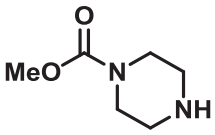
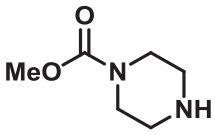
SUMMARY

[0007] Provided herein is piperazine methyl carboxylate (PMEC) phosphate salt, e.g., a PMEC phosphate hydrate salt. PMEC is alternatively referred to as methyl piperazine-1-carboxylate.

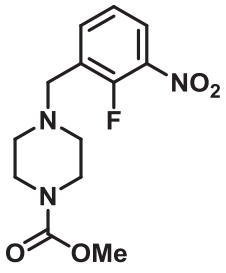
[0007a] In one aspect, the present disclosure refers to piperazine methyl carboxylate

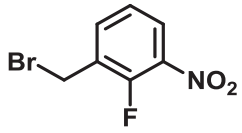


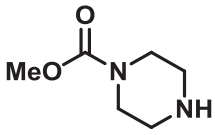
("PMEC") phosphate hydrate.

[0007b] In another aspect, the present disclosure refers to a process for synthesizing piperazine methyl carboxylate 

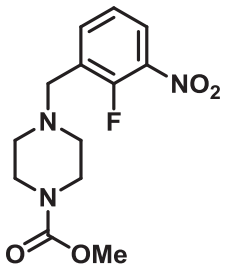
("PMEC") phosphate hydrate comprising (a) admixing piperazine and methyl chloroformate to form PMEC; (b) admixing the PMEC and 0.5 molar equivalents of phosphoric acid to form PMEC phosphate hydrate; and (c) optionally filtering the PMEC phosphate hydrate from the admixture of step (b).

[0007c] In yet another aspect, the present disclosure refers to a process for synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate 

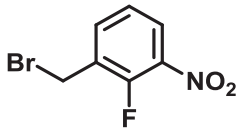
(PIPN) comprising (a) admixing 2-fluoro-3-nitrotoluene, sodium bromate, and sodium bisulfite in isopropylacetate and water to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene 

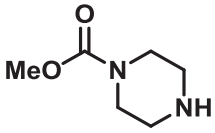
(FNB); (b) optionally washing the FNB with aqueous sodium thiosulfate, with aqueous sodium chloride, or both; and (c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate 

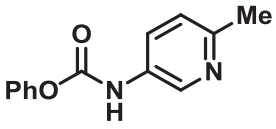
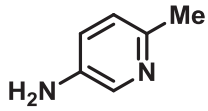
("PMEC") phosphate hydrate to form PIPN.

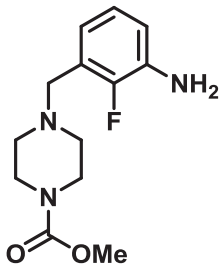
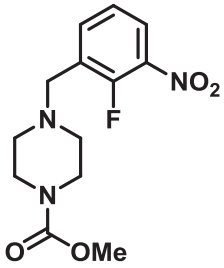
[0007d] In yet another aspect, the present disclosure refers to a process for synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate 

(PIPN) comprising (a) admixing 2-

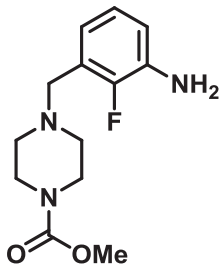
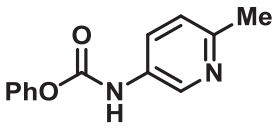
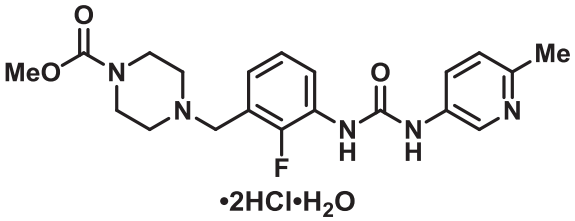
fluoro-3-nitrotoluene, benzoyl peroxide, N-bromosuccinimide and acetic acid at a temperature of 70 to 95°C to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene  (FNB); (b) optionally extracting FNB with toluene, washing FNB with an aqueous basic solution, or both;

(c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate  ("PMEC") phosphate hydrate to form PIPN.

