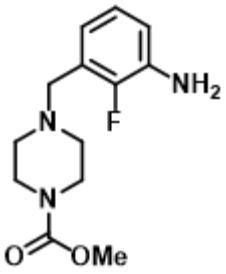
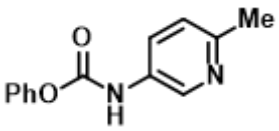
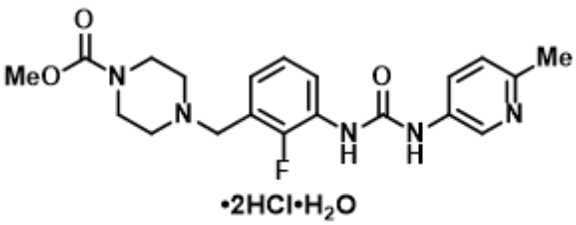
pyrrolidinone (NMP). In some cases, the admixing is performed at a temperature of 15 to 30°C for 1 to 15 hours. In various cases, the PCAR is formed as a hydrochloride salt. In some cases, the process can further comprise preparing APYR by a process comprising: (i) hydrogenating 2-methyl-5-nitropyridine (NPYR) in the presence of a palladium catalyst to form crude APYR; and (ii) crystallizing APYR from the crude APYR in isopropyl acetate and heptane. In various cases, the process can further comprise, prior to step (i), washing NPYR in isopropyl acetate with aqueous sodium hydroxide, followed by admixing the washed NPYR in isopropyl acetate with charcoal. In some cases, the process can further comprise, prior to admixing the APYR and phenyl chloroformate, purifying APYR by a process comprising: (i) washing an isopropyl acetate solution of crude APYR, wherein the crude APYR comprises up to 10 wt% APYR hydrochloride, with aqueous sodium hydroxide, and admixing the washed APYR with charcoal to form, after filtration, an APYR solution; and (ii) crystallizing APYR from the APYR solution of step (i) from isopropyl acetate and heptane. In various cases, the process can further comprise crystallizing PCAR.

[0011] Also provided herein are processes for synthesizing methyl 4-(3-amino-2-fluorobenzyl)piperazine-1-carboxylate (PIPA) comprising (a) admixing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate (PIPN), an aqueous solution of an inorganic base, and toluene to form a PIPN freebase solution; (b) hydrogenating the PIPN freebase solution in the presence of a palladium catalyst in a toluene and alcohol solvent mixture to form crude PIPA, wherein the alcohol comprises ethanol or isopropanol; and (c) crystallizing the PIPA from the crude PIPA in heptane and toluene. In various cases, the inorganic base comprises sodium hydroxide.

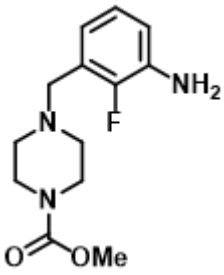
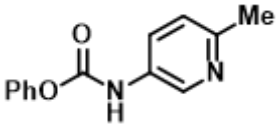
[0012] In one aspect, the present disclosure provides a process for preparing omecamtiv mecarbil dihydrochloride hydrate comprising (a) admixing methyl 4-(3-amino-2-fluorobenzyl)piperazine-1-carboxylate  (PIPA), phenyl (6-methylpyridin-3-yl) carbamate  (PCAR), and a trialkylamine in acetonitrile and tetrahydrofuran to form a solution of crude omecamtiv mecarbil; (b) isolating omecamtiv mecarbil free base from the solution of crude omecamtiv mecarbil; and (c) admixing the isolated omecamtiv mecarbil free base with 2 to 3 molar equivalents of hydrochloric acid in isopropanol and water to form omecamtiv mecarbil dihydrochloride hydrate  . Further provided herein are processes for preparing omecamtiv mecarbil dihydrochloride hydrate comprising (a) admixing

methyl 4-(3-amino-2-fluorobenzyl)piperazine-1-carboxylate (PIPA), phenyl (6-methylpyridin-3-yl) carbamate (PCAR), and a trialkylamine in acetonitrile and tetrahydrofuran to form a solution of crude omecamtiv mecarbil; (b) isolating omecamtiv mecarbil free base from the solution of crude omecamtiv mecarbil; and (c) admixing the isolated omecamtiv mecarbil free base with 2 to 3 molar equivalents of hydrochloric acid in isopropanol and water to form omecamtiv mecarbil dihydrochloride hydrate. In various cases, the trialkylamine comprises diisopropylethylamine or triethylamine. In some cases, the isolation of step (b) comprises crystallizing omecamtiv mecarbil free base by adding water to the solution of crude omecamtiv mecarbil from step (a) and filtering the crystallized omecamtiv mecarbil free base. In various cases, the process can further comprise crystallizing the omecamtiv mecarbil dihydrochloride hydrate from isopropanol and water. In some cases, the PCAR is prepared using a process as disclosed herein.

