VOLTAGE-GATED SODIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

In general, the present invention relates to uses of voltage-gated sodium channel blocker compounds, which include corresponding precursors, intermediates, monomers and dimers, corresponding pharmaceutical compositions, compound preparation and treatment methods for respiratory and respiratory tract diseases.

In particular, the present invention also relates to methods and uses for treatment of respiratory or respiratory tract diseases, which comprises administering to a subject in need thereof an effective amount of a compound of the present invention.

BACKGROUND OF THE INVENTION

Sodium channels play a significant role in the neuronal network by transmitting electrical impulses rapidly throughout cells and cell networks, which aid in coordinating higher processes ranging from locomotion to coginition in mammals.

In general, sodium channels are described in the art as large transmembrane proteins, which are able to switch between different states to enable selective permeability for sodium ions. For such a process, an action potential, a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, is needed to depolarize transmembranes, in which sodium channels are voltage-gated.

Voltage-gated sodium channels are responsible for generation of the action potentials of axonal nerve fibers via fast, selective transport of sodium ions across cell membranes resulting to rapid transmission of depolarizing impulses throughout cells and cell networks. Thus, voltage-gated sodium channels are responsible for initial phase of action potential, which is a wave of electrical depolarisation usually initiated at the soma of the neuron and propagated along the nerve axon to the terminals. At the terminals, the action potential triggers the influx of calcium and the release of neurotransmitter.

Research in this area has shown that voltage-gated sodium channels could be targeted, either selectively or in combination with other cellular processes, for the treatment of different diseases, which include, but are not limited to, for example, treatment of stroke, epilepsy and several types of neuropathic pain.

A key feature of these drugs is their use-dependent mechanism of action. The mechanism by which sodium channels are able to inactivate has been the subject of extensive study. It is clear that these channels are able to inactivate through both a

fast (milliseconds) and slow (seconds to minutes) pathway and that the interplay between activation and inactivation pathways is held in a delicate balance.

The drugs are thought to stabilise an inactivated configuration of the channel that is adopted rapidly after the channel opens. This inactivated state provides a refractory period before the channel returns to its resting (closed) state ready to be reactivated. As a result, use-dependent sodium channel blockers retard the firing of neurons at high frequency, for example in response to painful stimuli, and will help to prevent repetitive firing during periods of prolonged neuronal depolarisation that might occur, for example, during a seizure. Action potentials triggered at low frequencies, for example in the heart, will not be significantly affected by these drugs, although the safety margin differs in each case, since at high enough concentrations each of these drugs is capable of blocking the resting or open states of the channels.

The voltage-gated sodium channel family is made up of 10 subtypes, four of which are brain specific, NaV1.1, 1.2, 1.3 and 1.6. Of the other subtypes, NaV1.4 is found only in skeletal muscle, NaV1.5 is specific to cardiac muscle, and NaV1.7, 1.8, and 1.9 are found predominantly in sensory neurons. The hypothesised binding site for use-dependent sodium channel blockers is highly conserved between all the subtypes. As a result, drugs such as lidocaine, lamotrigine and carbamazepine do not distinguish between the subtypes. However, selectivity can be achieved as a result of the different frequencies at which the channels normally operate.

In general, drugs that interact with sodium channels to block ion flux cause the channels to inactivate to a greater extent and with smaller depolarizations than normal. Other sodium channel blockers, such as lamotrigine and carbamazepine are used to treat epilepsy. In the latter case, partial inhibition of voltage-gated sodium channels reduces neuronal excitability and reduces seizure propagation. In the case of local anaesthetics, regional block of sodium channels on sensory neurons prevents the conduction of painful stimuli.

Drugs that block voltage-gated sodium channels in a use-dependent manner are also used in the treatment of bipolar disorder, either to reduce symptoms of mania or depression, or as mood stabilisers to prevent the emergence of mood episodes. Clinical and preclinical evidence also suggests that use-dependent sodium channel blockers may help to reduce the symptoms of schizophrenia. For example, lamotrigine has been shown to reduce symptoms of psychosis induced by ketamine in healthy human volunteers, and furthermore, studies in patients suggest that the drug can augment the antipsychotic efficacy of some atypical antipsychotic drugs, such as

clozapine or olanzapine. It is hypothesised that efficacy in these psychiatric disorders may result in part from a reduction of excessive glutamate release. The reduction in glutamate release is thought to be a consequence of use-dependent sodium channel inhibition in key brain areas, such as the frontal cortex. However, interaction with voltage-gated calcium channels may also contribute to the efficacy of these drugs.

Propagation of nerve impulses arising from tussive stimuli is mediated, at least in part, via voltage-gated Na^+ channels (NaV). Generation of the action potential is blocked by local anesthetics such as Lidocaine. Drugs, such as lidocaine, that block voltage-gated sodium channels are used as local anaesthetics.

Lidocaine reduces the inward sodium current which elicits neuronal impulses (Butterworth, J.F.T. & Strichartz, G.R. , g.r. (1990). Molecular mechanisms of local anesthesia: a review. Anesthesiology, 72, 711-34.; McCleane, G. . (2007). Intravenous lidocaine: an outdated or underutilized treatment for pain? J Palliat Med, 10, 798-805.). Common modes of drug action on Na^+ channels: local anesthetics, antiarrhythmics and anticonvusants. TiPS, 8, 57-65.; Hille, B. (1966). Common mode of action of three agents that decrease the transient change in sodium permeability in nerves. Nature, 210, 1220-2.; Taylor, R.E., (1959). Effect of procaine on electrical properties of squid axon membrane. Am J Physiol, 196, 1071-8.) Indeed, blockade of neuronal Na+ channels is one of the most powerful and well described analgesic principles (Catterall, W.A. & Mackie, K. (2005). Chapter 14: Local Anesthetics. In Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition. ed Brunton, L.) Lidocaine, a pan-NaV inhibitor, is used to minimize gagging and cough during bronchoconscopy (Reed, A.P. . (1992). Preparation of the patient for awake flexible fiberoptic bronchoscopy. Chest, 101, 244-53.) and to limit airway intubation-induced post operative cough and sore throat (Diachun, C.A. , Tunink, B.P. & Brock-Utne, J.G. (2001). Suppression of cough during emergence from general anesthesia: laryngotracheal lidocaine through a modified endotracheal tube. J Clin Anesth, 13, 447-51.).

In general, coughing is produced in a variety of airway diseases, which may enhance and intensify the cough response. The cough reflex protects the airway from potential harm by aiding the clearance of luminal debris. Within the airway epithelium, irritant sensing vagal nerve endings transmit information arising from the presence of tussive stimuli to the brain stem evoking an urge to cough. Chronic cough, often thought as dry and unproductive, is associated with progressive irreversible lung damage such as occurs in chronic obstructive pulmonary disease (COPD). The persistence and intensity of this form of cough robs patients of quality of life. It is this

inappropriate chronic cough, a common symptom of chronic respiratory disease that therapy aims to resolve.

Based on the foregoing, there is evidence suggesting that short-term administration of intravenous lidocaine may produce pain relief that far exceeds both the duration of infusion and the half-life of the drug (McCleane, 2007). Although widely investigated, the mechanism remains unknown. One possibility is that local anesthetics inhibit central sensitization, i.e., the long-term increase in the excitability of the central nervous system in response to on-going or repeated activation of nociceptors. Blockade of sensory nerve input even for a short time would allow restoration of normal nerve function, a similar long-lasting effect on intractable dry cough could be expected.

In light of the above, a need exists to develop treatment methods or uses for diseases associated with mediation or modulation of voltage-gated sodium channels, which include, but are not limited to respiratory diseases or associated disorders, where suitable compounds or corresponding pharmaceutical compositions are described herein.

The present invention is directed to overcoming these and other problems encountered in the art.

SUMMARY OF THE INVENTION

In general, the present invention relates to uses of voltage-gated sodium channel blocker compounds, which include corresponding precursors, intermediates, monomers and dimers, corresponding pharmaceutical compositions, compound preparation and treatment methods for respiratory and respiratory tract diseases.

In particular, the present invention also relates to methods and uses for treatment of respiratory or respiratory tract diseases, which comprises administering to a subject in need thereof an effective amount of a compound of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

In general, the present invention relates to uses of voltage-gated sodium channel blocker compounds, , which include corresponding precursors, intermediates, monomers and dimers, corresponding pharmaceutical compositions, compound preparation and treatment methods for respiratory and respiratory tract diseases.

In particular, the present invention also relates to methods and uses for treatment of respiratory or respiratory tract diseases, which comprises administering to a subject in need thereof an effective amount of a compound of the present invention.

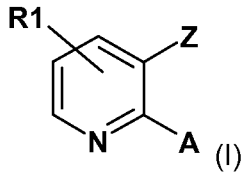
COMPOUNDS

A. Precursors, Intermediates and Monomers

In general, the present invention relates to uses of voltage-gated sodium channel blocker compounds, which include corresponding precursors, intermediates, monomers and dimers, corresponding pharmaceutical compositions, compound preparation and treatment methods for respiratory and respiratory tract diseases.

In particular, the present invention relates to uses of novel compounds of Formulas (I) to (XVI) and corresponding pharmaceutical compositions, respectively, which are suitable for use in the present invention.

In one aspect, the present invention relates to use of a compound of Formula (I):

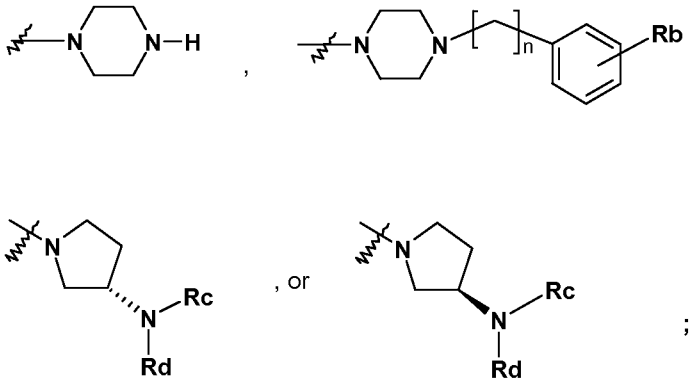


(I)

wherein:

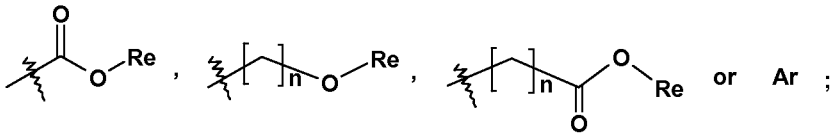
R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_a$, $-SR_a$ or $-OR_a$;

A is



;

Z is



;

wherein:

n is 0 or an integer from 1 to 5;

halogen is selected from bromo, chloro, fluoro or iodo;

R_a is phenyl or substituted phenyl;

R_b is H, halogen, –C(O)H, –C(O)-OH, -C(O)-OR_{1a}, -(CH)O$(R_{1b})_2$, -$(CH_2)_m$N-R_{1c}, -NH_2, -NHC(O)-phenyl, -NHC(O)-substituted phenyl, -NO_2, -SH, or -SR_{1d};

R_c is H, straight or branched C_{1-6} alkyl, cycloalkyl; phenyl or heteroaryl;

R_d is H, straight or branched C_{1-6} alkyl or cycloalkyl;

R_e is H, straight or branched C_{1-6} alkyl or cycloalkyl;

Ar is aryl or heteroaryl;

wherein:

for each variable R_a, R_b, R_c, R_d or R_e :

halogen as defined for Rb is bromo, chloro, fluoro or iodo;

R_{1a}, R_{1b}, R_{1c}, or R_{1d} is H or straight or branched C_{1-6} alkyl; or a pharmaceutically acceptable salt thereof.

Representative compounds of Formula (I) suitable for use in the present invention, may include, but are not limited to, the following compounds:

1-methylethyl 2-{(3R)-3-[{[(1,1-dimethylethyl)oxy]carbonyl} (ethyl)amino]-1-pyrrolidinyl}-4-iodo-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[{[(1,1dimethylethyl)oxy] carbonyl} (ethyl) amino]-1-pyrrolidinyl} -4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethylamino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

(R)- Isopropyl 2-[3-(ter-butoxycarbonylamino)pyrrolidine-1-yl]nicotinate;

(R)- Isopropyl 2-{3-[tert-butoxycarbonyl(ethyl)amino] pyrrolidin-1-yl}nicotinate;

1-Methylethyl 2-[(3*S*)-3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-Methylethyl 2-[(3*S*)-3-amino-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl} (ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-[(3*S*)-3-(ethylamino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1,1-Dimethylethyl [(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl]carbamate;

1,1-Dimethylethyl ethyl[(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl]carbamate;

1-Methylethyl 2-[(3*R*)-3-({[(1,1-dimethylethyl)oxy]carbonyl} amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*R*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl} (ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 4-iodo-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-Methylethyl2-{4-[(4-mercaptophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1,1-Dimethylethyl4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinecarboxylate;

1-Methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate;

1-Methylethyl2-[4-({4-[bis(ethyloxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-Methylethyl 2-{4-[(4-formylphenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-Methylethyl2-{4-[(3-nitrophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-{4-[(3-aminophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-[4-({3-[(phenylcarbonyl)amino]phenyl} methyl) -1-piperazinyl]-3-pyridinecarboxylate;

1-Methylethyl 2-{4-[(4-nitrophenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

1-Methylethyl 2-{4-[(4-aminophenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

1-Methylethyl 2-[4-({4-[(phenylcarbonyl)amino]phenyl}methyl) -1-piperazinyl]-3-pyridine carboxylate;

3-{[4-(3-{[(1-Methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl]methyl}benzoic acid;

4-{[4-(3-{[(1-Methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl]methyl}benzoic acid;

1-Methylethyl 2-{[((2*S*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-pyrrolidinyl)methyl] oxy}-3-pyridinecarboxylate;

1-Methylethyl 2-{[((2*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-pyrrolidinyl)methyl] oxy}- 3-pyridinecarboxylate;

1,1-Dimethylethyl ethyl{(3*R*)-1-[3-(hydroxymethyl)-2-pyridinyl]-3-pyrrolidinyl}

carbamate;

(2-{(3*R*)-3-[{[(1,1-Dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinyl)methyl benzoate;

{2-[(3*R*)-3-(Ethylamino)-1-pyrrolidinyl]-3-pyridinyl}methyl benzoate;

