

(*R*)-5-methyl-4-(piperazin-1-yl)-5,6-dihydro-7H-cyclopenta[d]pyrimidin-7-one, or the *N*-protected derivative thereof, wherein R^1 is hydrogen or an amino protecting group

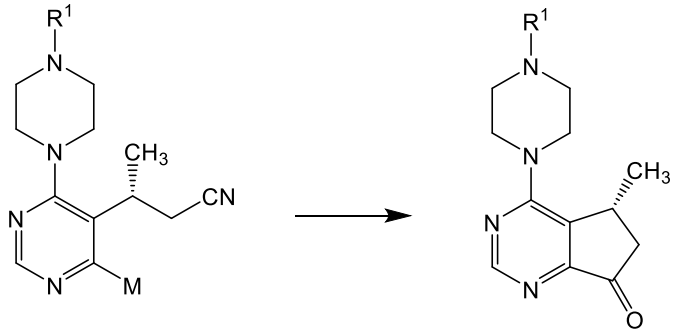
However, it is known that scale-up of chemical processes can result in unexpected conditions such as, for example, increased impurities or decreased yields. Accordingly, there is a need for improved processes for the synthesis of Ipatasertib that increase yields and/or decrease impurities.

SUMMARY

Provided herein are solutions to the problems above and other problems in the art.

Provided herein is a process for preparing *(R)*-5-methyl-4-(piperazin-1-yl)-5,6-dihydro-7H-cyclopenta[d]pyrimidin-7-one (compound of formula (1) wherein R^1 is hydrogen) wherein the process comprises a continuous flow reaction. Also provided is a process for preparing N-protected derivatives thereof (compound of formula (1) wherein R^1 is an amino protecting group).

In one example the continuous flow reaction mentioned above comprises cyclizing a compound of formula (II), or pharmaceutically acceptable salt thereof, to provide a compound of formula (I), or pharmaceutically acceptable salt thereof:



(II) (I)

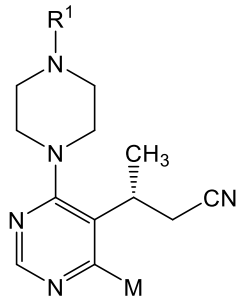
wherein:

R^1 is hydrogen or an amino protecting group; and

M is Li or MgX, wherein X is Br or I.

In certain examples, R^1 is an amino protecting group.

In one example the continuous flow reaction described above comprises cyclizing a compound of formula (II)



(II)

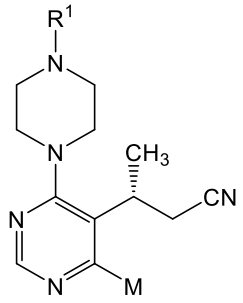
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or an amino protecting group; and

M is Li or MgX, wherein X is Br or I.

In certain examples, R^1 is an amino protecting group.

In one example the continuous flow reaction described above comprises cyclizing a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein:

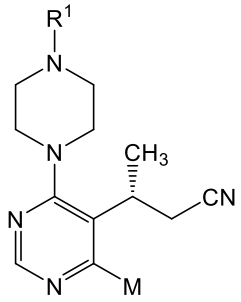
R^1 is hydrogen or an amino protecting group; and

M is MgX, wherein X is Br or I.

In certain examples, R^1 is an amino protecting group.

In certain examples, M is MgBr. In certain examples, R^1 is an amino protecting group and M is MgBr.

In certain examples, the continuous flow reaction described above comprises cyclizing a compound of formula (II):



(II)

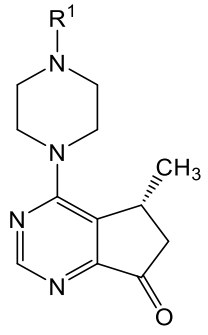
or a pharmaceutically acceptable salt thereof,

wherein:

R^1 an amino protecting group; and

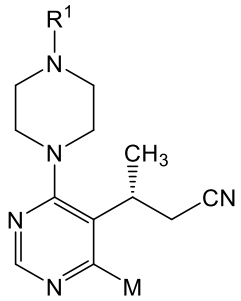
M is MgBr.

Thus, in one aspect, the present disclosure provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

wherein the process comprises a continuous flow reaction, which continuous flow reaction comprises cyclization of a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof,

wherein:

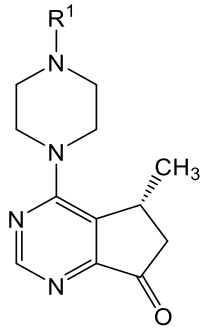
R^1 is an amino protecting group; and

M is MgX wherein X is Br.

In one example, the continuous flow reaction comprises iPrMgBr as metalating reagent.

The iPrMgBr permits continuous mode processing with a very fast reaction, reduced levels of dimerization by-products (amongst others), and easily isolated final products.

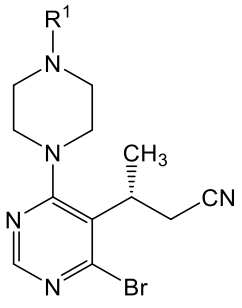
In another aspect, the present disclosure provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

the process comprising the steps of:

(a) solubilizing a compound of formula (IV)



(IV)

in a mixture of toluene and MeTHF;

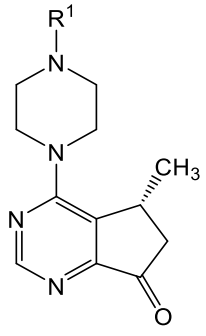
(b) adding iPrMgBr in MeTHF to the solubilized compound of step (a) thereby forming a Mg-imine complex as a solid in suspension;

(c) adding an aqueous acid salt;

(d) adding a base in water; and

(e) isolating the compound of formula (I).

