves, and hence in a further aspect of the invention, there is provided:
  -   a compound of formula (I) or a derivative thereof
20   -   a compound of formula (III) or a derivative thereof , for instance in at least greater than 50%ee
  -   a compound of formula (II), (IV) or (IVA) or a derivative thereof
In an embodiment of the invention, there is provided a process for the preparation of ibrutinib:

25
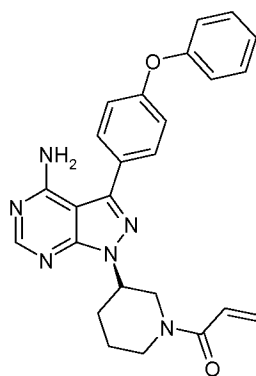
which process comprises a process as defined herein, followed by conversion to ibrutinib, for example:
  -   a process for the preparation of a compound of formula (I) as herein described, followed by conversion to ibrutinib

- a process for the preparation of a compound of formula (IV) or (IVA) as herein described, followed by conversion to ibrutinib, for example by deprotection (i.e. removal of the R^1 group) followed by acylation with acryl chloride

- a process for the preparation of a compound of formula (III) as hereinbefore described, followed by conversion to ibrutinib, for example in accordance with the procedures described herein

Hence, there is also provided the use of certain compounds (e.g. the use of a compound of formula (I), (IV), (IVA) and/or (III)) as intermediates in the preparation of ibrutinib.

There is then further provided a process for the preparation of a pharmaceutical formulation comprising ibrutinib, which process comprises bringing into association ibrutinib (or a pharmaceutically acceptable salt thereof), which is prepared in accordance with the processes described hereinbefore, with (a) pharmaceutically acceptable excipient(s), adjuvant(s), diluents(s) and/or carrier(s).

In general, the processes described herein, may have the advantage that the compounds prepared may be produced in a manner that utilises fewer reagents and/or solvents, and/or requires fewer reaction steps (e.g. distinct/separate reaction steps) compared to processes disclosed in the prior art.

The process of the invention may also have the advantage that the compound(s) prepared is/are produced in higher yield, in higher purity, in higher selectivity (e.g. higher regioselectivity), in less time, in a more convenient (i.e. easy to handle) form, from more convenient (i.e. easy to handle) precursors, at a lower cost and/or with less usage and/or wastage of materials (including reagents and solvents) compared to the procedures disclosed in the prior art. Furthermore, there may be several environmental benefits of the process of the invention.

Examples

The following examples are intended to illustrate the present invention and should not be construed as a limitation of the scope of the present invention.
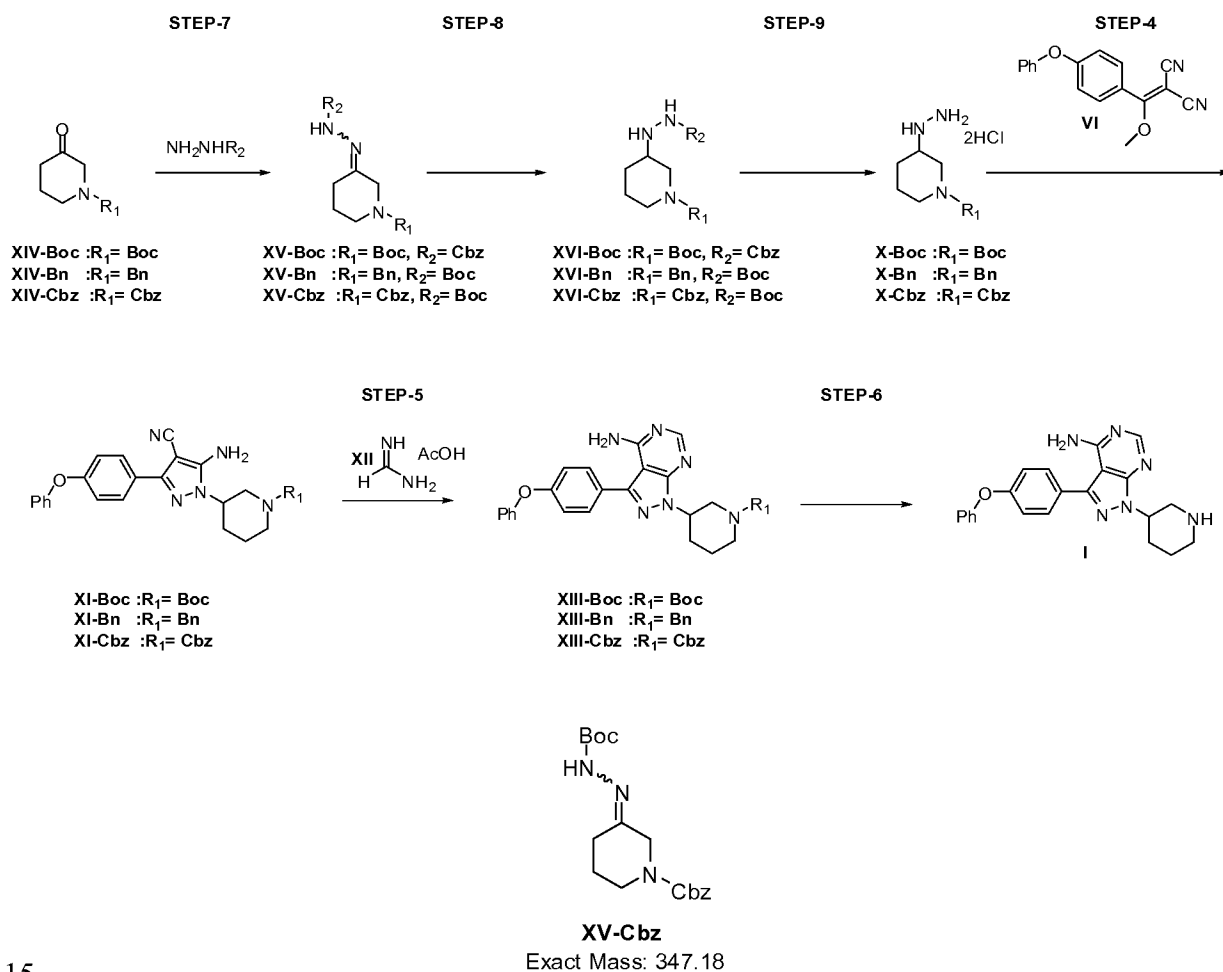
Experimental Section

