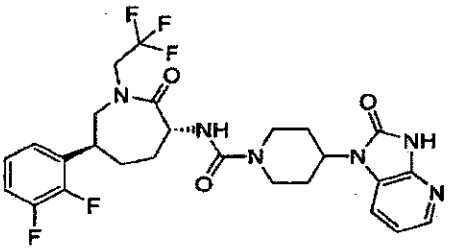
TITLE OF THE INVENTION

PROCESS FOR THE PREPARATION OF PYRIDINE HETEROCYCLE CGRP ANTAGONIST INTERMEDIATE

BACKGROUND OF THE INVENTION

International patent applications PCT/US2004/010851, filed April 9, 2004 (published as WO2004/092166 on October 28, 2004) and PCT/US2004/011280, filed April 9, 2004 (published as WO2004/092168 on, October 29, 2004), and U.S application Serial Number 10/838,835 (issued as U.S. Patent Number 6,953,790 on October 11, 2005) disclose compounds useful for the treatment of diseases or conditions of humans or other species which can be treated with inhibitors, modulators or promoters of the Calcitonin Gene-Related Peptide (CGRP) receptor function. Such diseases or conditions include those mentioned in the referenced applications, and specifically include migraine and cluster headache.

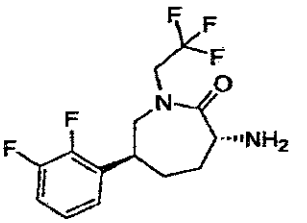
N-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**:



1

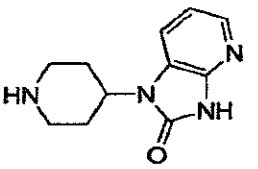
is a potent CGRP modulator. The laboratory preparation of compound **1** is described in international patent applications PCT/US2004/010851 and PCT/US2004/011280, and in U.S patent application Serial Number 10/838,835.

The laboratory preparation of certain intermediates employed in the synthesis of compound **1** is likewise described in the above-listed applications. Such intermediates include the intermediate (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**:



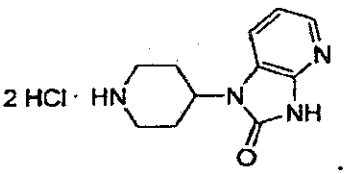
2 ;

and the intermediate 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, **3**:



3

and salts thereof, including 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride:



Prior techniques for synthesizing compound **1**, including syntheses of intermediates **2** and **3**, are relatively inefficient and costly from the standpoint of production and/or may result in sub-optimal salt and/or solvate forms for further synthesis and/or development.

With respect to intermediate **2**, it has been found that prior techniques of synthesis require an inordinate number of steps, including a large number of isolation steps, making the overall synthetic process slow as well as costly. Thus there remains a need for an improved synthetic route to compound **1** wherein the synthetic route to compound **2** is efficient and economical.

Prior techniques for making intermediate **3** are likewise costly and inefficient. Such known routes start with a reductive alkylation of 2,3-diaminopyridine ("DAP") followed by CDI-mediated cyclic urea formation and, lastly, acidic Boc-group deprotection/salt formation. This "DAP" route is characterized by high-cost starting materials and reagents as well as a low

yielding first step, resulting in prohibitive overall costs. Thus, there remains a need for an improved synthetic route to compound **1** wherein the synthetic route to intermediate **3** is efficient and economical.

Finally, prior techniques for making compound **1**, which techniques employ 4-nitrophenyl chloroformate as the carbonyl source, result in less than optimal yields. Such prior techniques further require that the neutral form of compound **1** be isolated prior to conversion to preferred salt forms. Moreover, previous laboratory-made forms of compound **1**, including free base forms and salt forms, possessed les than ideal properties with respect to stability and bioavailability. Thus, there remains a need for an improved synthetic route to compound **1**, and pharmaceutically acceptable salts thereof, which is amenable to large scale production formulation, storage and distribution.

SUMMARY

The disclosure provides an efficient synthesis for the preparation of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, by coupling the intermediates (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**, particularly the hydrochloride form thereof; and 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, **3**, particularly the dihydrochloride form, with 1,1'-carbonyldiimidazole as carbonyl source. The disclosure further provides an efficient preparation of potassium salt forms of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1** including the potassium ethanolate form.

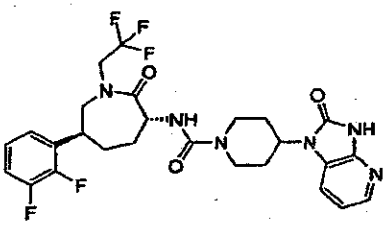
Additionally, the disclosure provides an efficient syntheses for the preparation of intermediates (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**, particularly the hydrochloride form; and 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, **3**, particularly the dihydrochloride form.

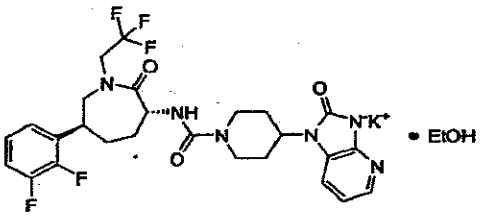
In a first aspect, there is provided a process for the preparation of an acid salt of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, said process comprising the steps of: (1) reductively alkylating 3-amino-2-chloropyridine with C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate to form C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate; (2) reacting the C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with chlorosulfonyl isocyanate to form C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate; (3) reacting the C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with Pd catalyst to form C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-1-yl)piperidine-1-carboxylate; and (4) reacting the C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate with a strong acid, or with a strong base followed by a strong acid.

The disclosure additionally resides in the superior properties of the potassium salt of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, including the potassium salt ethanolate and potassium salt hydrate.

DETAILED DESCRIPTION OF THE INVENTION

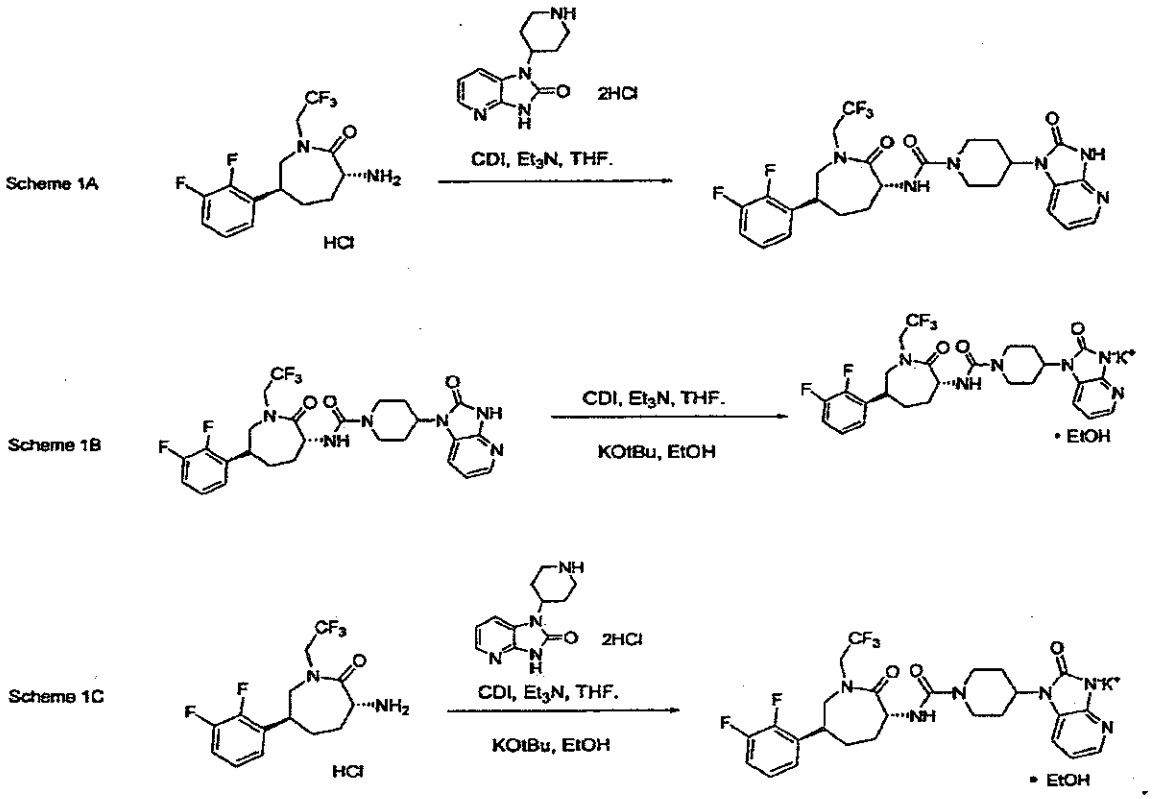
The present invention provides a process for the preparation of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, and its potassium salt ethanoate:





The syntheses of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, and its potassium salt ethanoate, is depicted in Scheme 1:

Scheme 1



Scheme 1A depicts an efficient method of synthesizing the neutral form of compound **1** from intermediates **2** and **3** using 1,1'-carbonyldiimidazole as the carbonyl source; **Scheme 1B** depicts an efficient method of synthesizing a potassium salt form of compound **1** starting from the neutral form of compound **1**; and **Scheme 1C** depicts the efficient synthesis of a potassium salt form of compound **1** directly from intermediates **2** and **3** using 1,1'-carbonyldiimidazole as the carbonyl source, without isolation of the neutral form of compound **1**.

Thus, in one embodiment of the invention provides a process for the preparation of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, comprising reacting (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one hydrochloride and 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride in the presence of 1,1'-carbonyldiimidazole.

Another embodiment of the invention provides a process for the preparation of the potassium salt ethanolate form of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, comprising the steps of:

(1) reacting (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one hydrochloride and 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride in the presence of 1,1'-carbonyldiimidazole;

(2) isolating *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**; and

(3) reacting said *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, with potassium *tert*-butoxide and ethanol.

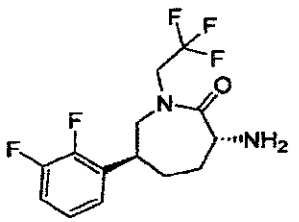
Yet another embodiment of the invention provides a process for the preparation of the potassium salt ethanolate form of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, without the necessity to isolate the neutral form of compound **1**, comprising the steps of:

(1) reacting (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one hydrochloride and 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride in the presence of 1,1'-carbonyldiimidazole; and

(2) reacting of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, **1**, with potassium *tert*-butoxide and ethanol.

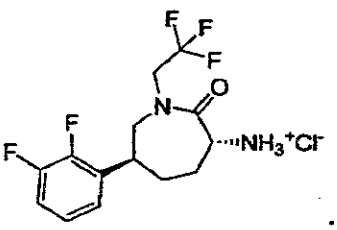
As described in the reaction schemes and Examples contained herein, the potassium salt ethanolate form of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide is obtained under anhydrous conditions. When the described reaction is performed in the presence of water, the reaction produces either pure ethanolate, pure hydrate or a mixed ethanolate / hydrate, depending on water content. The isolated potassium salt ethanolate or mixed ethanolate/hydrate converts to the hydrate over time due to the presence of water in the air.