(2-{(3*R*)-3-[{[(1,1-Dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinyl)methyl 3,3-dimethylbutanoate;

(2-{(3*R*)-3-[{[(1,1-Dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinyl)methyl 3,3-dimethylbutanoate;

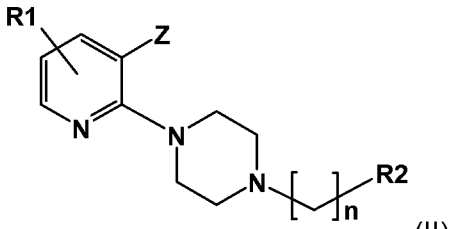
{2-[(3*R*)-3-(Ethylamino)-1-pyrrolidinyl]-3-pyridinyl}methyl 3,3-dimethylbutanoate;

1-Methylethyl 2-{[(2*S*)-2-pyrrolidinylmethyl]oxy}-3-pyridinecarboxylate;

1-Methylethyl 2-{[(2*R*)-2-pyrrolidinylmethyl]oxy}-3-pyridinecarboxylate; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (II) suitable for use in the present invention:



(II)

wherein:

n is 0 or an integer from 1 to 5;

R_1 is -H, -halogen,-straight or branched C_{1-6} alkyl, -phenyl, -substituted phenyl, -NHR_a, -SR_a or -OR_a;

wherein as defined for R_1:

-halogen is bromo, chloro, fluoro or iodo;

R_a is -phenyl or -substituted phenyl;

R_2 is aryl or heteroaryl;

wherein aryl is selected from -phenyl or -substituted phenyl;

wherein heteroaryl is selected from mono, bicyclic or tricyclic heterocyclic aromatic ring compounds containing 1-3 hetero atoms independently selected from nitrogen, oxygen and sulphur;

wherein aryl or heteroaryl further optionally is substituted by one or more substituents from Group A selected from:

-H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, aryl or heteroaryl, $-O(CH_2)_xOR_{1a}$, $-C(O)R_{1b}$, ,$-C(O)OR_{1c}$, aryl or heteroaryl, $-(CH_2)_x$-aryl, $-(CH_2)_x$-substituted aryl, $-(CH_2)_x$-heteroaryl, $-(CH_2)_x$-substituted heteroaryl, $-O-(CH_2)_x$-aryl, $-O-(CH_2)_x$ -substituted aryl, $-O-(CH_2)_x$-heteroaryl, $-O-(CH_2)_x$ -substituted heteroaryl, S-aryl, $-S(CH_2)_x$ aryl, $-S(CH_2)_x$ substituted aryl, S-heteroaryl, $-S(CH_2)_x$ heteroaryl, $-S(CH_2)_x$ substituted heteroaryl; , NH-aryl, $-NR(CH_2)_x$ aryl, $-NR(CH_2)_x$ substituted aryl, NR-heteroaryl, $-NR(CH_2)_x$ heteroaryl, $-NR(CH_2)_x$ substituted heteroaryl, $-(CH_2)_x$ $-N(R_{1d})$ $-(CH_2)_x$ $R_{1e;}$;

wherein:

R_{1a} ,R_{1b}, R_{1c}, or R_{1d} as defined in R_2 above is H or straight or branched C_{1-6} alkyl;

R_{1e} is H or straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5,

wherein:

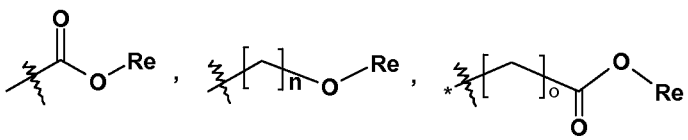
each substitutent as defined in Group A above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$ -OH, $-O(CH_2)_y$ CN, -OC(O)OH, $-OC(O)R_{1f}$, $-C(O)OR_{1g}$, $-O(CH_2)_yOR_{1h}$,- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1i}R_{1j}$, $-SO_2R_{1k}$, $-S(CH_2)_yR_{1l}$, $-NR_{1m}C(O)R_{1n}$, aryl or heteroaryl;

wherein:

y as defined for variables defined for Group A above is 0 or an integer from 1 to 5,

R_{1f}, R_{1g}, R_{1h}, R_{1i}, R_{1j}, R_{1k}, R_{1l}, R_{1m} or R_{1n} is H or straight or branched C_{1-6} alkyl;

Z is



;

wherein:

R_e is H or straight or branched C_{1-6} alkyl or cycloalkyl;

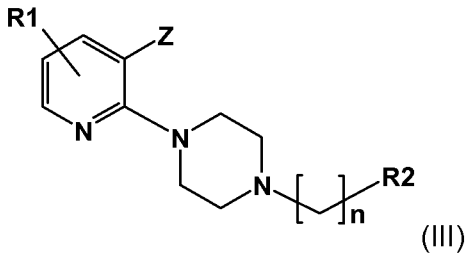
Ar is aryl;

n is 0 or an integer from 1 to 5;

o is 0 or an integer from 1 to 5; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (III) suitable for use in the present invention:



(III)

wherein:

n is 0 or an integer from 1 to 5;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_2 is phenyl, substituted phenyl, $-(CH_2)_x$-phenyl, furanyl,$-(CH_2)_x$ furanyl, -thienyl, $-(CH_2)_x$ thienyl, $(CH_2)_x$ thiazolyl, $-(CH_2)_x$ pyrazolyl, $-(CH_2)_x$ isoxazolyl, $-(CH_2)_x$ pyrrolidinyl, $-(CH_2)_x$ pyridinyl, $-(CH_2)_x$ substituted pyridinyl, $-(CH_2)_x$ pyrazinyl, $-(CH_2)_x$ substituted pyrazinyl, -phenoxy, $-(CH_2)_x$ -phenoxy, $-(CH_2)_x$ -substituted phenoxy, $-(CH_2)_x$ -substituted phenoxy, $-(CH_2)_x$-dibenzofuranyl, $-(CH_2)_x$-substituted dibenzofuranyl,$-(CH_2)_x$-carbazolyl, $-(CH_2)_x$-substituted carbazolyl, $-(CH_2)_x$-1,2,3,4 tetrahydro isoquinolinyl, $-(CH_2)_x$- substituted 1,2,3,4 tetrahydro isoquinolinyl, $-(CH_2)_x$-fluorenyl, or $-(CH_2)_x$-substituted fluorenyl;

wherein:

R_{1a}, R_{1b} or R_{1c} as defined for R_1 is phenyl or substituted phenyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5,

R_2 further optionally is substituted with at least one or more substituents selected from Group A:

-H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, aryl or heteroaryl,-

$O(CH_2)_yOR_{1d}$, $-C(O)R_{1e}$, ,$-C(O)OR_{1f}$, $-(CH_2)_y$ $-N(R_{1g})$ $-(CH_2)_y$ R_{1h}, aryl or heteroaryl, $-(CH_2)_y$-aryl, $-(CH_2)_y$-substituted aryl, $-(CH_2)_y$-heteroaryl, $-(CH_2)_y$-substituted heteroaryl, $-O-(CH_2)_y$-aryl, $-O-(CH_2)_y$ -substituted aryl, $-O-(CH_2)_y$-heteroaryl, $-O-(CH_2)_y$ -substituted heteroaryl, S-aryl, $-S(CH_2)_y$ aryl, $-S(CH_2)_y$ substituted aryl, S-heteroaryl, $-S(CH_2)_y$ heteroaryl, $-S(CH_2)_y$ substituted heteroaryl; NH-aryl, $-NR(CH_2)_y$ aryl, $-NR(CH_2)_y$substituted aryl, NR-heteroaryl, $-NR(CH_2)_y$ heteroaryl, $-NR(CH_2)_y$ substituted heteroaryl, $-(CH_2)_y$ $-N(R_{1g})$ $-(CH_2)_z$ $R_{1h;}$

wherein:

R_{1d}, R_{1e}, R_{1f}, or R_{1g} as defined in R_2 is H or straight or branched C_{1-6} alkyl;

R_{1h} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

y as defined for substituents defined above is 0 or an integer from 1 to 5,

wherein:

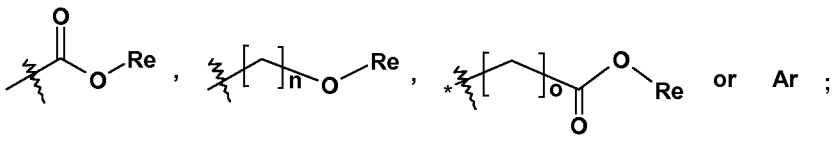
each substitutent as defined in Group A above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_z$ -OH, $-O(CH_2)_z$ CN, $-OC(O)OH$, $-OC(O)R_{1i}$, $-C(O)OR_{1j}$, $-O(CH_2)_zOR_{1k}$,- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1l}R_{1m}$, $-SO_2R_{1n}$, $-S(CH_2)_zR_{1o}$, $-NR_{1p}C(O)R_{1q}$, aryl or heteroaryl;

wherein:

z as defined for variables above is 0 or an integer from 1 to 5;

R_{1i}, R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} or R_{1q} is H or straight or branched C_{1-6} alkyl;

Z is



;

wherein:

n is 0 or an integer from 1 to 5;

o is 0 or an integer from 1 to 5;

R_e is H, straight or branched C_{1-6} alkyl or or cycloalkyl;

Ar is aryl or heteroaryl; or

a pharmaceutically acceptable salt thereof.

Representative compounds of Formula (III), suitable for use in the present invention, may include, but are not limited to:

1-methylethyl 2-{4-[(5-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-2-pyridinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(6-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-3-pyridinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(6-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-3-pyridinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate trihydrochloride;

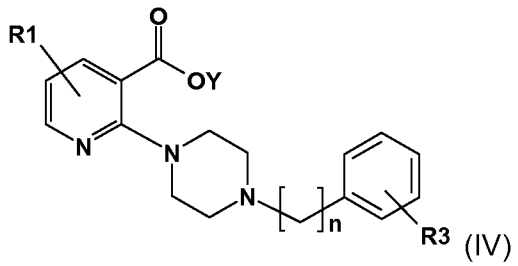
1-methylethyl2-[4-({2-[(2-chloro-6-fluorophenyl)methyl]-1,2,3,4-tetrahydro-6-isoquinolinyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl 2,2,3,3-tetramethylcyclopropanecarboxylate;(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl 3,3-dimethylbutanoate;

(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl 2-methylpropanoate;(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl acetate;1-methylethyl2-{4-[(5-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-2-pyrazinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl cyclopropanecarboxylate;(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl propanoate; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (IV), suitable for use in the present invention:



(IV)

wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or C_{3-6}-cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, -NHR_{1a}, -SR_{1b} or -OR_{1c};

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -$O(CH_2)_xOR_{1d}$, -$C(O)R_{1e}$, -$C(O)OR_{1f}$, -phenyl,-$(CH_2)_x$-phenyl, -$(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted phenyloxy, -$(CH_2)_x$-phenyloxy, -$(CH_2)_x$-piperazinyl, -$(CH_2)_x$-substituted piperazinyl, -$(CH_2)_x$-N-substituted piperazinyl, -$(CH_2)_x$ NRC(O)-phenyl, -$(CH_2)_x$ NRC(O)-substituted phenyl, -O-$(CH_2)_x$-phenyl, -O-$(CH_2)_x$ -substituted phenyl, -$O(CH_2)_x$ -1,4-benzodioxinyl, -$O(CH_2)_x$ -naphthalenyl, -$O(CH_2)_x$-tetrazolyl, -S-phenyl, -$S(CH_2)_x$ phenyl, -SO_2R_{1g}, -$SO_2N(R_{1g})_2$, -$(CH_2)_x$ -$N(R_{1h})$ -$(CH_2)_x$ R_{1i};

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, -NO_2,-halogen, -$(CH_2)_y$-OH, -$O(CH_2)_y$ CN, -OC(O)OH, -$OC(O)R_{1j}$, -$C(O)OR_{1k}$, -$O(CH_2)_yOR_{1l}$,- straight or branched C_{1-6} alkyl,-

straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy, - $NR_{1m}R_{1n}$, $-SO_2R_{1o}$, $-S(CH_2)_yR_{1p}$, $-NR_{1q}C(O)R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$ -OH, -OC(O)OH, $-OC(O)R_{1s}$, $-C(O)OR_{1t}$,--$SO_2N(R_{1u})_2$-,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

wherein:

R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof.

