Figure 5-32 shows TGA/DSC curves of Type J.

Figure 5-33 shows ^{1}H NMR of Type J.

Figure 5-34 shows XRPD pattern of Type K.

Figure 5-35 shows TGA/DSC curves of Type K.

Figure 5-36 shows ^{1}H NMR of Type K.

Figure 5-37 shows XRPD pattern of Type L.

Figure 5-38 shows TGA/DSC curves of Type L.

Figure 5-39 shows ^{1}H NMR of Type L.

Figure 5-40 shows XRPD pattern of Type M.

Figure 5-41 shows TGA/DSC curves of Type M.

Figure 5-42 shows ^{1}H NMR of Type M.

Figure 5-43 shows XRPD pattern of Type N.

Figure 5-44 shows TGA/DSC curves of Type N.

Figure 5-45 shows ^{1}H NMR of Type N.

Figure 5-46 shows XRPD pattern of Type O.

Figure 5-47 shows TGA/DSC curves of Type O.

Figure 5-48 shows ^{1}H NMR of Type O.

Figure 5-49 shows XRPD pattern of Type P.

Figure 5-50 shows TGA/DSC curves of Type P.

Figure 5-51 shows ^{1}H NMR of Type P.

Figure 5-52 shows XRPD pattern of Type Q.

Figure 5-53 shows TGA/DSC curves of Type Q.

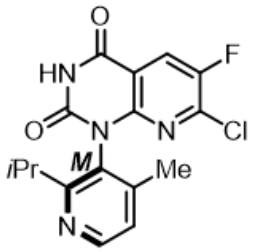
Figure 5-54 shows ^{1}H NMR of Type Q.

Figure 6-1 shows HPLC of M-5 from resolution with 1,3-diphenyl-3-oxopropanesulfonic acid.

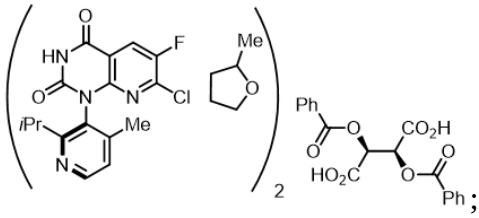
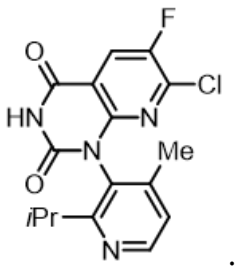
Figure 6-2 shows HPLC of 5 (P-atropisomer excess) from resolution with 1,3-diphenyl-3-oxopropanesulfonic acid.

SUMMARY

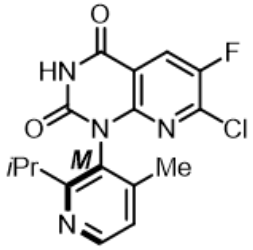
The present disclosure relates to improved preparation of a compound having the following chemical structure:



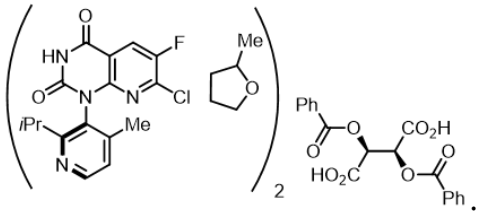
and key intermediates thereof, i.e., compositions and compounds comprising the following chemical structures:


; and 
.

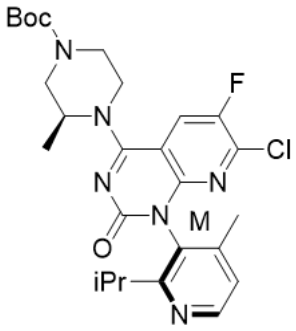
The present disclosure additional relates to a method of preparing Compound 5M having the following chemical structure


.

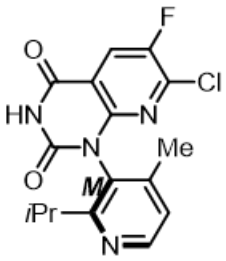
The present disclosure additional relates to a composition comprising a structure


.