Another aspect the invention provides a process for the preparation of the intermediate (3*R*,6*S*)-3-Amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**:



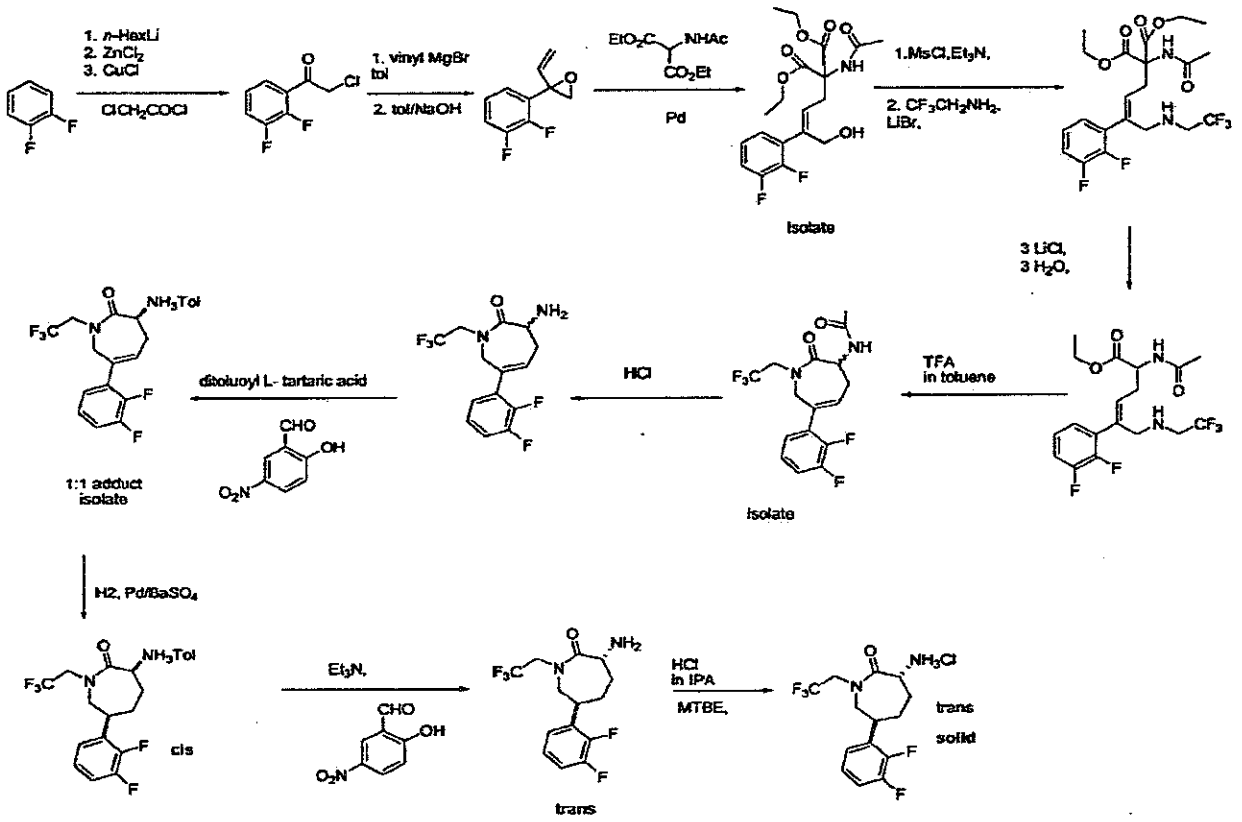
2

and salts thereof, in particular its hydrochloride salt:



The syntheses of (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2** and its hydrochloride salt is depicted in Scheme 2:

Scheme 2



Scheme 2 depicts the direct formation of the chloroacetophenone from cheap and readily available difluorobenzene; the selective formation of the Z-allylic alcohol using palladium catalysis; the use of a crystallization driven asymmetric transformation to set the amine stereocenter; followed by a cis-selective hydrogenation and epimerization to set the benzylic stereocenter and trans geometry.

Thus, an embodiment of the invention provides a process for the preparation of the intermediate (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**, comprising the steps of:

(1) hydrogenating a (3*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1*H*-azepin-3-ammonium salt, in the presence of a *cis*-selective catalyst, to form a (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium salt;

(2) reacting the (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium salt with R_3N , wherein each R is independently C_{1-4}alkyl, and a hydroxyl nitrobenzaldehyde, to form (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**.

An additional embodiment of the invention provides a process for the preparation of the intermediate (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one hydrochloride, comprising the steps of:

(1) hydrogenating a (3*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1*H*-azepin-3-ammonium salt, in the presence of a *cis*-selective catalyst, to form a (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium salt;

(2) reacting the (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium salt with R_3N , wherein each R is independently C_{1-4}alkyl, and a hydroxyl nitrobenzaldehyde, to form (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one; and

(3) reacting (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one with HCl.

A further embodiment of the invention provides a process for the preparation of the intermediate (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**, comprising the steps of:

(1) hydrogenating (3*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1*H*-azepin-3-ammonium di-toluoyl tartrate salt, in the presence of a heterogeneous palladium catalyst, to form (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium di-toluoyl tartrate salt;

(2) reacting (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium di-toluoyl tartrate salt with Et_3N and 2-hydroxy-5-nitrobenzaldehyde to form (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**.

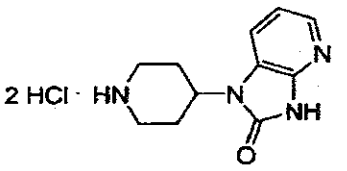
A still further embodiment of the invention provides a process for the preparation of (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one hydrochloride, comprising the steps of:

(1) hydrogenating (3*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1*H*-azepin-3-ammonium di-toluoyl tartrate salt, in the presence of a heterogeneous palladium catalyst, to form (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium di-toluoyl tartrate salt;

(2) reacting (3*S*,6*S*)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-ammonium di-toluoyl tartrate salt with Et_3N and 2-hydroxy-5-nitrobenzaldehyde to form (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one; and

(3) reacting (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one with HCl.

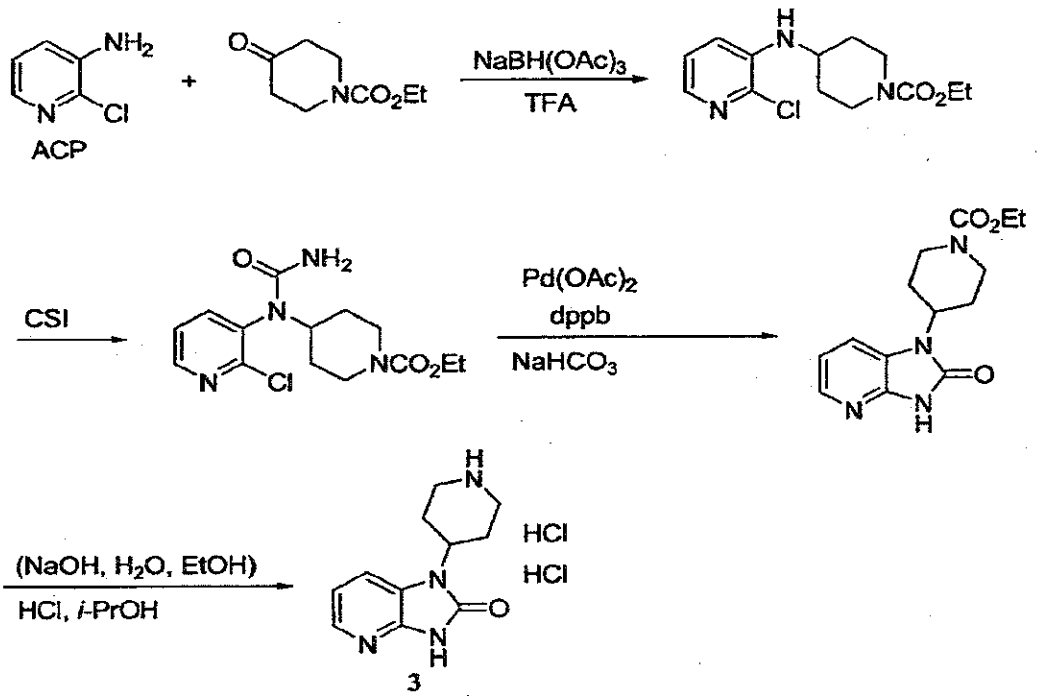
In still another aspect the invention provides a process for the preparation of the intermediate 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride, **3**:



3

and salts thereof, including the dihydrochloride salt, and those derived from reaction with alternative acids such as hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and other acids. The syntheses of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, **3**, and 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride, is depicted in Scheme 3:

Scheme 3



In **Scheme 3**, 3-Amino-2- chloropyridine ("ACP") is reductively alkylated in a first step. 3-amino-2-chloropyridine is reacted with ethyl 4-oxo-1-piperidinecarboxylate in the presence of IPAC, trifluoroacetic acid and sodium triacetoxyborohydride ("STAB") to form the amine ethyl 4-[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate. In a second step, a urea is formed in a reaction of the amine with chlorosulfonyl isocyanate (CSI), typically in the presence of H_2O and THF. In a third step, the urea is cyclized in the presence of a palladium catalyst. Typically, the urea is reacted in the presence of $NaHCO_3$, *i*-PrOH, $Pd(OAc)_2$ and bis-(diphenylphosphino)butane (dppb) to obtain the cyclic urea.

In a further ethyl carbamate deprotection step, the bis-HCl salt **3** may be accessed directly by treatment of the carbamate with concentrated hydrochloric acid followed by precipitation from i-PrOH. Alternatively, the cyclic urea may be reacted in the presence of NaOH and EtOH and water, followed by HCl to obtain the pyridine heterocycle bis-HCl salt **3**. In this alternative procedure, other bases or combinations of bases including LiOH and KOH may be used in this final step, and other acceptable salt forms may be made by substituting acids, including HBr, HI, H_2SO_4, HNO_3 and other acids, for HCl.

As described above and in the Examples which follow, this ACP route comprises four synthetic steps and features a reductive alkylation, primary urea formation using chlorosulfonyl isocyanate, Pd-catalyzed cyclization of the primary urea and hydrolysis of the ethyl carbamate. The starting materials/reagents for the ACP route are significantly less expensive than those required for the DAP route and all the steps are high yielding.