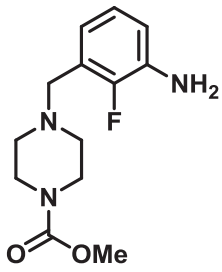
[0007e] In yet another aspect, the present disclosure refers to a process for synthesizing phenyl (6-methylpyridin-3-yl) carbamate  (PCAR) comprising admixing 5-amino-2-methylpyridine  (APYR) and phenyl chloroformate in acetonitrile to form PCAR, wherein the admixing is performed in the absence of N-methyl pyrrolidinone (NMP).

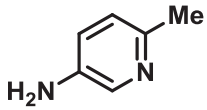
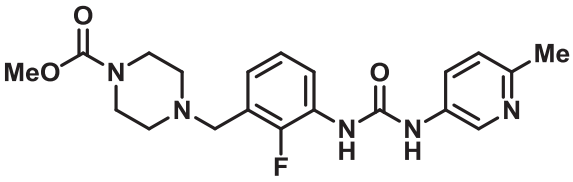
[0007f] In yet another aspect, the present disclosure refers to a process for synthesizing methyl 4-(3-amino-2-fluorobenzyl)piperazine-1-carboxylate  (PIPA) comprising (a) admixing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate  (PIPN), an aqueous solution of an inorganic base, and toluene 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.

[0007g] In yet another aspect, the present disclosure refers 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 .

[0007h] In yet another aspect, the present disclosure refers a process 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 hydrochloric acid in isopropanol and water to form omecamtiv mecarbil dihydrochloride hydrate.

[0008] Further provided herein are processes of synthesizing PMEC phosphate salt comprising a) admixing piperazine and methyl chloroformate to form PMEC; (b) admixing the PMEC and 0.5 molar equivalents of phosphoric acid to form PMEC phosphate ; and (c) optionally filtering the PMEC phosphate from the admixture of step (b). In some cases, step (a) is performed in an aqueous solution which generates PMEC phosphate hydrate with a PMEC to water ratio of about 2:1. In various cases, step (a) is performed at a temperature of 20 to 55°C for 1 to 12 hours. In some cases, the PMEC formed in step (a) is isolated as a solution in methylene chloride, dichloroethane, 2-methyltetrahydrofuran, or mixture thereof. More specifically, the isolation can be performed by (i) washing the resulting PMEC from step (a) with an organic solvent; (ii) modifying the pH to 8 to 14 by adding a base to form a basic aqueous solution; and (iii) extracting the PMEC from the basic aqueous solution of step (ii) with methylene chloride, dichloroethane, 2-methyl tetrahydrofuran, or mixture thereof.

[0009] Also provided herein are processes of synthesizing methyl 4-(2-fluoro-3-nitrobenzyl)piperazine-1-carboxylate (PIPN) comprising (a) admixing 2-fluoro-3-nitrotoluene, sodium bromate, and sodium bisulfite in isopropylacetate and water to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene (FNB); (b) optionally washing the FNB with aqueous sodium thiosulfate, with aqueous sodium chloride, or both; and (c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate ("PMEC") phosphate, e.g., PMEC phosphate hydrate, to form PIPN. In some cases, the FNB is washed with aqueous sodium thiosulfate, and aqueous sodium chloride. Alternatively, PIPN can be prepared by (a) admixing 2-fluoro-3-nitrotoluene, benzoyl peroxide, N-bromosuccinimide and acetic acid at a temperature of 70 to 95°C to form 1-(bromomethyl)-2-fluoro-3-nitrobenzene (FNB); (b) optionally extracting FNB with toluene, washing FNB with an aqueous basic solution, or both; (c) admixing FNB, a trialkylamine base, and piperazine methyl carboxylate ("PMEC") phosphate, e.g., PMEC phosphate hydrate, to form PIPN. In some cases, FNB is extracted with toluene and washed with aqueous sodium hydroxide. In either process for preparing PIPN, the PIPN can be formed as a hydrochloride salt. In either process for preparing PIPN, the PMEC phosphate, e.g., PMEC phosphate hydrate, can be prepared as disclosed herein. In either process for preparing PIPN, the trialkylamine base comprises diisopropylethylamine or triethylamine. In either process for preparing PIPN, prior to admixing the FNB, the trialkylamine base, and the PMEC, the process can further comprise adding diethylphosphite and a trialkylamine, and admixing the resulting mixture at a temperature of 30 to 65°C.

[0010] Further provided herein are processes for synthesizing phenyl (6-methylpyridin-3-yl) carbamate (PCAR) 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). 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] 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