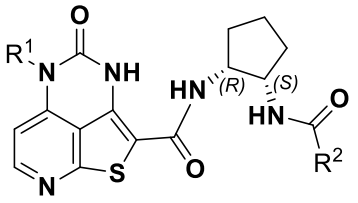


Formula (I)

**[0004a]** In one aspect, there is provided a method of synthesizing a compound of Formula (I):

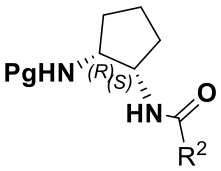


Formula (I)

wherein:

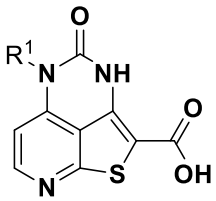
$R^1$ is selected from $C_{5-10}$ aryl and $C_{4-9}$ heteroaryl wherein the aryl or heteroaryl are optionally substituted with one or more groups independently selected from $C_{1-6}$ alkyl; and

$R^2$ is selected from $C_{1-6}$ alkyl and $C_{2-6}$ alkenyl;



CMPD-01

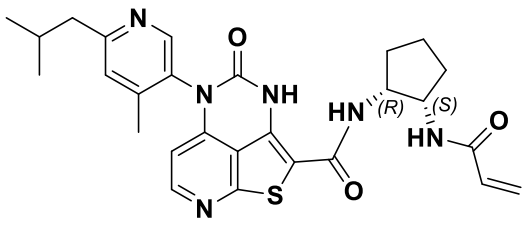
comprising contacting the compound with an acid and a first solvent



CMPD-02

followed by contacting with the compound in the presence of one or more coupling reagents, an amine base, and a second solvent to obtain the compound of Formula (I).

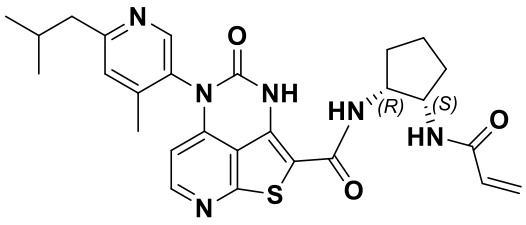
**[0005]** Also disclosed are methods of synthesizing a compound of Formula (II), including a solvate or a pharmaceutically acceptable salt form thereof:



Formula (II)

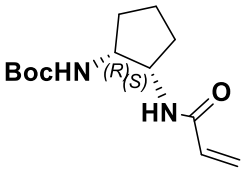
The compound of Formula (II) is also known as *N*-((1*R*,2*S*)-2-acrylamidocyclopentyl)-5-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide. In some examples, the compound of Formula (II) exists as a mixture of atropisomers- *P* and *M* forms.

**[0005a]** In another aspect, there is provided a method of synthesizing a compound of Formula (II):



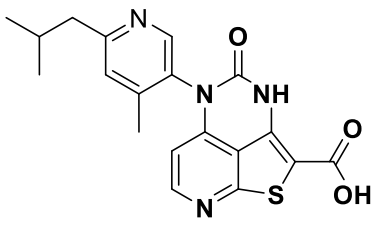
Formula (II)

comprising contacting the compound



CMPD-10

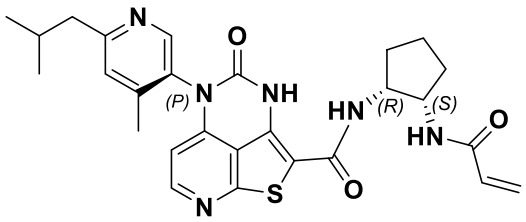
with an acid and a first solvent followed by contacting with the compound



CMPD-11

in the presence of one or more coupling reagents, an amine base, and a second solvent to obtain the compound of Formula (II).

**[0006]** Some examples further comprise converting the compound of Formula (II) into its P form:



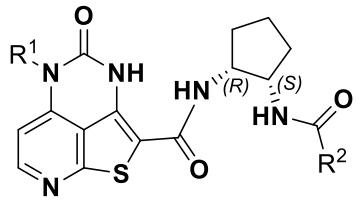

Formula *P*-(II)

The compound of Formula *P*-(II) is also known as *N*-((1*R*,2*S*)-2-acrylamidocyclopentyl)-5-(*S*)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

**[0007]** The compound of Formula *M*-(II) is also known as *N*-((1*R*,2*S*)-2-acrylamidocyclopentyl)-5-(*R*)-(6-isobutyl-4-methylpyridin-3-yl)-4-oxo-4,5-dihydro-3*H*-1-thia-3,5,8-triazaacenaphthylene-2-carboxamide.

