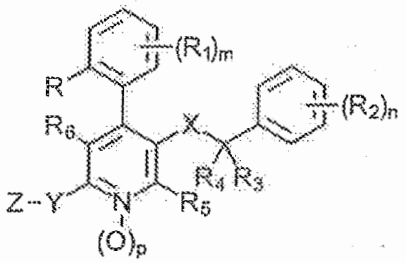
CLAIMS

What is claimed is:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,



Formula (I)

wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, $-OR^{101}$, $-NR^{101}R^{102}$, $-NR^{101}C(O)R^{102}$, $-C(O)R^{101}$, $-C(O)OR^{101}$, $-C(O)NR^{101}R^{102}$, $-alkylNR^{101}R^{102}$, $-S(O)_2R^{102}$, $-SR^{101}$, $-S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, $-OR^{101}$, $-NR^{101}R^{102}$, $-NR^{101}C(O)R^{102}$, $-C(O)R^{101}$, $-C(O)OR^{101}$, $-C(O)NR^{101}R^{102}$, $-alkylNR^{101}R^{102}$, $-S(O)_2R^{102}$, $-SR^{101}$, $-S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, $-OR^{101}$, $-NR^{101}R^{102}$, $-NR^{101}C(O)R^{102}$, $-C(O)R^{101}$, $-C(O)OR^{101}$, $-C(O)NR^{101}R^{102}$, $-alkylNR^{101}R^{102}$, $-S(O)_2R^{102}$, $-SR^{101}$, $-S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl

and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

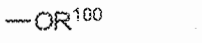
R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, $-OR^{101}$, $-NR^{101}R^{102}$, $-NR^{101}C(O)R^{102}$, $-C(O)R^{101}$, $-C(O)OR^{101}$, $-C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, $-S(O)_2R^{102}$, $-SR^{101}$, $-S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

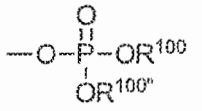
X is selected from the group consisting of $-C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, $-NR^{101}C(O)$ and $-NR^{101}$alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

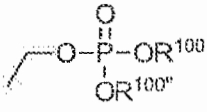
Y is selected from the group consisting of $-NR^{101}R^{102}$, $-NR^{101}$alkylOH, $-NR^{101}S(O)_2$alkyl, $-NR^{101}S(O)_2$phenyl, $-N{=}CH{-}NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

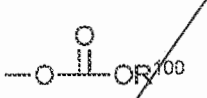
Z is a structural formula selected from the group consisting of


(Ia),

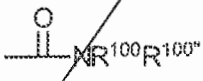

(Ib),

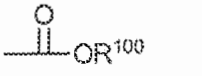

(Ic),

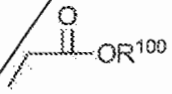

(Id),


(Ie),


(If),


(Ig),


(Ih) and


(Ii),

where formula (Ia) refers to an oxide;

R^{100}, $R^{100"}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, $-NO_2$, $-OR^{104}$, oxide, hydroxy, amino, alkyl, alkenyl,

cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, $-C(O)R^{104}$, $-C(O)OR^{104}$, $-C(O)NR^{104}R^{105}$, $-NR^{104}R^{105}$, $-NR^{104}S(O)_2R^{105}$, $-NR^{104}C(O)R^{105}$, $-S(O)_2R^{104}$, $-SR^{104}$ and $-S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, $-NO_2$, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

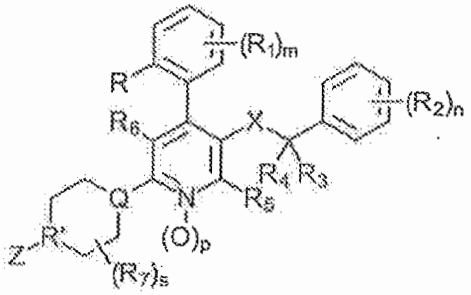
with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, $-OR^{101}$ and CF_3.

