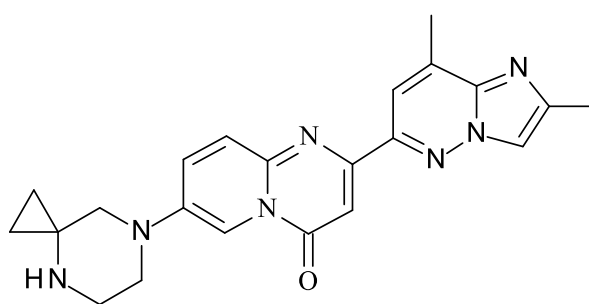


PROCESS FOR THE PREPARATION OF 7-(4,7-DIAZASPIRO[2.5]OCTAN-7-YL)-2-(2,8-DIMETHYLMIDAZO[1,2-B]PYRIDAZIN-6-YL)PYRIDO[1,2-A]PYRIMIDIN-4-ONE DERIVATIVES

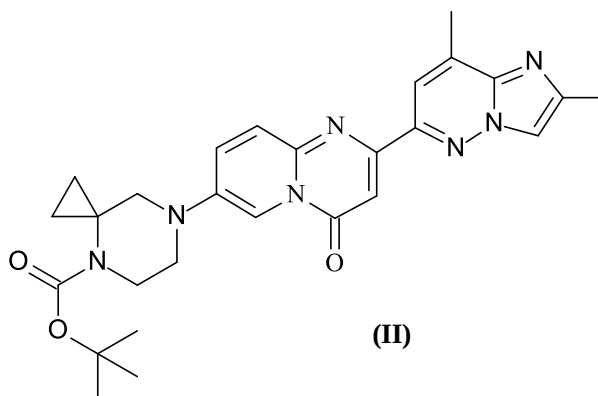
The present invention relates to a process for the preparation 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido[1,2-a]pyrimidin-4-one useful as pharmaceutically active compounds.

The present disclosure provides a process for the preparation of a compound of formula (I)
5 or the HCl salt thereof:



(I)

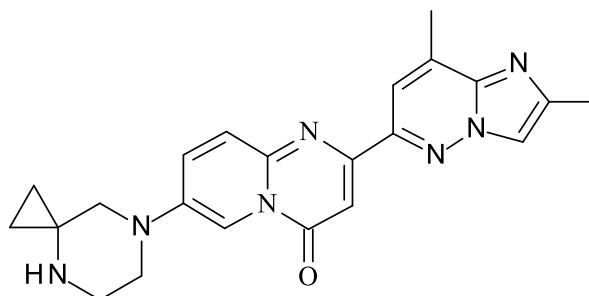
which comprises reacting compound of formula (II):



(II)

10 with a strong acid, in particular HCl.

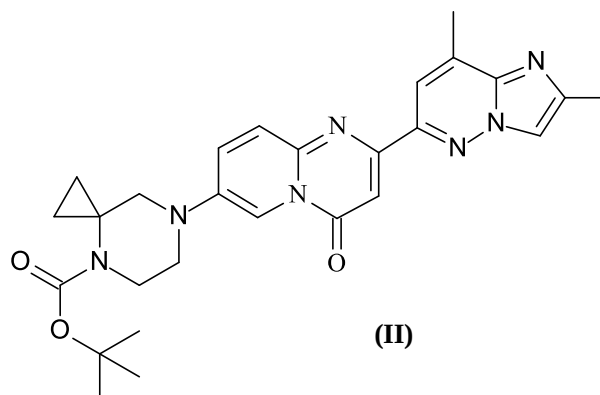
In a first aspect, the present disclosure provides a process for the preparation of a compound of formula (I) or the HCl salt thereof:



(I)

which comprises reacting compound of formula (II):

5



(II)

with a strong acid.

The process according to the first aspect, wherein the HCl is made *in situ* in the presence of 1-propanol and acetyl chloride.

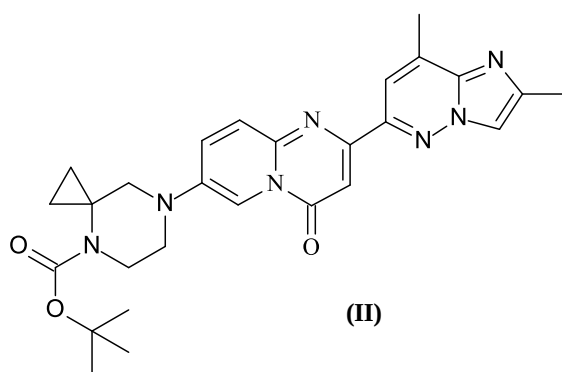
- 10 In particular, the preparation of compound of formula (I) is being carried out in a solvent such as an alcohol, an aqueous alcohol, ethyl-acetate, 1-propylacetate, toluene, acetonitrile, THF or dichloromethane. More preferably the preparation of compound of formula (I) is being carried out in the presence of 1-propanol and toluene.

“Transition metal hydrogenation catalyst” includes but is not limited to, a Raney catalyst (e.g. Ra-Ni, Ra-Co,) Pd/C, Pd(OH)₂/C, Au/TiO₂, Rh/C, Ru/Al₂O₃, Ir/CaCO₃, Pt-V/C or Pt/C, in particular Pt-V/C.

“Tertiary amine” refers to an amine of formula R^aN(R^b)R^c wherein R^a, R^b and R^c

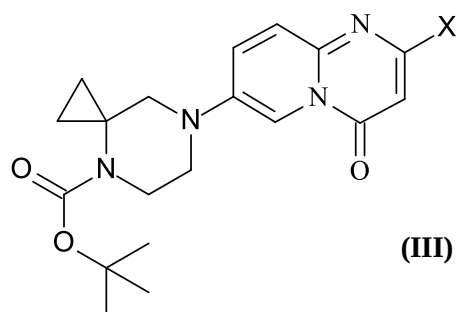
- 5 independently are selected from (C₁-C₆)alkyl or phenyl. Representative examples include, but are not limited to, triethylamine, tributylamine, di-ethyl-methylamine, dimethyl-ethylamine, di-isopropylethylamine, N,N-dimethylaniline and methylethylbutylamine. Preferably, the tertiary amine is chosen from triethylamine or di-isopropylethylamine. The most preferred tertiary amine is triethylamine.
- 10 The term “treating”, “contacting” or “reacting” used interchangeably refers to adding, bringing together or mixing two or more chemical substances (referred usually as reagents or reactants), more particularly under appropriate conditions, to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the
- 15 combination of two or more reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product. “

The present disclosure provides a process for the preparation of a compound of formula (II)