Example 1

### Prepare I from XI with Cbz protecting group

The synthesis route from XIV-Cbz to I has been performed in the laboratory with the total yield of ~50%. Structure of I from this route has been confirmed by comparing HPLC, HNMR and CNMR with reference standard I.
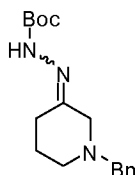

XV-Cbz
Exact Mass: 347.18

100 g (1.0 eq.) of XIV-Cbz and 56.66 g (1.0 eq.) Boc-NHNH$_2$ was dissolved in 500 mL solvent (methanol, 5.0 V), Na$_2$SO$_4$ was added and the mixture was stirred for 4h at 28°C. The solvent was evaporated by reduce pressure to get 148g of XV-Cbz as a yellow oil. MS (ESI):m/z =370 (M+23(Na))

CbzHN−N

NBoc
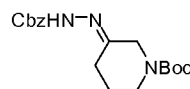
XV-Boc
Exact Mass: 347.18

45.8g (1.0 eq.) of XIV-Boc and 38.2 g (1.0 eq.) Cbz-NHNH₂ was dissolved in 230 mL
solvent (methanol, 5.0 V), the mixture was stirred for 2h at 28°C. The solvent was
5   evaporated by reduce pressure to get 78g of XV-Boc as a yellow oil. MS (ESI):m/z =
370 (M+23(Na))

Boc
HN
N

N
Bn

XV-Bn
Exact Mass: 303.19

100 g (1.0 eq.) of XIV-Bn.HCl.H₂O/Bn and 54.22 g (1.0 eq.) Boc-NHNH₂ was
10   dissolved in 500 mL solvent (methanol, 5.0 V), Na₂SO₄ was added and the mixture was
stirred for 2h at 25°C. The solvent was evaporated by reduce pressure to get 122g of
XV-Bn as orange foam. MS (ESI):m/z =304 (M+1)

BocHN−NH

NCbz
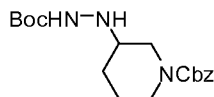
XVI-Cbz
Exact Mass: 349.20

33.11g (1.0 eq) of XV-Cbz was dissolved in 160mL of MeOH, cool 5°C and stirred
15   under nitrogen. 2.0 eq. NaBH₃CN was then added to the reaction mixture. Then, 1.0eq
of AcOH was added dropwise and stirred at 5 °C under nitrogen for 3h. The reaction
mixture was stirred for another 3.5h at 25 °C, cooled to 10°C, and then saturated
aq.NH4Cl was added dropwise until pH~6. (A lot of white solid separated out). The
mixture was filtered and the solid washed with H₂O. The cake was dried under vacuum
20   at 45-50°C for 16hrs and isolated in 81.1% yield. MS (ESI):m/z =372 (M+23(Na))

-21-

CbzHN
NH
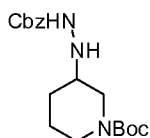
XVI-Boc
Exact Mass: 349.20

28.4g (1.0 eq) of XV-BOC was dissolved in 145mL of THF and 30mL of MeOH, cool
5°C and stirred under nitrogen. 6.18g (2.0 eq) of $NaBH_4$ was then added to the reaction
mixture and stir at 5 °C under nitrogen for 3h. It was allowed to stir for another 15h at
5   20 °C. 15% aq. NH_4Cl was added dropwise until pH~6-7. Then 10V of Ethyl acetate
was charged/added into the mixture. The phase was separated, and the aqueous was
extracted twice with 8V of ethyl acetate. The organic layers were combined and
washed twice with 10V of water. The organic solution was concentrated to 3-4V and
then cooled to 0-5°C. PE was added dropwise to crystallize XVI-Boc as white solid.
10   The mixture was filtered and the cake dried under vacuum at 40-45°C. 25g of
XVI-Boc was obtained with 97.54% HPLC purity in the yield of 87.7%.

HN^NHBoc
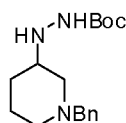
XV-Bn
Exact Mass: 305.21

A MeOH solution of XV-Bn (37.6g in 130mL MeOH) was cooled to 5°C under N_2.
15   2.0 eq. $NaBH_3CN$ was charged under N_2 keeping the temperature at 5-10 °C. 1.0eq of
AcOH was added dropwise at 5-10°C. The mixture was warmed to 25 °C and stirred
under N_2 for 16h. The reaction mixture was cooled to 10°C. Saturated aq.$NH4Cl$ was
added dropwise into R1 to pH~6. The mixture was concentrated under vacuum and
then aqueous phase was extracted with EA (100ml*3). The organic phase was
20   concentrated. The mixture was filtered and the filter cake washed with MTBE. The
cake was dried under vacuum at 45-50°C for 16hrs to get 23g XVI-Bn as white solid
97.9% purity. MS (ESI):m/z =306 (M+1)