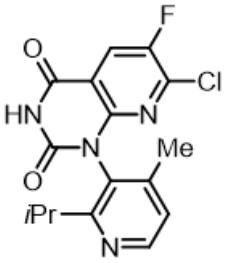
In one aspect, the present disclosure provides for a method of making a compound of Formula (6)


(6)

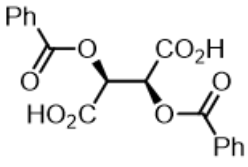
the method comprising: obtaining a compound of Formula (5M)


(5M)

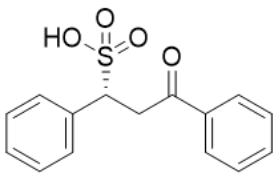
from a compound of Formula (4)


(4)

through cocrystallization with (+)-2, 3-dibenzoyl-D-tartaric acid of Formula (B1),

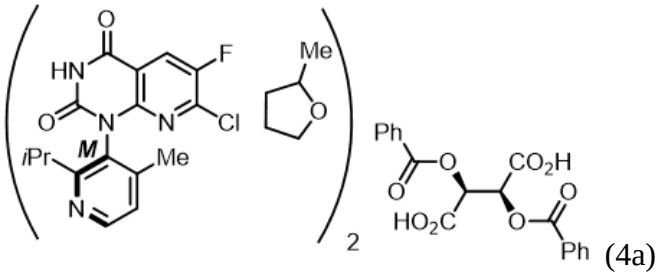

(B1),

or with (-) 1,3-diphenyl-3-oxopropanesulfonic acid of Formula (11b),


(11b); and

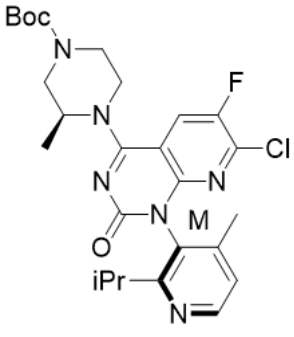
reacting the compound of Formula (5M) with phosphoryl chloride followed by (s)-1-boc-3-methylpiperazine.

In another aspect, the present disclosure provides for a use of a compound of Formula (4a)



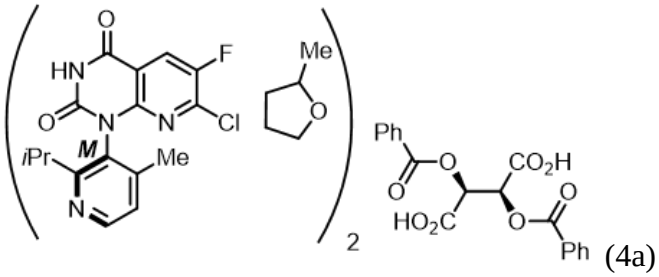
(4a)

for the preparation of a compound of: Formula (6)



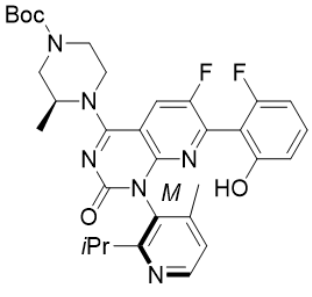
(6).

In another aspect, the present disclosure provides for a use of a compound of Formula (4a)



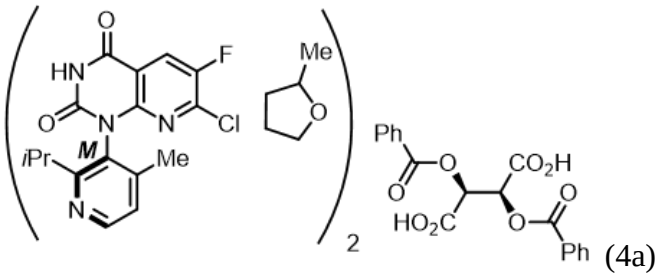
(4a)

for the preparation of a compound of: Formula (7)



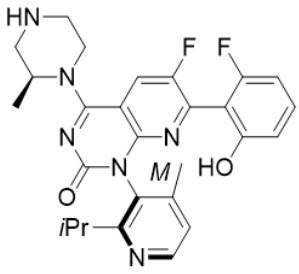
(7).

