

X^1 represents a suitable leaving group,

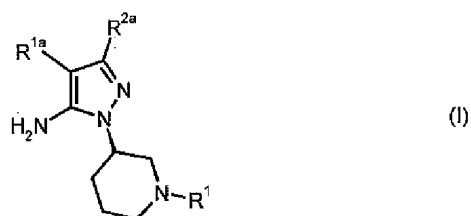
with a compound of formula III,



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

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

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



or a salt or solvate thereof, wherein

15 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});

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;

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which process comprises reaction of a compound of formula II,

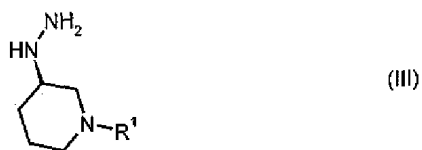


25 or a salt or solvate thereof, wherein

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

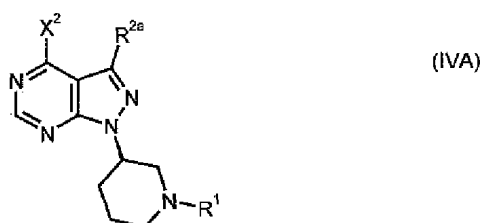
X^1 represents a suitable leaving group,

with a compound of formula III,



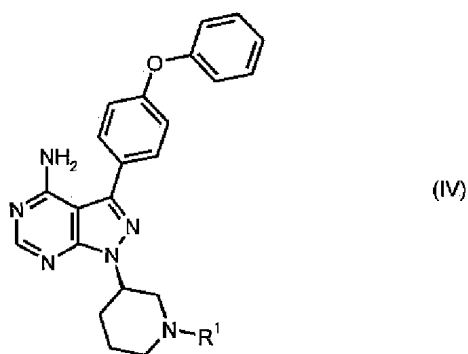
5 or a salt or solvate thereof, wherein R¹ is as defined above.

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



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

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



20 or a salt or solvate thereof, wherein R¹ is as hereinbefore defined, which process comprises a process for the preparation of a compound of formula (I) as defined herein followed by conversion of a compound of formula (I) as defined herein by

reaction with either:

- (i) formamide (HCONH₂);
- (ii) formamidine or a formamidine salt H-C(=NH)-NH₃⁺X⁻, wherein X⁻ represents a suitable counterion selected from a halide or an oxy anion;
- 5 (iii) alkyl formimidate, or a salt thereof;
- (iv) ethylorthoformate followed by ammonium acetate.

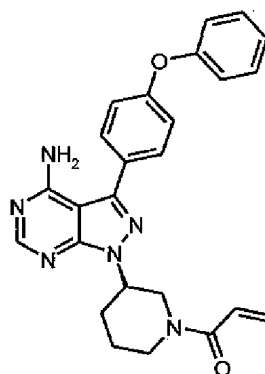
In another aspect, there is provided a compound of formula (III), as depicted herein, characterised in that it has an ee of greater than 50%.

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In another aspect, there is provided a compound of formula (I) or (IVA) 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

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



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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
- 25 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.

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 derivative thereof as defined herein as intermediates in the preparation of ibrutinib.

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- 10 In another aspect, there is provided a process for the preparation of a pharmaceutical formulation comprising ibrutinib, which process comprises a process for preparing ibrutinib as defined herein, followed by bringing into association ibrutinib or a pharmaceutically acceptable salt thereof, so prepared, with (a) pharmaceutically acceptable excipient(s), adjuvant(s), diluents(s) and/or carrier(s).

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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:

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- (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).

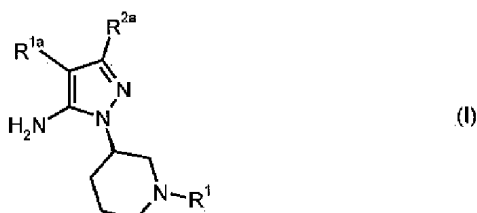
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Claims

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



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

R^{2b} represents hydrogen or phenyl;

which process comprises reaction of a compound of formula II,

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or a salt or solvate thereof, wherein

