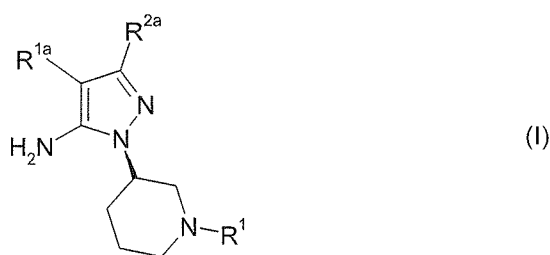


pyrazole moiety). As indicated in the above scheme, this is done by means of a Mitsunobu reaction – more specifically by converting the hydroxy moiety of the Boc-protected 3-hydroxypiperidine-1-carboxylate to a better leaving group, thereby allowing a substitution reaction with the -NH moiety of the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

- 10 This process has a number of disadvantages, such as those associated with cost, 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.

- 15 There is now provided, in a first aspect, a process for the preparation of a compound of formula I,

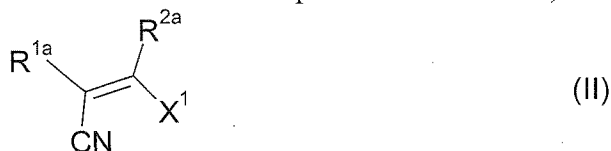


or a derivative thereof, wherein

- R¹ represents hydrogen or, more preferably, a nitrogen protecting group;
 20 R^{1a} represents -CN, -C(O)OR^{1b} or -C(O)N(R^{1c})(R^{1d});
 R^{1b}, R^{1c} and R^{1d} each independently represent C₁₋₆ alkyl, aryl or heteroaryl;
 R^{2a} represents:

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

which process comprises reaction of a compound of formula II,



or a derivative thereof, wherein

- 30 R^{1a} and R^{2a} are as defined above;

X¹ represents a suitable leaving group,

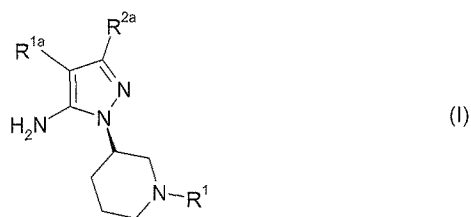
with a compound of formula III,



5 or a derivative thereof, wherein R¹ is as defined above,

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

10 In one aspect, there is provided a process for the preparation of a compound of formula I.



or a derivative thereof, wherein

15 R¹ represents hydrogen or, preferably, a nitrogen protecting group;

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

R^{1b}, R^{1c} and R^{1d} each independently represent C₁₋₆ alkyl, aryl or heteroaryl;

R^{2a} represents phenyl substituted at the 4-position with halo or -O-R^{2b};

R^{2b} represents hydrogen or phenyl;

20 which process comprises reaction of a compound of formula II.

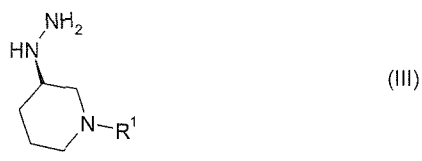


25 or a derivative thereof, wherein

R^{1a} and R^{2a} are as defined above;

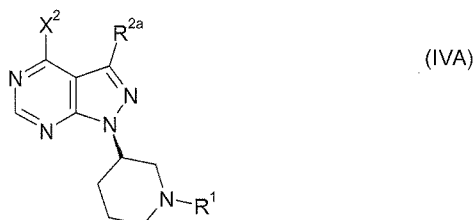
X¹ represents a suitable leaving group.

with a compound of formula III,



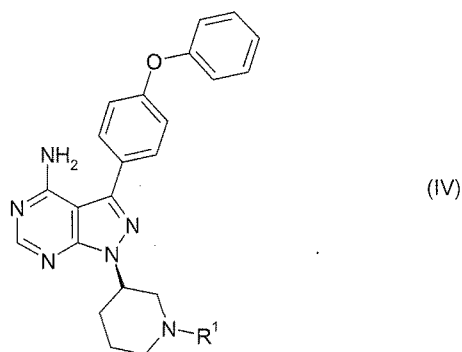
5 or a derivative thereof, wherein R¹ is as defined above.

In another aspect, there is provided a process for the preparation of a compound of formula (IVA), which process comprises conversion of a compound of formula (I) as defined herein to a compound of formula (IVA) (and, in particular, comprises a process for the preparation of a compound of formula (I) as defined herein followed by conversion to a compound of formula (IVA),



15 or a derivative (including isomer), wherein X² represent -OH or -NH₂, and R¹ and R^{2a} are as defined herein.

In another aspect, there is provided a process for the preparation of a compound of formula (IV),



20 or a derivative thereof, wherein R¹ is as hereinbefore defined, which process comprises conversion of a compound of formula (I) as defined herein by (and, in particular,

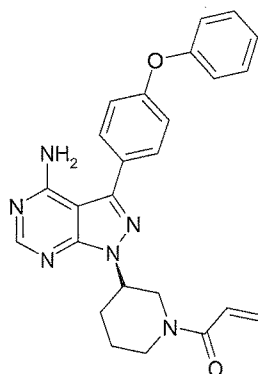
comprises a process for the preparation of a compound of formula (I) as defined herein followed by) reaction with either:

- (i) formamide (HCONH₂);
 - (ii) formamidine or a formamidine salt H-C(=NH)-NH₃⁺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;
- ethylorthoformate followed by ammonium acetate.

In another aspect, there is provided a compound of formula (III), characterised in that it has an ee of greater than 50%.

