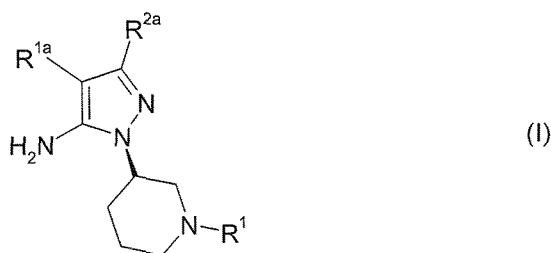


pyrazole moiety). As indicated in the above scheme, this is done by means of a Mitsunobu reaction – more specifically by converting the hydroxy moiety of the Boc-protected 3-hydroxypiperidine-1-carboxylate to a better leaving group, thereby allowing a substitution reaction with the -NH moiety of the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

R^1 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,



30 or a derivative thereof, wherein

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

X¹ represents a suitable leaving group,

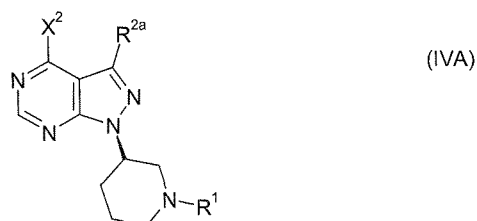
with a compound of formula III,



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

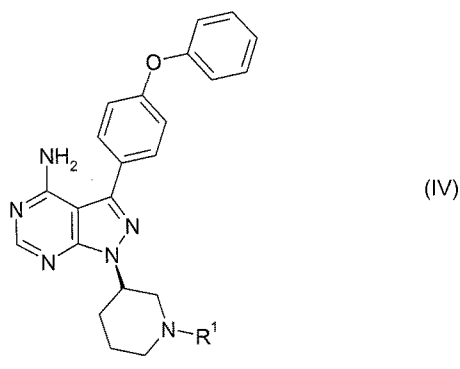
which process is hereinafter referred to as a “process of the invention”.

10 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.

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



25 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,

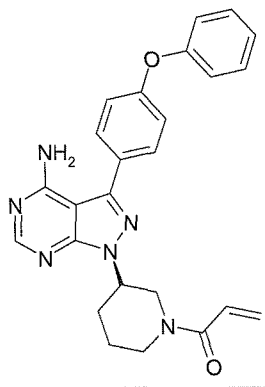
comprises a process for the preparation of a compound of formula (I) as defined herein followed by) reaction with either:

- (i) formamide (HCONH_2);
 - (ii) formamidine or a formamidine salt $\text{H}-\text{C}(=\text{NH})-\text{NH}_3^+\text{X}^-$, 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.

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 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 herein, followed by conversion to ibrutinib.

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

5 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).

10

In the embodiment of the ~~invention-disclosure~~ described above, it is indicated that R¹ may represent hydrogen or a nitrogen-protecting group. The ~~disclosure 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:

15

- (i) R¹ represents hydrogen; and
- (ii) R¹ represents a nitrogen-protecting group,

and the ~~disclosure invention~~ may be directed to either one of these two aspects (or sub-embodiments). For instance, in aspect (ii), R¹ is a nitrogen-protecting group, and the process of the ~~disclosure invention~~ may be performed on a compound of formula (III) in which R¹ is a protecting group to provide a compound of formula (I) also containing that R¹ protecting group. That R¹ 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),
25 R¹ 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 R¹ 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
30 described in the examples (see Example 2).

In the processes of the ~~disclosure invention~~ described herein, it is indicated that “derivatives” may be employed, which includes salts and solvates. Hence, for instance
35 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