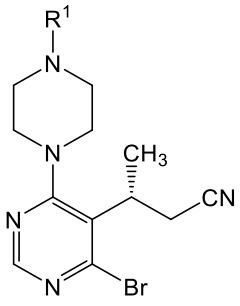
In another aspect, the present disclosure provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

the process comprising the steps of:

(a) solubilizing a compound of formula (IV)



(IV)

in a mixture of toluene and MeTHF in a first continuous stirred tank reactor (CSTR);

(b) adding iPrMgBr in MeTHF to the solubilized compound of step (a) in the first CSTR, thereby forming a Mg-imine complex as a solid;

(c) transferring the contents of the first CSTR to a second CSTR to which iPrMgBr in MeTHF is added, thereby forming a Mg-imine complex as a solid;

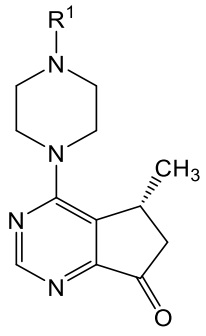
(d) transferring the contents of the second CSTR to a third CSTR to which toluene is added, thereby forming a Mg-imine complex as a solid;

(e) transferring the contents of the third CSTR to a fourth CSTR to which aqueous $NaHSO_4$ is added to set a pH about 2, thereby forming the compound of formula (I) and allowing the reaction to proceed;

(f) transferring the contents of the fourth CSTR to a fifth CSTR to which NaOH in water is added to set a pH of about 5 and allowing the reaction to proceed; and

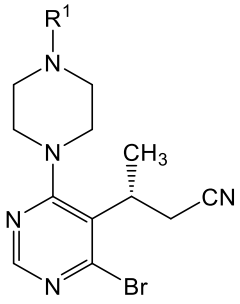
(g) transferring the contents of the fifth CSTR to a first separation vessel to separate the compound of formula (I) in the organic phase.

In another aspect, the present disclosure provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof,


(I)

the process comprising the steps of:

(a) solubilizing a compound of formula (IV)


(IV)

in a mixture of toluene and MeTHF in a first continuous stirred tank reactor (CSTR);

(b) adding iPrMgBr in MeTHF to the solubilized compound of step (a) in the first CSTR and wherein the first CSTR has a residence time of about 15 min, thereby forming a Mg-imine complex as a solid;

(c) transferring the contents of the first CSTR to a second CSTR to which iPrMgBr in MeTHF is added wherein the second CSTR has a residence time of about 15 min, thereby forming a Mg-imine complex as a solid;

(d) transferring the contents of the second CSTR to a third CSTR to which toluene is added wherein the third CSTR has a residence time of about 15 min, thereby forming a Mg-imine complex as a solid;

(e) transferring the contents of the third CSTR to a fourth CSTR to which aqueous $NaHSO_4$ is added to set a pH about 2, thereby forming the compound of formula (I) and allowing the reaction to proceed for about 4.45 min;

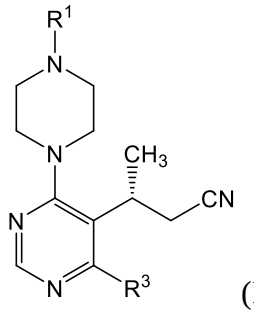
(f) transferring the contents of the fourth CSTR to a fifth CSTR to which NaOH in water is added to set a pH of about 5 and allowing the reaction to proceed for about 4.45 min; and

(g) transferring the contents of the fifth CSTR to a first separation vessel to separate the compound of formula (I) in the organic phase.

Provided herein is a process as exemplified by Figure 1.

Provided herein is a process as exemplified by Figure 2.

Provided herein is a process for the preparation of a compound of formula (I) as described herein or a pharmaceutically acceptable salt thereof the process comprising a continuous flow reaction wherein in step (a) the compound of formula (III) or a pharmaceutically acceptable salt thereof, wherein R^1 is as defined above, and R^3 is iodo or bromo, in a coordinating ethereal solvent or a non-coordinating apolar solvent, or a mixture of such solvents, is reacted with iPrMgBr in MeTHF to form a solid Mg-imine complex and wherein in step (b) an aqueous acid salt is added to the mixture obtained from step (a), thereby forming the compound of formula (I) or a pharmaceutically acceptable salt thereof.



(III)

The processes described herein has one or more of the following advantages:

(i) improved yields by 10-20%,

(ii) precipitation of a transient reaction intermediate protects it from further decomposition,

(iii) improved process robustness and better controllability,

(iv) better purity,

(v) no additional re-crystallization required to meet specification,

(vi) minimal scale up factors and short hold times for production, and

(vii) significant cost savings in the scaled up process per ton of Ipatasertib.

The present examples can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting examples.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts one diagram of the process described herein showing continuous flow reaction of compound 4 to compound 1 (or a pharmaceutically acceptable salt thereof). Arrows indicate flow between continuous stirred tank reactors (CSTRs). Flow rates are determined as described herein.

Figure 2 depicts one diagram of the process described herein showing continuous flow reaction of compound 4 to compound 1 (or a pharmaceutically acceptable salt thereof). Arrows indicate flow between continuous stirred tank reactors (CSTRs). Flow rates are determined as described herein.

DETAILED DESCRIPTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art. See, *e.g.*, Singleton