[0013] Also provided herein are processes for preparing omecamtiv mecarbil dihydrochloride hydrate comprising (a) admixing methyl 4-(3-amino-2-fluorobenzyl)piperazine-1-caboxylate (PIPA), triphosgene, and a trialkylamine in acetonitrile and tetrahydrofuran to form PIPA isocyanate; (b) admixing the PIPA isocyanate and 5-amino-2-methylpyridine (APYR) to form omecamtiv mecarbil free base; (c) admixing the omecamtiv mecarbil free base with 2 to 3 molar equivalents of

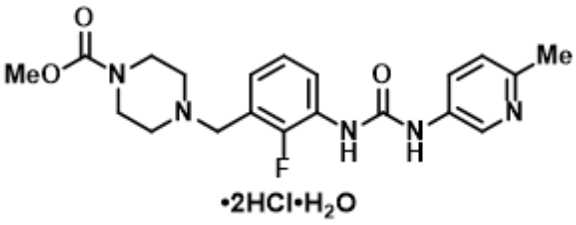
WHAT IS CLAIMED:

1. A process for preparing omecamtiv mecarbil dihydrochloride hydrate comprising

(a) admixing methyl 4-(3-amino-2-fluorobenzyl)piperazine-1-carboxylate  (PIPA), phenyl (6-methylpyridin-3-yl) carbamate  (PCAR), and a trialkylamine in acetonitrile and tetrahydrofuran to form a solution of crude omecamtiv mecarbil;

(b) isolating omecamtiv mecarbil free base from the solution of crude omecamtiv mecarbil; and

(c) admixing the isolated omecamtiv mecarbil free base with 2 to 3 molar equivalents of hydrochloric acid in isopropanol and water to form omecamtiv mecarbil dihydrochloride hydrate

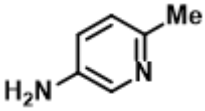


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2. The process of claim 1, wherein the trialkylamine comprises diisopropylethylamine or triethylamine.

3. The process of claim 1 or 2, wherein the isolating of step (b) comprises crystallizing omecamtiv mecarbil free base by adding water to the solution of crude omecamtiv mecarbil from step (a) and filtering the crystallized omecamtiv mecarbil free base.

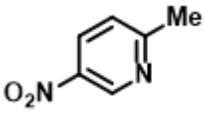
4. The process of any one of claims 1 to 3, further comprising crystallizing the omecamtiv mecarbil dihydrochloride hydrate from isopropanol and water.

5. The process of any one of claims 1 to 4, wherein the PCAR is prepared by a process comprising admixing 5-amino-2-methylpyridine  (APYR) and phenyl chloroformate in acetonitrile to form PCAR, wherein the admixing is performed in the absence of N-methyl pyrrolidinone (NMP).

6. The process of claim 5, wherein the admixing is performed at a temperature of 15 to 30°C for 1 to 15 hours.

7. The process of claim 5 or 6, wherein the PCAR is formed as a hydrochloride salt.

8. The process of any one of claims 5 to 7, further comprising preparing APYR by a process comprising:

(i) hydrogenating 2-methyl-5-nitropyridine 

(NPYR) in the presence of a palladium catalyst to form crude APYR ; and

(ii) crystallizing APYR from the crude APYR in isopropyl acetate and heptane.

9. The process of claim 8, further comprising, prior to step (i), washing NPYR in isopropyl acetate with aqueous sodium hydroxide, followed by admixing the washed NPYR in isopropyl acetate with charcoal.

10. The process of any one of claims 5 to 7, further comprising, prior to admixing APYR and phenyl chloroformate, purifying APYR by a process comprising:

(i) washing an isopropyl acetate solution of crude APYR, wherein the crude APYR comprises up to 10 wt% APYR hydrochloride, with aqueous sodium hydroxide, and admixing the washed APYR with charcoal to form an APYR solution after filtration; and

(ii) crystallizing APYR from the APYR solution of step (i) from isopropyl acetate and heptane.

11. The process of any one of claims 5 to 10, further comprising crystallizing PCAR.