2HCl H_2N
NH
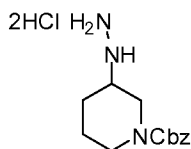
Exact Mass: 249.15

X-Cbz

-22-

16.12 g (1.0 eq.) XVI-Cbz was charged with 80 mL of methanol. 92.2mL MeOH
solution of HCl (4M) was charged and stirred for 3h at 28 °C. MeOH was switched to
EtOAc (a lot of white solid separated out). The solid was filtered under N₂ protection.
The filter cake was dried under vacuum at 35-40 °C for 16hrs to result in 11.9g (80.2%
5   Yield) with a purity of 94.97%. (ESI):m/z =249.9 (M+1)

2HCl
H₂N—NH

NBoc
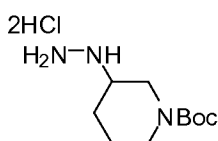
Exact Mass: 215.16
X-Boc

Pd(OH)₂/C was used as catalyst and 2.0eq HCl (2M MeOH solution) was added to
inhibit the generation of a dimmer by-product. Form LCMS, a strong MS signal of
10   X-Boc could be found. After the workup, 3.9g of X-Boc was obtained as foam in the
yield of 79.6%. **Procedure:** Charge 6.0 g (1.0 eq.) of XVI-Boc with 90 mL (15.0 V.)
Methanol, then charge 3.61 g (0.30 eq.) Pd(OH)2/C with 34.36mL(2.0 eq) of MeOH
solution of HCl (1M), stir for 1h at 28 °C under N₂. Swich the solvent to EtOAc to
separate the product out. Transfer the mother liquor out and dry the residue under
15   vacuum to get 3.9g of X-Boc as white foam (79.6% Yield). (ESI):m/z =216.0 (M+1)

2HCl H₂N

NH

N
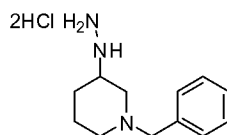
X-Bn
Exact Mass: 205.16

Charge 20g (1.0 eq) of XVI-Bn under N₂, add 11 eq. HCl MeOH solution (4M) into R1
20   under N₂ at 20-25°C and stir at 50 °C for 2h. Switch the solvent to EtOAc and then a
lot of white solid separated out. Filter the mixture under N₂ protection. The solid was
dried under vacuum at 45-50°C to yield 14g of X-Bn (76.9% Yield).

NC

NH₂

Ph
O

N-N

NCbz
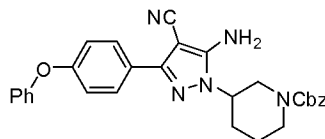
Exact Mass: 493.21
XI-Cbz

25   Charge 4.29 g (1.0 eq.) of VI under N₂ with 60mL (13 V.) ethanol and 43ml (10V) of
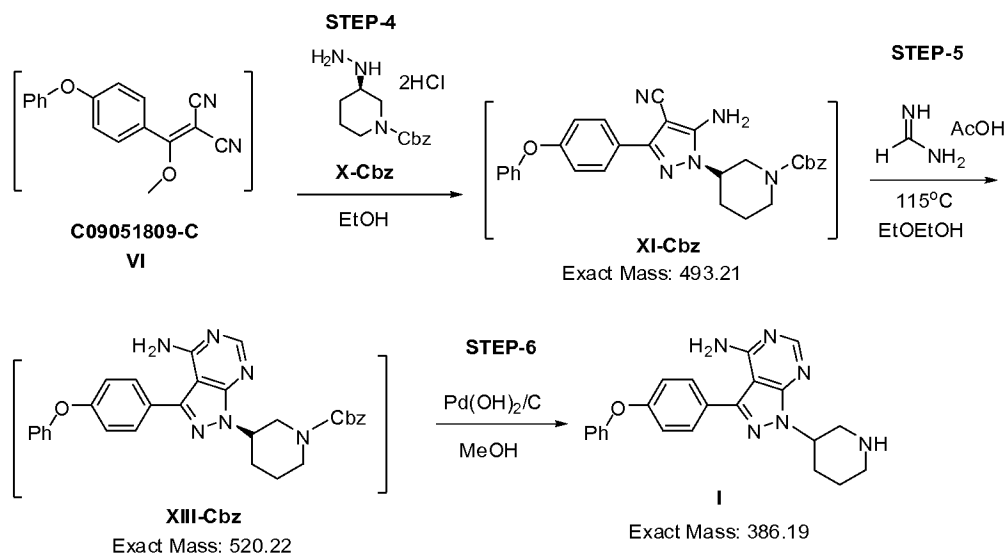
water. Cool the mixture to 5 °C. Add X-Cbz in three portions at 5-10 °C under N_2. Add dropwise 3.15g (2.0.eq.) NEt_3 at 5-10 °C. Warm to 25°C under N2 and stir for 1 h at 25°C (solid separate out). Add dropwise 17V H_2O into the reaction mixture at 25 °C. Cool the reaction mixture 0 -5°C and stir for 1h. Filter the mixture. The cake was dried under vacuum at 40-45 °C to result in 7.79g (100%Yield) with a purity of 99.81% (ESI):m/z =494.1 (M+1)