What is Claimed:

1. A method of synthesizing a compound of Formula (I):

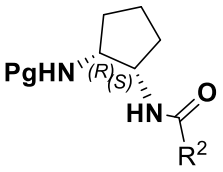


Formula (I)

wherein:

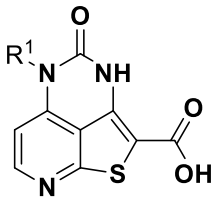
$R^1$ is selected from $C_{5-10}$ aryl and $C_{4-9}$ heteroaryl wherein the aryl or heteroaryl are optionally substituted with one or more groups independently selected from $C_{1-6}$ alkyl; and

$R^2$ is selected from $C_{1-6}$ alkyl and $C_{2-6}$ alkenyl;



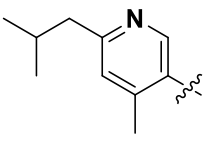
CMPD-01

comprising contacting the compound with an acid and a first solvent



CMPD-02

followed by contacting with the compound in the presence of one or more coupling reagents, an amine base, and a second solvent to obtain the compound of Formula (I).

2. The method of claim 1, wherein $R^1$ is .

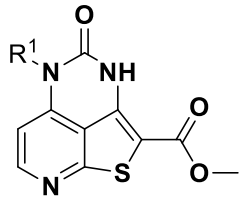
3. The method of claim 1 or 2, wherein $R^2$ is $C_{2-6}$ alkenyl.

4. The method of claim 1, 2 or 3 wherein the acid is methanesulphonic acid.

5. The method of any of claims 1-4, wherein the coupling reagent is selected from 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), hydroxybenzotriazole (HOBt), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), propylphosphonic anhydride (T3P), 1, 1'-carbonyldiimidazole (CDI), 2-hydroxypyridine-N-oxide (HOPO), and combinations thereof.

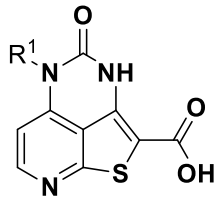
6. The method of any of claims 1-5, wherein the amine base is selected from *N*,*N*-diisopropylethylamine (DIPEA), triethylamine, tributylamine, N-methyl morpholine, and N-methyl piperidine. In some aspects the second solvent is selected from dichloromethane, ethyl acetate, 2-methyltetrahydrofuran, tetrahydrofuran, and acetonitrile.

7. The method of any of claims 1-6, further comprising contacting the compound



CMPD-03

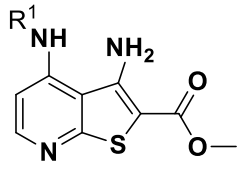
with a base and an ammonium salt in a solvent to form the compound



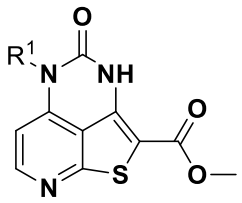
CMPD-02

.

8. The method of claim 7, further comprising contacting the compound

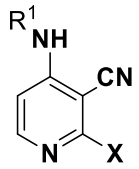


CMPD-04 with a carbonyl source and a solvent to form the compound

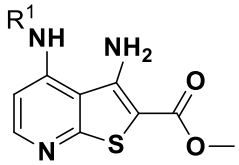


CMPD-03 .

9. The method of claim 8, further comprising contacting the compound

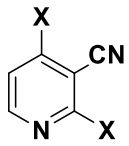


CMPD-05 with a sulfur reagent and a base in a solvent to form the compound



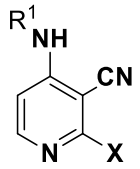
CMPD-04 and wherein X is selected from Cl and Br.

10. The method of claim 9, further comprising contacting the compound



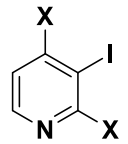
CMPD-06 with the compound $R^1$-$NH_2$ with a base, and an amine base in a solvent

system to form the compound

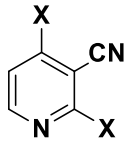


CMPD-05.

11. The method of claim 10, further comprising contacting the compound

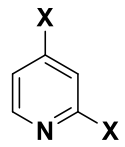


CMPD-07 with a cyano source and a solvent to form the compound

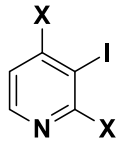


CMPD-06.

12. The method of claim 11, further comprising contacting the compound

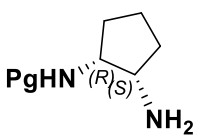


CMPD-08 with a base and an electrophilic halogen in a solvent to form the compound

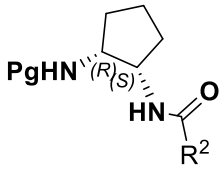


CMPD-07.

13. The method of claim 1, further comprising contacting the compound

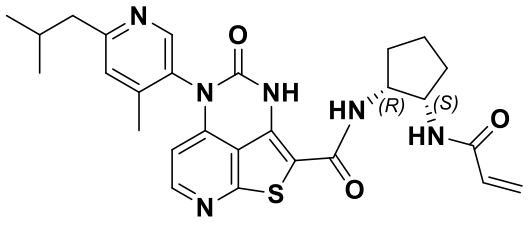


CMPD-09 with a base, , and a solvent to form the compound



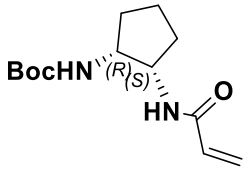
CMPD-01 .