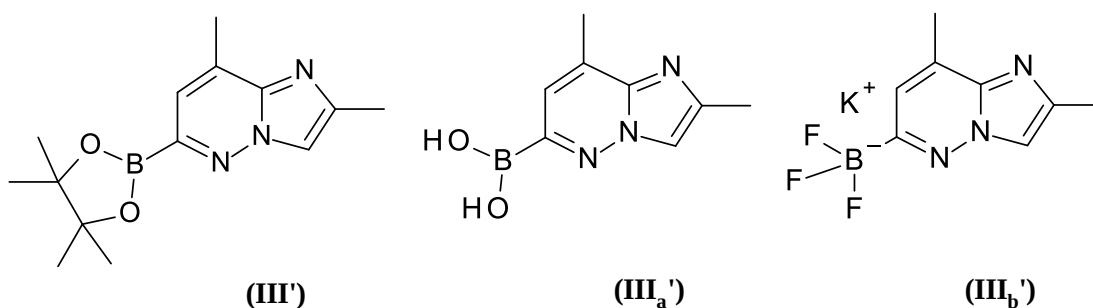
20

which comprises reacting a compound of formula (III)



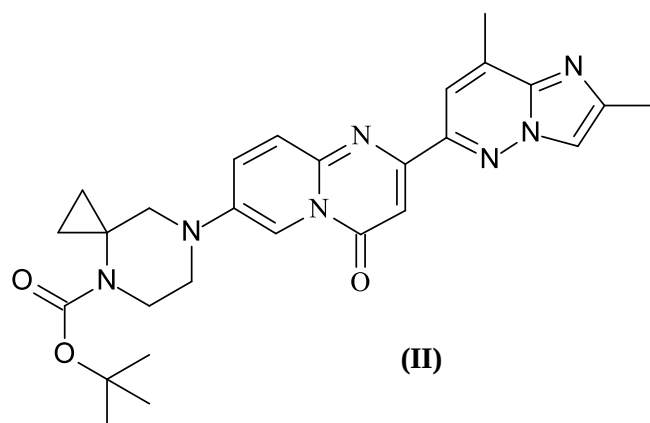
wherein X is an alkyl or aryl sulfonate (such as pTolSO₃⁻, CH₃SO₃⁻, phenyl-SO₃⁻), fluorinated alkyl or aryl sulfonates (such as CF₃SO₃⁻, nonaflate), or a halide (such as Cl, Br, or I),

- 5 with a compound of formula (III'), (III_a') or (III_b'), in particular with a compound of formula (III')

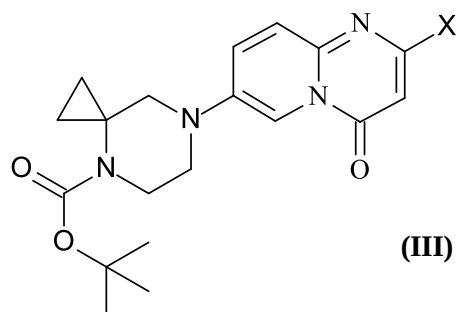


in the presence of a palladium catalyst or nickel catalyst, in particular in presence of a palladium catalyst.

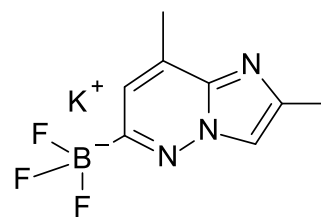
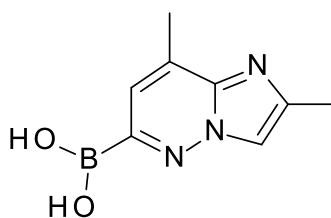
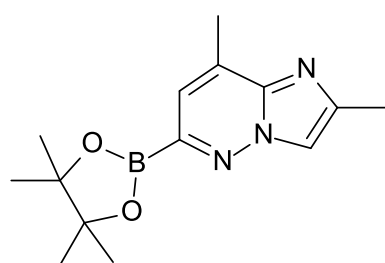
- 10 In another aspect (aspect 2), the present disclosure provides a process for the preparation of a compound of formula (II)



which comprises reacting a compound of formula (III)



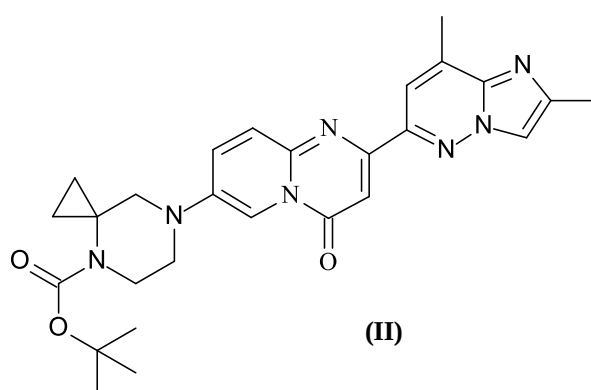
wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide, with a compound of formula (III'), (III_a') or (III_b')



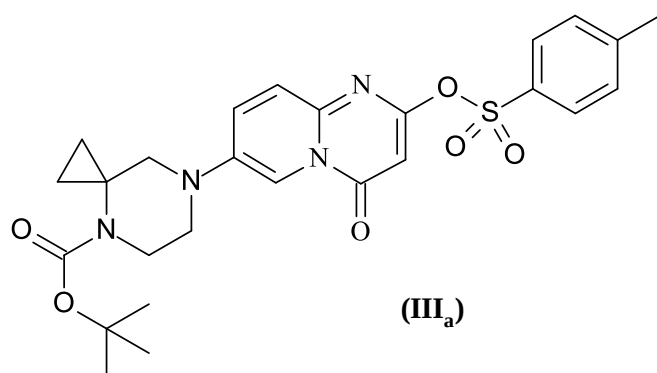
5

in the presence of a palladium catalyst or nickel catalyst.

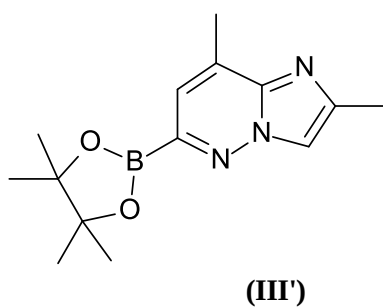
In a particular example of aspect 2, the present disclosure provides a process for the preparation of a compound of formula (II)



10 which comprises reacting a compound of formula (III)



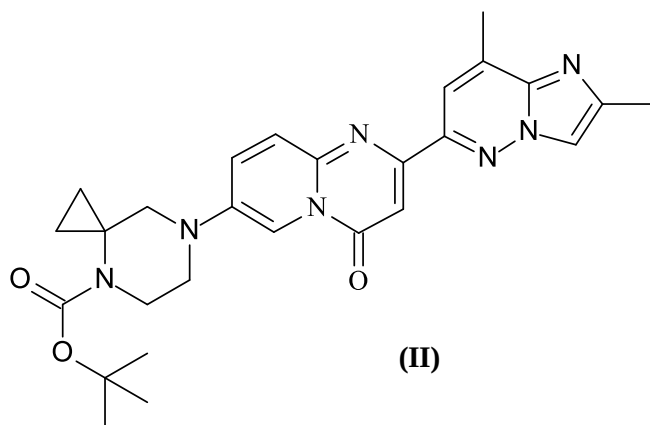
with a compound of formula (III')



in the presence of a palladium catalyst or nickel catalyst, in particular in presence of a
5 palladium catalyst.