XIII-Cbz
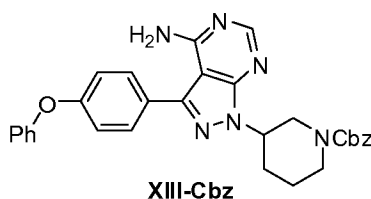
Exact Mass: 520.22

3g (1.0eq) of XI-Cbz was mixed with 9.5g (15.0 eq) of formamidine acetate and 40mL (13V) $C_2H_5OC_2H_4OH$ (degassed), the reaction mixture was stirred at 120 °C for 6hrs, Cool the reaction mixture to r.t. Add dropwise H2O (13V) and EA (15V). Separate the mixture and extract the aqueous phase with EA fro twice. Combine the organic phase and wash it with H_2O twice. Evaporate solvent under vacuum to get crude XIII-Cbz as yellow oil in 97.9% purity. (ESI):m/z = 521.4 (M+1)

STEP-4

C09051809-C
VI

X-Cbz

EtOH

XI-Cbz
Exact Mass: 493.21

STEP-5

AcOH

115°C
EtOEtOH

XIII-Cbz
Exact Mass: 520.22

STEP-6

$Pd(OH)_2/C$

MeOH

I
Exact Mass: 386.19

Telescope preparation of I from VI was carried out. In step-4, conversion of VI was 100% and XI-Cbz was generated with 99.8% area percent. In step-5, conversion of XI-Cbz was 97.7% and XIII-Cbz was generated with 94.2% area percent. In step-6, conversion of XIII-Cbz was 100% and I was obtained with 92.5% HPLC area percent. Procedure: Charge 4.29 g (1.0 eq.) VI under N2 with 10mL (16.6 V.) ethanol and 6ml
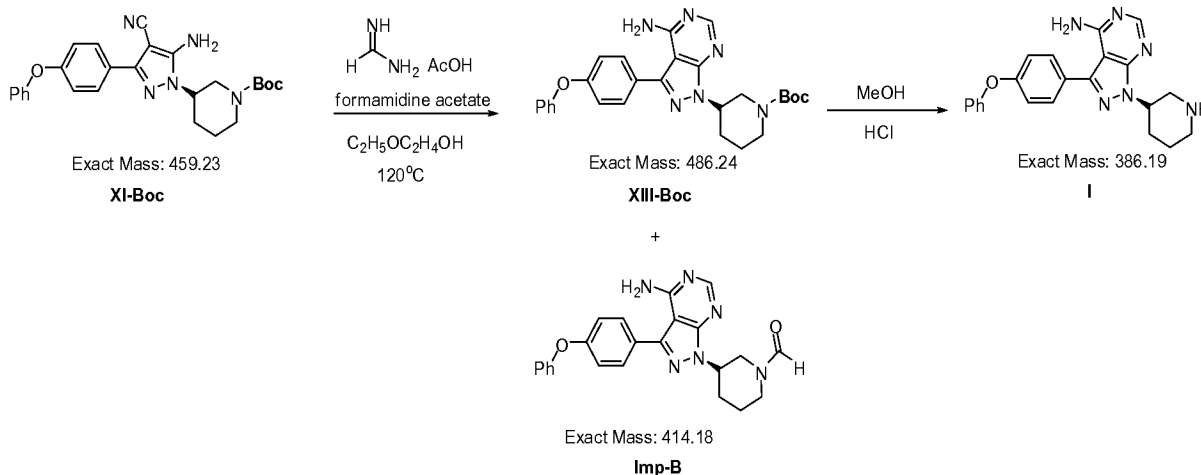
(10V.) Cool R1 to 5-10 °C. Add 0.7g (1.0.eq.) X-Cbz solution in water was added drop-wise over 15 min at 5-10 °C. Add 0.45g (2.0.eq.) NEt₃ drop-wise over 5min at 5-10 °C. Warm to 20~30 °C under N₂ and stir R1 for 1 h at 20~30 °C. Add 10V EA and then 10V H2O into the reaction mixture. Separate the mixture and extract the aqueous phase with 10V EA twice. Combine the organic phase and wash with 10V H2O. Switch the solvent to 13V EtOEtOH. Add 15eq formamidine acetate into the mixture. Heat to 120°C and stir for 5hrs at 120°C. Cool the mixture to r.t. and add 15V EA and 15V H2O into the mixture. Separate the mixture and extract the aqueous phase with 10V EA twice. Combine the organic phase and wash with 10V H2O twice. Switch the solvent to 10V MeOH. Add Pd(OH2)/C(0.3eq) and stir the mixture at 55-60 °C under 3Bar H₂. Filter the reaction mixture and wash the cake with MeOH. Combine the MeOH solution of crude I and concentrate to 2-3VAdd dropwise H2O (5-6V) into the MeOH solution (a lot of off-white solid separated out). Filter the mixture and wash the cake with MeOH/H2O (1V/1V). The solid was dried under vacuum at 40-45 °C to obtain I in 80% yield (over 3 steps) in 92.5% purity.

By comparing the HPLC, HNMR and CNMR of **I** with a reference of that compound e.g. known from the art (or derivatised therefrom), it could be concluded that **I** that is prepared by this synthesis had the same HPLC retention time, same HNMR and CNMR. Therefore, this synthesis route from SM-Cbz to **I** is an available working route.