Thus, in one aspect of the invention provides a process for the preparation of the intermediate 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride, **3**, comprising the steps of:

(1) reacting 3-amino-2-chloropyridine with C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate, in the presence of trifluoroacetic acid and sodium triacetoxyborohydride to form C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(2) reacting the C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with chlorosulfonyl isocyanate to form C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(3) reacting the C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate in the presence of NaHCO3, Pd(OAc)2 and bis-(diphenylphosphino)butane to form C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate;

(4) reacting the C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate with HCl to form 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride.

In another aspect, the invention provides a process for the preparation of the intermediate which is an acid salt of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, comprising the steps of:

(1) reacting 3-amino-2-chloropyridine with C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate, in the presence of trifluoroacetic acid and sodium triacetoxyborohydride to form C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(2) reacting the C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with chlorosulfonyl isocyanate to form C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(3) reacting the C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate in the presence of NaHCO3, Pd(OAc)2 and bis-(diphenylphosphino)butane to form C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate;

(4) reacting the C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate with a strong acid to form an acid salt of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine.

In yet another aspect of the invention there is provided a process for the preparation of an acid salt of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine, comprising the steps of:

(1) reacting 3-amino-2-chloropyridine with C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate, in the presence of trifluoroacetic acid and sodium triacetoxyborohydride to form C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(2) reacting the C_{1-4}alkyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with chlorosulfonyl isocyanate to form C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(3) reacting the C_{1-4}alkyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate in the presence of NaHCO3, Pd(OAc)2 and bis-(diphenylphosphino)butane to form C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate;

(4) reacting the C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate with a strong base, followed by a strong acid, to form an acid salt of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine.

An additional embodiment of the invention provides a process for the preparation of the intermediate 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride, 3, comprising the steps of:

(1) reacting 3-amino-2-chloropyridine with ethyl 4-oxo-1-piperidinecarboxylate, in the presence of trifluoroacetic acid and sodium triacetoxyborohydride to form ethyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(2) reacting the ethyl 4[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with chlorosulfonyl isocyanate to form ethyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(3) reacting the ethyl 4[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate in the presence of NaHCO3, Pd(OAc)2 and bis-(diphenylphosphino)butane to form ethyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate;

(4) reacting the ethyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate with HCl to form 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride.

The invention is not limited to specific embodiments described in this application, and in fact includes additional features not expressly described above, including but not limited to the use of particular solvents and reaction conditions, the use of particular reagent forms (including neutral forms of intermediates 2 and 3, and salt forms other than HCl salt forms), and the use or no-use of particular separation or isolation techniques, and other features. For instance, one skilled in the art could readily alternate reaction conditions employing alternates to the recited trifluoroacetic acid, sodium triacetoxyborohydride, NaHCO3, Pd(OAc)2, bis-(diphenylphosphino)butane and other features.

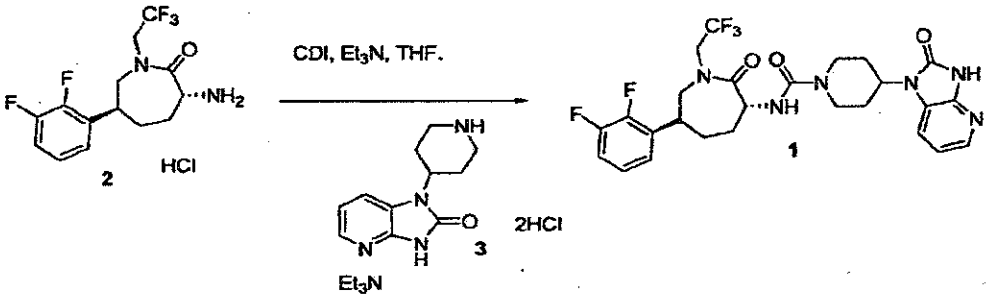
Several abbreviations, acronyms and other shorthand is presented herein. Although these terms are known to those skilled in the art, presented below is a table summarizing these terms:

IPAc	isopropylacetate
IPA	ispropanol
nHexLi	n-hexyl lithium
THF	tetrahydrofuran
BOC	*tert*-butyloxycarbonyl
CDI	1,1'-carbonyldiiidazole
MTBE	Methyl tert-butyl ether
tol	toluoyl or toluene
dppe	bis-(diphenylphosphino)ethane
dppb	bis-(diphenylphosphino)butane
DMAc	dimethylacetamide
TFA	trifluoroacetic acid
ACP	3-amino-2-chloropyridine
STAB	sodium triacetoxyborohydride

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Example 1

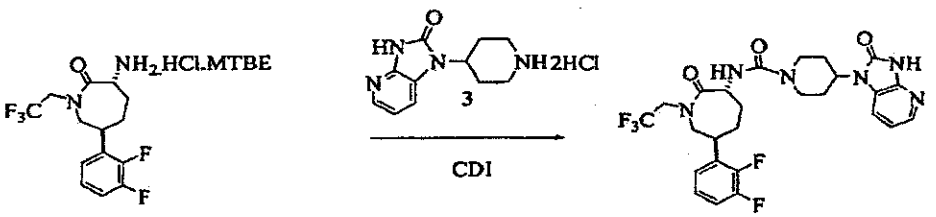
***N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide**



To a 12 L 4 necked flask equipped with overhead stirrer, thermocouple and nitrogen inlet was charged Caprolactam HCl salt **2** - MTBE solvate (412 g corrected as HCl salt; MTBE solvate typically 78-79 wt % HCl salt) . THF was then added at room temperature (4.1 L; 10 mL/g) followed by triethylamine (194 ml; 1.2 eq). The slurry was aged at room temperature. To a separate 22 L 4 necked flask equipped with overhead stirrer, thermocouple and nitrogen inlet was charged CDI (233 g; 1.25 eq) and THF (2.3 L; 10 ml/g relative to CDI). The solution was aged at room temperature. The caprolactam slurry solution was added to the CDI solution over 1 – 1.5 h at room temperature then aged at room temperature over 1 hour after which the reaction was assayed for conversion to the caprolactam acyl imidazole intermediate (>98.5 LCAP conversion). The piperidine heterocycle **3** (418 g; 1.25 eq) was then added followed by Et_3N (419 mL; 2.6 eq). The slurry was heated to 60 °C and held overnight at that temperature. HPLC assay showed 97.4 LCAP conversion. Water was then added (190 mL; ~ 3 vol % relative to THF) and reaction mixture aged at 60 °C for an additional 2.5 hours after which LC assay showed 99.8 LCAP conversion. The reaction mixture was then cooled to 15 °C then quenched with MTBE (3.1 L; 7.5 ml/g) and washed with 10 % (w/w) aq citric acid soln (4 x 2L; 5 ml/g). The organic layer was then assayed for imidazole and piperidine acyl imidazole impurities (<0.2 LCAP) The organic layer was then washed with 5 % (w/w) aq sodium bicarbonate solution (2 L; 5 ml/g) then water (2L; 5 ml/g) then passed through an inline filter to give 620 g assay of desired product. (95.3 % assay yield, 98 LCAP purity).

Example 2

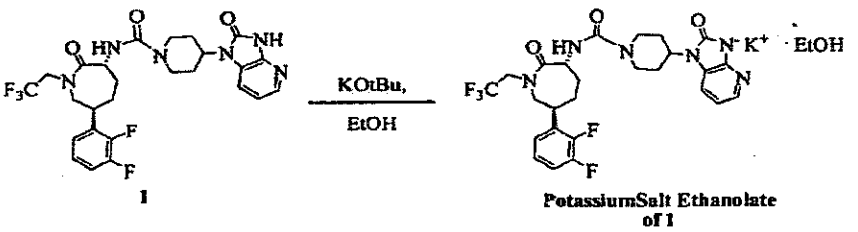
***N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide**



Caprolactam **2**(8.23 kg ≡ 5.60 kg caprolactam HCl salt based on 68 wt% assay)) was charge to an inerted vessel A with THF (66.4 L) and triethylamine (1.90 kg). A vessel B was charged with CDI (3.163 kg) and THF (30 L). The contents of vessel A were transferred to vessel B over 1.5h and the mixture in vessel B aged for 1h. At that point HPLC analysis showed the formation of caprolactam acylimidazole to be complete. The piperidine heterocycle **3** (5.0 kg) was charged to vessel B followed by triethylamine (4.12 kg). The batch was heated to 60°C and aged overnight when HPLC analysis showed the coupling was complete (<0.2 LCAP caprolactam-CDI adduct remaining). MTBE (49 l) and 10% aqueous citric acid (29 l) were added and the phases separated. The organic phase was washed again with 10% aqueous citric acid (29 L) and then with 5% $NaHCO_3$ solution (2 x 28 L). The pH of the last aqueous phase was 9 at that point. The organic phase was washed with DI water (27 L) and the MTBE solution was assayed for compound **1**, with the assay yield of neutral compound **1** equal to 8.49 kg, 96.0%. The HPLC assay also showed still 1.0 LCAP of the N-acylimidazole adduct remaining. Therefore, the MTBE solution was washed again with 10% aqueous citric acid (2 x 29 L), 5% aqueous $NaHCO_3$ (2 x 28 L) and water (27 L). HPLC assay of the MTBE solution was performed again. Assay yield neutral 454 = 8.27 kg, 93.5%, 98.9 LCAP, <0.1 LCAP N-acylimidazole adduct.

Example 3

***N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, potassium salt ethanolate**

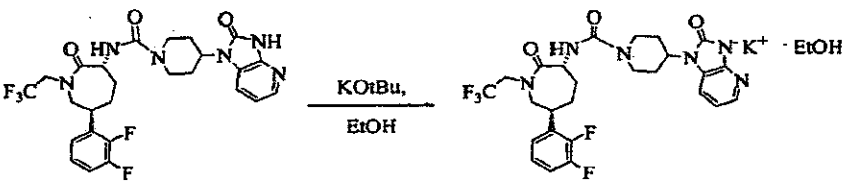


1 PotassiumSalt Ethanolate of 1

The MTBE solution of compound 1 (8.27 kg) was charged to an inerted vessel through a 0.1μm cartridge filter and concentrated down to 30 L using partial vacuum and keeping T<40 °C. Ethanol (116 L) was charged and the solution concentrated down to 30 L again under vacuum at <40 °C. Ethanol (116 L) was added and the solution analyzed for residual THF/MTBE content (none detected). Potassium *tert*-butoxide (1.720 kg) was charged as a solid to the vessel and the mixture warmed up to 45°C to dissolve all solids. The batch was then concentrated down to a final volume of 58 L (7 ml/g based on neutral 454) at <40°C. The resulting slurry was left cooling to room temperature overnight before filtering. The filter cake was washed with cold ethanol (25 L) and the solid dried under vacuum at 40 °C. The solid was de-lumped using a co-mill. Yield = 7.97 kg, 84%.