In another aspect, the present disclosure provides for a use of a compound of Formula (4a)



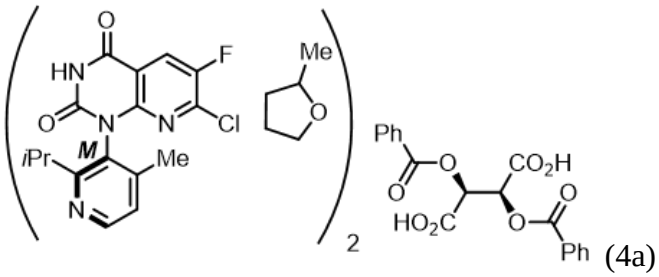
(4a)

for the preparation of a compound of Formula (8)



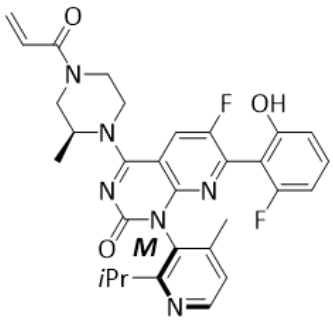
(8).

In another aspect, the present disclosure provides for a use of a compound of Formula (4a)



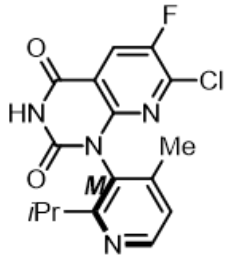
(4a)

for the preparation of a compound of: Formula (9)



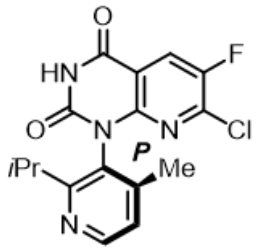
(9).

In another aspect, the present disclosure provides for a use of a compound of Formula (5M)



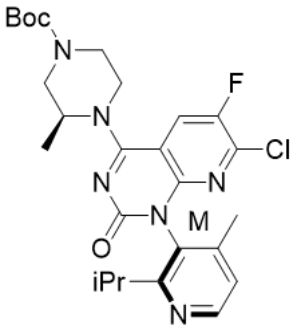
(5M)

that has been separated from a compound of Formula (5P) through cocrystallization



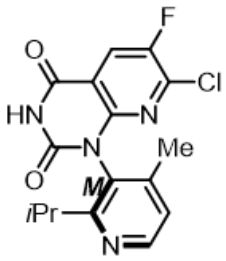
(5P)

for the preparation of a compound of: Formula (6)



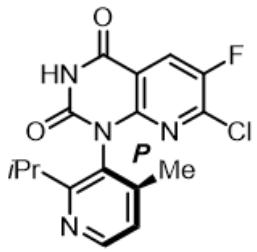
(6).

In another aspect, the present disclosure provides for a use of a compound of Formula (5M)



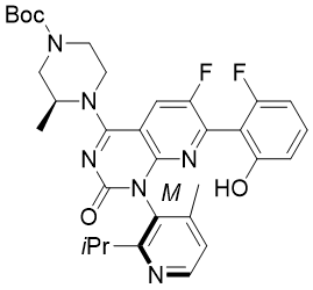
(5M)

that has been separated from a compound of Formula (5P) through cocrystallization



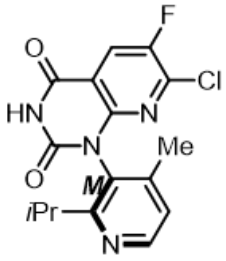
(5P)

for the preparation of a compound of: Formula (7)



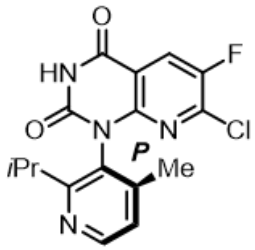
(7).