STEP-4'
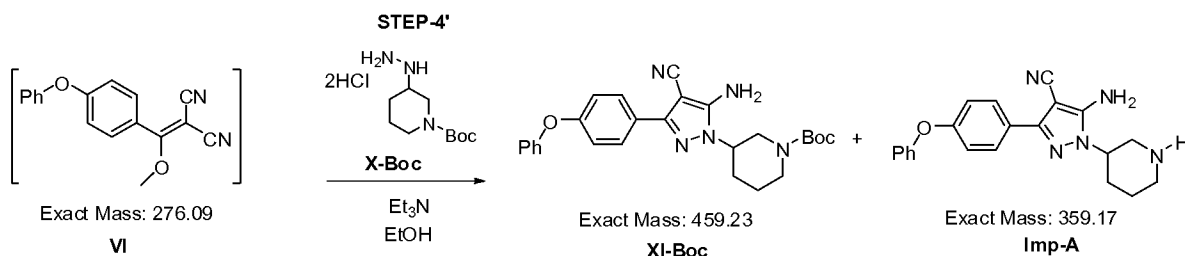
Charge 0.41 g (1.0 eq.) of VI (in THF solution). Dissolve 0.32g (1.0 eq.) of X-Boc in EtOH(2V) /H2O(0.5mL, 1.5V)/ Et3N (3.0eq). Add drop-wise X-Boc to R1 at 5-10°C. Warm to 25 °C under N2 and stir R1 for 1h at 25 °C. Add water (10V) drop-wise at 5-10 °C. Concentrate the mixture under vacuum and extract it with ethyl acetate (20ml*3). Wash the organic phase with H2O. Evaporate solvent under vacuum to get crude XI-Boc as yellow oil. The de-Boc compound, Imp-A, was generated as the main product. XI-Boc was obtained in 29% yield with 96% purity by column chromatography

-25-

Exact Mass: 459.23
XI-Boc

formamidine acetate
$C_2H_5OC_2H_4OH$
120°C

Exact Mass: 486.24
XIII-Boc

MeOH
HCl

Exact Mass: 386.19
I

+

Exact Mass: 414.18
Imp-B

Charge XI-Boc (0.3g, 1.0eq.) at r.t under N2. Charge formamidine acetate (15eq) into
R1 under N2. Charge $C_2H_5OC_2H_4OH$ (13V) into R1 under N2. Heat to 120°C (inter
temp) and stir the mixture at 120°C for 8hrs. In this reaction mixture,4.3% of Imp-B
also could be observed. Cool the reaction mixture to r.t. Add dropwise H_2O
(40mL,13V) and EA (15V). Separate the mixture and extract the aqueous phase with
EA twice. Combine the organic phase and switch the solvent to MeOH. Add HCl
(10eq, MeOH solution) into the mixture. Heat to 50°C and stir for 3hrs. Cool to r.t,
concentrate the reaction mixture to 2-3mL. Add 3mL H2O and then add dropwise 30%
aq. NaOH to adjust pH to 10. Filter the mixture and dry the cake under vacuum at
45°C. **I** could be isolated by crystallization form MeOH/H_2O with 95.6% purity in the
total yield of 87.3%

By comparing the HPLC, HNMR and CNMR of **I** with a reference of that compound
e.g. known from the art (or derivatised therefrom), it could be concluded that **I** that is
prepared by this synthesis had the same HPLC retention time, same HNMR and
CNMR. Therefore, this synthesis route from SM-Boc to **I** is an available working route.
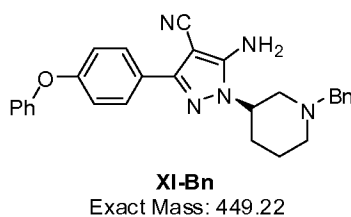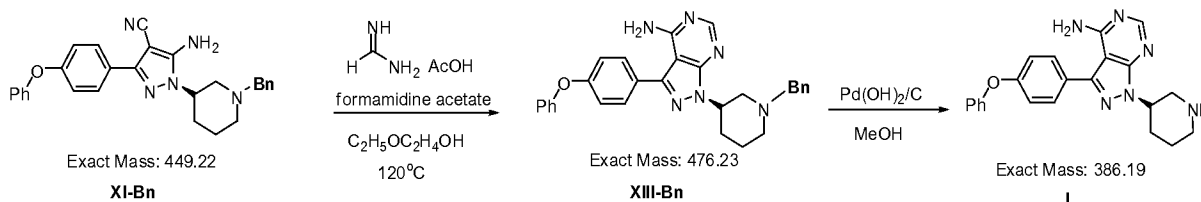

XI-Bn
Exact Mass: 449.22

Charge 0.496 g (1.0 eq.) of VI under N2 with 4mL (8V.) ethanol. Cool the mixture to
5°C. Add X-Bn (dissolve in 5V EtOH and 10V H_2O) in three portions at 5-10 °C under
N2. Add dropwise 0.51g (2.0.eq.) NEt₃ at 5-10 °C. Warm to 25-30°C under N2 and stir
for 1 h at 25-30°C (solid separate out). Add dropwise 17V H_2O into the reaction

mixture at 25 °C. Cool the reaction mixture 0 -5°C and stir for 1h. Filter the mixture. The cake was dried under vacuum at 40-45 °C to yield 0.65g of XI-Bn (80% Yield) with 94.03% purity. (ESI):m/z =450 (M+1)

5

One batch to prepare XIII-Bn was carried out from 1.72g XI-Bn. In the first ring closure step, Conversion of XI-Bn was 100% and XIII-Bn was generated with 99.12% LCMS purity. Even been stirred for 21hrs at 120°C, no decomposition could be observed. In the second step, we tried two conditions. One added 2eq of HCl (4M MeOH solution) and the other one was without HCl. The batch adding HCl was faster than the other one. However, conversion of XIII-Bn was only 20%. Procedure: Charge XI-Bn at r.t with formamidine acetate (15eq) and $C_2H_5OC_2H_4OH$ (13V) under N_2. Heat to 120°C and stir the mixture at 120°C for 8hrs. Cool the reaction mixture to r.t. Add dropwise H_2O (13V) and EA (10V). Separate the mixture and extract the aqueous phase with 10V EA for twice. Combine the organic phase and wash it with 10V H_2O for three times. Switch the solvent to MeOH from EA. Charge 0.1eq $Pd(OH)_2/C$ and 2eq HCl(4M MeOH solution). Heat to 45-50°C Stir the mixture in R2 at 40-50°C. The desired product was obtained from this procedure. (ESI):m/z =387.0 (M+1)