Example 4

***N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, potassium salt ethanolate**

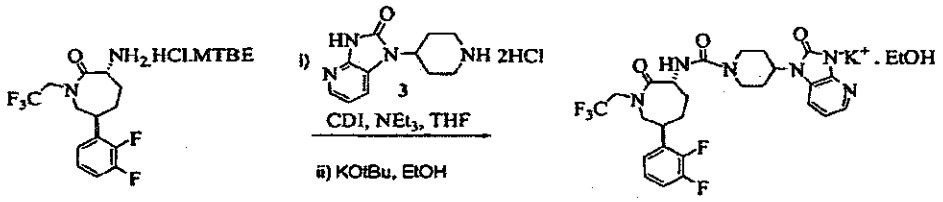


1 PotassiumSalt Ethanolate of 1

A 250 mL, 3-neck round bottom flask was equipped with a mechanical stirrer and claisen adapter with nitrogen inlet and thermocouple. Compound **1** (12.49 g) and punctilious ethanol (165 mL) were charged to the vessel. The suspension was warmed in a 60 °C oil bath and the suspension agitated. All the solids dissolved and a homogeneous solution was obtained when the internal temperature reached 38 °C. The temperature of the oil bath was reduced to 50 °C and the internal temperature was brought to 44 °C. The potassium *tert*-butoxide (2.72 g of 95% pure material) was then charged (slight exotherm to 46 °C observed). The resulting solution was then seeded with authentic Compound **1** potassium-salt ethanolate (20 mg). The temperature on the oil bath was reduced to 40 °C and the batch was aged about 1 hr. The heating on the oil bath was turned off and the suspension was cooled to 25 °C over about 1 h. The batch was then cooled in an ice bath to <5 °C and aged about 2 h. The batch was filtered through a medium porosity sintered funnel and the cake dried under vacuum and nitrogen tent until a constant weight was obtained or until the amount of residual EtOH present by NMR (DMSO-d6) was about 80 mol% relative to Compound **1**. The Compound **1** potassium-salt (11.15) was obtained as a tightly bound ethanol solvate in 78% yield (99.4 LCAP, 99.6 % *ee*).

Example 5

***N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, potassium salt ethanolate**

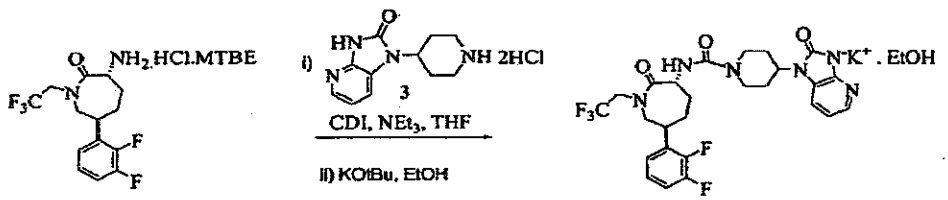


Caprolactam HCl salt **2** (30 g ≡ 20.4 g caprolactam HCl salt based on 68 wt% assay)) was charge to an inerted flask A with THF (240 ml) and triethylamine (6.91 g). To flask B was charged CDI (11.53 g) and THF (110 ml). The contents of vessel A were transferred to vessel B over 50 minutes and the mixture in vessel B aged for 1h. At that point HPLC analysis showed the formation of caprolactam acylimidazole to be complete. Piperidine heterocycle 3 (18.2g) was charged to vessel B followed by triethylamine (15.0 g). The batch was heated to 60°C and aged overnight when HPLC analysis showed the coupling was complete (<0.2 LCAP caprolactam-CDI adduct remaining). MTBE (180 ml) and 10% aqueous citric acid (105 ml) were added and the phases separated. The organic phase was washed again with 10% aqueous citric acid (105 ml) and then with 5% $NaHCO_3$ solution (2 x 100 ml). The pH of the last aqueous phase was 9 at that point. The organic phase was washed with DI water (100 ml) (5 ml saturated aqueous brine added to give good phase separation). HPLC assay of the MTBE solution gave an assay yield of neutral Compound 1 of 31.95 g, 99.1%, 98.8 LCAP. The MTBE solution of neutral Compound 1 (31.95 g) was concentrated down to low volume using partial vacuum and keeping T<40 °C. Ethanol (240 ml) was charged and the solution concentrated to low volume again under partial vacuum at <40 °C. Ethanol (116 L) was added to bring the volume of the solution to 420 ml and the solution assayed for neutral Compound 1: Result: 30.3 g, 53.5 mmol. Potassium *tert*-butoxide (6.3 g) was added and the mixture warmed to 45°C to dissolve all the solids. The solution was then concentrated down to a final volume of 210 ml (7 ml/g based on neutral 454) at <40°C. The resulting slurry was cooled to room temperature for 2 hours and the solid

collected by filtration. The filter cake was washed with cold ethanol (100 ml) and the solid dried under vacuum at 40 °C. Yield = 30.2 g, 87%.

Example 6

***N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide, potassium salt ethanolate**



Potassium Salt Ethanolate of 1

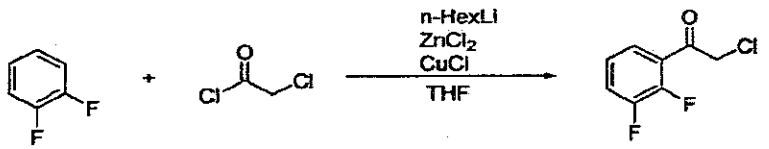
Caprolactam HCl salt **2** (8.23 kg ≡ 5.60 kg caprolactam HCl salt based on 68 wt% assay)) was charge to an inerted vessel A with THF (66.4 L) and triethylamine (1.90 kg). To vessel B was charged CDI (3.163 kg) and THF (30 L). The contents of vessel A were transferred to vessel B over 1.5h and the mixture in vessel B aged for 1h. At that point HPLC analysis showed the formation of caprolactam acylimidazole to be complete. The Piperidine heterocycle **3** (5.0 kg) was charged to vessel B followed by triethylamine (4.12 kg). The batch was heated to 60°C and aged overnight when HPLC analysis showed the coupling was complete (<0.2 LCAP caprolactam-CDI adduct remaining). MTBE (49 l) and 10% aqueous citric acid (29 l) were added and the phases separated. The organic phase was washed again with 10% aqueous citric acid (29 L) and then with 5% $NaHCO_3$ solution (2 x 28 L). The pH of the last aqueous phase was 9 at that point. The organic phase was washed with DI water (27 L) The HPLC profile showed still 1.0 LCAP of the caprolactam N-acylimidazole adduct impurity remaining. The MTBE solution was washed again with 10% aqueous citric acid (2 x 29 L), 5% aqueous $NaHCO_3$ (2 x 28 L) and water (27 L). HPLC assay of the MTBE solution gave an assay yield of neutral Compound 1 of 8.27 kg, 93.5%, 98.9 LCAP, <0.1 LCAP caprolactam N-acylimidazole adduct. The MTBE solution of neutral Compound 1 (8.27 kg) was charged to a vessel through a 0.1μm

cartridge filter and concentrated down to 30 L using partial vacuum and keeping T<40 °C. Ethanol (116 L) was charged and the solution concentrated down to 30 L again under partial vacuum at <40 °C. Ethanol (116 L) was added and the solution analysed for residual THF/MTBE (none detected). Potassium *tert*-butoxide (1.720 kg) was charged as a solid to the vessel and the mixture warmed up to 45°C to dissolve all solids. The batch was then concentrated down to a final volume of 58 L (7 ml/g based on neutral 454) at <40°C. The resulting slurry was left cooling to RT overnight before filtering. The filter cake was washed with cold ethanol (25 L) and the solid dried under vacuum at 40 °C. Yield = 7.97 kg, 84%.

Example 7

(3*R*,6*S*)-3-Amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one

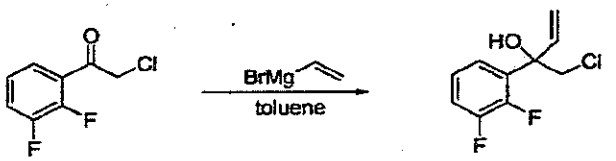
Step 1: 2-Chloro-1-(2,3-difluorophenyl)ethanone



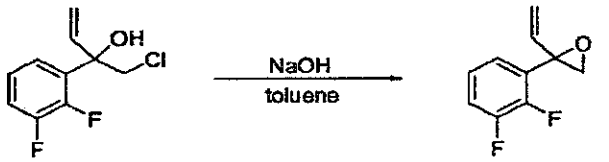
To a 5 L 4-necked round bottom flask was charged 1,2-difluorobenzene (130.0 g) and dry THF (1.3 L). This solution was cooled to < -60 while stirring under nitrogen. To this was added n-hexyllithium (455 mL of 2.5 M/hexane) dropwise such that T < -60 (~ 15 minute addition). The solution quickly turned into a stirrable slurry, which was aged for 1 hour cold. To this was added zinc chloride (2.3 L of 0.5 M/THF) such that T < -60 and the slurry quickly became a homogeneous solution. This was warmed to 0 °C followed by the addition of copper(I) chloride (11.3 g) and chloroacetyl chloride (142 g) such that T < 5 °C. The reaction was assayed after 20 minutes and judged complete by HPLC. The reaction was quenched with 1N HCl (2 L) and then the two phase system was transferred to a seperatory funnel and diluted with IPAc (2 L). The aqueous was cut and the organic washed again with 1N HCl (2 L) followed by 1N NH_4OH (2 x 2 L) and finally with water (2 L). The organic was concentrated to an oil. Assay yield = 78%. The oil is then diluted with heptane (800 mL - does not all go into solution) and stirred while cooling to – 30 °C. During cooling the oil turns over to a crystalline solid. The slurry is aged 1

hour at -30 °C, filtered and washed with cold heptane. Desired product isolated in 71 % yield (154 g).

Step 2: 2-(2,3-difluorophenyl)-2-vinyloxirane

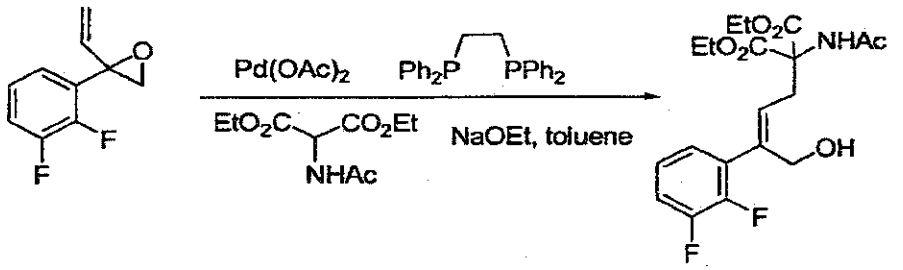


A solution of chloro acetophenone (40 g) in dry toluene (400 mL) was cooled to T < -60 while stirring under nitrogen. To this was added vinyl magnesium bromide (420 mL of 0.8 M in THF) dropwise such that T < -25 °C. After complete addition the reaction is warmed to 0 degrees and assayed for completion. The reaction is quenched with 1N HCl (250 mL) and transferred to a seperatory funnel and the aqueous layer cut. The organic is washed again with 1N HCl (250 mL) followed by saturated sodium bicarbonate (250 mL) and water (250 mL). The organic is concentrated to an oil and carried forward directly.