Representative compounds of Formula (IV), suitable for use in the present invention, may include, but are not limited to:

1-methylethyl 2-[4-({3-[(2-thienylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chloro-4-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-

pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-nitrophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(acetyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-[4-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylpropyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

[(3-{[4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl}phenyl) oxy]acetic acid;

1-methylethyl 2-[4-({3-[(2-hydroxyethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-(4-{[3-({2-[(2-chloroethyl)oxy]ethyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-

pyridinecarboxylate;

1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenyloxy)-3-pyridine carboxylate;

1-methylethyl 4-[(2-fluorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(3-chlorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(4-cyanophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(ethyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-({3-[(ethyloxy)carbonyl]phenyl}amino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(2-ethylphenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(methyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-(phenylamino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenylthio)-3-pyridine carboxylate;

1-methylethyl 4-{[2-(methyloxy)phenyl]thio}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[2-(trifluoromethyl)phenyl]amino}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[2-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylphenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({2-[(trifluoromethyl)oxy]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({3-(ethyloxy)carbonyl]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[2-fluoro-6-(trifluoromethyl)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(ethyloxy)phenyl]methyl}-1-piperazinyl)-4-phenyl-3-pyridine carboxylate;

1-methylethyl 4-phenyl-2-[4-(2-thienylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridine carboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridine carboxylate;

1-methylethyl 4-phenyl-2-[4-({4-[(trifluoromethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[4-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridine carboxylate;

1-methylethyl 4-phenyl-2-[4-({2-[(phenylmethyl)oxy] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-4-phenyl-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-fluoro-2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-

3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chloro-4-fluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({3-[(trifluoromethyl)oxy]phenyl} oxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chloro-4-fluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(ethyloxy)phenyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(3-furanylmethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(ethyloxy)phenyl]methyl}amino) methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(5-methyl-2-thienyl)methyl]amino} methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl}

phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[2-(ethyloxy)phenyl]methyl}amino) methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(methyloxy)phenyl]methyl}amino) methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-furanylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-thienylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({4-[(methyloxy)carbonyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridine carboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridine carboxylate;

1-methylethyl 4-methyl-2-(4-{[3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-{4-[(4-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-cyano-4-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3,5-dimethyl-4-isoxazolyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetylamino)phenyl]methyl}-1-piperazinyl)-4-methyl-3-

pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridine carboxylate;

1-methylethyl 4-methyl-2-(4-{[1-(3-pyridinyl)-1*H*-pyrrol-2-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(1*H*-tetrazol-5-yl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methylsulfonyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-[(cyanomethyl)oxy]-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({1,2,5-trimethyl-4-[(methyloxy)carbonyl]-1*H*-pyrrol-3-yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(1-piperidinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-methyl-1-piperazinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({1-[3-cyano-4-(methyloxy)-2-pyridinyl]-1*H*-pyrrol-2-yl}methyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2,4-dichlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-methyl-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(ethyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4,5-bis(methyloxy)-2-[(phenylmethyl)oxy] phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-[4-({3,5-dimethyl-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-hydroxy-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-

piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(methyloxy)-4-({[4-(methyloxy)phenyl]methyl} oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,4-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-bromophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(3-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-fluoro-3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(9*H*-fluoren-2-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(4-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-

pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-4-biphenylyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(9-ethyl-9*H*-carbazol-3-yl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-[4-(dibenzo[*b*,*d*]furan-4-ylmethyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-[4-({4-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-chloro-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-{4-[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-3-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-4-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-{[4-(1,1-dimethylethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-4-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3'-(methyloxy)-2-biphenylyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-{[3-(trifluoromethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-

3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(butyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(butyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(5-chloro-2-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-

pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({4-[(2-chloro-6-fluorophenyl)methyl]-1-piperazinyl} methyl)phenyl]methyl}1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(phenylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[4-(2-pyridinylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[3-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[4-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-Methylethyl-2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-Methylethyl-2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;1-Methylethyl-2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride;

1-Methylethyl-2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate dihydrochloride;

1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate;

1-methylethyl 2-(4-{[4-({ethyl[(2-{[(1-methylethyl)oxy]carbonyl}phenyl) methyl] amino} methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(3-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-[4-({3-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-[4-({4-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl 2-{4-[(4-{[({2-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl) amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[({3-[(dimethylamino)sulfonyl]phenyl}methyl) (ethyl) amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[({4[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl) amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-Methylethyl 2-{4-[(4-{[[2-(2-chloro-6-fluorophenyl)ethyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(3-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(4-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[[(2,6-difluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[[(2,6-dichlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[[(3-chlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-{4-[(4-{[[(4-chlorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-

piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chlorophenyl)methyl](ethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl][3-(2-oxo-1-pyrrolidinyl)propyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(2-methyl-3-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-fluorophenyl)methyl]amino}methyl)phenyl] ;methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(2-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] ;methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[3-(2-chloro-6-fluorophenyl)propyl](ethyl)amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)carbonyl]amino}methyl) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl) phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate quaternary hydrochloride1-methylethyl 2-(4-{[4-({[(2-fluorophenyl)carbonyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

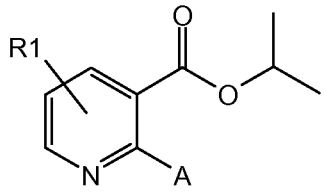
1-methylethyl 2-{4-[(4-{[(phenylcarbonyl)amino]methyl}phenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl) phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate trihydrochloride;1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (V) suitable for use in the present invention:



(V)

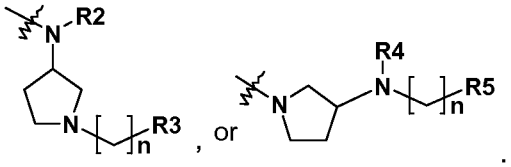
wherein:

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

A is:



;

wherein:

n is 0 or an integer from 1 to 5;

R_2 is H, straight or branched C_{1-6} alkyl or $(CH_2)_x$-cycloalkyl;

R_3 is phenyl or thienyl;

wherein R_3 optionally is substituted with at least one of the following substitutents straight or branched C_{1-6} alkyl, straight or branched C_{1-6} haloalkyl, C1-6-alkoxy, straight or branched C_{1-6}-halosubstituted alkoxy, phenyl, phenoxy, benzyloxy, 3-pyridinyl or 2-thienyl;

wherein phenoxy or benzyloxy optionally is substituted by at least one of following substituents: halogen, -CN, straight or branched C_{1-6} alkyl, straight

or branched C_{1-6}-alkoxy, $-O(CH_2)_nC(O)-N(Ra)_2$, SO_2R_b; $-C(O)R_c$;

wherein:

R_a is H, alkyl or cycloalkyl;

R_b is NH_2, alkyl, cycloalkyl, aryl, heteroaryl;

R_c is straight or branched C_{1-6} alkyl;

R_4 is H, straight or branched C_{1-6} alkyl; cycloalkyl, $(CH_2)_x$-cycloalkyl, $(CH_2)_x$-heterocycloalkyl;

R_5 is phenyl, furanyl, thienyl, piperidinyl, or pyridinyl;

wherein R_5 is optionally substituted with at least one of the following substitutents: phenyl, phenoxy, pyridinyl or thienyl;

wherein phenyl, phenoxy, pyridinyl or thienyl as defined for R_5 further is optionally substituted by at least one of the following substituents: halogen, straight or branched C_{1-6} alkyl, straight, straight or branched C_{1-6} haloalkyl, branched C_{1-6}-alkoxy, $-O(CH_2)_nC(O)R_x$, phenyl, substituted phenyl, phenoxy, benzyloxy, pyridinyl, thienyl or piperidinyl;

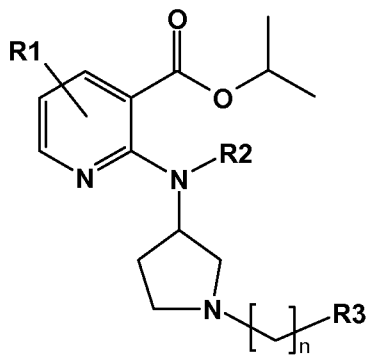
wherein:

R_x is straight or branched C_{1-6} alkyl

benzyloxy, phenoxy, substituted phenyl is optionally substituted by at least one of the following substituents halogen, -CN, straight or branched C_{1-6} alkyl straight or branched C_{1-6}-alkoxy, or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (VI) suitable for use in the present invention:



(VI);

wherein:

n is 0 or an integer from 1 to 5;

R_1 is H;

R_2 is C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

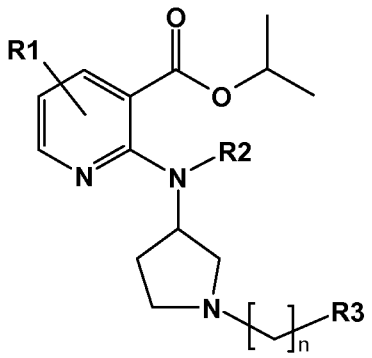
R_3 is C_{1-6} alkyl, alkoxyalkyl, phenyl, heteroaryl;

wherein R_3 optionally is substituted with at least one of following substitutents: straight or branched C_{1-6} alkyl, straight or branched C_{1-6} haloalkyl, C_{1-6}-alkoxy, phenyl, phenoxy or benzyloxy, heteroaryl, heteroaryloxy;

wherein phenoxy or benzyloxy optionally is substituted by at least one of following substituents: halogen, -CN, straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (VII) suitable for use in the present invention:



(VII);

wherein:

n is 0 or an integer from 1 to 5;

R_1 is H;

R_2 is C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

R_3 is C_{1-6} alkyl, alkoxyalkyl, phenyl, heteroaryl;

wherein:

x is 0 or an integer from 1 to 5;

R_3 optionally is substituted with at least one of following substitutents: straight or branched C_{1-6} alkyl, straight or branched C_{1-6} haloalkyl, C_{1-6}-alkoxy, phenyl, phenoxy or benzyloxy;

wherein:

phenoxy or benzyloxy optionally is substituted by at least one of following substituents: halogen, -CN, straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof.

In another aspect, in a compound of formula (VII), suitable for use in the present invention, where R_2 is methyl or ethyl; R_3 is phenyl or 2-thienyl; halogen is selected from fluoro or chloro.

In another aspect, the present invention relates to a compound, suitable for use in the present invention, which may include, but is not limited to :

1-methylethyl 2-[methyl((3*S*)-1-{[3-(phenyloxy)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*S*)-1-({4-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*S*)-1-({3-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*S*)-1-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-[((3*S*)-1-{[4-(hexyloxy)phenyl]methyl}-3-pyrrolidinyl)(methyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*S*)-1-{[4-(propyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*S*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-(methyl{(3*S*)-1-[(2-methylphenyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate;

1-methylethyl 2-[[(3*S*)-1-(2-biphenylylmethyl)-3-pyrrolidinyl] (methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[((3*S*)-1-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy) phenyl]methyl}-3-pyrrolidinyl)(methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*S*)-1-[(5-ethyl-2-thienyl)methyl]-3-pyrrolidinyl}(methyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-(methyl{(3*S*)-1-[(3-{[(4-methylphenyl)methyl]oxy} phenyl) methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*S*)-1-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl) methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*S*)-1-({3-(methyloxy)-2-[(phenylmethyl) oxy]phenyl}

methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*S*)-1-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl) methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[[(3*S*)-1-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl] (methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*S*)-1-({4-[(4-methylphenyl)oxy]phenyl} methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-(methyl{(3*S*)-1-[(2-{[4-(methyloxy)phenyl]oxy}phenyl) methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate;

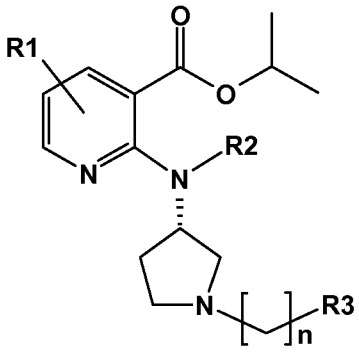
1-methylethyl 2-[[(3*S*)-1-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl] (methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*S*)-1-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl) methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*S*)-1-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl) methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention, relates to a compound of Formula (VIIIA) suitable for use in the present invention:



(VIIIA)

wherein:

n is 1

R_1 is H;

R_2 is $C_{1\text{-}6}$ alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

wherein:

x is 0 or an integer from 1 to 5;

R_3 is $C_{1\text{-}6}$ alkyl, alkoxyalkyl, phenyl, heteroaryl;

wherein:

R_3 optionally is substituted with at least one of following substitutents:

straight or branched C_{1-6} alkyl, straight or branched C_{1-6} haloalkyl, straight or branched C_{1-6}-alkoxy, straight or branched C_{1-6}-halosubstituted alkoxy, phenyl. phenoxy, benzyloxy, 3-pyridinyl or 2-thienyl;

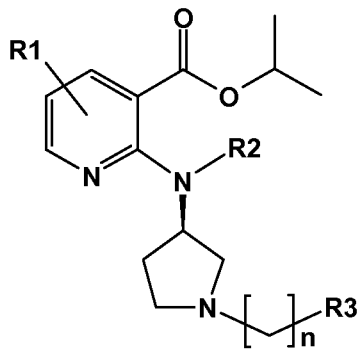
wherein:

phenoxy or benzyloxy optionally is substituted by at least one of following substituents: halogen, -CN, straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy, $-O(CH_2)_yC(O)-NH_2$, SO_2NH_2; $-C(O)CH_3$;

wherein y is 0 or an integer from 1 to 5; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention, relates to a compound of Formula (VIIIB) suitable for use in the present invention:



(VIIIB)

wherein:

n is 1

R_1 is H;

R_2 is C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

wherein:

x is 0 or an integer from 1 to 5;

R_3 is C_{1-6} alkyl, alkoxyalkyl, phenyl, heteroaryl;

wherein R_3 optionally is substituted with at least one of following substitutents: straight or branched C_{1-6} alkyl, straight or branched C_{1-6} haloalkyl, straight or branched C_{1-6}-alkoxy, straight or branched C_{1-6}-halosubstituted alkoxy, phenyl. phenoxy, benzyloxy, 3-pyridinyl or 2-thienyl;

wherein phenoxy or benzyloxy optionally is substituted by at least one of following substituents: halogen, -CN, straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy, $-O(CH_2)_yC(O)-NH_2$, SO_2NH_2; $-C(O)CH_3$;

wherein:

y is 0 or an integer from 1 to 5; or
a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a a compound of formula (VIII), suitable for use in the present invention, where R_2 is methyl, R_3 is phenyl, and halogen is selected from chloro or fluoro.

In another aspect, representative acompounds of Formula (VIII), suitable for use in the present invention, which may include, but are not limited to:

1-methylethyl 2-{methyl[(3*R*)-1-({2-[(trifluoromethyl)oxy]phenyl} methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-[[(3*R*)-1-({2-[(3-chlorophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*R*)-1-[(2-{[4-(aminosulfonyl)phenyl]oxy}phenyl) methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*R*)-1-({3-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*R*)-1-({3-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*R*)-1-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-[[(3*R*)-1-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[((3*R*)-1-{[4-(ethyloxy)phenyl]methyl}-3-pyrrolidinyl)(methyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*R*)-1-{[4-(phenyloxy)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*R*)-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-(methyl{(3*R*)-1-[(4-{[(2-methylphenyl)methyl]oxy}phenyl) methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate;

1-methylethyl 2-[[(3*R*)-1-({4-[(2-amino-2-oxoethyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*R*)-1-({4-[({4-[(methyloxy)carbonyl]phenyl} methyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*R*)-1-{[4-(3-pyridinyl)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*R*)-1-{[2'-(methyloxy)-4-biphenylyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*R*)-1-{[4-(2-thienyl)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-{methyl[(3*R*)-1-({2-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate;

1-methylethyl 2-[[(3*R*)-1-(4-biphenylylmethyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*R*)-1-[(4'-fluoro-3-biphenylyl)methyl]-3-pyrrolidinyl} (methyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-(methyl{(3*R*)-1-[(2'-methyl-3-biphenylyl)methyl]-3-pyrrolidinyl} amino)-3-pyridinecarboxylate;

1-methylethyl 2-[{(3*R*)-1-[(4'-fluoro-2-biphenylyl)methyl]-3-pyrrolidinyl} (methyl)amino]-3-pyridinecarboxylate;

1-methylethyl 2-(methyl{(3*R*)-1-[(2'-methyl-2-biphenylyl)methyl]-3-pyrrolidinyl} amino)-3-pyridinecarboxylate;

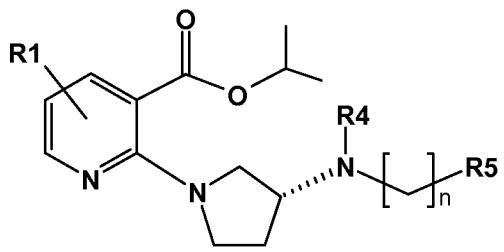
1-methylethyl 2-[methyl((3*R*)-1-{[3-(phenyloxy)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*R*)-1-{[3-(propyloxy)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate;

1-methylethyl 2-[methyl((3*R*)-1-{[4-(propyloxy)phenyl]methyl}-3-pyrrolidinyl) amino]-3-pyridinecarboxylate; or

a pharmaceutically acceptable salt thereof.