<u>Example 2</u>
Preparation of compound Y6 (also referred to as compound I above) from unprotected piperidine-hydrazine (referred to as Y20 below)

Exact Mass: 276.09
C09051809-C
Y3

S-1

Y20
NaOMe, MeOH

Exact Mass: 359.17
Y4

S-2

165-175°C
2h

Exact Mass: 414.18
Y16

S-3

35% HCl
55-65°C

Exact Mass: 386.19
Y6
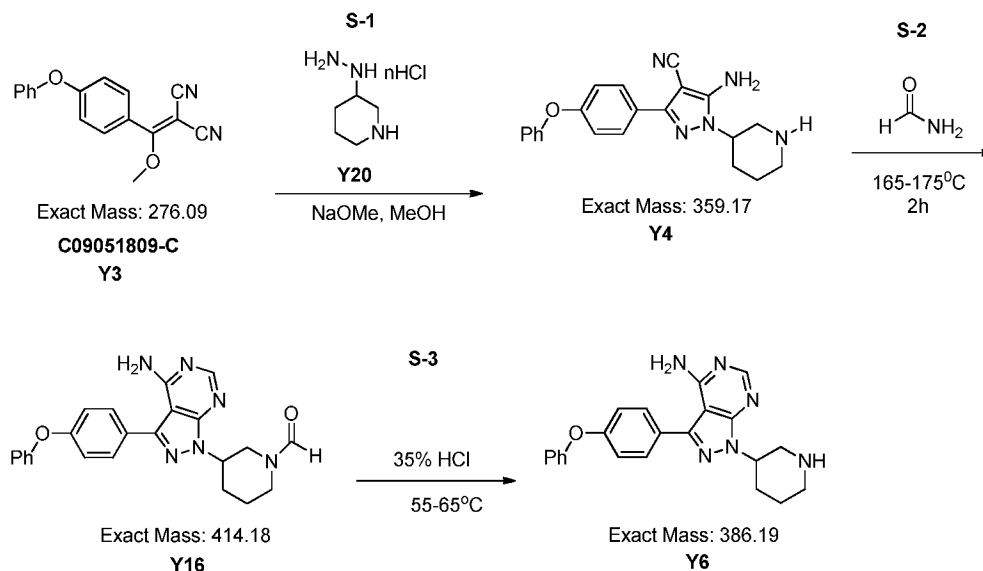
This example represents a further embodiment of the invention. The compound Y20 (the piperidine-hydrazine; also referred to herein as a compound of formula (III)),

5   which corresponds to the general compound X in previous Example 1 (but wherein in that case the N atom of the piperidine is protected with -Boc, -Bn or -CBz), is unsubstituted at the piperidine N atom, and is directly mixed with the compound Y3 (also referred to in Example 1 as compound VI, which is also a compound of formula (II) as defined herein). The reaction is similar to Step-4 in Example 1 but, unlike in

10   Example 1, this example shows that the piperidine-hydrazine need not be protected for the reaction with Y3 to proceed (see Procedure S-1 below). Indeed, the resultant product Y4 (also referred to herein as a compound of formula (I) as hereinbefore described) is advantageously produced without the need to protect the piperidine-hydrazine (and then subsequently deprotect it). The compound Y4 (which is still

15   unsubstituted at the piperidine N atom) may then be directly used in the next reaction step (i.e. without the need to add a protecting group), where a mixture containing Y4 and formamide (or another suitable reagent that achieves the same result, as described herein) are allowed to react (see Procedure S-2 below) thereby forming a compound Y16 (which is a protected version of a compound of formula (IV) as described herein

20   (or a protected version of compound I as specified in Example 1, i.e. XIII but in which R_1 represents -C(O)H). It is incidental that the N atom of the piperidine is acylated (by a -C(O)H group) during the cyclisation reaction to produce the pyrimidine moiety of the bicycle (pyrazole[3,4-d]pyrimidine), and this group may be removed by deprotection (for example as shown by the Procedure S-3 below).

25

Procedure S-1

The reaction procedure was followed in accordance with the following steps

1. Dissolve Y20 (0.058g, 1.5eq) in 0.5mL MeOH in a first reaction vessel

2. Add dropwise a MeOH solution of NaOMe into Y20 to adjust pH value to ~9

3. Add Y3 (1.0eq) and 0.45 mL MeOH into a second reaction vessel

4. Cool the reaction mixture in the second reaction vessel to 0-10°C

5. Add dropwise the MeOH solution of Y20 in the first reaction vessel to the reaction mixture in the second reaction vessel at 0-10°C