3. The compound of any of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein X is $-NR^{101}C(O)$.

4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) has a structure of formula (II):



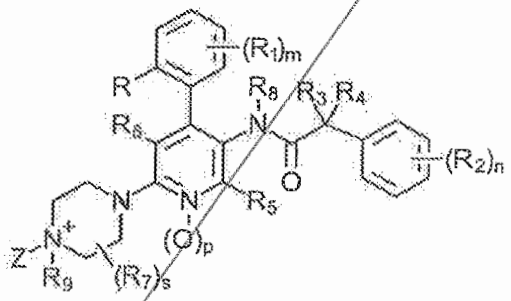
Formula (II)

where Q and R" are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents;

R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, $-OR^{101}$, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents;

s is 0, 1, 2, 3 or 4; and all other radicals are defined according to formula (I).

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) has a structure of formula (III):



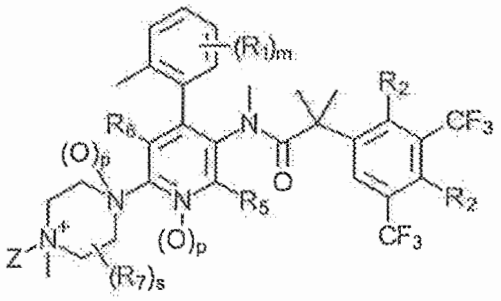
Formula (III)

where

R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined according to formula (I) and formula (II).

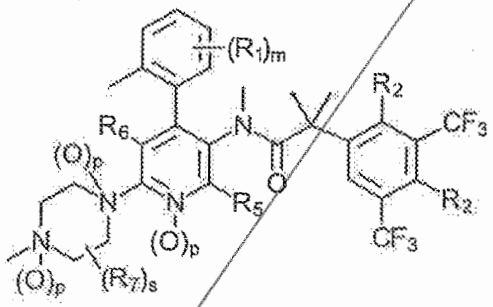
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) has a structure of formula (IV):



Formula (IV)

where p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II) and formula (III).

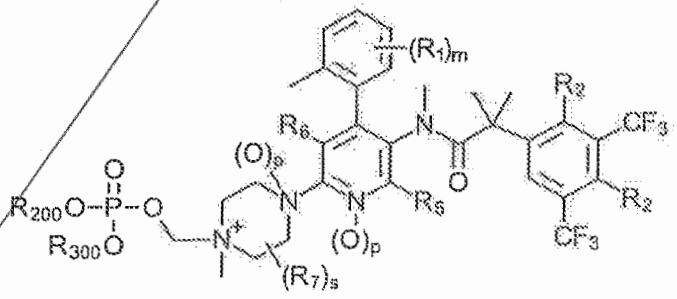
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) has a structure of formula (V):



Formula (V)

where p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III) and formula (IV).

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) has a structure of formula (VI):



Formula (VI)

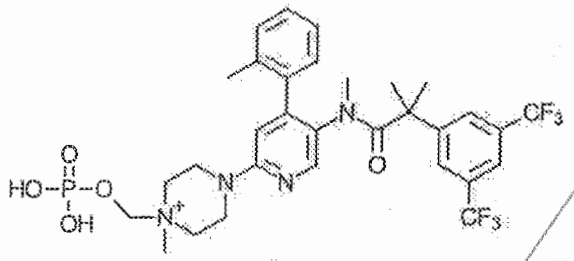
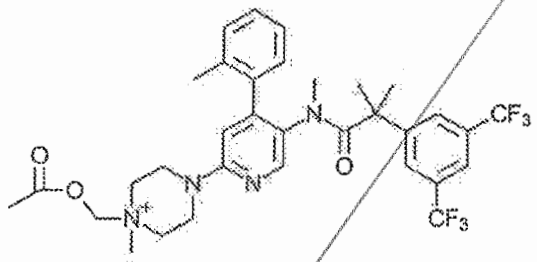
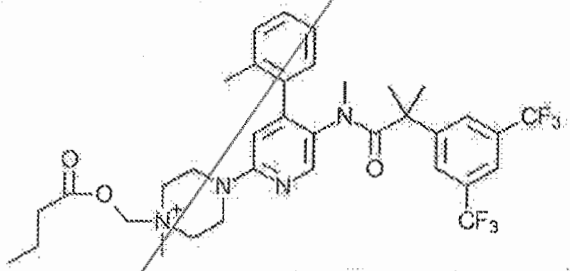
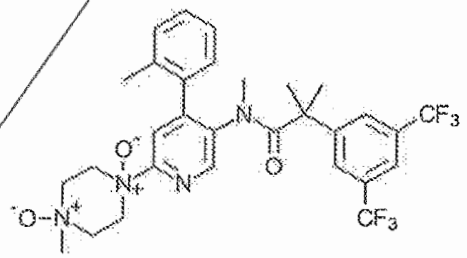
where