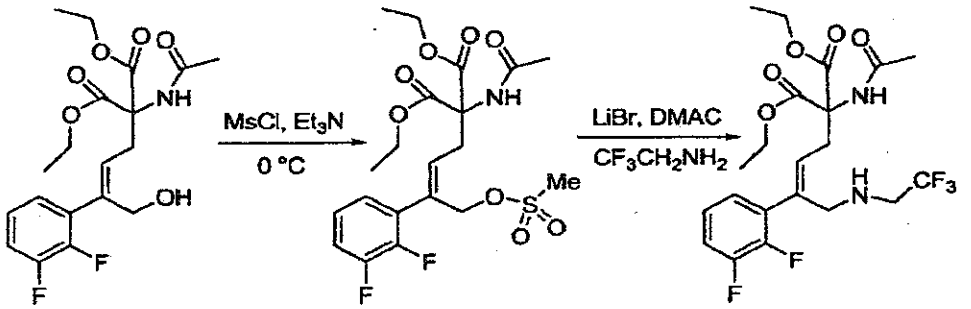
To a solution of tertiary alcohol (210 mmol) in toluene (400 mL) is added 1N NaOH (400 mL) and the two-phase system agitated for 4 hours at room temperature. The organic layer is assayed by HPLC for completion. At end of reaction the aqueous layer is cut and the organic washed with water (400 mL). The organic is concentrated/azeotropically dried in vacuo and used for the next step. Typical assay yield over both steps is 89 %.

Step 3: N-[(3Z)-4-(2,3-difluorophenyl)-5-hydroxy-1,1-dipropionylpent-3-en-1-yl]acetamide



A 1 liter 3-necked round bottom flask equipped with a vacuum/N2 Inlet, temperature probe, addition funnel and septa was charge with $Pd(OAc)_2$ (392 mg, 1.75 mmol, 2 mol%), DPPE (835 mg, 2.09 mmol, 2.4 mol%) , N-acetodiethyl malonate (43.8 g, 201 mol, 1.15 equiv), NaOEt (1.20 g, 17.5 mmol, 10 mol%), and flushed with N_2. The addition funnel was charged with the substrate vinyl epoxide (33.6 g, 174.8 mmol) in 100 mL of toluene (KF < 300 ppm). To the reaction flask was added 500 mL of toluene (< 300 ppm) and the resulting mixture flushed with N_2 and stirred at room temperature (20-25°C) for 10 min. The vinyl epoxide solution was added over 5 min and the resulting mixture stirred overnight(6-10 hrs) at room temperature (20-25°C).. Toluene (140 mL) and 1 N HCl (140 mL) was added to the flask and the biphasic mixture transferred to a separatory funnel. The organic layer was separated and washed with 140 mL of 1 N NaOH, 140 mL of brine and 140 mL of water. The final organic layer was treated with Darco-G60 (2-5 grams), stirred for 10 min, and filtered. The resulting solution was concentrated (T= 20-25 °C) to about 300 mL volume. The solution was heated to 40-45 °C and 600 mL of N-heptane added over 20 min. The slurry is stirred at 40-45 °C for 30 min and allowed to cool to room temperature overnight. The solution was filtered and the solids washed with 2 x 120 mL of 8:1 n-heptane:toluene. The solids were dried with vacuum and N_2 sweep(70 % yield).

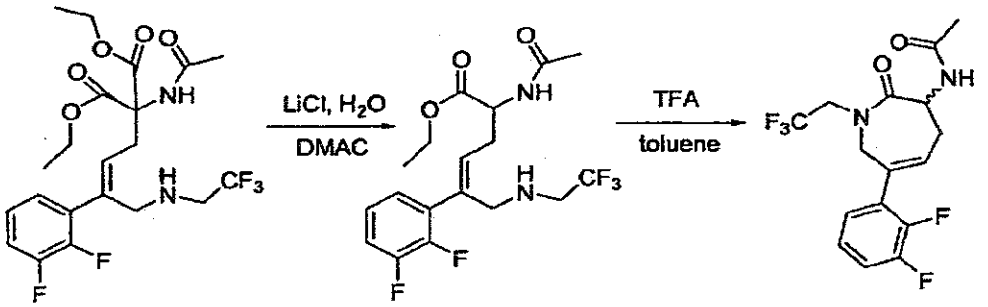
Step 4: N-{(3Z)-4-(2,3-difluorophenyl)-1,1-dipropionyl-5-[(2,2,2-trifluoroethyl)amino]pent-3-en-1-yl}acetamide



The compound of Step 3 (50.0 g, 125.2 mmol) in 400mL toluene (was treated with Et_3N (16.5g, 162.7 mmol) followed by a 25 mL toluene flush followed by MsCl (16.5 g, 162.7 mmol) in 120mL toluene followed by a 25 ml flush making sure the temperature did not exceed 3 °C . After a 30 min age, the slurry was treated with 250mL H_2O and then warmed to RT. The aqueous layer was drained away (a black rag layer is observed) and the organic phase washed with 1x200 mL 1N NaOH and 1x150 mL of 15 % NaCl solution. The solution was concentrated to ~150 mL and flushed with 300mL toluene. Addition of 375 mL of DMAC (KF ~400) afforded the solution ready for the next step .

To the orange solution was added $CF_3CH_2NH_2$ (37.2 g, 376 mmol, few degree temperature increase here) followed by LiBr (2.17g, 26 mmol) and the solution aged for 13 hours at 28-30 °C. The reaction was diluted with 250 mL IPAC and 150 mL H_2O. The aqueous layer was removed. The organic layer was washed with 150 mL 1N NaOH and 150 mL 15 % aqueous NaCl solution. Assay of the IPAC layer shows 92 % yield and the solution was concentrated to 150 mL volume and 375 mL DMAC added .

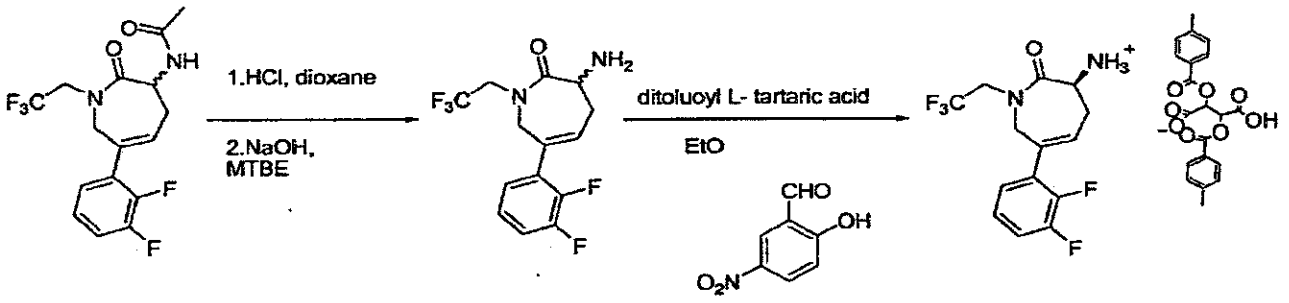
Step 5: N-[6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1H-azepin-3-yl]acetamide



To the DMAC solution of **6** (55 g, 114.49 mmol assay, 475 mL volume) was added LiCl (14.5g, 343.5 mmol) followed by H_2O (6.1 g, 343.5 mmol). The solution was aged at 113-115 °C for 12-14 hours (after 1 hour at 112 °C a white precipitate forms). After cooling to RT, 5g of Darco was added and the solution filtered through Solka-Floc. The filter cake was washed with 285 mL IPAC. The organic layer was split in half and cooled to 5-10°C. Each half was treated with 118.5 mL H_2O keeping the temperature ~15-20 °C. The aqueous was back extracted with 165 mL IPAC and the organic layer was washed with 220 mL 1N NaOH, 2 x220 mL 15% NaCl solution brine and 220 mL of water. The solvent was switched to toluene (450 mL volume, 45g assay).

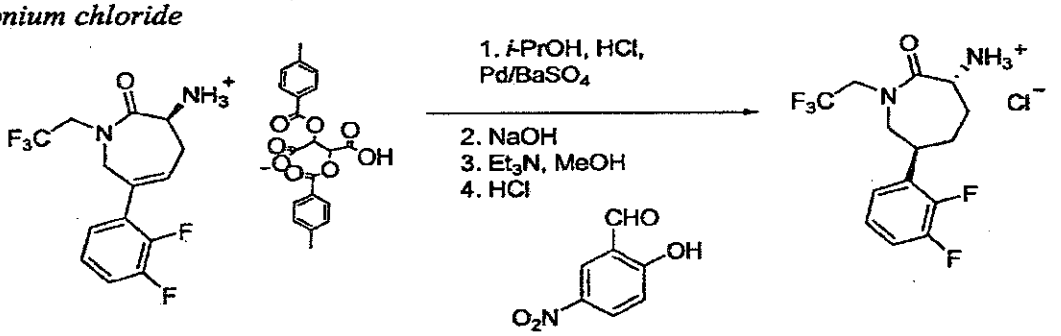
The toluene solution (45 g, 110 mmol of decarboxylated product) was treated with trifluoroacetic acid (143 mmol, 1.3 equiv. and a yellow oil separated from the toluene solution. The reaction is aged at 85-90 °C for 12-15 hours overnight under nitrogen. The solution was cooled to RT and then concentrated to 3 L/kg) based on starting material and diluted with IPAC (338 mL). The organic layer was washed with 1N NaOH (225 mL). This resulted in an emulsion, so the batch was charged with 10 wt % celite, filtered and the cake was washed with 180 mL IPAC. The aqueous phase was cut at this point. The organic layer was washed with 1N HCl (225 mL), 225 mL 1 % aqueous NaCl solution, and 5g Darco added. The solution was filtered through Solka-Floc, and the solution concentrated to 4L/kg (based on assay of product) and flushed with IPAC until KF<100. A total of 4 volumes of heptane was added and the slurry cooled to 0 °C. Filtration and washing with 0 °C 7:1 heptane:IPAC (150 mL) afforded the product as an off-white solid.