6. Stir the subsequent reaction mixture at 20-25°C for 2hrs

7. Cool the reaction mixture to 0-10°C

8. Add dropwise 2mL H2O into the reaction mixture (off-white solid separated out)

9. Filter the mixture and dry the product under vacuum

Procedure S-2

1. Charge Y4 into a first reaction vessel under N_2.

2. Charge 9.6X formamide into that reaction vessel.

3. Heat the mixture to 165-175 °C.

4. Stir the reaction mixture for 2 h at 165-175 °C.

5. Calculate Impact of Ion-Pair Reagents (IPC) on LCMS analysis

6. Cool the reaction mixture 40°C (solid separate out).

7. Add drop wise 6V water into the reaction vessel

8. Stir the reaction mixture for 0.5 h at 40°C

9. Cool the reaction mixture 20°C (or around room temperature)

10. Filter the mixture.

11. Dry the cake under vacuum at 40-45 °C for 16hrs

12. Crude yield: 92%

Procedure S-3

1. Charge 0.5g of Y16 (the material obtained directly from S-2 above) into a first reaction vessel under N_2.

2. Charge 0.5mL 35%HCl (5.0eq) into that first reaction vessel.

3. Heat the mixture to 55-65 °C.

4. Stir the mixture in the reaction vessel at 55-65°C (see table below).

5. Calculate Impact of Ion-Pair Reagents (IPC) on LCMS analysis (see table below)

6. Cool the reaction mixture to 20°C (or around room temperature).

7. Add, drop wise, KOH into the reaction vessel to adjust pH to 11-13 (solid separate out).

8. Stir the mixture in the reaction vessel for 0.5 h at 20°C

9. Filter the mixture.

10. Dry the solid under vacuum at 40-45°C for 16hrs.

11. Crude yield: 63%

| Rxn	Raw materials		Condition		IPC (a%), as shown by LCMS			Results		
	Y16 (g)	HCl eq.	Time (h)	T. (°C)	Conv	Y6	Y16	Purity (by LCMS)	Qty	Crude Yield
S-3	0.5g Of Material from S-2 96.6%	5.0eq.	4	55-65	90.64	88.9	9.36	98.9%	0.29g	63%
			5	55-65	99.46	97.6	0.54			

Example – Pharmaceutical Formulation

5   Ibrutinib may be formulated into a pharmaceutically acceptable formulation using standard procedures.

For example, there is provided a process for preparing a pharmaceutical formulation comprising ibrutinib, or a derivative thereof, which process is characterised in that it

10   includes as a process step a process as hereinbefore defined. The skilled person will know what such pharmaceutical formulations will comprise/consist of (e.g. a mixture of active ingredient (i.e. ibrutinib or derivative thereof) and pharmaceutically acceptable excipient, adjuvant, diluent and/or carrier).

15   There is further provided a process for the preparation of a pharmaceutical formulation comprising ibrutinib (or a derivative thereof), which process comprises bringing into association ibrutinib, or a pharmaceutically acceptable salt thereof (which may be formed by a process as hereinbefore described), with (a) pharmaceutically acceptable excipient(s), adjuvant(s), diluent(s) and/or carrier(s).

20

Claims

1.   A process for the preparation of a compound of formula I,

(I)

5
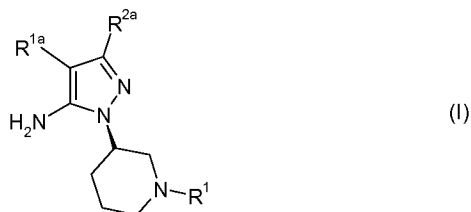
or a derivative thereof, wherein

R^1 represents hydrogen or, preferably, a nitrogen protecting group;

R^{1a} represents -CN, -C(O)OR^{1b} or -C(O)N(R^{1c})(R^{1d});

10   R^{1b}, R^{1c} and R^{1d} each independently represent C_{1-6} alkyl, aryl or heteroaryl;

R^{2a} represents:

(i) phenyl substituted at the 4-position with halo or -O-R^{2b}; or

(ii) hydrogen;

R^{2b} represents hydrogen or phenyl;

15

which process comprises reaction of a compound of formula II,

(II)
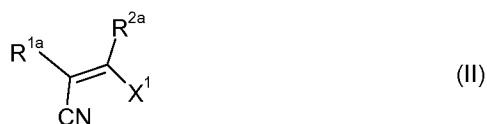
20   or a derivative thereof, wherein

R^{1a} and R^{2a} are as defined above;
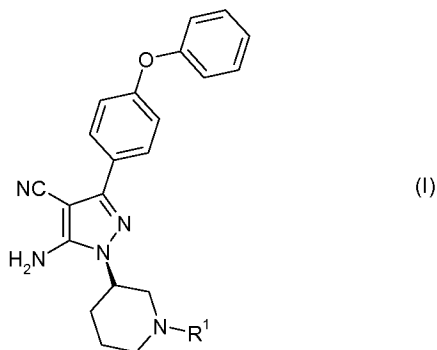
X^1 represents a suitable leaving group,

with a compound of formula III,

25

(III)

or a derivative thereof, wherein R^1 is as defined above.

2. A process for the preparation of a compound of formula I as claimed in Claim 1 wherein the process comprises preparation of the following compound of formula (I):

(I)

5

or a derivative thereof, wherein R^1 is as defined in Claim 1, which process comprises reaction of the following compound of formula (II),

(II)
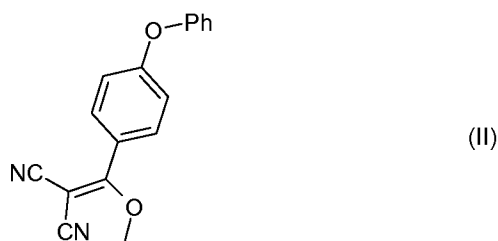
10   or a derivative thereof, with the following compound of formula III,

(III)
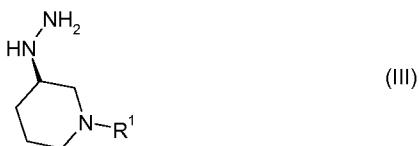
or a derivative thereof.