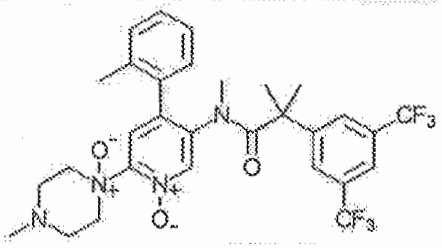
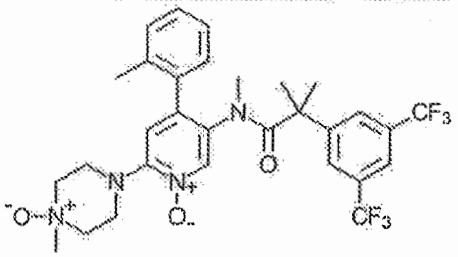
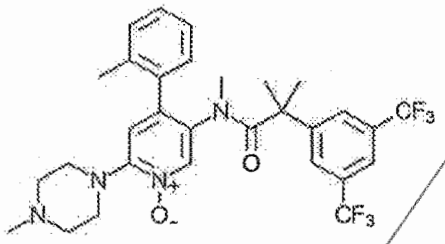
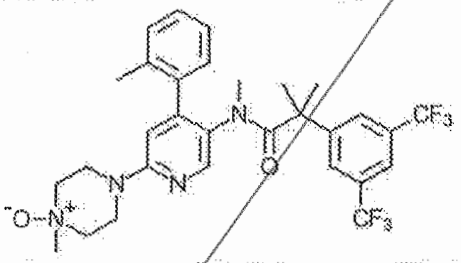
R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation;

p is independently 0 or 1; and

all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

10. A compound selected from the group consisting of:

GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,
GA2		1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,
GA3		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,
GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

GA5		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,
GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

or a pharmaceutically acceptable salt thereof.

11. A method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) according to any of claims 1-10.

12. The method of claim 11, wherein said emesis comprises chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

13. The method of either of claims 11-12, wherein said emesis is induced by moderately or highly emetogenic chemotherapy.

14. The method of any of claims 11-13, wherein emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy.

15. The method of claims 11-14, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

16. The method of any of claims 11-15, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

17. The method of any of claims 11-16, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is intravenously administered at a dosage of from about 10 mg to about 200 mg.

18. The method of any of claims 11-17, wherein said emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy, further comprising administering a 5-HT_3 antagonist and corticosteroid.

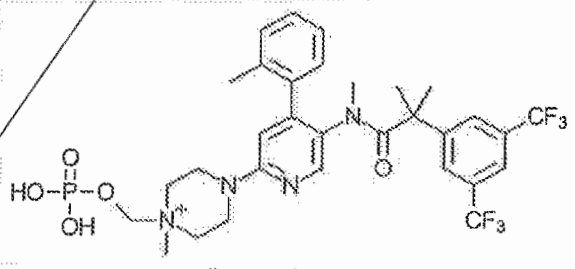
19. The method of claim 18, wherein said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

20. The method of any of claims 11-18, further comprising administering 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant).

21. The method of any of claims 11-20, wherein the subject is a human.

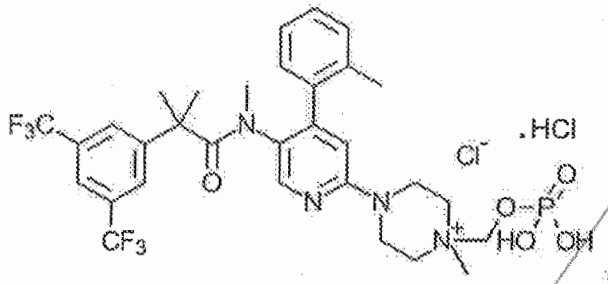
22. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-10, and one or more pharmaceutically acceptable excipients.