In another aspect, the present disclosure provides for a use of a compound of Formula (5M)



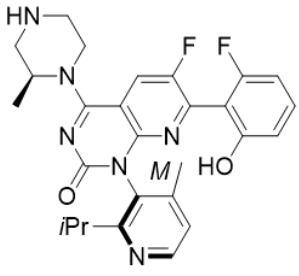
(5M)

that has been separated from a compound of Formula (5P) through cocrystallization



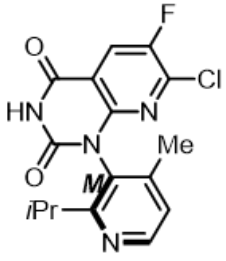
(5P)

for the preparation of a compound of: Formula (8)



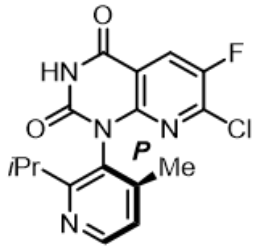
(8).

In another aspect, the present disclosure provides for a use of a compound of Formula (5M)



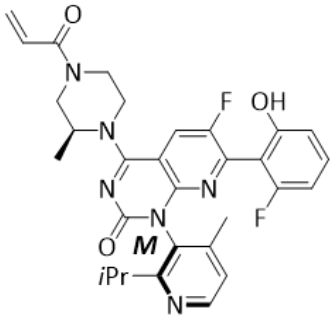
(5M)

that has been separated from a compound of Formula (5P) through cocrystallization



(5P)

for the preparation of a compound of: Formula (9)

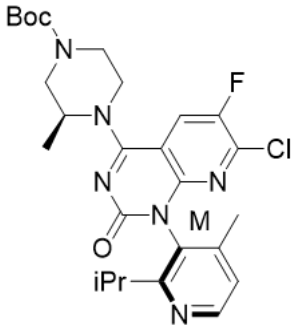


(9).

CLAIMS

What is claimed is:

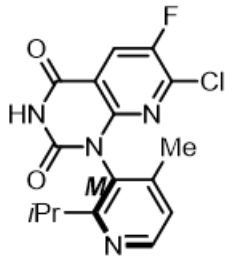
1. A method of making a compound of Formula (6)



(6)

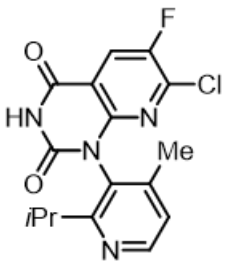
the method comprising:

obtaining a compound of Formula (5M)



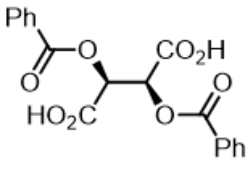
(5M)

from a compound of Formula (4)



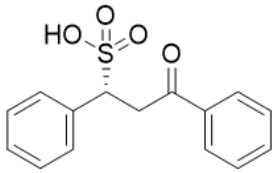
(4)

through cocrystallization with (+)-2, 3-dibenzoyl-D-tartaric acid of Formula (B1),



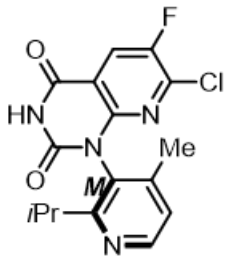
(B1),

or with (-) 1,3-diphenyl-3-oxopropanesulfonic acid of Formula (11b),


(11b); and

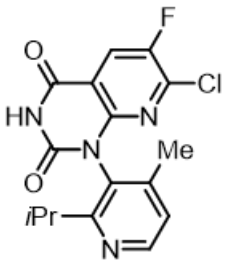
reacting the compound of Formula (5M) with phosphoryl chloride followed by (s)-1-boc-3-methylpiperazine.

2. The method according to claim 1, wherein the compound of Formula (5M)

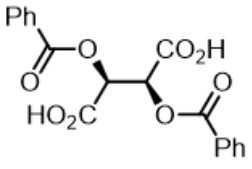

(5M)

is prepared by

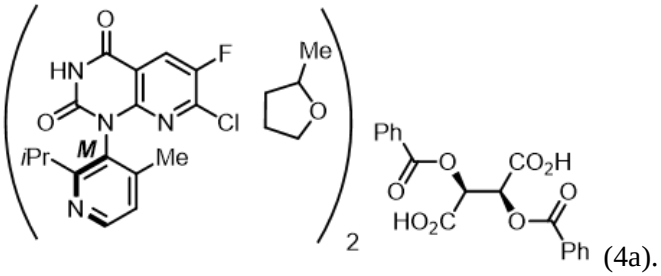
a) reacting the compound of Formula (4)