The present invention also relates to a compound of formula (IX) suitable for use in the present invention:



(IX)

wherein:

n is 1;

R_1 is H;

R_4 is C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

R_5 is C_{1-6} alkyl, alkoxyalkyl, phenyl or heteroaryl;

wherein R_5 is optionally substituted with at least one of the following substitutents: phenyl, phenoxy, 3-pyridinyl or 2-thienyl;

wherein phenyl, phenoxy, pyridinyl or thienyl is optionally substituted by at least one of the following substituents: halogen, straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (IX), where R_4 is ethyl; R_5 is phenyl or furanyl; R_4 is C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl and R_5 is C_{1-6} alkyl, alkoxyalkyl, phenyl, heteroaryl.

Representative compounds of Formula (IX), suitable for use in the present invention, which may include, but are not limited to:

1-methylethyl-2-{(3R)-3-[(3-biphenylylmethyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridine carboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4'-(methyloxy)-4-biphenylyl] methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[{[5-(2-chlorophenyl)-2-furanyl]methyl} (ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-((3R)-3-{ethyl[(5-phenyl-2-furanyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[(4-biphenylylmethyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

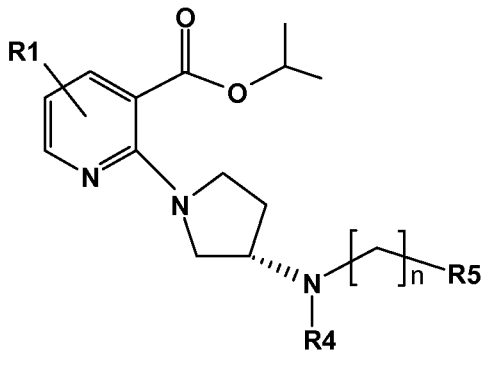
1-methylethyl 2-[(3R)-3-(ethyl{[4-(3-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4-(2-thienyl)phenyl]methyl} amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[3-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to use of a compound of formula (X):



(X)

wherein:

n is 1;

R_1 is H;

R_4 is ethyl;

R_5 is phenyl;

R_4 is C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

R_5 is C_{1-6} alkyl, alkoxyalkyl, phenyl, heteroaryl;

wherein R_5 is optionally substituted with at least one of the following substitutents: straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy, phenoxy or benzyloxy;

wherein phenoxy or benzyloxy is optionally substituted by at least one of the following substituents: halogen, straight or branched C_{1-6} alkyl, straight or branched C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (X), suitable for use in the present invention, where R_4 is ethyl and R_5 is phenyl or furanyl.

Representative examples of compounds of Formula (X), suitable for use in the present invention, which may include, but are not limited to::

1-methylethyl 2-{(3*S*)-3-[ethyl({4-(methyloxy)-3-[(phenylmethyl)oxy] phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridine carboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({4-[(4-fluorophenyl)oxy]phenyl} methyl)amino]-1-

pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3*S*)-3-(ethyl{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({3-(methyloxy)-2-[(phenylmethyl) oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({2-[(4-fluorophenyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3*S*)-3-(ethyl{[2-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[(3*S*)-3-(ethyl{[4-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({3-[(phenylmethyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({3-(methyloxy)-4-[(phenylmethyl)oxy] phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({2-(methyloxy)-4-[(phenylmethyl) oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3*S*)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3*S*)-3-(ethyl{[3-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-((3*S*)-3-{ethyl[(2-{[4-(methyloxy)phenyl]oxy} phenyl)methyl] amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

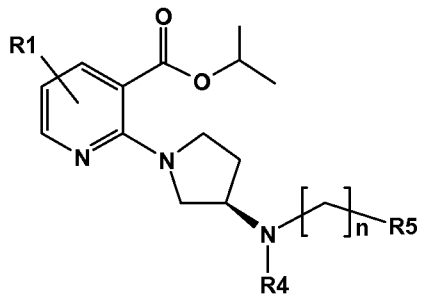
1-methylethyl 2-{(3*S*)-3-[({4-[(4-cyanophenyl)oxy]phenyl}methyl) (ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-((3*S*)-3-{ethyl[(4-{[4-(methyloxy)phenyl]oxy}phenyl) methyl] amino} -1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-((3*S*)-3-{ethyl[(3-{[4-(methyloxy)phenyl]oxy} phenyl)methyl] amino} -1-pyrrolidinyl)-3-pyridinecarboxylate; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a compound of Formula (XI) suitable for use in the present invention:



(XI)

wherein:

n is 1;

R_1 is H, methyl or phenyl;

R_4 is straight or branched C_{1-6} alkyl, cycloalkyl or $(CH_2)_x$-cycloalkyl;

R_5 is straight or branched C_{1-6} alkyl, alkoxyalkyl, phenyl, heteroaryl;

wherein R_5 optionally is substituted with at least one of the following substitutents straight or branched C_{1-6} alkyl, straight or branched C_{1-6} haloalkyl, straight or branched C_{1-6}-alkoxy, $-O(CH_2)_nC(O)R_x$, phenyl, substituted phenyl, phenoxy, benzyloxy, pyridinyl, thienyl, piperidinyl or $-(CH_2)_x -N(R_{1h}) -(CH_2)_x R_{1i;}$

wherein:

R_{1h} is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl or substituted phenyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5, wherein:

each phenyl or substituted phenyl substitutent as defined in R_{1i}, above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, -OC(O)OH, $-OC(O)R_{1j}$, $-C(O)OR_{1k}$,–$SO_2N(R_{1l})_2$, -straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy; or

R_x is straight or branched C_{1-6} alkyl

benzyloxy, phenoxy, substituted phenyl is optionally substituted by at least one of the following substituents halogen, -CN, straight or branched C_{1-6} alkyl straight or branched C_{1-6}-alkoxy;

wherein:

y is 0 or an integer from 1 to 5;

R_{1j} , R_{1k} or R_{1l} is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof.

The present invention also relates to use of a compound of formula (XI), suitable for use in the present invention, where R_4 is ethyl and R_5 is phenyl, furanyl, thienyl, piperidinyl, or pyridinyl.

Representative examples of compounds of Formula (XI), suitable for use in the present invention, include, but are not limited to:

1-methylethyl 2-{(3R)-3-[({2-[(difluoromethyl)oxy]phenyl} methyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[2-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[ethyl({2-[(4-fluorophenyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-((3R)-3-{ethyl[(2-{[2-(ethyloxy)-2-oxoethyl] oxy}phenyl)methyl] amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[3-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[({3-[(4-chlorophenyl)oxy]phenyl} methyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[[(3-{[4-(1,1-dimethylethyl)phenyl] oxy}phenyl)methyl] (ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[{[3-(butyloxy)phenyl]methyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[ethyl({4-[(1-methylethyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4-(hexyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-((3R)-3-{ethyl[(4-{[(4-fluorophenyl)methyl]oxy} phenyl)methyl] amino}-

1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[ethyl({4-[(2-methylpropyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-((3R)-3-{ethyl[(4'-ethyl-4-biphenylyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[[(2'-chloro-4-biphenylyl)methyl](ethyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[ethyl({2-[(phenylmethyl)oxy] phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[3-(2-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-((3R)-3-{ethyl[(4'-fluoro-3-biphenylyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[2-(3-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-((3R)-3-{ethyl[(4'-fluoro-2-biphenylyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[3-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;1-methylethyl 2-{(3*R*)-3-[ethyl(2-furanylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl(2-thienylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl(3-furanylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(5-methyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(methyloxy)carbonyl]phenyl} methylamino]-1-

pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({2-[(trifluoromethyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(2-methylphenyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(3-fluorophenyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({4-(methyloxy)-3-[(phenylmethyl) oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(3-fluoro-2-methylphenyl) methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({2-[(1-methylethyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(3-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({3-[(1-methylethyl)oxy]phenyl} methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(5-ethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(2-methylpropyl)oxy] phenyl}methyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl(3-pyridinylmethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl(3-furanylmethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(5-methyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(3-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[[1-(3-chlorophenyl)-4-piperidinyl](ethyl) amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(4'-fluoro-3-biphenylyl)methyl]amino}-1-pyrrolidinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-((3*R*)-3-{ethyl[(2'-methyl-2-biphenylyl)methyl] amino}-1-pyrrolidinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[({2-[(3-chlorophenyl)oxy]phenyl}methyl) (ethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[({3-[(4-chlorophenyl)oxy]phenyl}methyl) (ethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({3-[(2-methylpropyl)oxy]phenyl} methyl) amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[[(4,5-dimethyl-2-furanyl)methyl](ethyl) amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl(phenylmethyl)amino]-1-pyrrolidinyl}-4-methyl-3-

pyridinecarboxylate;

1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(1-methylethyl)oxy]phenyl}methyl) amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate;

1-Methylethyl-2-((3R)-3-{ethyl[(4'-fluoro-2-biphenylyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl} phenyl) methyl] (ethyl) amino] -1-pyrrolidinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino] methyl} phenyl)methyl](ethyl)amino]-1-pyrrolidinyl}-3-pyridine carboxylate; or

a pharmaceutically acceptable salt thereof.

In another aspect, additional representative compounds, suitable for use in the present invention, which are encompassed and defined by Formulas (I) to (XI), respectively of the present invention, include, but are not limited to:

1-Methylethyl2-{4-[(5-ethyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-{4-[(4,5-dimethyl-2-thienyl)methyl]-1-piperazinyl} -3-pyridine carboxylate;

1-Methylethyl 2-{4-[(4-ethylphenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

1-Methylethyl 2-{4-[(2-ethylphenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-Methylethyl 2-{methyl[(3*S*)-1-(phenylmethyl)-3-pyrrolidinyl]amino}-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-{methyl[(3*R*)-1-(phenylmethyl)-3-pyrrolidinyl]amino}-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-((3*S*)-3-{[(5-ethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{[(4,5-dimethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{[(3-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;1-Methylethyl 2-((3*S*)-3-{[(4-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{[(2-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[[(5-ethyl-2-thienyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[[(4,5-dimethyl-2-thienyl)methyl](methyl)amino]-1-

pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[[(3-ethylphenyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[[(4-ethylphenyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[[(2-ethylphenyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{ethyl[(5-ethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-{(3*S*)-3-[[(4,5-dimethyl-2-thienyl)methyl](ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{ethyl[(3-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{ethyl[(4-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-((3*S*)-3-{ethyl[(2-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride;

1-Methylethyl 2-{(3*R*)-3-[ethyl(phenylmethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

2-{(3*R*)-3-[Ethyl(phenylmethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylic acid;

1-Methylethyl2-{methyl[(3*R*)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate hydrochloride;

1-methylethyl 2-(4-{[3-(Phenylmethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride ;

1-Methylethyl 2-(4-{[4-(phenylmethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride;

1-Methylethyl2-[4-(2-phenylethyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride;

1-Methylethyl 2-(4-{[4-(3-phenylpropyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride;

1-Methylethyl2-[4-({3-[methyl(phenylcarbonyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride;

1-Methylethyl 2-[4-({4-[methyl(phenylcarbonyl)amino]phenyl}methyl)-1-piperazinyl]-

3-pyridinecarboxylate hydrochloride;

1-methylethyl 2-[4-({3-[(dimethylamino)carbonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride;

1-Methylethyl 2-[4-({4-[(dimethylamino)carbonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride;

1-Methylethyl 2-(4-{[4-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-(4-{[3-(phenylthio)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-(4-{[4-(phenylthio)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-[4-({3-[(phenylmethyl)thio]phenyl}methyl)-1-piperazinyl] -3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-[4-({4-[(phenylmethyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate hydrochloride;

1-Methylethyl 2-(4-{[3-(hydroxymethyl)phenyl]methyl}-1-piperazinyl) -3-pyridine carboxylate;

1-Methylethyl 2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl] amino} methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate; or a pharmaceutically acceptable salt thereof.

In another aspect, additional representative compounds, suitable for use in the present invention, which are encompassed and defined by Formulas (I) to (XI), respectively of the present invention are:

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino)(3S)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);

benzene-1,4-diylbis[methanediyl(ethylimino)(3R)-3,1-pyrrolidinediyl-2,3-pyridinediylmethanediyl] bis(3,3-dimethylbutanoate;

1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-

pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl) -3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4-({ethyl[(3R)-1-(1-{2-[(1-methylethyl)oxy]-2-oxoethyl}ethenyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{(3R)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate;

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(2S)-1,2-pyrrolidinediylmethanediyloxy]}di(3-pyridinecarboxylate); or

pharmaceutically acceptable salts thereof.

B. Dimer Compounds

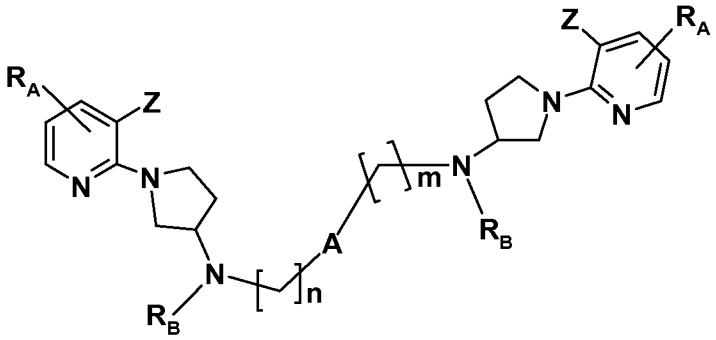
In general, the present invention relates to use of dimer compounds and corresponding dimer preparation methods, where the aforementioned dimers are formed from precursors, intermediates or monomeric compounds of Formulas (I) to (XI), respectively, of the present invention as defined above and a reactant containing a linker group A.