23. A compound of formula GA1,

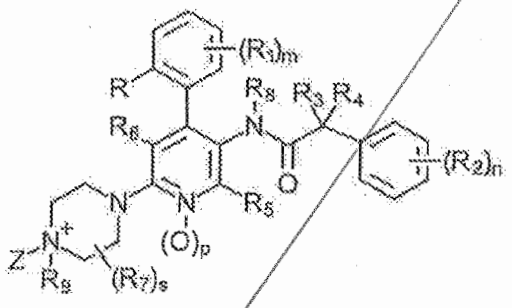
GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 23 as a chloride hydrochloride salt having the following chemical formula:



25. A method for making a compound of formula III



Formula (III)

comprising

a) providing a compound of claim 1 wherein Y is a 4-N-methyl-piperazine group and Z is not present;

b) providing a dialkyl (halomethyl) phosphate;

c) reacting an N atom of the piperazine group with the dialkyl (halomethyl) phosphate to obtain a quaternary ammonium methylene phosphate compound.

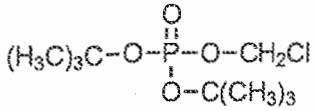
26. The synthetic method of claim 25, wherein the reaction is carried out in the presence of an iodide salt and in the absence of a proton scavenger.

27. The method of either of claims 25-26, wherein the reaction is carried out in the substantial absence of air and dioxygen.

28. The method of any of claims 25-27, wherein the quaternary ammonium methylene phosphate compound is obtained with a (phosphooxy)methyl group in dealkylated form without acidifying the reaction or the product.

29. A method for making a compound of claim 8 comprising: contacting a compound of formula V wherein p is 0 for the methylated 4-N atom of the piperazinyl ring, with a

compound of formula VII in the presence of an iodide salt, for a period of time sufficient to functionalize the methylated 4-N atom on the compound of formula V with the compound of formula VII and to dealkylate the compound of formula VII:



Formula (VII).

30. A method for making chloromethyl dialkylphosphate comprising:

a) contacting a dialkylphosphate salt with an acid in a first low alkyl alcohol solvent solution at a temperature below room temperature to obtain the corresponding ester of phosphoric acid, wherein the strength and quantity of the acid is sufficient to convert essentially all of the salt to the corresponding dialkyl ester of phosphoric acid;

b) contacting the dialkyl ester of phosphoric acid with a quaternary ammonium hydroxide base in a second low alkyl alcohol solvent solution at a temperature below room temperature, wherein the strength and quantity of the base is sufficient to convert the dialkyl ester of phosphoric acid to a monobasic salt of the same acid; and

c) contacting the monobasic salt with chloroiodomethane in a low alkyl ketone or aldehyde solvent to form the corresponding chloromethyl dialkyl phosphate.

31. The method of claim 30 wherein the dialkylphosphate salt is a di-(*tert*-butyl)phosphate salt, the acid is hydrochloric acid, and in each case the temperature below room temperature is approximately 0°C.

32. The method of either of claims 30-31 wherein both low alkyl alcohol solvent solutions are methanol solutions and the low alkyl ketone or aldehyde is acetone.

33. The method of any of claims 30-32 wherein following the reaction:

a) the solvent and any remaining chloroiodomethane are distilled off;

b) the distillation residue is suspended in *tert*-butyl methyl ether (TMBE) and then filtered;

c) the filtrate is washed with aqueous base; and

d) the washed filtrate is placed under reduced pressure to substitute the solvent with acetone.