(4)

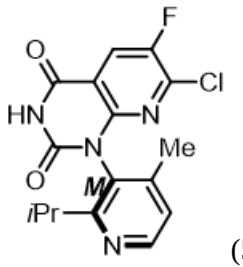
with a compound of Formula (B1)


(B1)

in the presence of 2-methyltetrahydrofuran to form a composition of Formula (4a)

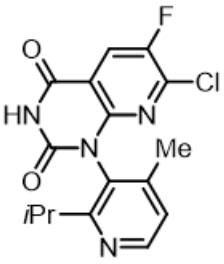

(4a).

3. The method according to claim 1, wherein the compound of Formula (5M)

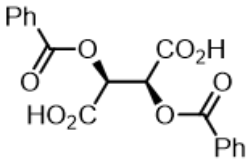

(5M)

is prepared by

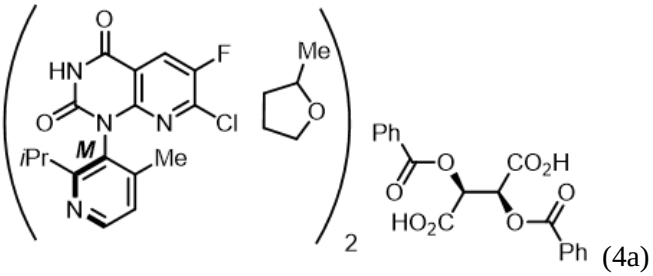
a) reacting the compound of Formula (4)


(4)

with a compound of Formula (B1)


(B1)

in the presence of 2-methyltetrahydrofuran to form a composition of Formula (4a)


(4a)

as crystals,

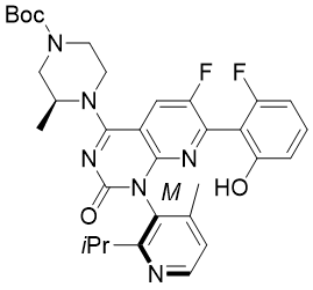
b) isolating the composition of Formula (4a), and

c) treating the isolated composition of Formula (4a) with a base to produce the compound of Formula (5M).

4. The method according to claim 3, wherein the base is Na_2HPO_4.

5. The method according to claim 3, wherein the base is $NaHCO_3$.

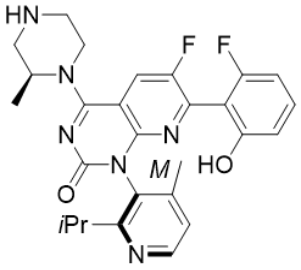
6. The method according to any one of claims 1 to 5, wherein the compound of Formula (6) is used to generate a compound of Formula (7)



(7).

7. The method according to claim 6, wherein the compound of Formula (7) is prepared by reacting the compound of Formula (6) with trifluoro(2-fluoro-6-hydroxyphenyl)borate in the presence of [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).

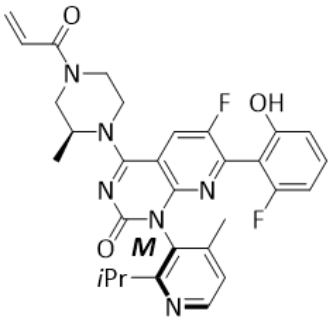
8. The method according to any one of claims 1 to 7, wherein the compound of Formula (6) is used to generate a compound of Formula (8):



(8).

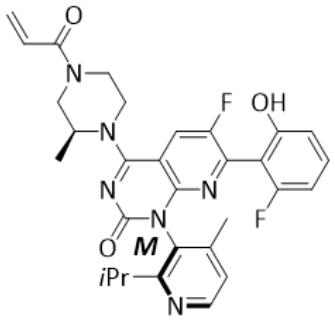
9. The method according to claim 8, wherein the compound of Formula (8) is prepared by reacting the compound of Formula (7) with trifluoroacetic acid.

10. The method according to any one of claims 1 to 8, wherein the compound of Formula (6) is used to generate a compound of Formula (9)



(9).