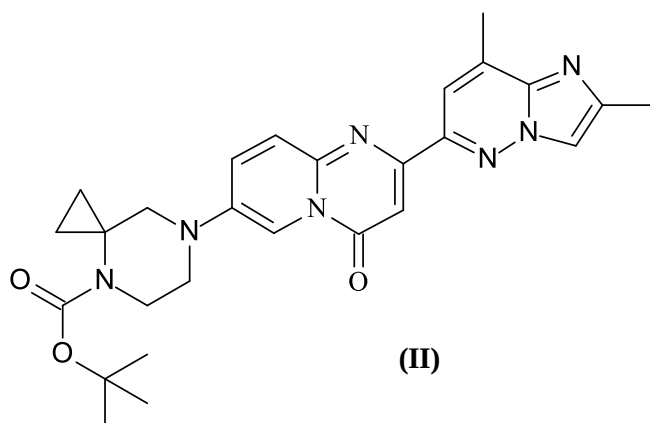
In particular, the process as described herein (i.e. aspect 2) which further comprises a base, particularly wherein the base is Na₂CO₃, K₂CO₃, Cs₂CO₃, KOAc or KOtBu more particularly wherein the base is K₂CO₃.

The present disclosure provides a process for the preparation of a compound of formula
10 (II)



in the presence of a palladium catalyst or nickel catalyst, in particular in presence of a palladium catalyst, to obtain a compound of formula (II).

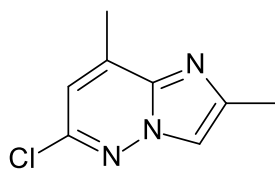
In another aspect (aspect 3), the present disclosure provides a process for the preparation of a compound of formula (II)



5

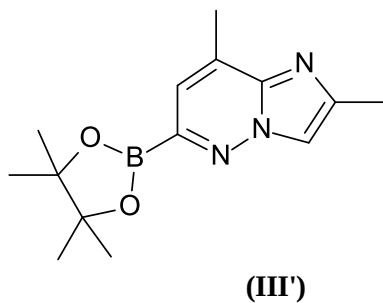
which comprises

- a) reacting a compound of formula (III'')



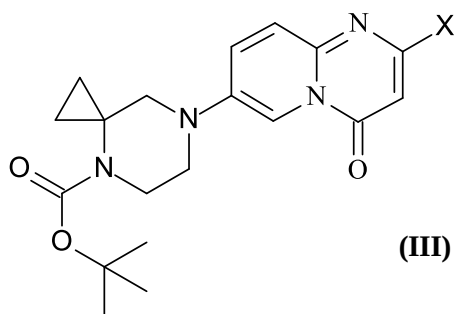
(III'')

with bis(pinacolato)diboron to obtain a compound of formula (III'):

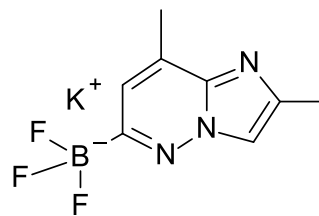
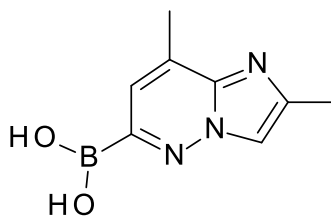
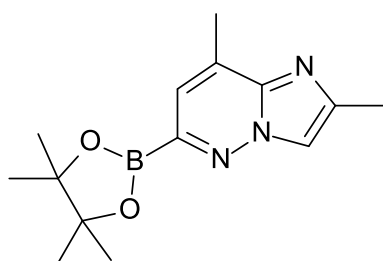


10

b) reacting a compound of formula (III)



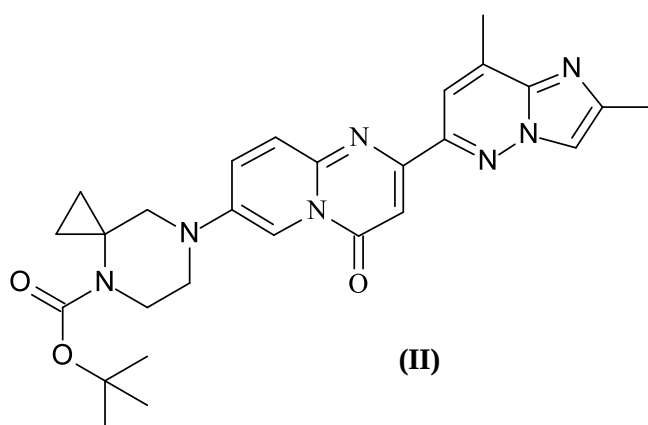
wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide with a compound of formula (III') , (III_a') or (III_b'),



5

in the presence of a palladium catalyst or nickel catalyst, to obtain a compound of formula (II).

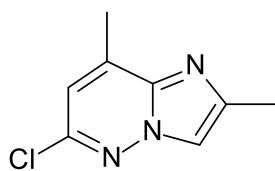
In a particular example of aspect 3, the present disclosure provides a process for the preparation of a compound of formula (II)



10

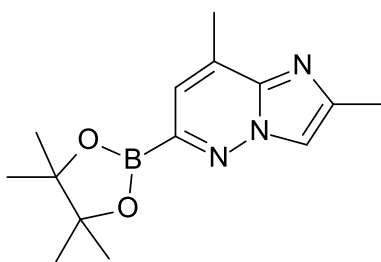
which comprises

a) reacting a compound of formula (III'')



(III'')

with bis(pinacolato)diboron to obtain a compound of formula (III'):



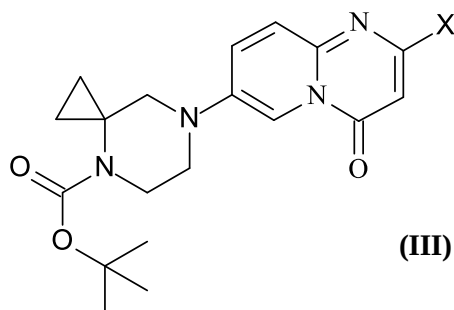
(III')

b) reacting a compound of formula (III)

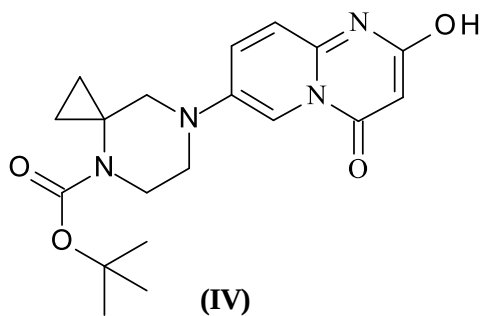
In particular the disclosure provides a process as described above, wherein the reaction of compound of formulae (III) or (III_a) with compound of formulae (III'), (III_a') or (III_b'), in particular with a compound of formula (III') in the presence of palladium catalyst or nickel catalyst, in particular in presence of a palladium catalyst as defined herein, is carried out in presence of a base, particularly wherein the base is Na₂CO₃, K₂CO₃, Cs₂CO₃, KOAc or KotBu more particularly wherein the base is K₂CO₃.