Step 6: (3S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1H-azepin-3-ammonium 3-carboxy-2,3-bis[(4-methylbenzoyl)oxy]propanoate (di-toluoyl tartrate salt)



To a 288 mL dioxane solution of the Step 5 compound (36 g, 99.4 mmol) was added 6 equiv of 3N HCL. The solution was heated at 85 °C for 12 hours. After cooling, the solution was diluted with 230 mL MTBE added and the pH adjusted to8-10 with 10N NaOH followed by 1N NaOH. After the phase cut, the aqueous was extracted with 230 mL MTBE and the combined organic layer washed with 390 mL 15% NaCl and assayed for product (25.4 g, 79.3 mmol, 80 % assay yield). The solution was concentrated to ~10 L/kg of amine and then solvent switched to IPA (~762 mL total volume). The KF of the solution was adjusted to 4000 ppm and then 2-hydroxy-5-nitrobenzaldehyde (7.9 mmol) was added followed by (-)-O,O'-di-toluoyl-L-tartaric acid (158.6 mmol) and the resulting slurry was aged at 65 °C for 130 hours. The slurry was then filtered and the solid washed with IPA.

Step 7: (3S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,7-tetrahydro-1H-azepin-3-ammonium chloride



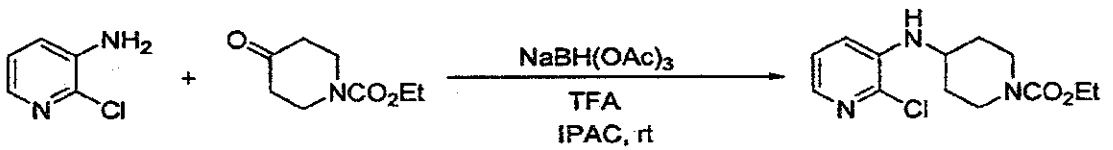
The compound of step 6 (10 g, 14.15 mmol) di-toluoyl tartrate salt was slurried in *i*-PrOH (93 mL). To this mixture was added 1N HCl (15.57 mL, 1.10 equiv) and the mixture became homogeneous. After sparging with nitrogen, 5% $Pd/BaSO_4$ (1.20 g, 4 mol%) was added and

hydrogenated at 80 psi of hydrogen for 20h, or until all consumed by HPLC. The solution was filtered through Solka Floc with MeOH (50 mL) to remove catalyst. The filtrate was concentrated to 2 mL/g and then diluted with MTBE (100 mL) and then 1N NaOH (80 mL). After the phase cut, the aqueous was back extracted with 70 mL of MTBE. The organic solution was washed with brine (70 mL) (HPLC assay for yield of cis form) and solvent switched to MeOH until <5% MTBE and KF ~1500ppm with a total volume of 45 mL and then treated with Et_3N (3.95 mL, 2 equiv. relative to cis form) and 2-hydroxy-5-nitrobenzaldehyde (237 mg, 10 mol% relative to cis form). The solution was stirred at room temperature for 20 hours which results in ~20:1 ratio of trans:cis forms of the title compound . The solution was diluted with MTBE (100 mL) and then 1N NaOH (80 mL) added. After the phase cut, the aqueous was back extracted with 70 mL of MTBE. The combined organics were then washed with 70 mL of brine, conc. to 25% volume and filtered. The organic solution was concentrated further and then MTBE was added until volume was 30 mL. To this was then added 15 mL of MeOH (KF ~1500ppm). After heating solution to 50 °C, 1% seed of the title copound was added followed by a 2 hour addition of 5N HCl in IPA (5.6 mL, 2.2 equiv. relative to cis form assay). This was then aged 1 hour at 50 °C and then cooled to room temperature over 3 hours. After aging overnight at RT, the slurry was filtered and washed with 3:1 MTBE:MeOH (2 x 15 mL). The cake was then dried 20h under vacuum at room temperature to give the title compound as an HCl salt • MTBE solvate in 85% yield (5.37 g, 99% ee,).

Example 8

2-Oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine

Step 1: Ethyl 4-[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate



To a 1 L three-neck RB-flask equipped with a mechanical agitator and temperature probe was charged 3-amino-2-chloropyridine (37.9 g, 0.294 mol, 100 mol%) and ethyl 4-oxo-1-piperidinecarboxylate (55.5 g, 0.324 mol, 110 mol%) followed by IPAC (500 mL). The mixture became homogeneous after 5 min agitation (16 °C). Trifluoroacetic acid (44 mL, 0.590 mol, 200

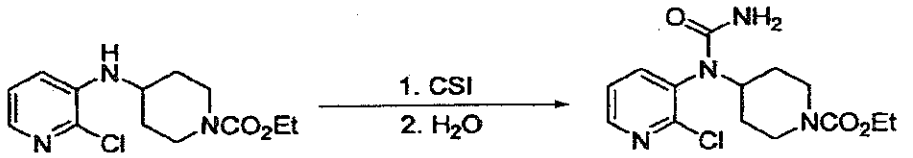
mol%) was charged to the mixture over 30 s, causing an increase in temperature to 25 °C (no cooling used). Sodium triacetoxyborohydride (75.0 g, 0.354 mol, 120 mol%) was added as a solid over 5 min and a further increase in temperature to 56 °C was observed. After 10 min agitation, the mixture was clear and homogeneous. LC analysis indicated consumption (< 0.5 A%) of 3-amino-2-chloropyridine and formation of the alkylated product. A solution of 10 wt% aqueous NaOH was added to the mixture at 50 °C over 10 min. When the pH of the mixture was 8-9, the phases were allowed to separate. The organic phase washed with brine (200 mL). The separated aqueous phase was 580 mL – 100 μL sample was diluted in 100 mL MeOH and LC analysis indicated 0.23g, 0.3% of product was present. The brine was assayed as above and contained negligible product. Azeotropic drying with IPAC was conducted at atmospheric pressure under constant volume conditions until the water content was < 500 ppm by KF titration. The solution was concentrated to a volume of 170 mL then THF (35 ppm H_2O, 230 mL) was added. This solution was used directly for the subsequent step. LC analysis gave 84 g, 101% AY of the desired reductively alkylated product and KF titration gave water content as < 500 ppm.

Step 1(alternate): Ethyl 4-[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate

To a 2 L three-neck Morton-type flask equipped with a mechanical agitator and temperature probe was charged 3-amino-2-chloropyridine and ethyl 4-oxo-1-piperidinecarboxylate followed by IPAC. The mixture became homogeneous after 5 min agitation (16 °C). Trifluoroacetic acid was charged to the mixture over 30 s, causing an increase in temperature to 26 °C (no cooling used). After 15 min age, a caplet of $NaBH_4$ (0.95 g, 0.025 mol) was added. The temperature was observed to increase to 28 °C over a 30 min period and the caplet dissolved completely within this time. This method of $NaBH_4$ addition was repeated, allowing each caplet to dissolve before adding the next, until a total of eight caplets had been added over 7 h. At this time, LC analysis indicated > 95% conversion of the 3-amino-2-chloropyridine. A solution of 10 wt% aqueous NaOH was added to the mixture at 30-40 °C (no cooling) over 10 min. When the pH of the mixture was 12-14, the phases were allowed to separate. The separated aqueous phase was 450 mL and LC assay indicated this contained 0.5 g, < 1.0% of product. The organic phase washed with brine then the separated organic phase was assayed. The separated brine wash was 275 mL and LC assay indicated this contained neglible product. The organic phase was 690 mL and LC assay indicated this contained 87.5 g, 97% AY of reductively alkylated product and 2.1 g, 5% of starting amine. The yellow organic phase was concentrated (45 °C bath temperature) to

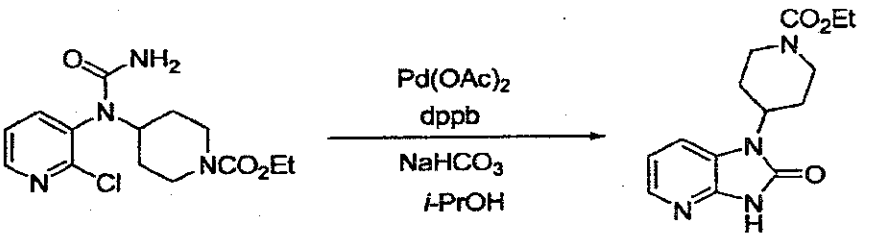
approximately one-third original volume. Fresh IPAC was added and this process was repeated until the water content was 110 μg/mL by KF titration. The solution was concentrated to a volume of 170 mL then THF (230 mL) was added. This solution was used directly for the subsequent step.

Step 2: Ethyl 4-[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate



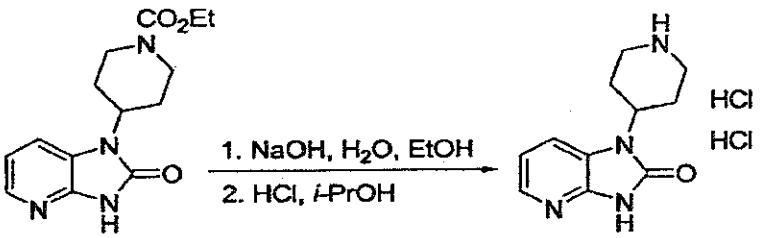
To a 1 L three-neck RB-flask equipped with a mechanical agitator and temperature probe was charged with THF (250 mL, KF 35 ppm H_2O) then chlorosulfonyl isocyanate (CSI) (30.7 mL, 0.353 mol, 120 mol%) was added at room temperature (negligible exotherm). The mixture was cooled to -10 °C using ice/MeOH. The solution of amine prepared above in Step 1 (83.42 g, 0.294 mol, 100 mol%) in THF : IPAC (~1:1) (400 mL, KF of this solution was 500 ppm) was added over a 20 min period via a dropping funnel. An exotherm was observed during this addition (max. temp. 2 °C). Upon completion of the amine solution addition LC analysis indicated consumption of the amine (< 1.0 A%) – sample was prepared by dilution in 0.1% H_3PO_4/MeCN (70:30) and rapid injection on the LC instrument indicated one major component. After 10 min, water (30 mL) was added dropwise over a 10 min period. A second exotherm was observed during the water addition (max. temp. 17 °C). The mixture was allowed to warm to rt and aged for 14 h. The pH at EOR was approximately 1. The hydrolysis was complete (< 0.5 A% intermediate) within 30 min of the water addition as monitored by LC analysis. The mixture was treated with 10% aq. NaOH until pH 8-9 and the separated organic phase was washed with brine (300 mL). The work-up was conducted at 50 °C to maintain solubility of the product. The separated aqueous volume was 500 mL - 100 μL sample was diluted in 100 mL of above sample diluent and LC analysis indicated 1.38 g, 1.4% of product was present. The brine was assayed as above and contained negligible product. Azeotropic drying with IPAC was conducted at atmospheric pressure under constant volume conditions until the water content was < 250 ppm by KF titration. The urea crystallized and the slurry was concentrated to ~ 5 volumes then allowed reach rt before the product urea was collected by filtration. The cake was rinsed with 2 bed volumes IPAC. After drying for 12 h at 50-60 °C under vacuum, the product urea was obtained as a white solid (81.41 g, 85% isolated yield, 96 wt%).