- In another aspect, there is provided a compound of formula (I), ~~(II)~~ or (IVA) ~~(or derivatives thereof)~~ as defined herein and wherein R¹ represents hydrogen (in the case of formula (I) only) or a nitrogen protecting group that results in the formation of an amide, optionally substituted *N*-alkyl, *N*-sulfonyl, a carbamate, a urea, trityl (triphenylmethyl), diphenylmethyl, or the like.

In another aspect, there is provided a process for the preparation of ibrutinib:



- which process comprises either:
- a process for the preparation of a compound of formula (I) as defined herein, followed by conversion to ibrutinib;
 - a process for the preparation of a compound of formula (IVA) or (IV) as defined herein, followed by conversion to ibrutinib, for example by deprotection (i.e. removal of the R¹ group) followed by acylation with acryl chloride; and/or

- a resolution process for the preparation of a compound of formula (III) as defined herein, followed by conversion to ibrutinib.

5 In another aspect, there is provided a use of a compound of formula (I) or derivative thereof as defined herein, a compound of formula (IVA) or derivative thereof as defined herein, a compound of formula (IV) or derivative thereof as defined herein and/or a compound of formula (III) (or derivatives thereof) as defined herein as intermediates in the preparation of ibrutinib.

10 In another aspect, there is 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 as defined herein, with (a) pharmaceutically acceptable excipient(s), adjuvant(s), diluents(s) and/or carrier(s).

15 In the embodiment of the disclosure described above, it is indicated that R^1 may represent hydrogen or a nitrogen-protecting group. The disclosure 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:

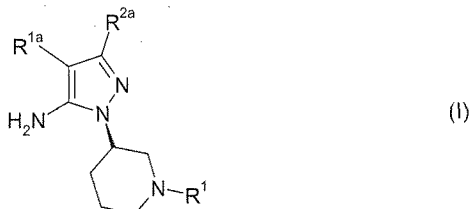
- (i) R^1 represents hydrogen; and
- (ii) R^1 represents a nitrogen-protecting group,

and the disclosure 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 disclosure 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 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 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).

In the processes of the disclosure 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
5 another salt

Claims

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



5

or a derivative thereof, wherein

R¹ 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 C₁₋₆ 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;

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which process comprises reaction of a compound of formula II,



20 or a derivative thereof, wherein

R^{1a} and R^{2a} are as defined above;

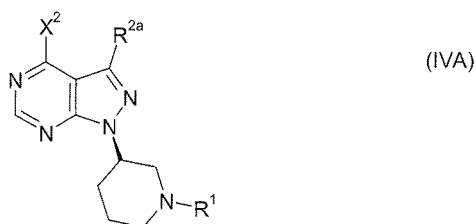
X¹ represents a suitable leaving group,

with a compound of formula III,

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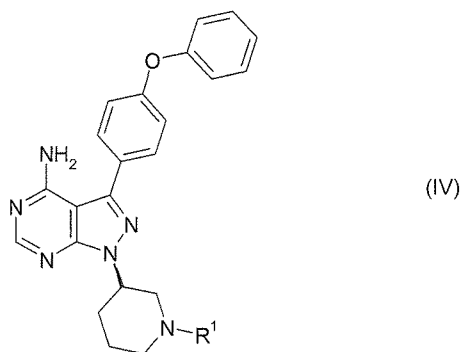


or a derivative thereof, wherein R¹ is as defined above.



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),



10 or a derivative thereof, wherein R^1 is as hereinbefore defined, which process comprises 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:

- 15 (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.

- 20 5. A process as claimed in Claim 3 or Claim 4, wherein the conversion/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 $160^\circ C$, for instance between $100^\circ C$ and $140^\circ C$.

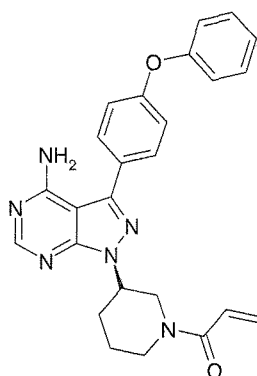
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7. A compound of formula (III), characterised in that it has an ee of greater than 50%.

8. A compound of formula (I), ~~(II)~~ or (IVA) ~~(or derivatives thereof)~~ as defined in any one of Claims 1, 2 or 3 and wherein R¹ represents hydrogen (in the case of formula (I) only) or a nitrogen protecting group that results in the formation of an amide, optionally substituted *N*-alkyl, *N*-sulfonyl, a carbamate, a urea, trityl (triphenylmethyl), diphenylmethyl, or the like.

9. A compound as claimed in Claim 8, wherein the nitrogen protecting group represents a protecting group forming a carbamate or substituted alkyl moieties.

10. ~~9~~10. A process for the preparation of ibrutinib:



which process comprises either:

- 15 - 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 ~~2-3~~ to 6, followed by conversion to ibrutinib, for example by deprotection (i.e. removal of the R¹ group) followed by acylation with acryl chloride; and/or
- 20 - 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~~11. A use of a compound of formula (I) or derivative thereof as defined in any one of Claim 1, 2, 8 or 9, a compound of formula (IVA) or derivative thereof as defined in claim 3, 8 or 9, a compound of formula (IV) or derivative thereof as defined in any one of claims 4 to 6 and/or a compound of formula (III) (or derivatives thereof) as defined in any of Claim 1, 2, 3, 7, or 8 as intermediates in the preparation of ibrutinib.

1112. 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 910,
with (a) pharmaceutically acceptable excipient(s), adjuvant(s), diluents(s) and/or
5 carrier(s).