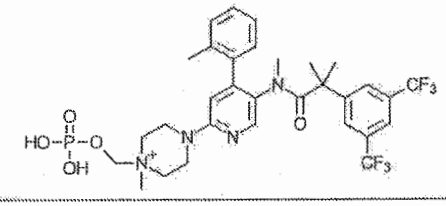
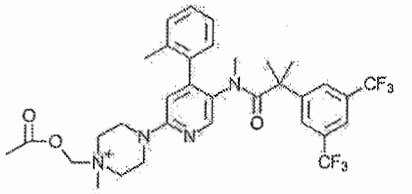
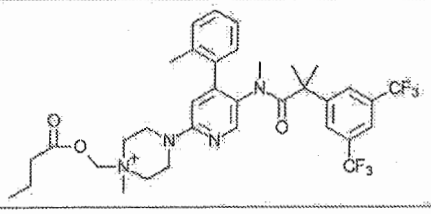
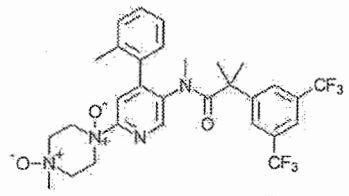
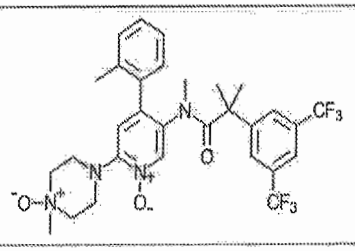
34. A method for stabilizing a compound of claim 23, comprising contacting the compound with two equivalents of hydrochloric acid.

35. The method of claim 34 wherein a compound of claim 23 is in methanolic solution and is contacted with 4M hydrochloric acid in dioxane, followed by distillation under reduced pressure to remove the methanol, dioxane and any excess hydrochloric acid.

36. The method of either of claim 34-35 wherein after distillation under reduced pressure the residue is purified by additional slurrying in acetone followed by filtering to collect the compound and washing it further with acetone and pentane.

CLAIMS

1. A compound selected from the group consisting of:

GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,
GA2		1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,
GA3		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,
GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,
GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 for use in a method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof.

3. The compound for the use according to claim 2, wherein said emesis comprises chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

4. The compound for the use according to either of claims 2-3, wherein said emesis is induced by moderately or highly emetogenic chemotherapy.

5. The compound for the use according to any of claims 2-4, wherein emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy.

6. The compound for the use according to any of claims 2-5, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

7. The compound for the use according to any of claims 2-6, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

8. The compound for the use according to any of claims 2-7, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is intravenously administered at a dosage of from about 10 mg to about 200 mg.

9. The compound for the use according to any of claims 2-8, wherein said emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy, further comprising administering a 5-HT_3 antagonist and corticosteroid.

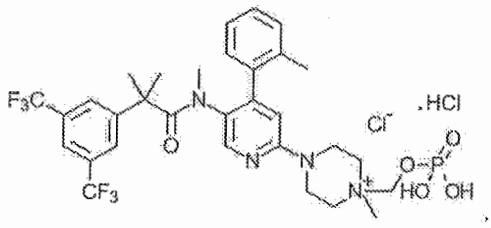
10. The compound for the use according to claim 9, wherein said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

11. The compound for the use according to any of claims 2-10, further comprising administering 2-(3,5- bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1.yl)-4-(o-tolyl)pyridin-3-yl) propanamide (netupitant).

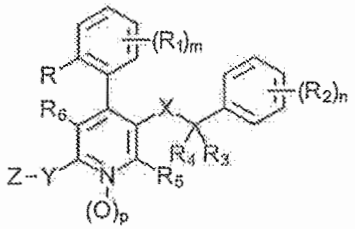
12. The compound for the use according to any of claims 2-11, wherein the subject is a human.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, and one or more pharmaceutically acceptable excipients.

14. The compound of claim 1, as a chloride hydrochloride salt having the following chemical formula:



15. A process of making a compound of formula (I):



Formula (I)

wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, -OR^{101}, -$NR^{101}R^{102}$, -$NR^{101}C(O)R^{102}$, -$C(O)R^{101}$, -$C(O)OR^{101}$, -$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, -$S(O)_2R^{102}$, -SR^{101}, -$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, -OR^{101}, -$NR^{101}R^{102}$, -$NR^{101}C(O)R^{102}$, -$C(O)R^{101}$, -$C(O)OR^{101}$, -$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, -$S(O)_2R^{102}$, -SR^{101}, -$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, -OR^{101}, -$NR^{101}R^{102}$, -$NR^{101}C(O)R^{102}$, -$C(O)R^{101}$, -$C(O)OR^{101}$, -$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, -$S(O)_2R^{102}$, -SR^{101}, -$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