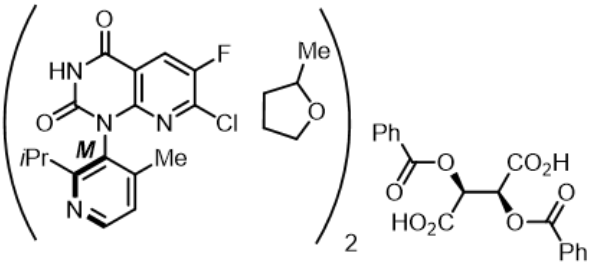
11. The method according to claim 8 or 9, wherein the compound of Formula (8) is reacted with acryloyl chloride to generate a compound of Formula (9)



(9).

12. The method according to claim 10 or 11, wherein the method further comprises mixing the compound of Formula (9) with at least one pharmaceutically acceptable excipient to form a pharmaceutical composition.

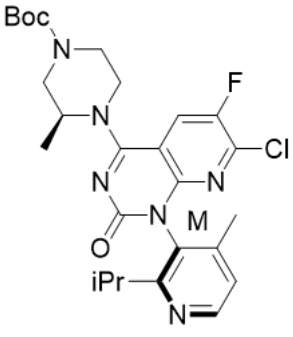
13. Use of a compound of Formula (4a)



(4a)

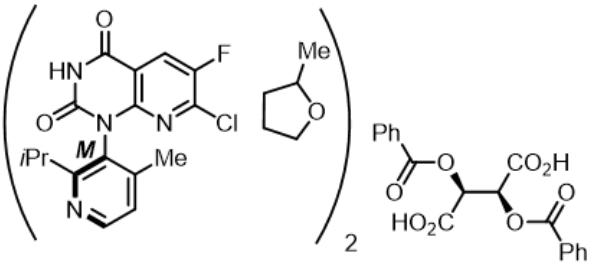
for the preparation of a compound of:

Formula (6)



(6).

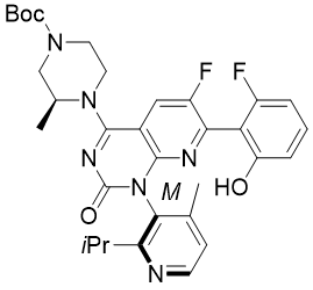
14. Use of a compound of Formula (4a)



(4a)

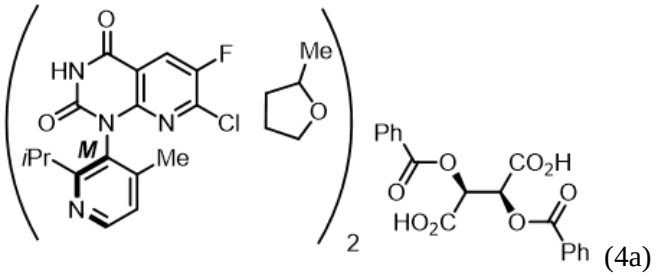
for the preparation of a compound of:

Formula (7)



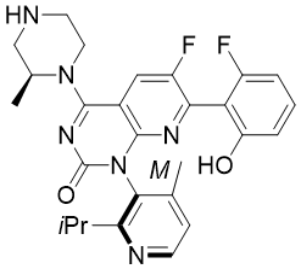
(7).

15. Use of a compound of Formula (4a)



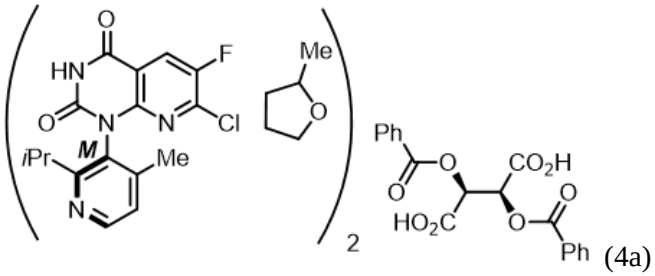
(4a)

for the preparation of a compound of Formula (8)



(8).