14. A method of synthesizing a compound of Formula (II):

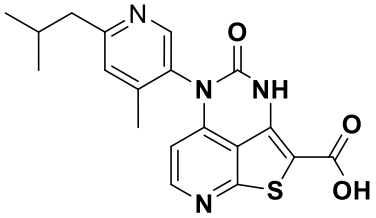


Formula (II)

comprising contacting the compound

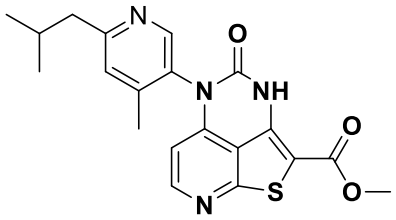


CMPD-10 with an acid and a first solvent followed by contacting with the compound

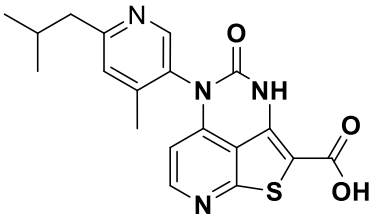


CMPD-11 in the presence of one or more coupling reagents, an amine base, and a second solvent to obtain the compound of Formula (II).

15. The method of claim 14, further comprising contacting the compound

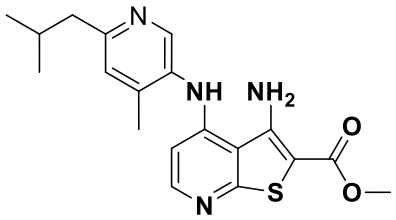


CMPD-12 with a base and an ammonium salt in a solvent to form

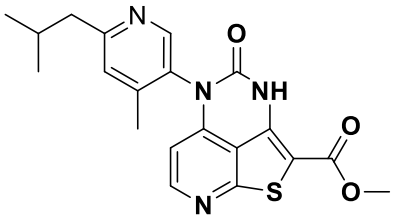


the compound CMPD-11 .

16. The method of claim 15, further comprising contacting the compound

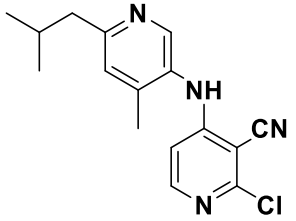


CMPD-13 with a carbonyl source and a solvent to form the



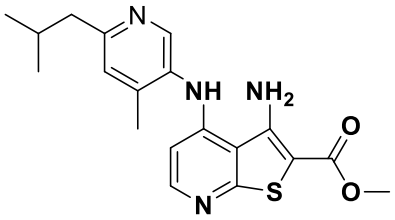
compound CMPD-12 .

17. The method of claim 16, further comprising contacting the compound



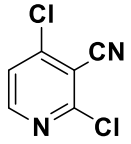
CMPD-14 with a sulfur reagent and a base in a solvent to form the

compound

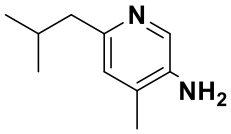


CMPD-13 .

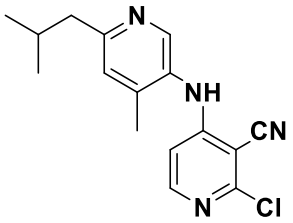
18. The method of claim 17 further comprising contacting the compound



CMPD-15 with the compound

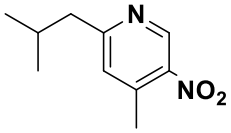


CMPD-16 with a base, and an amine base in a solvent system to form the

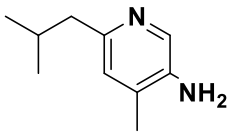


compound CMPD-14 .

19. The method of claim 18, further comprising contacting the compound

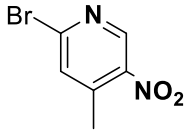


CMPD-17 with a hydride source, a catalyst, and a solvent system to form the

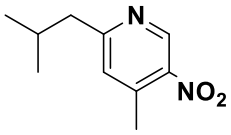


compound CMPD-16 .

20. The method of claim 19, further comprising contacting the compound

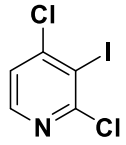


CMPD-20 with a catalyst, phosphorus reagent, a boron reagent, a first base, a second base and a solvent system to form the compound

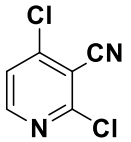


CMPD-17 .

21. The method of claim 20, further comprising contacting the compound

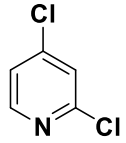


CMPD-18 with a cyano source and a solvent to form the compound

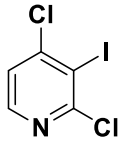


CMPD-15 .

22. The method of claim 21, further comprising contacting the compound



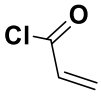
CMPD-19 with a base and an electrophilic halogen in a solvent to form the compound



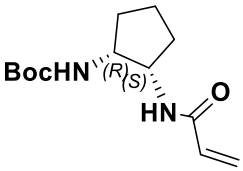
CMPD-18 .

23. The method of claim 22, further comprising contacting the compound




CMPD-20 with a base, 

, and a solvent to form the compound




CMPD-10 .

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