In another aspect, dimer compounds suitable for use in the present invention may be structurally symmetric or asymmetric as formed based upon selection of corresponding precursors, intermediates or monomeric compounds of Formulas (I) to (XI), respectively, as defined in the present specification above.

In one aspect, as suitable for use in the present invention is reactant containing a linker group A may include, but is not limited to the following functional groups straight or branched C_1-C_6-alkyl, straight or branched C_1-C_6-thioalkyl, straight or branched C_1-C_6-aminoalkyl, substituted straight or branched C_1-C_6-aminoalkyl straight or branched C_1-C_6-alkoxy, C_4-C_7cycloalkyl, aryl, heterocycloalkyl or heteroaryl as

defined above in the section entitled Substituents.

In one aspect, the present invention relates to a dimer compound of formula (XII) suitable for use in the present invention:



(XII)

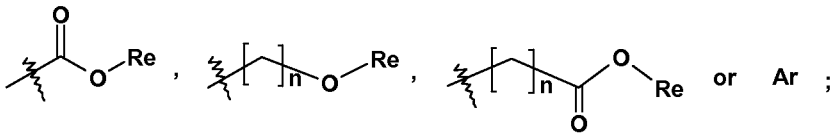
wherein:

n is 0 or an integer from 1 to 5;

m is 0 or an integer from 1 to 5;

A is straight or branched C_{1-6} alkyl, aryl or heteroaryl;

Z is



;

R_A is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_a$, $-SR_a$ or $-OR_a$;

R_B is H, straight or branched C_{1-6}alkyl or cycloalkyl;

wherein:

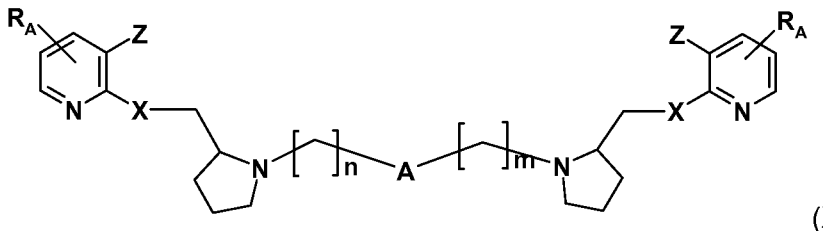
R_a is selected from phenyl or substituted phenyl;

R_e is H, straight or branched C_{1-6} alkyl or cycloalkyl; or

a pharmaceutically acceptable salt thereof.

The present invention also relates to a dimer compound of Formula (XII), suitable for use in the present invention, where A is isopropyl, dimethylpentyl or phenyl.

In another aspect, the present invention relates to a dimer compound of Formula (XIII) suitable for use in the present invention:



(XIII)

wherein:

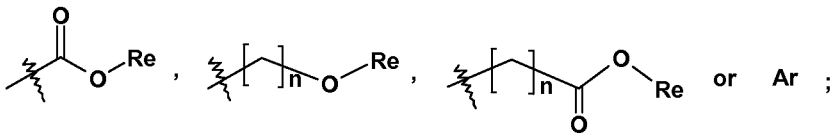
n is 0 or an integer from 1 to 5;

m is 0 or an integer from 1 to 5;

A is straight or branched C_{1-6} alkyl, phenyl or heteroaryl;

X is O, N or S;

Z is



R_A is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_a$, $-SR_a$ or $-OR_a$;

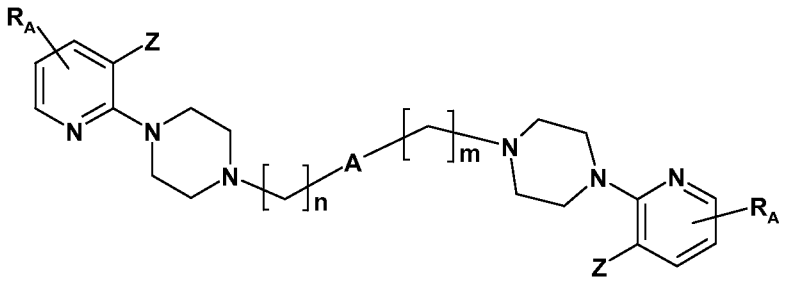
wherein:

R_a is selected from phenyl or substituted phenyl;

R_e is H, straight or branched C_{1-6} alkyl or cycloalkyl; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a dimer compound of Formula (XIV) suitable for use in the present invention:



(XIV)

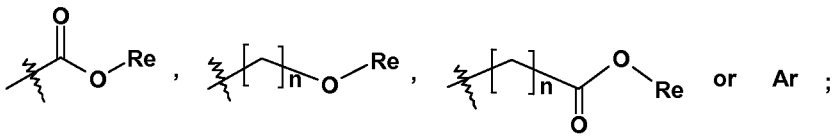
wherein:

n is 0 or an integer from 1 to 5;

m is 0 or an integer from 1 to 5;

A is straight or branched C_{1-6} alkyl, phenyl or heteroaryl;

Z is



R_A is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_a$, $-SR_a$ or $-OR_a$;

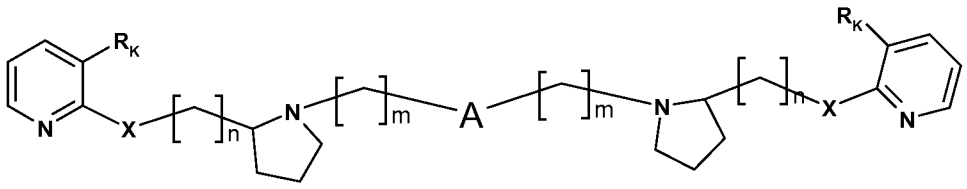
wherein:

R_a is selected from phenyl or substituted phenyl;

R_e is H, straight or branched C_{1-6} alkyl or cycloalkyl; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a dimer compound of Formula (XV) suitable for use in the present invention:



(XV)

wherein:

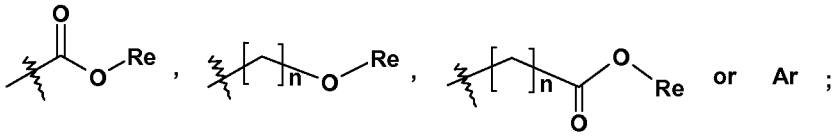
n is 0 or an integer from 1 to 5;

m is 0 or an integer from 1 to 5;

A is straight or branched C_{1-6} alkyl, phenyl or heteroaryl;

X is O, N or S;

R_K is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_a$, $-SR_a$, $-OR_a$; or



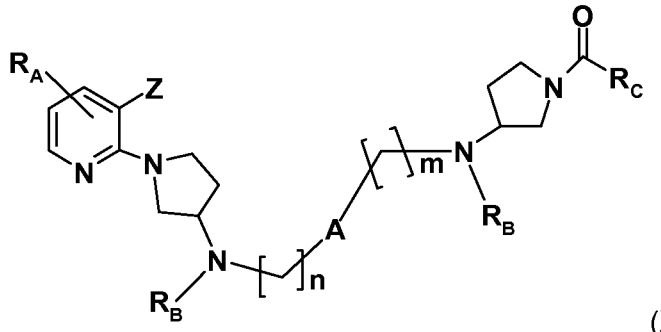
wherein:

R_a is selected from phenyl or substituted phenyl;

R_e is H, straight or branched C_{1-6} alkyl or cycloalkyl; or

a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to a dimer compound of Formula (XVI) suitable for use in the present invention:



(XVI)

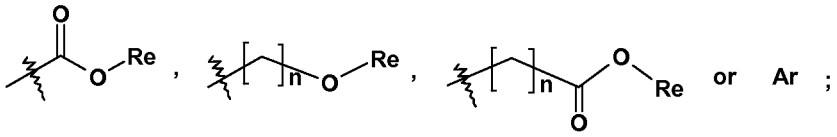
wherein:

n is 0 or an integer from 1 to 5;

m is 0 or an integer from 1 to 5;

A is straight or branched C_{1-6} alkyl, phenyl or heteroaryl;

Z is



R_A is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_a$, $-SR_a$ or $-OR_a$;

R_B is H, straight or branched C_{1-6}alkyl or cycloalkyl;

R_C is H, straight or branched C_{1-6}alkyl, phenyl or $-OR_b$;

wherein:

R_a is selected from phenyl or substituted phenyl;

R_b is H, straight or branched C_{1-6} alkyl or cycloalkyl;

R_e is H, straight or branched C_{1-6} alkyl or cycloalkyl; or

a pharmaceutically acceptable salt thereof.

In one aspect of the present invention, representive dimer compounds of Formulas (XII) to (XVI), suitable for use in the present invention, which may include, but are not limited to:

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);

bis(1-methylethyl) 2,2'-{benzene-1,3-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);

1-methylethyl 2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*S*)-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

bis(1-methylethyl) 2,2'-{benzene-1,3-diylbis[methanediyl(2*S*)-1,2-pyrrolidinediyl methanediyloxy]}di(3-pyridinecarboxylate);

benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) hydrochloride;

benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] dibenzoate hydrochloride;

bis(1-methylethyl)2,2'-[benzene-1,4-diylbis(methanediyl-4,1-piperazinediyl)]di(3- pyridinecarboxylate);

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(2*S*)-1,2-pyrrolidinediyl methanediyloxy]}di(3-pyridinecarboxylate);

1-Methylethyl 2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl] amino} methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*S*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate) or

a pharmaceutically acceptable salt thereof.

In another aspect of the present invention, a representive dimer compound suitable for use in the present invention , may include, but is not limited to: bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate) or a pharmaceutically acceptable salt thereof.

In another aspect of the present invention, a representive dimer compound suitable for use in the present invention , may include, but is not limited to: bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate); or a pharmaceutically acceptable salt thereof.

In another aspect, dimer compounds of the present invention, suitable for use in the present invention, may be structurally symmetric or asymmetric as

formed based upon selection of corresponding precursors, intermediates or monomeric compounds of Formulas (I) to (XVI), respectively, as defined in the present specification above.

Additional representative examples of such dimers suitable for use in the present invention, include, but are not limited to:

Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);

Bis(1-methylethyl) 2,2'-{benzene-1,3-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridine carboxylate);

1-Methylethyl 2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*S*)-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

Bis(1-methylethyl) 2,2'-{benzene-1,3-diylbis[methanediyl(2*S*)-1,2-pyrrolidinediyl methanediyloxy]}di(3-pyridinecarboxylate);

Benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) hydrochloride;

Benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl -2,3-pyridinediylmethanediyl] dibenzoate hydrochloride;

Bis(1-methylethyl) 2,2'-[benzene-1,4-diylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridinecarboxylate);

Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(2*S*)-1,2-pyrrolidinediyl methanediyloxy]}di(3-pyridinecarboxylate);

Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*S*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);

Bis(1-methylethyl) 2,2'-[(ethylimino)bis(methanediylbenzene-4,1-diylmethanediyl-4,1-piperazinediyl)]di(3-pyridinecarboxylate);

(3*R*)-*N*,*N*-diethyl-*N*-{[4-({ethyl[(3*R*)-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-3-pyrrolidinaminium;

1H-pyrazole-3,5-diylbis[methanediyl(ethylimino)(3R)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) quaternary hydrochloride;2,5-pyrazinediylbis[methanediyl(ethylimino)(3R)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) hydrochloride;

Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediylimino(3R)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);Bis(1-methylethyl) 2,2'-[2,5-

pyrazinediylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridine carboxylate); or pharmaceutically acceptable salts thereof.

It is recognized that the compounds of Formulas (I) to (XVI), respectively, suitable for use in the present invention as defined above may exist in forms as stereoisomers, regioisomers, or diastereiomers. These compounds may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. For example, compounds of the present invention may exist as a racemic mixture of R(+) and S(-) enantiomers, or in separate respectively optical forms, i.e., existing separately as either the R(+) enantiomer form or in the S(+) enantiomer form. All of these individual compounds, isomers, and mixtures thereof are included within the scope of the present invention.

SUBSTITUENT DEFINITIONS

As used herein, the term "alkyl" represents a saturated, straight or branched hydrocarbon moiety, which may be unsubstituted or substituted by one, or more of the substituents defined herein. Exemplary alkyls include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and the like. The term "C1-C6" refers to an alkyl containing from 1 to 6 carbon atoms.

When the term "alkyl" is used in combination with other substituent groups, such as "haloalkyl" or "hydroxyalkyl", "arylalkyl", the term "alkyl" is intended to encompass a divalent straight or branched-chain hydrocarbon radical. For example, haloalkyl is intended to mean a saturated, straight or branched hydrocarbon moiety substituted with one or more halogen groups, where halogen is fluoro, chloro, bromo or iodo. Representative haloalkyls include, but are not limited to trifluoromethyl ($-CF_3$). tetrafluoroethyl ($-CF_2CHF_2$), pentafluoroethyl ($-CF_2CF_3$) and the like. For example, hydroxyalkyl is intended to mean a saturated, straight or branched hydrocarbon moiety substituted with one or more hydroxy groups. .

As used herein, the term "alkenyl" refers to a straight or branched hydrocarbon moiety containing at least 1 and up to 3 carbon-carbon double bonds. Examples include ethenyl and propenyl.

As used herein, the term "alkynyl" refers to a straight or branched hydrocarbon moiety containing at least 1 and up to 3 carbon-carbon triple bonds. Examples include ethynyl and propynyl.

As used herein, the term “cycloalkyl” refers to a non-aromatic, saturated, cyclic

hydrocarbon ring. The term "(C_3-C_8)cycloalkyl" refers to a non-aromatic cyclic hydrocarbon ring having from three to eight ring carbon atoms. Exemplary "(C3-C8)cycloalkyl" groups useful in the present invention include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

"Alkoxy" refers to a group containing an alkyl radical attached through an oxygen linking atom. The term "(C_1-C_6)alkoxy" refers to a straight- or branched-chain hydrocarbon radical having at least 1 and up to 6 carbon atoms attached through an oxygen linking atom. Exemplary "(C_1-C_4)-alkoxy" groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, s-butoxy, and t-butoxy. Representative haloalkoxy include, but are not limited to difluoromethoxy (-$OCHCF_2$), trifluoromethoxy (-OCF_3), tetrafluoroethoxy (-OCF_2CHF_2) and the like.