In a particular example, the present disclosure provides the process herein described wherein steps a) and b) are telescoped.

The present disclosure provides a process for the preparation of a compound of formula (III)



wherein X is an alkyl or aryl sulfonate (such as pTolSO₃⁻, CH₃SO₃⁻, phenyl-SO₃⁻), fluorinated alkyl or aryl sulfonates (such as CF₃SO₃⁻, nonaflate), or a halide (such as Cl, Br, or I), which comprises reacting a compound of formula (IV)

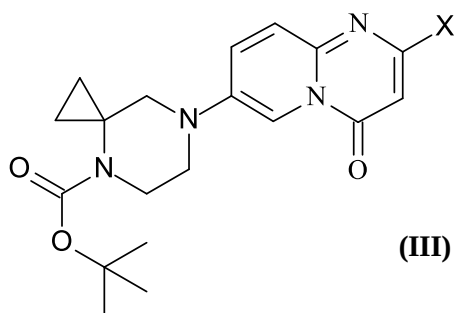


- with tosyl chloride when X is pTol-SO₃⁻, methanesulfonyl chloride when X is CH₃SO₃⁻, triflyl chloride when X is CF₃SO₃⁻ or phenylsulfonylchloride when X is phenyl-SO₃⁻, and in the presence of a base, in particular wherein the base is an organic base or basic alkali metal salts, more particularly wherein the base

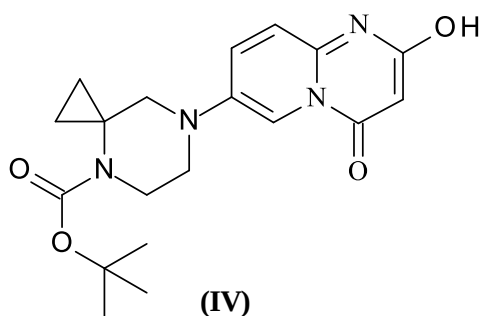
is nitrogen-containing heterocycle, tertiary amine or basic alkali metal salts, most particularly wherein the base is a tertiary amine;

- with POCl_3 when X is Cl;
 - with POBr_3 when X is Br; or
- 5 - with Ph_3PI_2 or POCl_3 followed by NaI or CuI, when X is I.

In another aspect (aspect 4), the present disclosure provides a process for the preparation of a compound of formula (III)



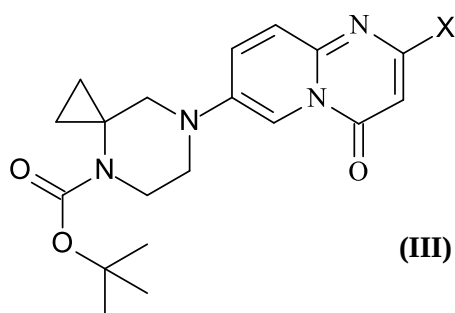
- wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide,
- 10 which comprises reacting a compound of formula (IV)



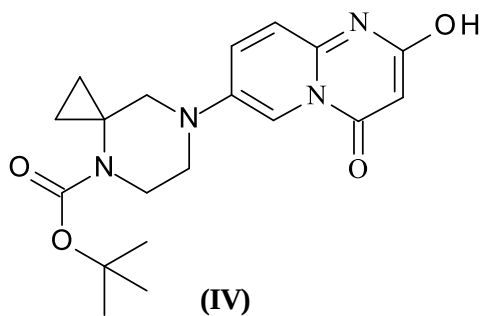
- with tosyl chloride when X is pTol-SO₃-, methanesulfonyl chloride when X is CH₃SO₃-, triflyl chloride when X is CF₃SO₃- or phenylsulfonylchloride when X is phenyl-SO₃-, and in the presence of a base;

- with POCl_3 when X is Cl;
- with POBr_3 when X is Br; or
- with Ph_3PI_2 or POCl_3 followed by NaI or CuI, when X is I.

In a particular example of aspect 4, the present disclosure provides a process for the
5 preparation of a compound of formula (III)



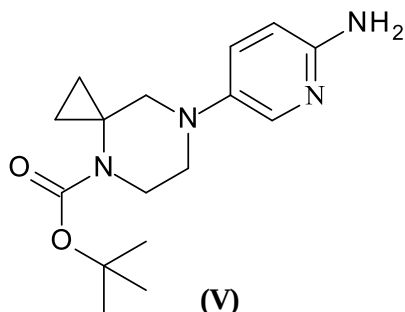
wherein X is an alkyl or aryl sulfonate (such as pTolSO_3^- , CH_3SO_3^- , phenyl- SO_3^-),
fluorinated alkyl or aryl sulfonates (such as CF_3SO_3^- , nonaflate), which comprises reacting
a compound of formula (IV)



10

with tosyl chloride, methanesulfonyl chloride, phenylsulfonylchloride or triflyl chloride
respectively and in the presence of a base, in particular wherein the base is an organic base
or basic alkali metal salts, more particularly wherein the base is nitrogen-containing
heterocycle, tertiary amine or basic alkali metal salts, most particularly wherein the base is
15 a tertiary amine.

In a more particular example of aspect 4, the present disclosure provides a process for the
preparation of a compound of formula (III_a)



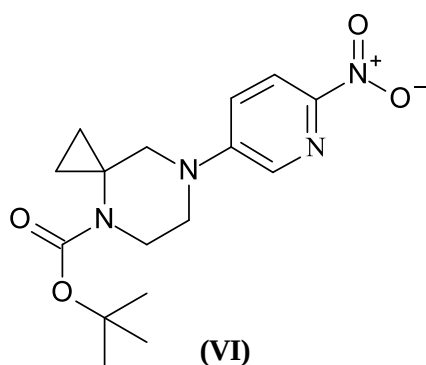
b) reacting a compound of formula (V) with di-tert-butyl malonate to obtain a compound of formula (IV).

In particular, the process for the preparation (i.e aspects 5 to 7) of a compound of formula (IV) which comprises reacting a compound of formula (V) with di-tert-butyl malonate, is carried out in the presence of xylene, dichlorobenzene, toluene or anisole, in particular in the presence of anisole.

In more particular, the preparation of compound of formula (IV), wherein the transition metal hydrogenation catalyst is Raney catalyst (e.g. Ra-Ni, Ra-Co,) Pd/C, Pd(OH)₂/C, Au/TiO₂, Rh/C, Ru/Al₂O₃, Ir/CaCO₃, Pt-V/C or Pt/C or combination thereof, in particular Pt-V/C, more particularly Pt 1% and V 2% on activated carbon.-

In a particular example, the present disclosure provides the process herein described wherein steps a) and b) are telescoped.