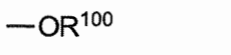
R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, -OR^{101}, -$NR^{101}R^{102}$, -$NR^{101}C(O)R^{102}$, -$C(O)R^{101}$, -$C(O)OR^{101}$, -$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, -$S(O)_2R^{102}$, -SR^{101}, -$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

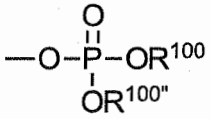
X is selected from the group consisting of -$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, -$NR^{101}C(O)$ and -NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

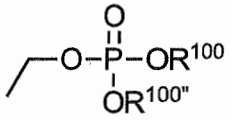
Y is selected from the group consisting of $-NR^{101}R^{102}$, $-NR^{101}$alkylOH, $-NR^{101}S(O)_2$alkyl, $-NR^{101}S(O)_2$phenyl, $-N=CH-NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

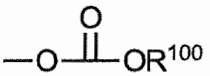
Z is a structural formula selected from the group consisting of

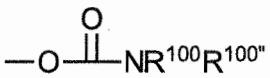
 (Ia),

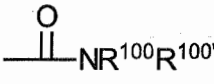
 (Ib),

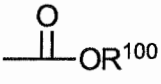
 (Ic),

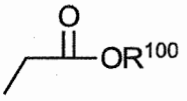
 (Id),

 (Ie),

 (If),

 (Ig),

 (Ih) and

 (Ii),

where formula (Ia) refers to an oxide;

R^{100}, $R^{100"}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, $-NO_2$, $-OR^{104}$, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, $-C(O)R^{104}$, $-C(O)OR^{104}$, $-C(O)NR^{104}R^{105}$, $-NR^{104}R^{105}$, $-NR^{104}S(O)_2R^{105}$, $-NR^{104}C(O)R^{105}$, $-S(O)_2R^{104}$, $-SR^{104}$ and $-S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100"}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, $-NO_2$, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one,

said process comprising:
a) providing a compound of formula (I) wherein Y is a 4-N-methyl-piperazine group and Z is not present;
b) providing a dialkyl(halomethyl)phosphate;
c) reacting an N atom of the piperazine group with the dialkyl(halomeihyl)phosphate to obtain a quaternary ammonium methylene phosphate compound,

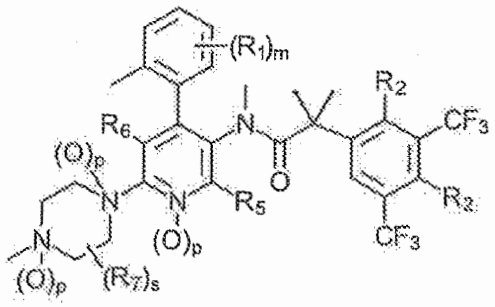
where said process is performed to obtain the compound GA-1 according to claim 1.

16. The process of claim 15, wherein the reaction is carried out in the presence of an iodide salt and in the absence of a proton scavenger.

17. The process of either of claims 15-16, wherein the reaction is carried out in the substantial absence of air and dioxygen.

18. The process of any of claims 15-17, wherein the quaternary ammonium methylene phosphate compound is obtained with a (phosphooxy)methyl group in dealkylated form without acidifying the reaction or the product.

19. A process of making a compound of formula (V):



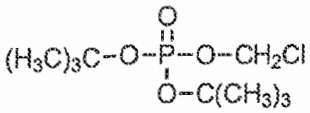
Formula (V)

where:
R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, $-OR^{101}$, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents;
and all other radicals are defined according to formula (I) in claim 15,

comprising:

contacting a compound of formula V wherein p is 0 for the methylated 4-N atom of the piperazinyl ring, with a compound of formula VII in the presence of an iodide salt, for a

period of time sufficient to functionalize the methylated 4-N atom on the compound of formula V with the compound of formula VII and to dealkylate the compound of formula VII:



Formula (VII).

where said process is performed to obtain the compound GA-1 according to claim 1.