"Alkylthio-" refers to a group containing an alkyl radical atoms attached through an sulfur linking atom. The term "(C1-C4)alkylthio-" refers to a straight- or branched-chain hydrocarbon radical having at least 1 and up to 4 carbon atoms attached through a sulfur linking atom. Exemplary "(C1-C4)alkylthio-" groups useful in the present invention include, but are not limited to, methylthio-, ethylthio-, n-propylthio-, isopropylthio-, n-butylthio-, s-butylthio-, t-butylthio- and the like.

"Cycloalkyloxy", "cycloalkylthio", "cycloalkylamino" refers to a group containing a saturated carbocyclic ring atoms attached through an oxygen, nitrogen or sulfur linking atom, respectively.

"Aryl" represents a group or moiety comprising an aromatic, monovalent monocyclic or bicyclic hydrocarbon radical containing from 6 to 10 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents defined herein, and to which may be fused one or more cycloalkyl rings, which may be unsubstituted or substituted by one or more substituents defined herein. Representative aryl groups suitable for use in the present invention, may include, but are not limited to phenyl, naphthalenyl, fluorenyl, and the like.

Heterocyclic groups may be heteroaryl or heterocycloalkyl groups.

"Heterocycloalkyl" represents a group or moiety comprising a non-aromatic, monovalent monocyclic or bicyclic radical, which is saturated or partially unsaturated, containing 3 to 10 ring atoms, which includes 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents defined herein. Illustrative examples of heterocycloalkyls include, but are not limited to, azetidinyl, pyrrolidyl (or pyrrolidinyl),

piperidinyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl (or tetrahydrofuranyl), dihydrofuryl, oxazolinyl, thiazolinyl, pyrazolinyl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl, 1,5,9-triazacyclododecyl and the like.

Generally, in the compounds of this invention, heterocycloalkyl groups are 5-membered and/or 6-membered heterocycloalkyl groups, such as pyrrolidyl (or pyrrolidinyl), tetrahydrofuryl (or tetrahydrofuranyl), tetrahydrothienyl, dihydrofuryl, oxazolinyl, thiazolinyl or pyrazolinyl, piperidyl (or piperidinyl), piperazinyl, morpholinyl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxanyl, tetrahydro-2H-1,4-thiazinyl, 1,4-dioxanyl, 1,3-oxathianyl, and 1,3-dithianyl.

"Heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic or bicyclic radical, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. This term also encompasses bicyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 10 ring atoms, including 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. Illustrative examples of heteroaryls include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl (or furanyl), isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl (or pyridinyl), pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, tetrazolyl, benzo[b]thienyl, isobenzofuryl, 2,3-dihydrobenzofuryl, chromenyl, chromanyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthridinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, isothiazolyl, carbazolyl, 1,2,3,4 tetrahydro isoquinolinyl and the like.

Generally, the heteroaryl groups present in the compounds of this invention are 5-membered and/or 6-memebred monocyclic heteroaryl groups. Selected 5-membered heteroaryl groups contain one nitrogen, oxygen or sulfur ring heteroatom, and optionally contain 1, 2 or 3 additional nitrogen ring atoms. Selected 6-membered heteroaryl groups contain 1, 2, 3 or 4 nitrogen ring heteroatoms. Selected 5- or 6-membered heteroaryl groups include thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, triazolyl, and tetrazolyl or pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl.

"Oxo" represents a double-bonded oxygen moiety; for example, if attached directly to a carbon atom forms a carbonyl moiety (C=O), or attached to an N or S forms oxides, N-oxides, sulfones or sulfoxides.

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Hydroxy" or "hydroxyl" is intended to mean the radical –OH.

As used herein, the term "compound(s) of the invention" means a compound of Formulas (I) to (XVI), respectively (as defined above) in any form, i.e., any salt or non-salt form (e.g., as a free acid or base form, or as a pharmaceutically acceptable salt thereof) and any physical form thereof (e.g., including non-solid forms (e.g., liquid or semi-solid forms), and solid forms (e.g., amorphous or crystalline forms, specific polymorphic forms, solvates, including hydrates (e.g., mono-, di- and hemi- hydrates)), and mixtures of various forms.

As used herein, the term "optionally substituted" means that a group, such as, which may include, but is not limited to alkyl, aryl, heteroaryl, etc., may be unsubstituted, or the group may be substituted with one or more substituent(s) as defined. In the case where groups may be selected from a number of alternative groups the selected groups may be the same or different.

The term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

The alternative definitions for the various groups and substitutent groups of Formulas (I) to (XVI), respectively, provided throughout the specification are intended to particularly describe each compound species disclosed herein, individually, as well as groups of one or more compound species. The scope of this invention includes any combination of these group and substituent group definitions.

ENANTIOMERS, DIASTEREOMERS AND POLYMORPHS

The compounds according to Formulas (I) to (XVI), suitable for use in the present invention, may contain one or more asymmetric center (also referred to as a chiral center) and may, therefore, exist as individual enantiomers, diastereomers, or other stereoisomeric forms, or as mixtures thereof. Chiral centers, such as chiral carbon atoms, may also be present in a substituent such as an alkyl group. Where the stereochemistry of a chiral center present in Formula (I), or in any chemical structure illustrated herein, is not specified the structure is intended to encompass all individual stereoisomers and all mixtures thereof. Thus, compounds according to Formula (I)

containing one or more chiral center may be used as racemic mixtures, enantiomerically enriched mixtures, or as enantiomerically pure individual stereoisomers.

Individual stereoisomers of a compound according to Formulas (I) to (XVI), suitable for use in the present invention, which contain one or more asymmetric center may be resolved by methods known to those skilled in the art. For example, such resolution may be carried out (1) by formation of diastereoisomeric salts, complexes or other derivatives; (2) by selective reaction with a stereoisomer-specific reagent, for example by enzymatic oxidation or reduction; or (3) by gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. The skilled artisan will appreciate that where the desired stereoisomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired form. Alternatively, specific stereoisomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. When a disclosed compound or its salt is named or depicted by structure, it is to be understood that the compound or salt, including solvates (particularly, hydrates) thereof, may exist in crystalline forms, non-crystalline forms or a mixture thereof. The compound or salt, or solvates (particularly, hydrates) thereof, may also exhibit polymorphism (i.e. the capacity to occur in different crystalline forms). These different crystalline forms are typically known as “polymorphs.” It is to be understood that when named or depicted by structure, the disclosed compound, or solvates (particularly, hydrates) thereof, also include all polymorphs thereof. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. One of ordinary skill in the art will appreciate that different polymorphs may be produced, for example, by changing or adjusting the conditions used in crystallizing/recrystallizing the compound.

SALTS

Because of their potential use in medicine, the salts of the compounds of Formulas (I) through Formula (XVI) suitable for use in the present invention are preferably pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts include

those described by Berge, Bighley and Monkhouse J.Pharm.Sci (1977) 66, pp 1-19.

When a compound suitable for use in the present invention is a base (contain a basic moiety), a desired salt form may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, phenylacetates, phenylpropionates, phenylbutrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates mandelates, and sulfonates, such as xylenesulfonates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates and naphthalene-2-sulfonates.

If an inventive basic compound suitable for use in the present invention is isolated as a salt, the corresponding free base form of that compound may be prepared by any suitable method known to the art, including treatment of the salt with an inorganic or organic base, suitably an inorganic or organic base having a higher pK_a than the free base form of the compound.

When a compound suitable for use in the present invention , may include, but is not limited to: is an acid (contains an acidic moiety), a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary), an alkali metal or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as ethylene diamine, dicyclohexylamine, ethanolamine, piperidine, morpholine, and piperazine, as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

Certain of the compounds suitable for use in the present invention, may form salts with one or more equivalents of an acid (if the compound contains a basic moiety) or a base (if the compound contains an acidic moiety). The present invention includes within its scope all possible stoichiometric and non-stoichiometric salt forms.

Because the compounds of this invention may contain both acid and base moieties, pharmaceutically acceptable salts may be prepared by treating these compounds with an alkaline reagent or an acid reagent, respectively. Accordingly, this invention also provides for the conversion of one pharmaceutically acceptable salt of a compound of this invention, e.g., a hydrochloride salt, into another pharmaceutically acceptable salt of a compound of this invention, e.g., a sodium salt.

SOLVATES

For solvates of the compounds of the invention, or salts thereof, suitable for use in the present invention, that are in crystalline form, the skilled artisan will appreciate that pharmaceutically-acceptable solvates may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

PURITY

Because the compounds of the present invention are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

SYNTHETIC SCHEMES AND GENERAL METHODS OF PREPARATION

The present invention also relates to use of processes for making compounds of Formulas (I) to (XVI), respectively, which are suitable for use in the present invention.

The present invention also relates to methods or uses for treatment of respiratory or respiratory tract diseases, which comprises administering to a subject in need thereof an effective amount of a compound of Formulas (I) to (XVI), respectively, which are suitable for use in the present invention.

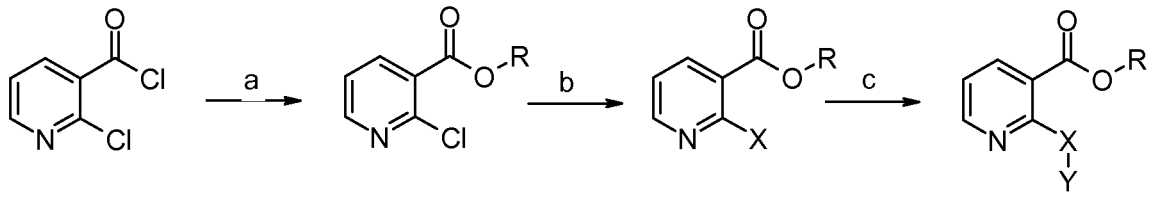
The compounds described herein, which are suitable for use in the present invention may be obtained by using synthetic procedures illustrated in Schemes 1 to 6 below or by drawing on the knowledge of a skilled organic chemist.

The synthesis provided in these Schemes 1 to 6 are applicable for producing compounds of the invention as defined by Formulas (I) to (XVI), respectively, having a variety of different functional groups as defined employing appropriate precursors, which are suitably protected if needed, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, where needed, affords compounds of the nature generally disclosed. While the Schemes 1 to 6, respectively, are shown with compounds only as defined therein, they are illustrative of processes that may be used to make the compounds of the invention.

Intermediates (compounds used in the preparation of the compounds of the invention) also may be present as salts. Thus, in reference to intermediates, the phrase "compound(s) of formula (number)" means a compound having that structural formula or a pharmaceutically acceptable salt thereof.

Synthetic Schemes

Scheme 1



1 2 3 4

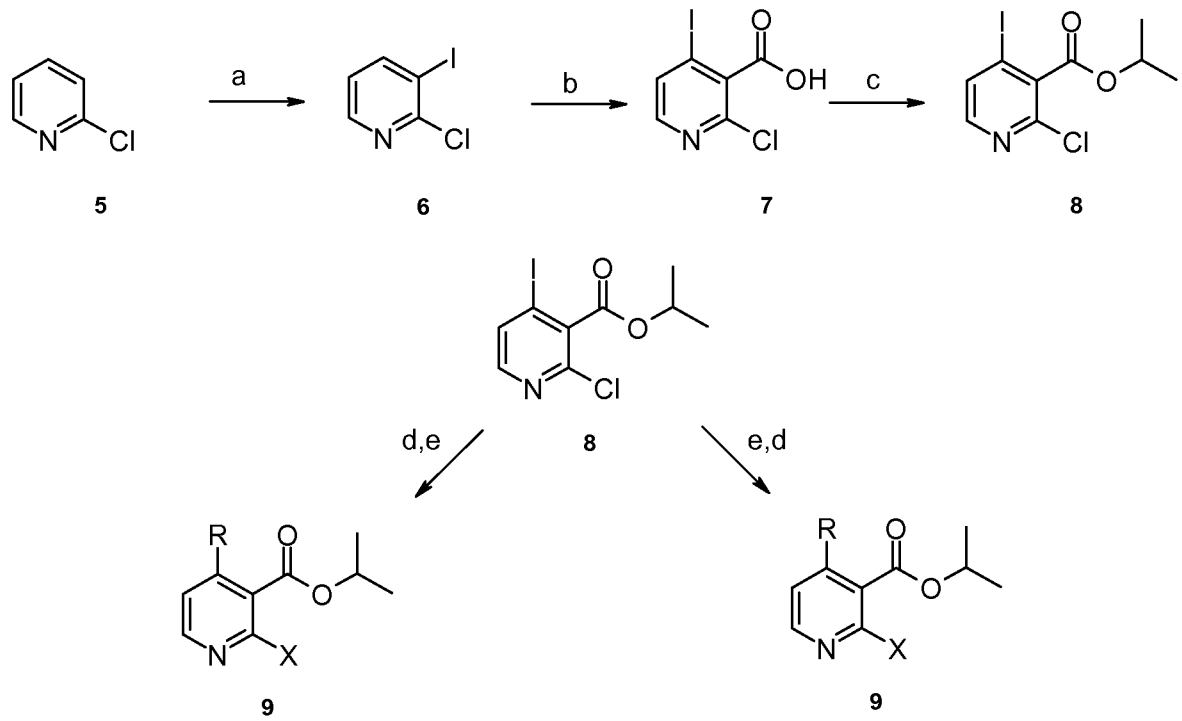
Conditions: a) ROH; b) NR1R2, DMF; c) RCHO, $Na(OAc)_3BH$;

Scheme 1 represents a general scheme for the preparation of compounds according to Compounds (3) and (4) as shown above, where X is attached to the pyridine ring via a nitrogen atom. Compound 1, (2-chloronicotinyl chloride – commercially available from Aldrich) depicted as starting material is available from commercial vendors.

Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of 2-chloronicotinyl chloride 1 in an alcoholic solvent produces the desired ester 2. Ester 2 is further transformed to aminopyridine 3 via reaction with the appropriate amine. In the case where X contains a suitable protecting group, removal of the protecting group under the appropriate conditions and further transformation to other products of the present invention may be accomplished. Subsequent transformation of the amine function of the group X to the subsequent alkylamine XY can be performed with the appropriate aldehyde of Y via a reductive amination protocol. It will be appreciated by the skilled artisan that upon conversion to the alkylamine XY the resulting product may require further elaboration. This can include but is not limited to suitable protecting and functional group manipulations and reactions with alcohols, aryl halides, phenols, anilines, and amines.