The present application discloses the preparation of a compound of formula (VI)

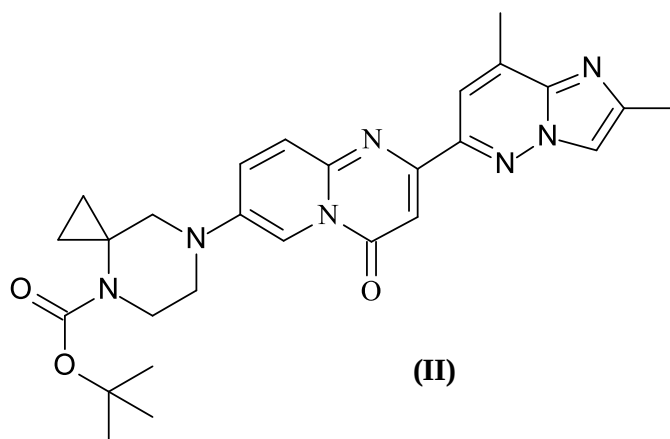


15

which comprises reacting a compound of formula (VII)

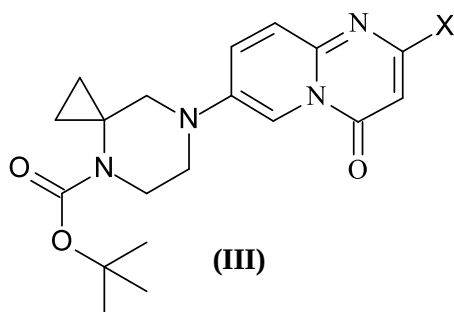
in particular: tBuDavePhos) and a base (such as Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , KOtBu , NaOtBu ($(\text{CH}_3)_3\text{CONa}$), KOAc or lithium-bis(trimethylsilyl)amid; in particular lithium-bis(trimethylsilyl)amid), in particular in tetrahydrofuran.

In another aspect, the present disclosure provides a compound of formula (II):



5

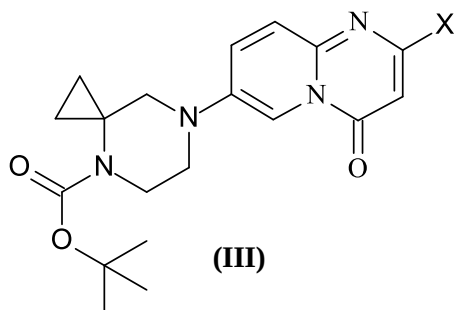
The present disclosure provides a compound of formula (III):



wherein X is an alkyl or aryl sulfonate (such as pTolSO_3^- , CH_3SO_3^- , phenyl- SO_3^-), fluorinated alkyl or aryl sulfonates (such as CF_3SO_3^- , nonaflate), or a halide (such as Cl, Br, or I).

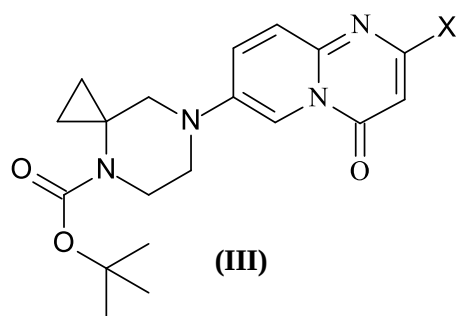
10

In another aspect, the present disclosure provides a compound of formula (III):



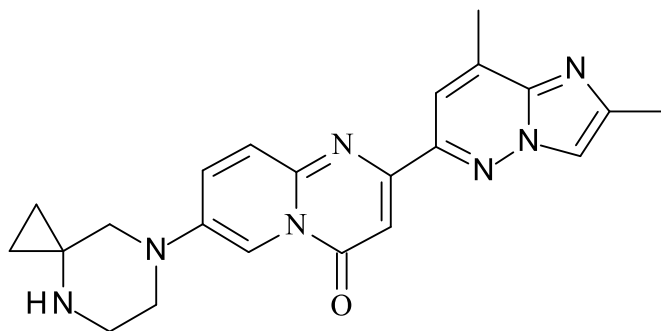
wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide.

In yet another example, the present disclosure provides a compound of formula (III):



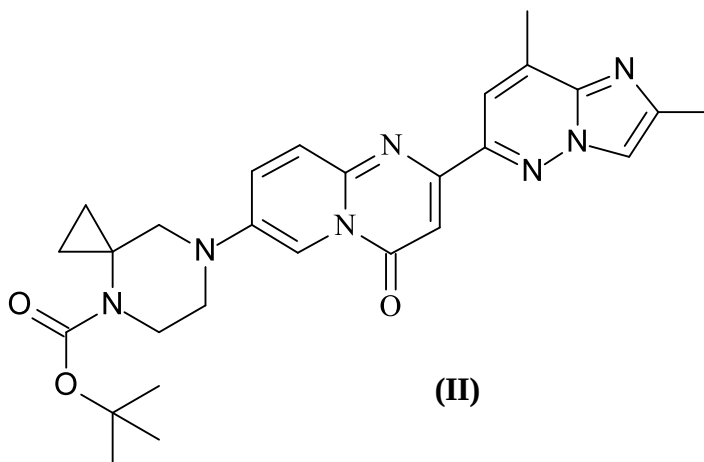
Claims

1. A process for the preparation of a compound of formula (I) or the HCl salt thereof:



(I)

which comprises reacting compound of formula (II):

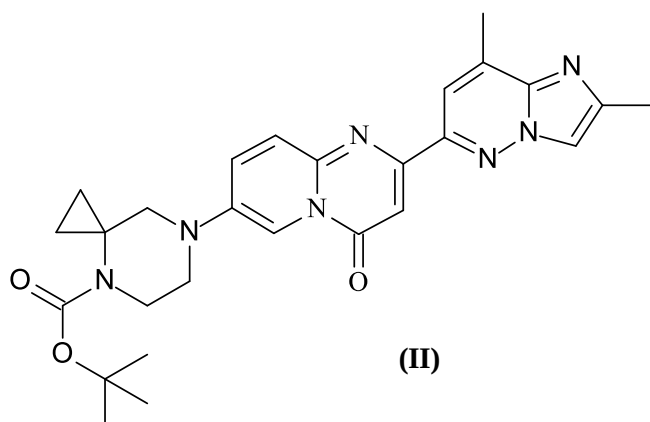


(II)

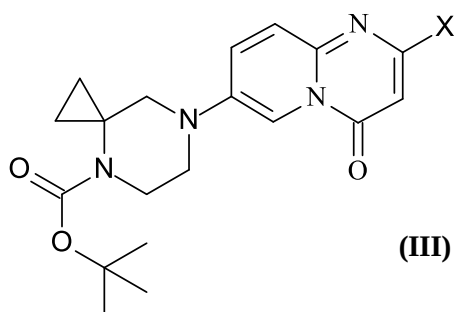
5

with a strong acid.