15

3. A process for the preparation of a compound of formula (IVA), which process comprises conversion of a compound of formula (I) as defined in Claim 1 to a compound of formula (IVA) (and, in particular, comprises a process for the preparation of a compound of formula (I) as defined in Claim 1 followed by conversion to a compound of

20   formula (IVA),

-32-

(IVA)

or a derivative (including isomer), wherein X^2 represent -OH or -NH$_2$, and R^1 and R^{2a} are as defined in Claim 1.

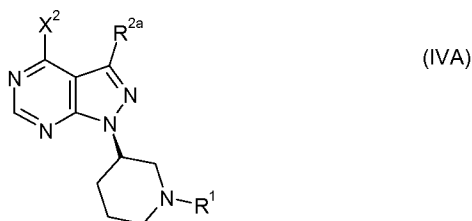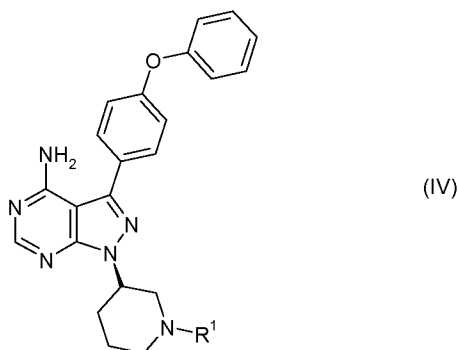5   4.   A process for the preparation of a compound of formula (IV),

(IV)

or a derivative thereof, wherein R^1 is as hereinbefore defined, which process comprises
10   conversion of a compound of formula (I) as defined in Claim 2 by (and, in particular,
comprises a process for the preparation of a compound of formula (I) as claimed in
Claim 1 followed by) reaction with either:

(i)   formamide (HCONH$_2$);

(ii)   formamidine or a formamidine salt H-C(=NH)-NH$_3^+$X$^-$, wherein X$^-$ represents
15   a suitable counterion, such as a halide (e.g. Cl$^-$) or an oxy anion (e.g. acyl-O$^-$),
so forming for example formamidine HCl or formamidine acetate or the like;

(iii)   alkyl (e.g. ethyl) formimidate, or a salt thereof, such as ethyl formimidate HCl;

(iv)   ethylorthoformate followed by ammonium acetate.

20   5.   A process as claimed in Claim 3 or Claim 4, wherein the reaction is with (ii) a
formamidine salt in which the counterion is a halide or oxygen-based anion.

6.   A process as claimed in any one of Claim 3 to 5, wherein the reaction is performed at
a temperature of below 160°C, for instance between 100°C and 140°C.
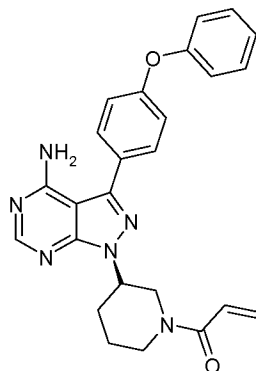
25

7.   A compound of formula (III), characterised in that it has an ee of greater than 50%.

8.   A compound of formula (I), (II) or (IVA) (or derivatives thereof) as defined in any one of Claims 1, 2 or 3.

9.   A process for the preparation of ibrutinib:

which process comprises either:
-   a process for the preparation of a compound of formula (I) as defined in Claim 1 or Claim 2, followed by conversion to ibrutinib;
-   a process for the preparation of a compound of formula (IVA) or (IV) as defined in any one of Claims 2 to 6, followed by conversion to ibrutinib, for example by deprotection (i.e. removal of the R^1 group) followed by acylation with acryl chloride; and/or
-   a resolution process for the preparation of a compound of formula (III) as defined in Claim 1 or Claim 7, followed by conversion to ibrutinib.

10. A use of a compound of formula (I), (IVA), (IV) and/or (III) (or derivatives thereof) as defined in any of Claim 1, 2, 3, 7 or 8 as intermediates in the preparation of ibrutinib.

11. A process for the preparation of a pharmaceutical formulation comprising ibrutinib, which process comprises bringing into association ibrutinib (or a pharmaceutically acceptable salt thereof), which is prepared as claimed in Claim 9, with (a) pharmaceutically acceptable excipient(s), adjuvant(s), diluents(s) and/or carrier(s).

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04   A61K31/519   A61P29/00   A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

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X	WO 2012/003544 A1 (INST MEDICAL W & E HALL [AU]; LUDWIG INST FOR CANCER RES LTD [US]; LES) 12 January 2012 (2012-01-12)	8
Y	page 83 - page 86; example 74 -----	1-7,9-11
Y	WO 2013/010136 A2 (PHARMACYCLICS INC [US]; CHEN WEI [US]; LOURY DAVID J [US]; MODY TARAK) 17 January 2013 (2013-01-17) Scheme 1; page 96 -----	1-11

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X	Further documents are listed in the continuation of Box C.		X	See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2014	03/04/2014

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Bissmire, Stewart

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INTERNATIONAL SEARCH REPORT

C(Continuation).   DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	disclosure of enyntiomerically pure ibrutinib; page 82, line 31 - line 32, paragraph 365 page 119; compound 1 -----	1-7,9-11
X	TAKAYAMA T ET AL: "Pyrrole derivatives as potent inhibitors of lymphocyte-specific kinase: Structure, synthesis, and SAR", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 20, no. 1, 1 January 2010 (2010-01-01), pages 108-111, XP026808783, ISSN: 0960-894X [retrieved on 2009-11-12] Scheme 1; page 109; compound 4 -----	8

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Information on patent family members

International application No

PCT/EP2014/054621

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