Scheme 2

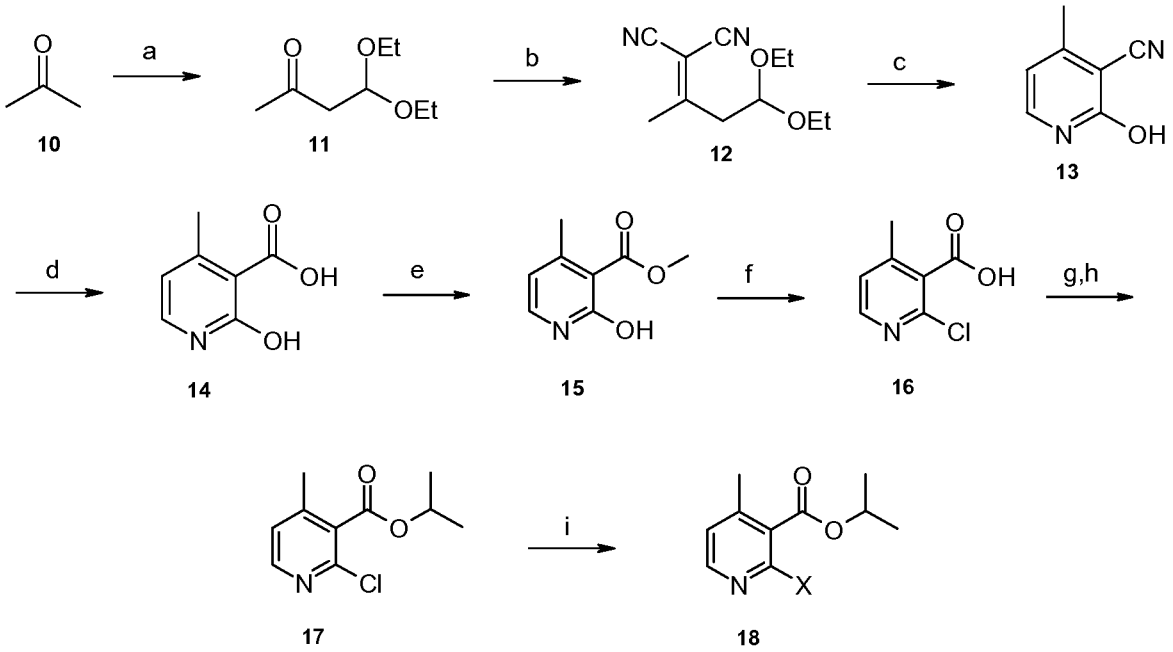


Conditions: a) 2,2,6,6-tetramethylpiperidine, n-BuLi, I_2; b) LDA, CO2; c) i-PrBr, K_2CO_3; d) NR1R2, DMF; e) $Pd(OAc)_2$, $RB(OH)_2$, (or) $RB(OR')_2$, K_2CO_3

Scheme 2 represents a general scheme for the preparation of compounds according to Compound (9) as defined above, where X is attached to the pyridine ring via a nitrogen atom and C4 is substituted. Compound 5, (2-chloropyridine) depicted as starting material is available from commercial vendors. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Deprotonation of 2-chloropyridine 5 followed by reaction with iodine produces the intermediate iodide 6. This is further transformed to the C3 acid/C4 iodide 7 via deprotonation using LDA followed by quenching with CO_2. The intermediate acid is then converted to the ester to produce the key compound 8 via treatment with isopropylbromide and potassium carbonate. With this material is hand, a 2 step sequence provides access to compounds of structure 9. In the first instance reaction with amine X where X may contain a suitable protecting group, followed by reaction of the C4 iodide provides access to 9 where the C4 substituent may be varied in the last step. Alternatively, the C4 substituent may be installed initially followed by incorporation of the C2 amine X allowing variation of the C2 position in the last step. Installation of the substituent R can be accomplished via a transition metal mediated coupling using an appropriate catalyst and coupling partner. As an example of such a transformation, for the case in Scheme 1 condition “e”, a Suzuki cross-coupling reaction can be completed using a boronic ester or acid in the presence of $Pd(OAc)_2$, Ph_3P, and K_2CO_3. Removal of any protecting group under the appropriate conditions and further transformation to other products may be accomplished. Subsequent transformation of the amine function of the group X to the subsequent alkylamine XY can be performed with the appropriate aldehyde of Y via a reductive amination protocol. It will be appreciated by the skilled artisan that upon conversion to the alkylamine XY the resulting product may require further elaboration. This can include but is not limited to suitable protecting and functional group manipulations and reactions with alcohols, aryl halides, phenols, anilines, and amines.

Scheme 3



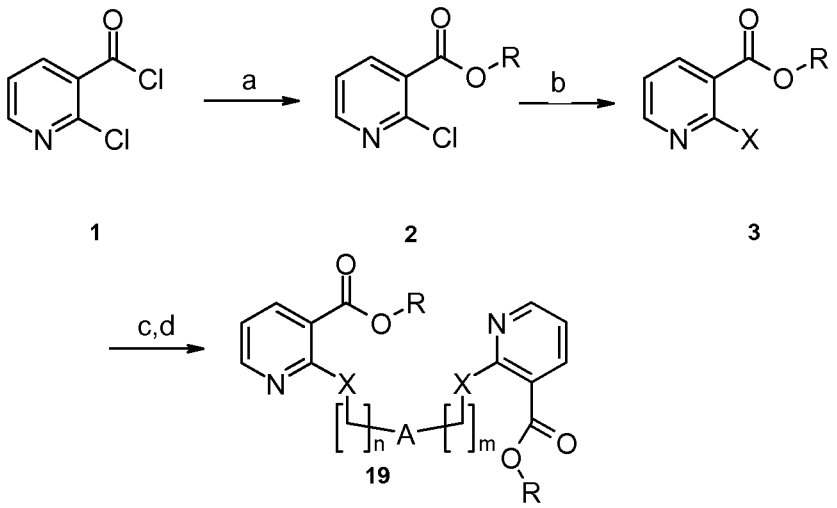
Conditions: a) $HC(OEt)_3$, $BF_3{\cdot}Et_2O$; b) malononitrile, HOAc, piperidine; c) *conc*. H_2SO_4; d) 50% H_2SO_4; e) MeOH, H_2SO_4; f) $POCl_3$; g) 20% NaOH, MeOH; h) *i*-PrI, K_2CO_3; i) NR1NR2, DMF

Scheme 3 represents a general scheme for the preparation of compounds according to Compound (18) as defined above, where X is attached to the pyridine ring via a nitrogen atom and C4 is substituted with a methyl group. Compound 10, (acetone) depicted as starting material is commercially available from commercial vendors. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of acetone with triethyl orthoformate produces the homologated ketone 11. Condensation with malononitrile and subsequent cyclization under acidic conditions produces pyridine 12. With this intermediate in hand, conversion through to the intermediate chloride 17 results from a series of functional group manipulations including hydroysis of the nitrile to the acid, conversion of the acid to the methylester, reaction with POCl3 to produce the C2 chloride, hydrolysis of the ester to the acid and subsequent transformation of the acid to the isopropyl ester. Compound 17 can then

be transformed to final products of the invention using conditions described in Scheme 3 above.

Scheme 4

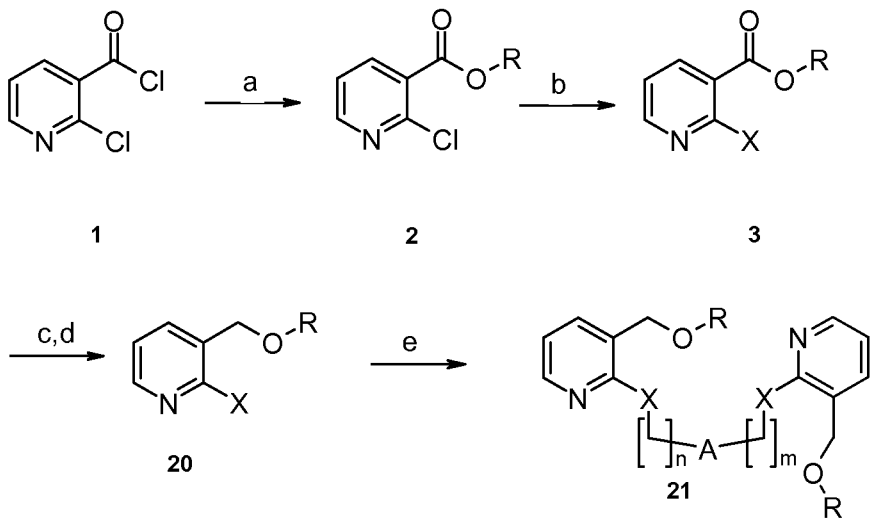


Conditions: a) ROH; b) NR1R2, DMF; c) NaH, RBr, d) RBr, K_2CO_3

Scheme 4 represents a general scheme for the preparation of dimeric compounds (19) according to Compound 19 as defined above, where X is attached to the pyridine ring via a nitrogen atom. Compound 1, (2-chloronicotinyl chloride) depicted as starting material is available from commercial vendors. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of 2-chloronicotinyl chloride 1 in an alcoholic solvent produces the desired ester 2. Ester 2 is further transformed to aminopyridine 3 via reaction with the appropriate amine. In the case where X contains a suitable protecting group, removal of the protecting group under the appropriate conditions and further transformation to other products may be accomplished. In the case where the amine used to transform 2 to 3 is 3-Boc-aminopyrrolidine, installation of the alkyl group is achieved prior to removing the protecting group. With the protecting group removed, completion of the dimeric analogs 19 can be achieved via reaction with the appropriate benzyl or alkyl bromide under basic conditions. For the case where X is piperazine, the dimer analog can be made by reacting with the appropriate aldehyde bromide under basic conditions initially followed by reductive amination as described for Scheme 1.

Scheme 5

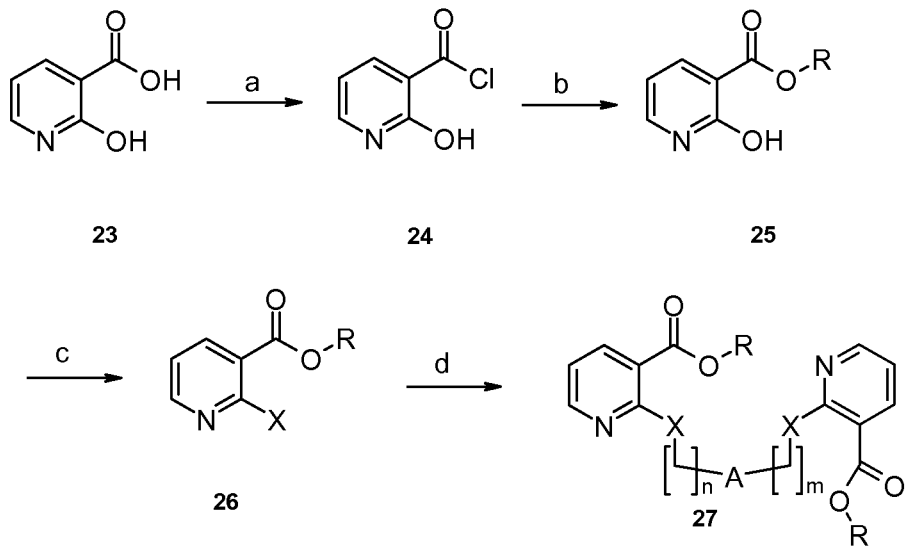


Conditions: a) ROH; b) NR1R2, DMF; c) LAH, THF; d) RCOCl, TEA, DCM; e) RBr, K_2CO_3

Scheme 5 represents a general scheme for the preparation of dimeric compounds (21) according to Compound 21, where X is attached to the pyridine ring via a nitrogen atom. Compound 1, (2-chloronicotinyl chloride) depicted as starting material is available from commercial vendors. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of 2-chloronicotinyl chloride 1 in an alcoholic solvent produces the desired ester 2. Ester 2 is further transformed to aminopyridine 3 via reaction with the appropriate amine. In the case where the amine used to transform 2 to 3 is 3-Boc-aminopyrrolidine, installation of the N-alkyl group can be achieved with the appropriate alkyl halide. Reduction of the ester to alcohol can then be achieved under reducing conditions using a reagent like lithium aluminium hydride. Formation of the ester is then accomplished via reaction with the appropriate acid chloride under basic conditions or with the appropriate acid in the presence of a coupling reagent. In the case where X contains a suitable protecting group, removal of the protecting group under the appropriate conditions and further transformation to other products may be accomplished. With the protecting group removed, completion of the dimeric analogs 21 can be achieved via reaction with the appropriate benzyl or alkyl bromide under basic conditions or in some cases via reaction with the appropriate dialdehyde under reductive amination conditions. For the case where X is piperazine, the dimer analog can be made by reacting initially with the appropriate aldehyde bromide under basic conditions followed by reductive amination as described for Scheme 1.