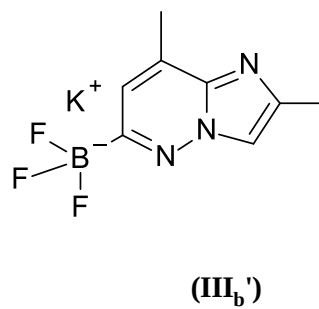
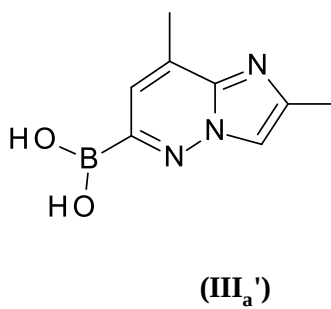
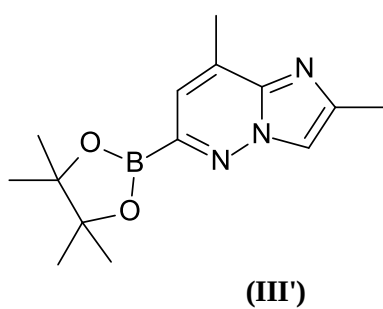
2. The process according to claim 1, wherein the HCl is made *in situ* with 1-propanol and acetyl chloride.
3. A process for the preparation of a compound of formula (II)



which comprises reacting a compound of formula (III)

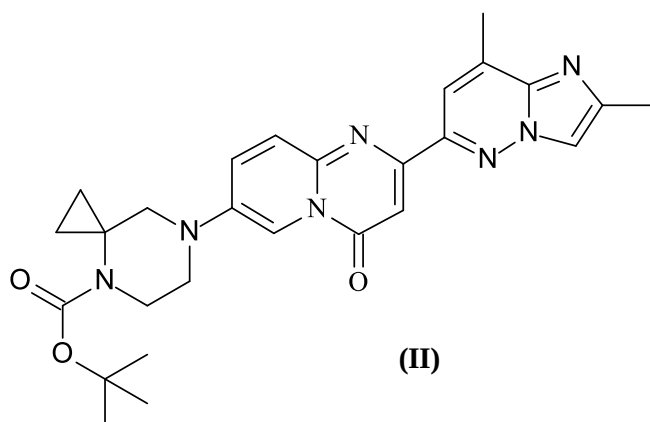


wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide,
5 with a compound of formula (III'), (III_a') or (III_b')



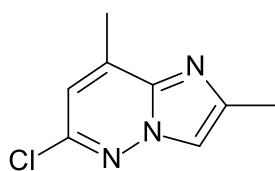
in the presence of a palladium catalyst or nickel catalyst.

10 4. A process for the preparation of a compound of formula (II)

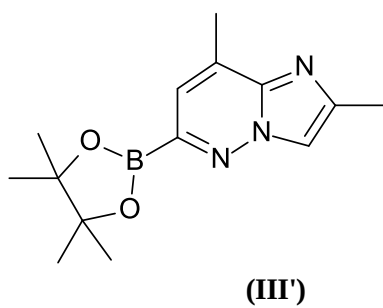


which comprises

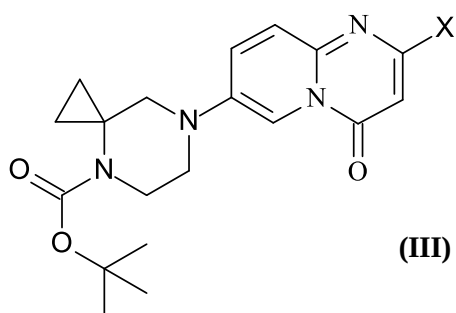
- a) reacting a compound of formula (III'')



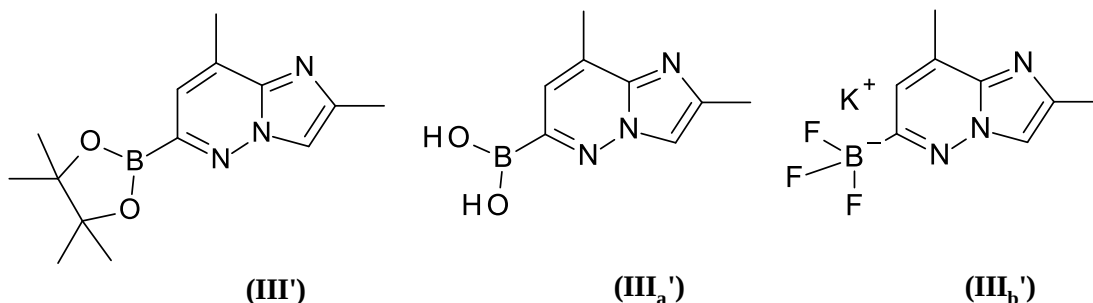
- 5 with bis(pinacolato)diboron to obtain a compound of formula (III'):



- b) reacting a compound of formula (III)

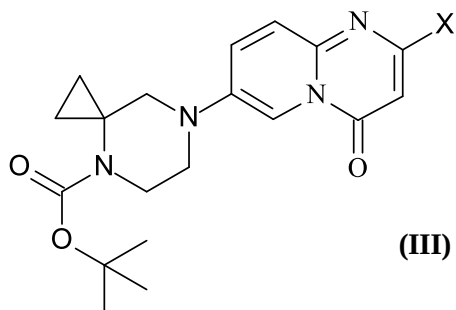


wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide with a compound of formula (III'), (III_a') or (III_b'),

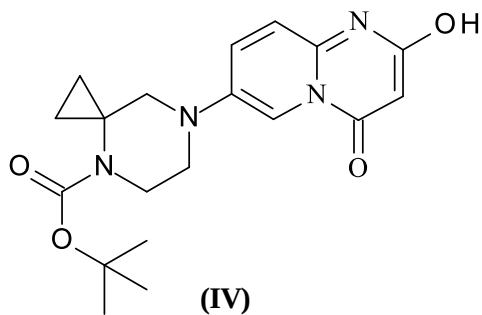


in the presence of a palladium catalyst or nickel catalyst, to obtain a compound of formula (II).

5. The process according to claim 2 or 4, carried out in presence of a base.
6. The process according to any one of claims 4 to 5, wherein steps a) and b) are telescoped.
7. A process for the preparation of a compound of formula (III)

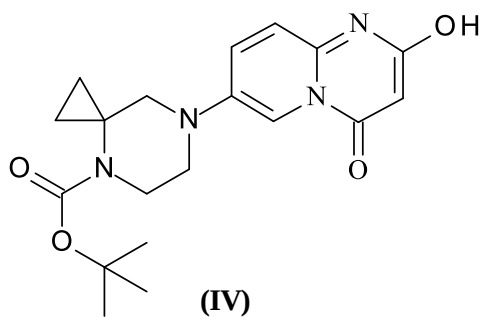


wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide, which comprises reacting a compound of formula (IV)

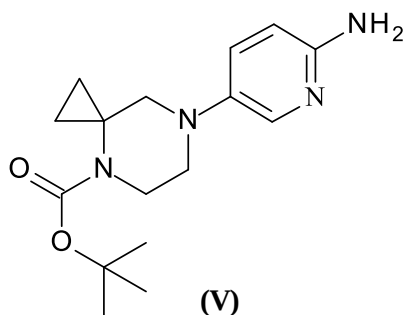


- with tosyl chloride when X is pTol-SO₃-, methanesulfonyl chloride when X is CH₃SO₃-, triflyl chloride when X is CF₃SO₃- or phenylsulfonylchloride when X is phenyl-SO₃-, and in the presence of a base;
- with POCl₃ when X is Cl;
- 5 - with POBr₃ when X is Br; or
- with Ph₃PI₂ or POCl₃ followed by NaI or CuI, when X is I.