Step 3: Ethyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate



To a 500 mL three-neck Morton-type flask equipped with a mechanical agitator, reflux condenser and temperature probe was charged $NaHCO_3$ (25.21 g, 0.300 mol, 300 mol%), urea of Step 2, above (32.69 g, 0.100 mol, 100 mol%), and *i*-PrOH (KF 1415 ppm, 320 mL). The heterogeneous mixture was agitated and purged with N_2 using an M-fritted gas dispersion tube. After 1 h, the $Pd(OAc)_2$ (0.224 g, 0.001 mol, 1 mol%) and bis-(diphenylphosphino)butane (dppb) 0.854 g, 0.002 mol, 2 mol%) were added as solids and the N_2 purge continued for a further 30 min. The pink mixture was then heated to 83 °C (reflux) for 24 h. After this time, LC analysis of the yellow mixture indicated > 99.5 : 0.5 A% ratio of product to starting material. Atmospheric pressure distillation of the *i*-PrOH was initiated and continued until 200 mL *i*-PrOH distillate had been collected. IPAC (200 mL) and water (100 mL) were added and the temperature was maintained at 60 °C. After 30 min agitation, the phases were allowed to separate. The organic phase was clear yellow and the aqueous was colorless. The separated aqueous volume was 75 mL - 100 μL sample was diluted in 100 mL of MeOH and LC analysis indicated 0.03 g, 0.1% of product was present. The organic phase was washed with brine (3 × 75 mL). Azeotropic drying with IPAC was conducted at atmospheric pressure under constant volume conditions until the water content was < 150 ppm measured by KF titration. The product crystallized to produce a slurry at 90 °C. The slurry was concentrated to ~ 5 volumes and allowed to cool to rt before it was filtered and the cake was washed with 2 bed volumes IPAC. The solid was dried in a vacuum oven @ 50-60 °C under an nitrogen sweep for 16 h. A cyclic urea was obtained as a white solid (27.4 g, 94% isolated, 96 wt%).

Step 4: 1-piperidin-4-yl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride



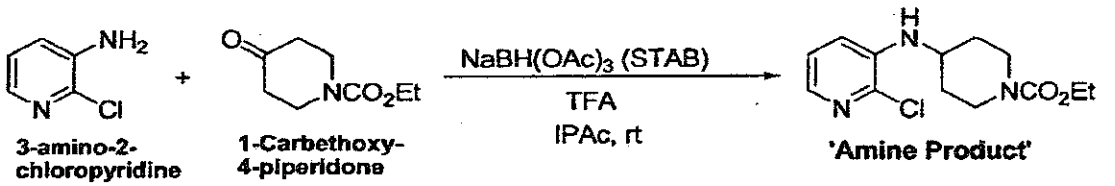
3

To a 100 mL three-neck RB-flask equipped with a mechanical agitator, reflux condenser and temperature probe was charged the cyclic urea made in Step 3, above (4.80 g, 16.48 mmol, 100 mol%) followed by EtOH (10 mL). To the resultant slurry was added aqueous NaOH (13 mL of 50 wt% solution diluted with 12 mL water, 246.0 mmol, 1500 mol%) and the mixture was heated to 82 °C (reflux) for 14 h. LC analysis indicated consumption (< 0.5 A%) of the cyclic urea and formation of the amine product **3** - sample was prepared by dilution in 0.1% H_3PO_4/MeCN (70:30). Water (25 mL) and *i*-BuOH (25 mL) were added and the mixture was agitated for 10 min then the phases were allowed to separate. The separated aqueous volume was 41 mL - 100 μL sample was diluted in 100 mL of above diluent and LC analysis indicated 0.26 g, 5% of product was present. The separated aqueous volume was 54 mL - 100 μL sample was diluted in 100 mL of above diluent and LC analysis indicated 4.13 g, 86% of product was present. Azeotropic drying with *i*-PrOH was conducted at atmospheric pressure under constant volume conditions until the water content was 150 ppm measured by KF titration. The volume was adjusted to 100 mL and the temperature allowed to reach 50 °C. HCl in *i*-PrOH (5-6 N, 20 mL, 0.100 mol, 600 mol%) was added, causing an immediate white precipitate. After cooling to rt, the slurry was filtered and the cake was rinsed with 2 bed volumes *i*-PrOH. The white solid was dried in a vacuum oven @ 50-60 °C under a nitrogen sweep for 24 h. The title pyridine heterocycle bis-HCl salt was obtained as a white solid (5.54 g @ 78 wt% giving 89% isolated yield, with the residual wt% consisting of NaCl).

Example 9

2-Oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine

Step 1: Ethyl 4-[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate



IPAc (369 kg) was charged to 300 gallon vessel and KF was determined to be 180 ug/mL). Next, 39.1 kg of 3-amino-2-chloropyridine (ACP) was charged to the vessel, followed a 5 kg IPAc sprayball flush and a 20 kg IPAc sprayball flush. 57.2 kg of 1-carbethoxy-4-piperidone was then pumped to the vessel followed by a 10 kg IPAc line flush. The mixture was aged 15 minutes to ensure ACP was in solution. Then, 68.6 kg trifluoroacetic acid was charged to the vessel followed by a 10 kg IPAc line flush. 79.7 kg STAB was then charged to the vessel over ~2.5 hrs, maintaining the temperature between 22-27°C. (Due to the generation of hydrogen from STAB reaction with residual water in the solvent, the vessel was vented to the atmosphere beginning with the addition of STAB until the excess STAB was quenched with NaOH.) After all of the STAB was charged to the vessel, a 5 kg IPAc PSL sprayball flush was charged to the vessel, followed by a 20 kg IPAc vessel sprayball flush. The mixture was aged for 30 minutes at 20-25°C.

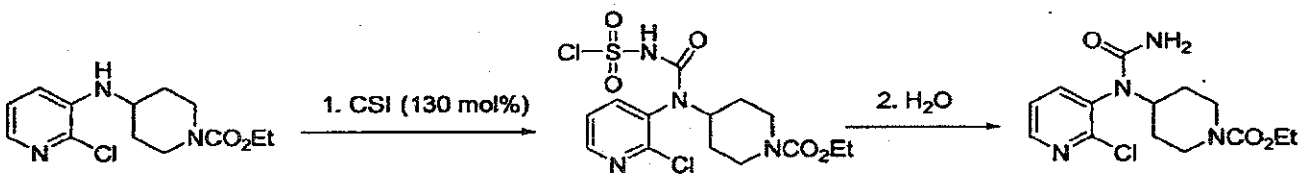
After confirming the reaction was complete, the batch was adjusted to a neutral pH by addition of 17wt% NaOH while recycling around a pH cart. The initial pH of the system was 2.1. After addition of 354.9 kg of 17wt% NaOH the pH of the batch was 9.7. The batch temperature during the pH adjustment was maintained between 20-25°C. The mixture was adjusted to a pH of 11 via addition of 16.7 kg 17wt% NaOH. Temperature was then raised to 55-60°C, agitated for 25 minutes, and settled for 1 hr. The aqueous waste layer (464.7 kg) was cut to a 500 gallon vessel.

To the mixture was then added 224 kg 15wt% NaCl followed by a 10 kg DI water line flush. The mixture was maintained at 55-60°C during a 15 minute age and 45 minute settle. The waste, aqueous layer (248.3 kg) was cut to a 500 gallon vessel. The amine product in IPAc is stable after the cuts and was aged overnight prior to drumming. The drummed 'amine product in wet

IPAc' solution weighed 530.1 kg. The concentration of the batch after the cuts was measured as 16wt%, correlating to 84.8 assay kg and a ~100% yield (target yield 95-100%, see mol balance).

343 kg of 'amine product in wet IPAc' was charged to a 200 gallon vessel followed by a 50 kg IPAc line flush. The batch in ST-30F was then concentrated to ~210 L (~2.5 volumes vs. amine product), and the remainder of the 'amine product in wet IPAc' (187 kg) was fed to the vessel to maintain a constant volume distillation. After the entirety of the 'amine product in IPAc' had been fed to the vessel, the batch was azeotropically dried via constant-level feed and bleed distillation with dry IPAc. Conditions during the distillation were 160-200 mmHg vacuum and 47-54°C. About 410 L (~2 batch volumes) of IPAc was fed to the vessel during the feed and bleed. After breaking vacuum on the distillation, with the temperature maintained at 40-50°C, 183 kg of dry monoglyme (2.5 volumes vs. amine product) was charged to the vessel to bring the volume to ~420 L (~ 5 volumes vs amine product). The batch in approximately 50:50 v:v IPAc:DME was then cooled to 20-25°C. The batch was a slurry at room temperature, which was aged and stirred 144 hrs until used in step 2.

Step 2: Ethyl 4-[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate



'Amine Product' of Step 1
2
$C_{13}H_{18}ClN_3O_2$
283.75

Reaction Intermediate
3

Urea Product
4
$C_{14}H_{19}ClN_4O_3$
326.78

After purging a 300 gallon vessel, 220 kg of Monoglyme (DME) was charged to the vessel. The solvent was sampled to check KF. After the monoglyme was confirmed as dry, the contents of the vessel were cooled to -12 to -14°C. After cooling the vessel, 55.5 kg of chlorosulfonyl isocyanate (CSI) was pumped to the vessel, followed by a 10 kg monoglyme line flush. The CSI/monoglyme mixture was then cooled to -16°C and the 'amine product' slurry was charged to the vessel over 95 minutes. The batch temperature in the vessel during the reaction remained

below -5°C. 30 kg of monoglyme was charged to the vessel via the vessel sprayball as a follow flush. The mixture was then aged 15 minutes at -8 to -10°C.

After the CSI reaction was confirmed as complete, 31 kg DI water was charged to the vessel over the course of 20 minutes. The temperature rose from -12°C to 14°C and the mixture turned into a slurry. The mixture was then warmed to 20 – 25°C and aged for 30 minutes prior to sampling for end of hydrolysis reaction.

After confirming the reaction was complete, the mixture was adjusted to a neutral pH by addition of 17wt% NaOH while recycling around a pH cart. The initial pH of the system was 0.4. After addition of 274.1 kg 17wt% NaOH, pH was 9.5. Temperature during the pH adjustment increased from 22°C to 58°C with the addition of NaOH. The batch temperature during the extraction was maintained at 55-60°C. After pH reached 9.5 the mixture was agitated for 15 minutes and settled for 45 minutes. The aqueous waste layer (281.1 kg) was removed. 215 kg 15wt% NaCl was added to the vessel, followed by a 10 kg DI water line flush. The batch was maintained at 55-60°C during the 15 minute age and 45 minute settle. The aqueous waste layer (267.8 kg) was removed and the vessel cooled to 15 – 25°C.