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

20 X¹ represents a suitable leaving group,

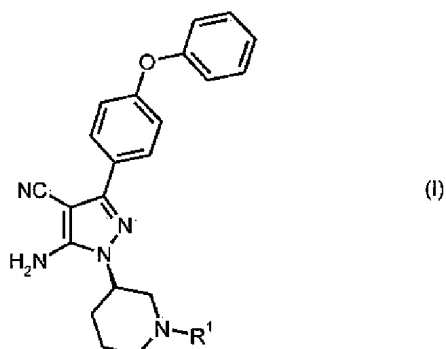
with a compound of formula III,



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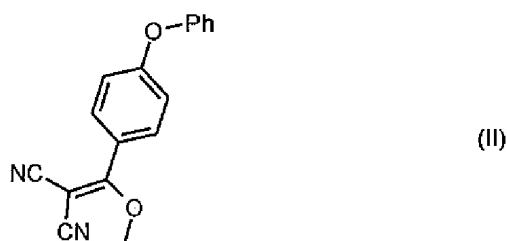
or a salt or solvate thereof, wherein R¹ is as defined above.

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):



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



- 10 or a salt or solvate thereof, with the following compound of formula III,

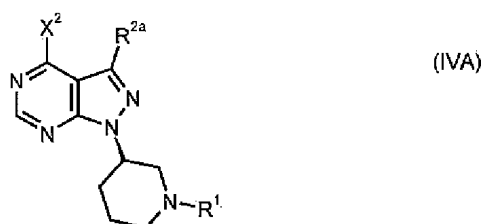


or a salt or solvate thereof.

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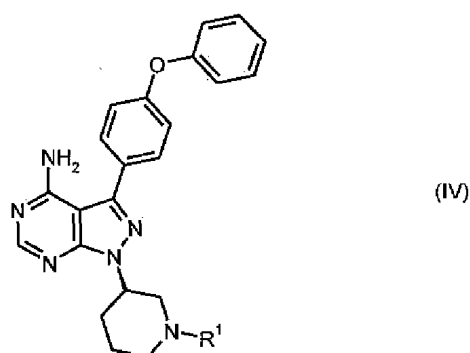
3. A process for the preparation of a compound of formula (IVA), which process comprises a process for the preparation of a compound of formula (I) as defined in Claim 1 followed by conversion to a compound of formula (IVA),

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or a salt or solvate (including isomer), wherein X^2 represent -OH or -NH₂, and R¹ 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 salt or solvate thereof, wherein R¹ is as hereinbefore defined, which process comprises a process for the preparation of a compound of formula (I) as claimed in Claim 1 followed by conversion of a compound of formula (I) as defined in Claim 2 by reaction with either:

- 15 (i) formamide (HCONH₂);
 (ii) formamidine or a formamidine salt H-C(=NH)-NH₃⁺X⁻, wherein X⁻ represents a suitable counterion selected from a halide or an oxy anion;
 (iii) alkyl formimidate, or a salt thereof;
 (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°C.

- 25 7. A compound of formula (III), as depicted in Claim 1, characterised in that it has an ee of greater than 50%.

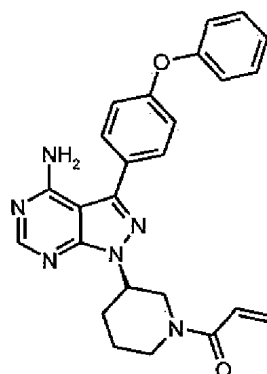
8. A compound of formula (I) or (IVA) as defined in any one of Claims 1, 2 or 3 and wherein R^1 represents hydrogen, in the case of formula (I) only, or a nitrogen protecting group that results in the formation of an amide, optionally substituted *N*-alkyl, *N*-sulfonyl, a carbamate, a urea, trityl (triphenylmethyl),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

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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. A process for the preparation of ibrutinib:

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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 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
- 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.

11. A use of a compound of formula (I) or salt or solvate thereof as defined in any one of Claim 1, 2, 8 or 9, a compound of formula (IVA) or salt or solvate thereof as defined in claim 3, 8 or 9, a compound of formula (IV) or salt or solvate thereof as defined in any one of claims 4 to 6 and/or a compound of formula (III) or salt or solvate thereof as defined in Claim 7 as intermediates in the preparation of ibrutinib.

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12. A process for the preparation of a pharmaceutical formulation comprising ibrutinib, which process comprises a process for preparing ibrutinib as claimed in Claim 10, followed by bringing into association ibrutinib or a pharmaceutically acceptable salt thereof, so prepared, with (a) pharmaceutically acceptable excipient(s), adjuvant(s),
5 diluent(s) and/or carrier(s).