8. A process for the preparation of a compound of formula (IV)



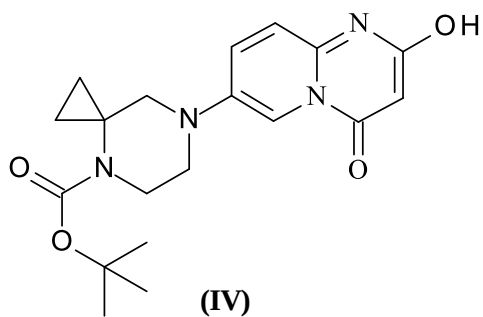
which comprises reacting a compound of formula (V)



10

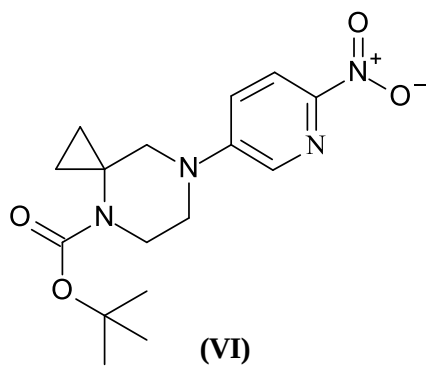
with di-tert-butyl malonate.

9. A process for the preparation of a compound of formula (IV)

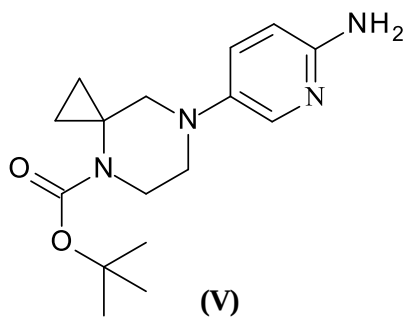


which comprises :

- a) reduction of a compound of formula (VI)

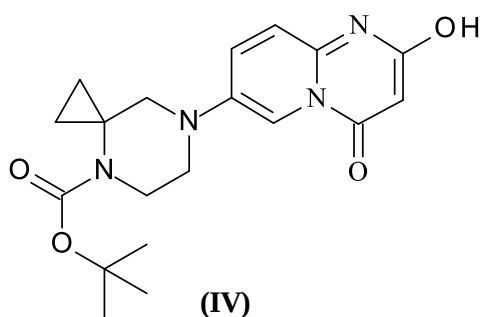


- 5 to a compound of formula (V)



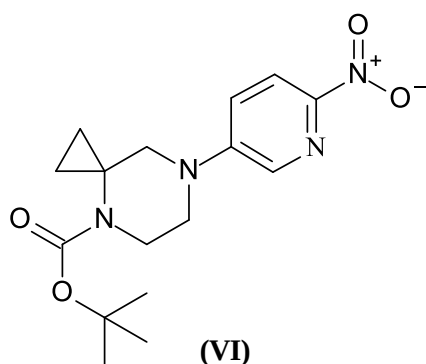
- b) reacting a compound of formula (V) with di-tert-butyl malonate to obtain a compound of formula (IV).

10. A process for the preparation of a compound of formula (IV)

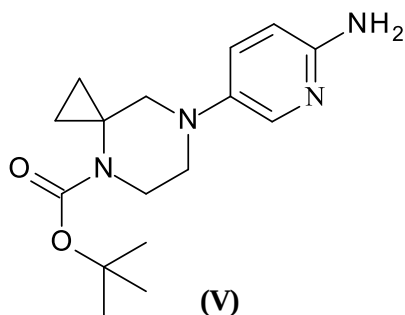


which comprises :

- a) reacting a compound of formula (VI)



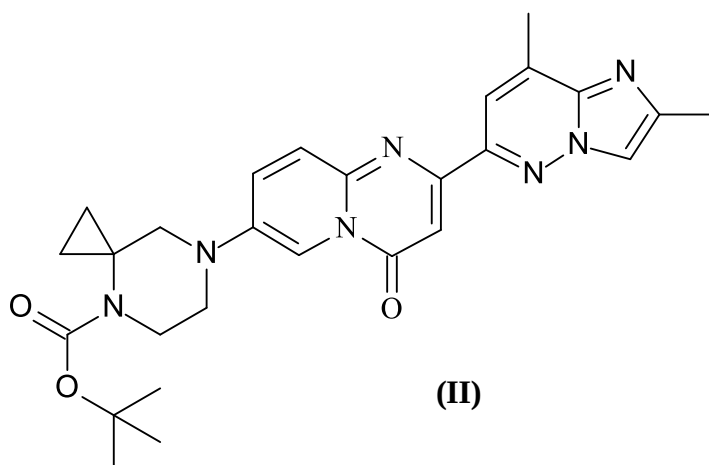
- 5 with a transition metal hydrogenation catalyst to obtain a compound of formula (V)



- b) reacting a compound of formula (V) with di-tert-butyl malonate to obtain a compound of formula (IV).
- 10 11. The process according to any one of claims 8 to 10, which comprises reacting a compound of formula (V) with di-tert-butyl malonate, carried out in the presence of xylene, dichlorobenzene, toluene or anisole.
12. The process according to any one of claims 10 to 11, wherein the transition metal hydrogenation catalyst is Raney catalyst (e.g. Ra-Ni, Ra-Co,) Pd/C, Pd(OH)₂/C, Au/TiO₂, Rh/C, Ru/Al₂O₃, Ir/CaCO₃, Pt-V/C or Pt/C or combination thereof.

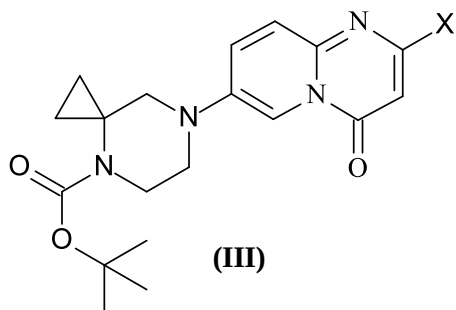
13. The process according to any one of claims 9 to 12, wherein steps a) and b) are telescoped.