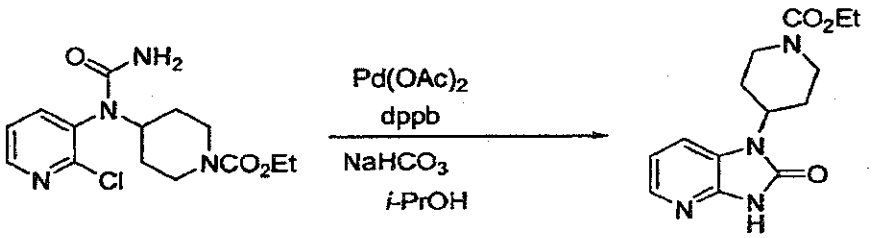
The mixture was concentrated via distillation to ~422 L (~5 volumes vs. starting material). The distillation conditions during the concentration were 200 mmHg vacuum and 45-46°C. After the volume reached ~422 L, the mixture was solvent switched to IPAc via constant-level feed and bleed distillation using 1299 kg IPAc (3.5 bed volumes). Conditions during the feed and bleed distillation were 167 – 200 mmHg vacuum and 46-51°C. Crystallization was observed throughout this process. The constant level feed and bleed distillation continued until the full 3.5 bed volumes of IPAc had been distilled. The mixture was then cooled to 20-25°C . The supernatant concentration of urea product was 5 g/L (target - 5 g/L) and the batch KF was < 100 ug/mL.

Due to filter volume constraints, the batch was filtered in two drops. The slurry and the filter were both maintained at 20-25°C throughout the filtration. The first drop filtered in ~10

minutes; the filtration flux was ~2600 L/(m^2*hr) and the cake height was 22 cm. The cake was washed with a 100 kg IPAc displacement wash, followed by a 100 kg IPAc slurry wash, followed by a final 100 kg IPAc displacement wash. The cake was then blown with nitrogen for 40 minutes prior to sampling for cake purity. The cake was blown with nitrogen for an additional 90 minutes prior to discharging the cake into a stainless steel Heinkel can. 36.6 kg of urea product wetcake was collected in the first drop. The second drop was filtered in ~15 minutes; the filtration flux was ~1900 L/(m^2*hr) and the cake height was 30 cm. The cake was washed with an 80 kg IPAc displacement wash, followed by an 80 kg IPAc slurry wash, followed by a final 80 kg IPAc displacement wash. The cake was then blown with nitrogen for 20 minutes prior to sampling for cake purity. The cake was blown with nitrogen for an additional 35 minutes prior to discharging the cake into a stainless steel Heinkel can. 59.3 kg of urea product wetcake was collected in the second drop.

The urea product wetcake was transferred to tray dryer and dried with full vacuum and 35°C on the jacket for 58 hours prior to sampling for solvent content. A loss on drying sample indicated < 0.2wt% solvent remaining. Tg assay confirmed the solvent content of the cake was < 0.2wt% (target < 0.5wt% solvent). A total of 84.0 physical kg of urea product was packaged (97.5 wt%; 81.9 assay kg). The yield was 84.1% based on converting 84.5 assay kg of amine to 81.9 assay kg urea product.

Step 3: Ethyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate



Urea Product, Step 2

Ethyl Carbamate

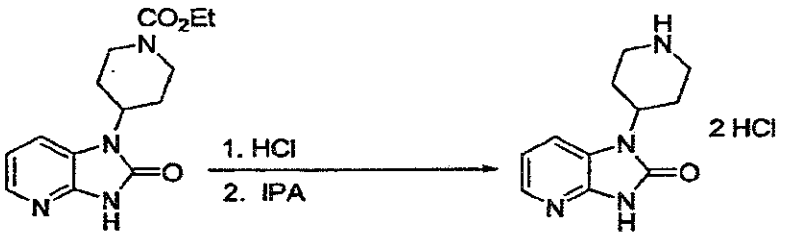
After purging a 300 gallon vessel, 585 kg of isopropyl alcohol was charged to the vessel. The solvent was then sampled for KF. The KF of the isopropyl alcohol was 237 ppm. After the KF measurement, 0.67 kg of water was charged to the vessel followed by 62.8 kg of sodium bicarbonate and 83.4 kg of the urea product. Isopropyl alcohol (5 kg) was then charged to the vessel spray ball cap, followed by a 15 kg charge of isopropyl alcohol to the vessel spray ball. The vessel was then pressure purged with nitrogen 7x using 20-25 psig and venting < 1 psig between purges. After the pressure purges, 2.2 kg of 1,4-bis(diphenylphosphino butane) and 0.56 kg of palladium (II) acetate were charged to the vessel. Next, 5 kg of degassed isopropyl alcohol was charged to the vessel spray ball cap and 15 kg of degassed isopropyl alcohol was charged to the vessel spray ball. The isopropyl alcohol used for the follow-flush was degassed with nitrogen purges in an agitated blowcan prior to the charge to the vessel. Following the isopropyl alcohol follow-flush, the vessel was pressure purged with nitrogen 7x using 20-25 psig and venting < 1 psig between purges. The heterogeneous reaction mixture was then heated to 83 °C and aged for 24 hr. After the reaction age, the batch was cooled to 50 °C.

The mixture was concentrated via distillation to ~300 L (~3.7 volumes vs. urea product). The temperature during the distillation ranged from 80-83 °C, and the pressure was 760 mmHg. After the batch volume reached ~300 L, 439 kg isopropyl acetate and 249 kg water were charged to ST-20A while maintaining the batch temperature between 60-65°C. The mixture was agitated for 15 min, allowed to settle for 30 min, and the aqueous layer (225 kg) was removed.

The mixture was concentrated via distillation to ~410 L (~5 volumes vs. urea product). The temperature and pressure during the distillation were 75-89 °C and 760 mmHg, respectively. Once volume reached ~410 L, the mixture was azeotropically dried with isopropyl acetate (1091.4 kg, ~3 bed volumes) via a constant-volume distillation. The ethyl carbamate product crystallized throughout the distillation. After ~3 bed volumes of isopropyl acetate had been fed/bled during the constant volume distillation, the mixture was cooled to 50 °C and KF of the sample was determined to be 200 ppm (target <600 ppm). The batch was then cooled to 20 °C, aged for 3 hr. Concentration of the ethyl carbamate product was 11 g/L (target < 6 g/L). The batch was aged for ~14 hr. Concentration of the ethyl carbamate product was 9 g/L.

The batch was filtered and washed in one drop and the cake height was ~30 cm. Both the slurry and the filter were maintained at 20-25°C throughout the filtration. The cake was displacement washed twice with isopropyl acetate; 215 kg (wash 1) and 98.8 kg (wash 2) were used for the wash sequence. The wet-cake was then blown with nitrogen for ~1 hr, with LC assay of the wet-cake indicating LCAP > 98% (target LCAP >98%). The ethyl carbamate product wet-cake was dried under full vacuum at 35°C for 85 hrs. TG analysis of a dry-cake gave 0.1 wt% loss up to 138 °C. A total of 66.7 physical kg of ethyl carbamate product was packaged (95.3 wt%; 63.6 assay kg). The yield was 88% based on converting 81.3 assay kg of urea to 63.6 assay kg ethyl carbamate product.

Step 4: 1-piperidin-4-yl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one dihydrochloride



ethyl carbamate **pyridine heterocycle bis-HCl**

After purging a 200 gallon vessel, 66.7 kg of ethyl carbamate was charged through the manway. The vessel was then purged and 136.7 kg of 12.1 N HCl was charged through the vessel spray ball. The reaction mixture was then heated to 82 °C and aged for 24 hr. After the reaction age, the batch was cooled to 50 °C. LC assay determined 0.1 LCAP ethyl carbamate.

Isopropyl alcohol was charged to the vessel in two segments while maintaining the batch temperature between 50-55 °C. The first segment, 65.4 kg of isopropyl alcohol, was charged over 3 hr. The second segment, 615 kg of isopropyl alcohol, was also charged over 3 hr. After the isopropyl alcohol charges were complete, the batch was cooled to 20 °C, aged for 10 hr. LC assay indicated the supernatant concentration of the pyridine heterocycle bis-HCl product was 0.78 g/L.

After confirming the supernatant concentration, the batch was filtered and washed in one drop with an average flux of ~2300 LMH. The cake height was ~30 cm. Both the slurry and filter were maintained at 20-25°C throughout the filtration. A displacement/slurry/displacement wash sequence was then used to wash the cake; 105 kg of isopropyl alcohol was used for each wash. The wet-cake was then blown with nitrogen for ~1 hr. LC assay of the wet-cake indicated LCAP > 99%. The Pd level in the isolated wet-cake was 7 ppm. The cake was blown with nitrogen for an additional 0.5 hr prior to drying. The pyridine heterocycle bis-HCl product wet-cake was dried under full vacuum at 50°C for ~14 hr. TG analysis of the dry-cake sample gave 0.2 wt% loss when the sample was heated from 24 °C -160 °C. KF results gave 1.2 wt% water (target < 0.5 wt%). The wet-cake was dried for an additional 4 hr in FD-80A under full vacuum with 50 °C on the jacket. KF results gave 0.04 wt% water and residual solvent analysis by GC gave 0.14 wt% IPA , isopropyl acetate was non detectable.

A total of 64.7 physical kg of pyridine heterocycle bis-HCl product was obtained (96.6 wt%; 62.5 assay kg). The yield was 98% based on converting 63.9 assay kg of ethyl carbamate to 62.5 assay kg pyridine heterocycle bis-HCl product.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A process for the preparation of an acid salt of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine , said process comprising the steps of:

(1) reductively alkylating 3-amino-2-chloropyridine with C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate to form C_{1-4}alkyl 4-[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(2) reacting the C_{1-4}alkyl 4-[(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with chlorosulfonyl isocyanate to form C_{1-4}alkyl 4-[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate;

(3) reacting the C_{1-4}alkyl 4-[(aminocarbonyl)(2-chloropyridin-3-yl)amino]piperidine-1-carboxylate with a Pd catalyst to form C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate; and

(4) reacting the C_{1-4}alkyl 4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate with a strong acid, or with a strong base followed by a strong acid.

2. A process according to claim 1 wherein said strong base is selected from NaOH, LiOH and KOH, and wherein said strong acid is selected from HCl, HBr, HI, H_2SO_4 and HNO_3.

3. A process according to any previous claim wherein step (1) comprises reacting 3-amino-2-chloropyridine with C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate in the presence of trifluoroacetic acid and sodium triacetoxy borohydride.

4. A process according to any previous claim wherein step (3) comprises reacting the C_{1-4}alkyl 4-[(aminocarbonyl)(2-chloropyridin-3-

yl)amino]piperidine-1-carboxylate in the presence of NaHCO3, Pd(OAc)2 and bis(diphenylphosphino)butane.

5. A process according to any previous claim wherein said C_{1-4}alkyl 4-oxo-1-piperidinecarboxylate is ethyl 4-oxo-1-piperidinecarboxylate.

6. A process according to any previous claim which is for the preparation of 2-oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-b]pyridine dihydrochloride.