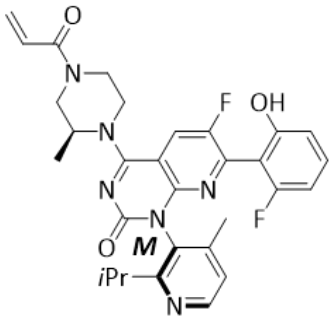
16. Use of a compound of Formula (4a)



(4a)

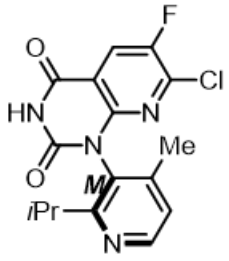
for the preparation of a compound of:

Formula (9)



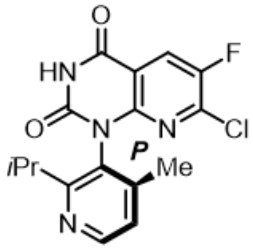
(9).

17. Use of a compound of Formula (5M)



(5M)

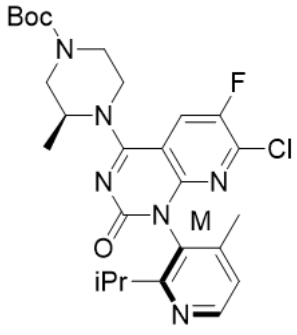
that has been separated from a compound of Formula (5P) through cocrystallization



(5P)

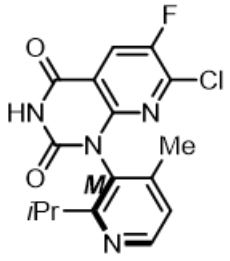
for the preparation of a compound of:

Formula (6)



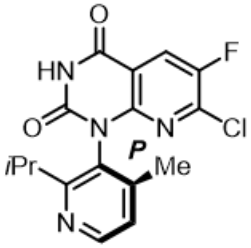
(6).

18. Use of a compound of Formula (5M)



(5M)

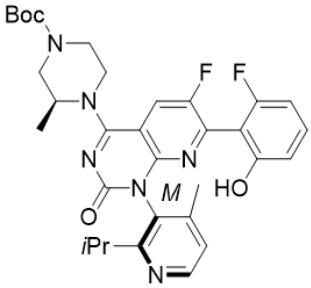
that has been separated from a compound of Formula (5P) through cocrystallization



(5P)

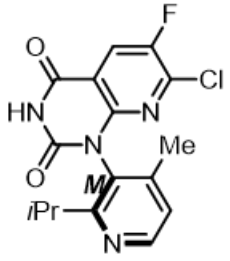
for the preparation of a compound of:

Formula (7)



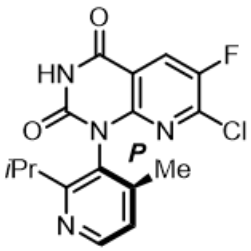
(7).

19. Use of a compound of Formula (5M)



(5M)

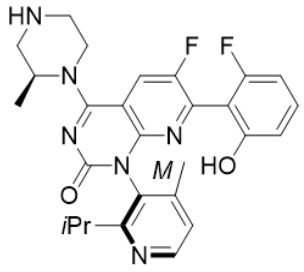
that has been separated from a compound of Formula (5P) through cocrystallization



(5P)

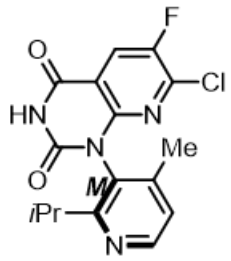
for the preparation of a compound of:

Formula (8)



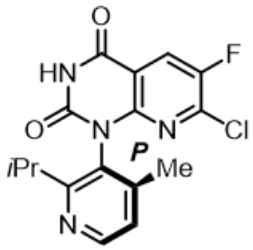
(8).

20. Use of a compound of Formula (5M)



(5M)

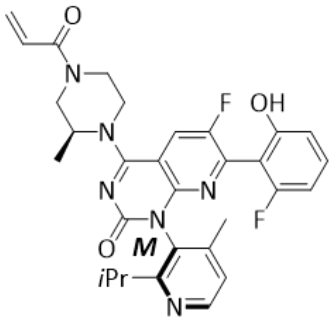
that has been separated from a compound of Formula (5P) through cocrystallization



(5P)

for the preparation of a compound of:

Formula (9)



(9).