14. A compound of formula (II):



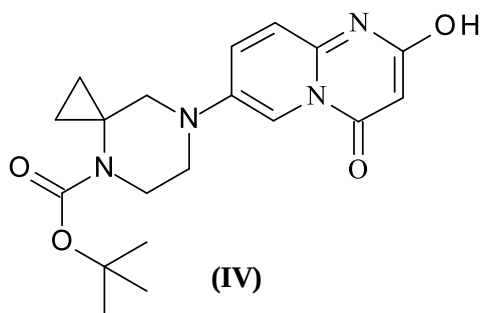
5

15. A compound of formula (III):

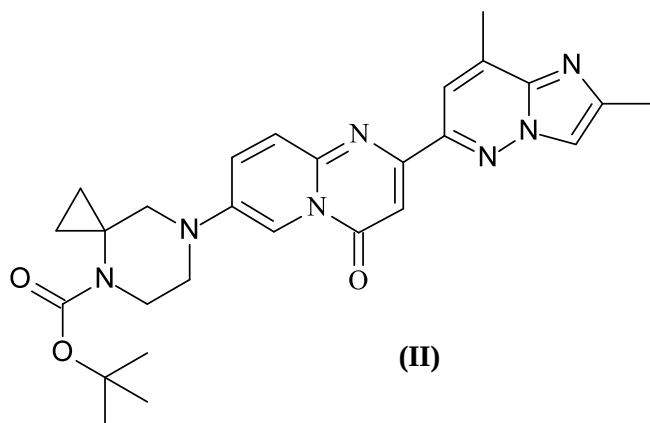


wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide.

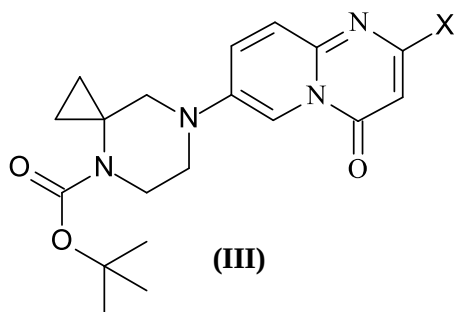
10 16. A compound of formula (IV):



17. The process according to any one of claims 1 to 2, which further comprises the preparation of a compound of formula (II)

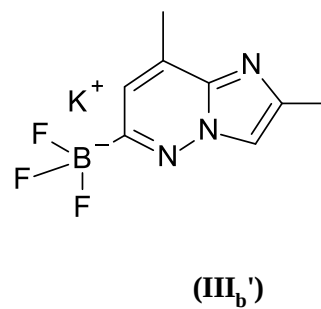
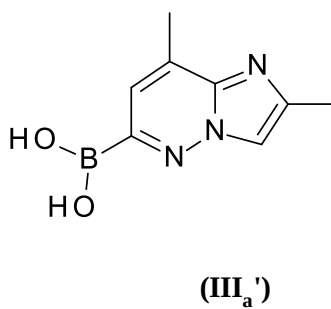
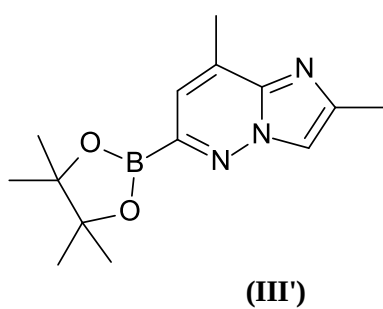


by reacting a compound of formula (III)



5

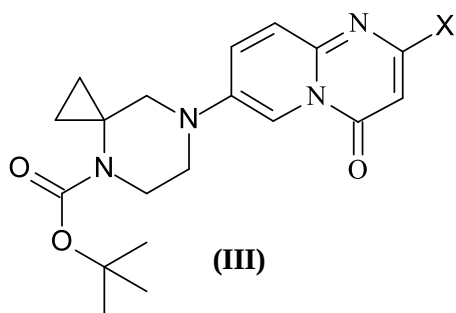
wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide, with a compound of formula (III'), (III_a') or (III_b'),



in

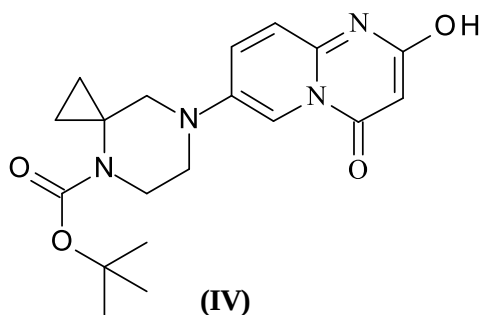
the presence of a palladium catalyst or nickel catalyst.

- 10 18. The process according to claim 17, wherein in addition to the palladium catalyst a base is present.
19. The process according to claim 17 or 18, which further comprises the preparation of a compound of formula (III)



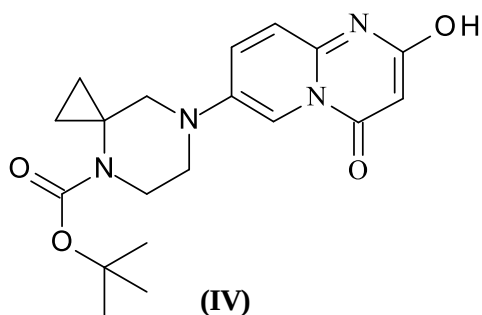
wherein X is an alkyl or aryl sulfonate, fluorinated alkyl or aryl sulfonates, or a halide;

by reacting a compound of formula (IV)

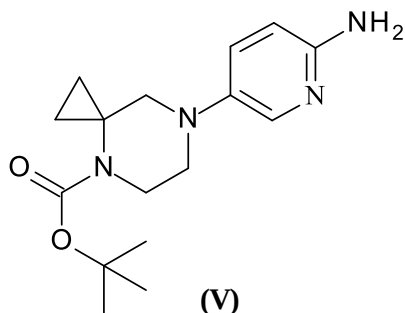


- 5 - with tosyl chloride when X is pTol-SO₃-, methanesulfonyl chloride when X is CH₃SO₃-, triflyl chloride when X is CF₃SO₃- or phenylsulfonylchloride when X is phenyl-SO₃-, and in the presence of a base;
- with POCl₃ when X is Cl;
- with POBr₃ when X is Br; or
- 10 - with Ph₃PI₂ or POCl₃ followed by NaI or CuI, when X is I.

20. The process according to claim 19, which further comprises the preparation of a compound of formula (IV)



by reacting a compound of formula (V)



with di-tert-butyl malonate.

21. The process according to any one of claims 3, 4, 7, 15, 17 and 19 wherein X is
5 pTolSO₃-, CH₃SO₃-, phenyl-SO₃-, CF₃SO₃-, nonaflate, Cl, Br, or I.
22. The process according to any one of claims 3, 4, 7, 15, 17 and 19 wherein X is
pTolSO₃.
23. The process according to claim 5 or 18 wherein the base is Na₂CO₃, K₂CO₃, Cs₂CO₃,
KOAc or KOtBu.
- 10 24. The process according to claim 5 or 18 wherein the base is K₂CO₃.
25. The process according to claim 7 or 19, wherein the base is an organic base or basic
alkali metal salts.
26. The process according to claim 7 or 19, wherein the base is nitrogen-containing
heterocycle, tertiary amine or basic alkali metal salts.
- 15 27. The process according to claim 7 or 19, wherein the base is a tertiary amine.
28. The process according to claim 1, wherein the strong acid is HCl.