Scheme 6



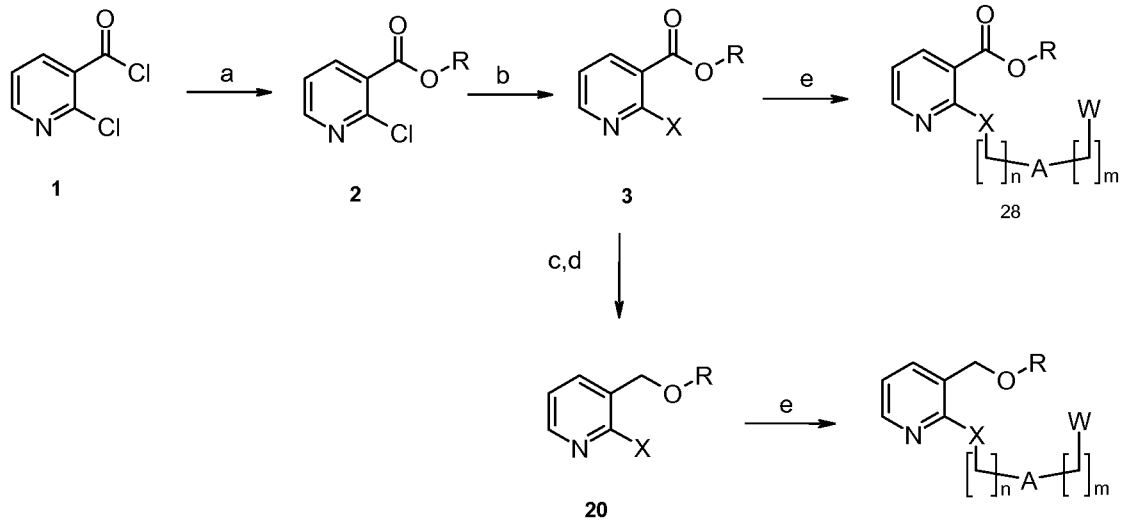
Conditions: a) Oxalyl chloride, DCM, DMF; b) ROH, TEA; b) ROH, DIAD, Ph_3P; c) RBr, K_2CO_3

Scheme 6 represents a general scheme for the preparation of dimeric compounds (27) according to Compound (27) as defined above, where X is attached to the pyridine ring via an oxygen atom. Compound 23, (2-hydroxynicotinic acid) depicted as starting material is available from commercial vendors. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of 2-hydroxynicotinic acid 23 with oxalyl chloride produces the desired acid chloride 24. Acid chloride 24 is further transformed to ester 25 via reaction with the appropriate alcohol in presence of triethylamine. Conversion of the phenol to the requisite ether is then achieved under Mitsunobu conditions. In the case where X contains a suitable protecting group, removal of the protecting group under the appropriate conditions and further transformation to other products may be accomplished. With the protecting group removed, completion of the dimeric analogs 27 can be achieved via reaction with the appropriate benzyl or alkyl bromide under basic conditions or in some cases via reaction with the appropriate dialdehyde under reductive amination conditions. Alternatively, the dimer analog may be made by

reacting initially with the appropriate aldehyde bromide under basic conditions followed by reductive amination as described for Scheme 1.

Scheme 7



Conditions: a) ROH; b) NR1R2, DMF; c) LAH, THF; d) RCOCl, TEA, DCM; e) RBr, K_2CO_3

Scheme 7 represents a general scheme for the preparation of dimeric compounds (28) and (29), respectively. Compound 1, (2-chloronicotinyl chloride) depicted as starting material is commercially available. Reaction conditions are as described above in the scheme; however, the skilled artisan will appreciate that certain modifications in the reaction conditions and/or reagents used are possible.

Treatment of 2-chloronicotinyl chloride 1 in an alcoholic solvent produces the desired ester 2. Ester 2 is further transformed to aminopyridine 3 via reaction with the appropriate amine. In the case where the amine used to transform 2 to 3 is 3-Boc-aminopyrrolidine, installation of the N-alkyl group can be achieved with the appropriate alkyl halide.

In the case where X contains a suitable protecting group, removal of the protecting group under the appropriate conditions and further transformation to other products may be accomplished. With the protecting group removed, reaction with a benzyl or alkyl bromide, or benzyl or alkyl aldehyde, followed by an appropriate amine group “W” results completion of the dimeric analog (28).

Alternatively, reduction of the ester to alcohol can then be achieved under reducing conditions using a reagent like lithium aluminium hydride. Formation of the ester is then accomplished via reaction with the appropriate acid chloride under basic

conditions or with the appropriate acid in the presence of a coupling reagent. In the case where X contains a suitable protecting group, removal of the protecting group under the appropriate conditions and further transformation to other products may be accomplished. With the protecting group removed, completion of the dimeric analog (29), respectively, can be achieved via reaction with the appropriate benzyl or alkyl bromide under basic conditions or in some cases via reaction with the appropriate dialdehyde under reductive amination conditions. For the case where X is piperazine, the dimer analog can be made by reacting initially with the appropriate aldehyde bromide under basic conditions followed by reductive amination as described for Scheme 1.

PHARMACEUTICAL COMPOSITIONS, DOSAGE FORMS AND REGIMENS

The present invention relates to compounds of Formulas (I) to (XVI) and corresponding pharmaceutical compositions comprising compounds of Formulas (I) to (XVI), respectively, which are suitable for use in the present invention.

The compounds suitable for use in the present invention will normally, but not necessarily, be formulated into a pharmaceutical composition prior to administration to a patient.

Accordingly, the present invention is directed to pharmaceutical compositions or formulations suitable for use in the present invention, which comprise a compound of the invention and pharmaceutically-acceptable excipient(s). In particular, the present invention also may relate to a use of a pharmaceutical composition or formulation, which comprises a compound as defined by Formulas (I) to (XVI), respectively, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable adjuvants, carriers or excipients, and optionally one or more other therapeutic ingredients.

The pharmaceutical compositions suitable for use in the present invention may be prepared and packaged in bulk form wherein an effective amount of a compound of the invention can be extracted and then given to the patient such as with powders, syrups, and solutions for injection. Alternatively, the pharmaceutical compositions suitable for use in the present invention may be prepared and packaged in unit dosage form. For oral application, for example, one or more tablets or capsules may be administered. A dose of a pharmaceutical composition suitable for use in the present invention contains at least a therapeutically effective amount of a compound of this invention (i.e., a compound of Formula (I) or a salt, particularly a pharmaceutically

acceptable salt, thereof). When prepared in unit dosage form, the pharmaceutical compositions or formulations may contain from 1 mg to 1000 mg of a compound of this invention.

The pharmaceutical compositions or formulations as defined herein typically contain one compound as defined above suitable for use in the present invention.

However, in certain embodiments, the pharmaceutical compositions may contain more than one compound of the present invention. In addition, the pharmaceutical compositions of the present invention may optionally further comprise one or more additional pharmaceutically active compounds.

As used herein, "pharmaceutically-acceptable excipient" means a material, composition or vehicle involved in giving form or consistency to the composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a patient and interactions which would result in pharmaceutical compositions that are not pharmaceutically-acceptable are avoided. In addition, each excipient must of course be of sufficiently high purity to render it pharmaceutically-acceptable.

Suitable pharmaceutically-acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically-acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically-acceptable excipients may be chosen for their ability to facilitate the carrying or transporting the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically-acceptable excipients may be chosen for their ability to enhance patient compliance. Moreover, pharmaceutical compositions, formulations, dosage forms, and the like, etc. may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the

desired formulation.

Suitable pharmaceutically-acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anti-caking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically-acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically-acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically-acceptable excipients and may be useful in selecting suitable pharmaceutically-acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The compounds suitable for use in the present invention as described herein and the pharmaceutically-acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration.

With regard to the present invention, conventional dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols and solutions; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

The pharmaceutical compositions or formulations suitable for use in the present invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in

Remington's Pharmaceutical Sciences (Mack Publishing Company).

In general, pharmaceutical compositions suitable for use in the present invention are prepared using conventional materials and techniques, such as mixing, blending and the like.

The term "active agent" is defined for purposes of the present invention as any chemical substance or composition of the present invention, which can be delivered from the device into an environment of use to obtain a desired result.

The percentage of the compound in compositions can, of course, be varied as the amount of active in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It will be appreciated that the actual preferred dosages of the compounds being used in the compositions of this invention will vary according to the particular composition formulated, the mode of administration, the particular site of administration and the host being treated.

The active compounds suitable for use in the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they can be enclosed in hard or soft shell capsules, or they can be compressed into tablets, or they can be incorporated directly with the food of the diet, etc.

In one aspect, compounds of Formulas (I) to (XVI) suitable for use in the present invention may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For administration by inhalation the compounds suitable for use in the present invention as described herein may be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as tetrafluoroethane or heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine or blisters of

for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di or poly-saccharides (e.g. lactose or starch). Use of lactose is preferred. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients.

Suitably, the packing/medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

In the case of multi-dose delivery, the formulation can be pre-metered (e.g. as in Diskus, see GB 2242134, US Patent Nos. 6,632,666, 5,860,419, 5,873,360 and 5,590,645 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Patent No.s 4,778,054, 4,811,731, 5,035,237, the disclosures of which are hereby incorporated by reference) or metered in use (e.g. as in Turbuhaler, see EP 69715 or in the devices described in US Patents No. 6,321,747 the disclosures of which are hereby incorporated by reference). An example of a unit-dose device is Rotahaler (see GB 2064336 and US Patent No. 4,353,656, the disclosures of which are hereby incorporated by reference).

The Diskus inhalation device comprises an elongate strip formed from a

base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) or (Ia) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament there from.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disc-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.
In one aspect, the multi-dose blister pack is defined between two members peelably secured to one another. US Patent No.'s 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of medicament upon each actuation by means of the valve, which can be opened either

by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Where the medicament container is an aerosol container, the valve typically comprises a valve body having an inlet port through which a medicament aerosol formulation may enter said valve body, an outlet port through which the aerosol may exit the valve body and an open/close mechanism by means of which flow through said outlet port is controllable.

The valve may be a slide valve wherein the open/close mechanism comprises a sealing ring and receivable by the sealing ring a valve stem having a dispensing passage, the valve stem being slidably movable within the ring from a valve-closed to a valve-open position in which the interior of the valve body is in communication with the exterior of the valve body via the dispensing passage.

Typically, the valve is a metering valve. The metering volumes are typically from 10 to 100 μl, such as 25 μl, 50 μl or 63 μl. Suitably, the valve body defines a metering chamber for metering an amount of medicament formulation and an open/close mechanism by means of which the flow through the inlet port to the metering chamber is controllable. Preferably, the valve body has a sampling chamber in communication with the metering chamber via a second inlet port, said inlet port being controllable by means of an open/close mechanism thereby regulating the flow of medicament formulation into the metering chamber.

The valve may also comprise a 'free flow aerosol valve' having a chamber and a valve stem extending into the chamber and movable relative to the chamber between dispensing and non-dispensing positions. The valve stem has a configuration and the chamber has an internal configuration such that a metered volume is defined there between and such that during movement between is non-dispensing and dispensing positions the valve stem sequentially: (i) allows free flow of aerosol formulation into the chamber, (ii) defines a closed metered volume for pressurized aerosol formulation between the external surface of the valve stem and internal surface of the chamber, and (iii) moves with the closed metered volume within the chamber without decreasing the volume of the closed metered volume until the metered volume communicates with an outlet passage thereby allowing dispensing of the metered volume of pressurized aerosol formulation. A valve of this type is described in U.S. Patent No. 5,772,085. Additionally, intra-nasal delivery of the present compounds is effective.

To formulate an effective pharmaceutical nasal composition, the

medicament must be delivered readily to all portions of the nasal cavities (the target tissues) where it performs its pharmacological function. Additionally, the medicament should remain in contact with the target tissues for relatively long periods of time. The longer the medicament remains in contact with the target tissues, the medicament must be capable of resisting those forces in the nasal passages that function to remove particles from the nose. Such forces, referred to as 'mucociliary clearance', are recognised as being extremely effective in removing particles from the nose in a rapid manner, for example, within 10-30 minutes from the time the particles enter the nose.

Other desired characteristics of a nasal composition are that it must not contain ingredients which cause the user discomfort, that it has satisfactory stability and shelf-life properties, and that it does not include constituents that are considered to be detrimental to the environment, for example ozone depletors.

A suitable dosing regime for the formulation of the present invention when administered to the nose would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is manually compressed. This procedure would then be repeated for the other nostril.

In one aspect, the means for applying a formulation of the present invention to the nasal passages is by use of a pre-compression pump. Most preferably, the pre-compression pump will be a VP7 model manufactured by Valois SA. Such a pump is beneficial as it will ensure that the formulation is not released until a sufficient force has been applied, otherwise smaller doses may be applied. Another advantage of the pre-compression pump is that atomisation of the spray is ensured as it will not release the formulation until the threshold pressure for effectively atomising the spray has been achieved. Typically, the VP7 model may be used with a bottle capable of holding 10-50ml of a formulation. Each spray will typically deliver 50-100μl of such a formulation, therefore, the VP7 model is capable of providing at least 100 metered doses.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of Formula (I) optionally in combination with another therapeutically active ingredient and a

suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants, e.g., oleic acid or lecithin and cosolvents, e.g. ethanol. Pressurised formulations will generally be retained in a canister (e.g. an aluminium canister) closed with a valve (e.g. a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means e.g., by micronization. The desired fraction may be separated out by air classification or sieving. Suitably, the particles will be crystalline in form. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulization may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

For all methods and uses disclosed herein for the compounds of Formulas (I) to (XVI), suitable for use in the present invention, the daily oral dosage regimen will preferably be from about 0.05 to about 80 mg/kg of total body weight, preferably from about 0.1 to 30 mg/kg, more preferably from about 0.5 mg to 15mg/kg, administered in one or more daily doses. For example, the daily parenteral dosage regimen about 0.1

to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg, administered in one or more daily doses. The daily topical dosage regimen will preferably be from 0.01 mg to 150 mg, administered one to four times daily. The daily inhalation dosage regimen will preferably be from about 0.05 microgram/kg to about 5 mg/kg per day, or from about 0.2 microgram/kg to about 20 microgram/kg, administered in one or more daily doses.

It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formulas (I) to (XVI), respectively, or a pharmaceutically acceptable salt thereof, suitable for use in the present invention, will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formulas (I) to (XVI), respectively, or a pharmaceutically acceptable salt, suitable for use in the present invention, thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The amount of a compound of Formulas (I) to (XVI), respectively, or a pharmaceutically acceptable salt thereof, suitable for use in the present invention, which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

The compounds as described herein suitable for use in the present inventionmay be administered by inhalation at a dose of from 0.0005 mg to 400 mg. In another aspect, the compounds as described herein suitable for use in the present invention may be administered by inhalation at a dose of from 0.00 5mg to 40 mg, such as at a dose of from 0.05mg to 0.5mg. The dose range for adult humans is generally from 0.0005mg to 10mg per day; such as at a dose of from 0.01mg to 1mg per day or from 0.05mg to 0.5mg per day.

ADMINISTRATION

Treatment regimen for the administration of compounds, pharmaceutical compositions, or controlled-release formulations or dosage forms as described herein suitable for use in the present invention also may be determined readily by those with ordinary skill in art.

The quantity of the compound, pharmaceutical composition, or dosage form as described herein suitable for use in the present invention administered may vary over a wide range to provide in a unit dosage in an effective amount based upon the body weight of the patient per day to achieve the desired effect and as based upon the mode of administration.

The scope of the present invention includes all compounds, pharmaceutical compositions, or controlled-release formulations or dosage forms as described herein, which is contained in an amount effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art.

The compounds as described herein suitable for use in the present invention may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation.

Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion.

Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages.

In one aspect, pharmaceutical compositions, formulations, dosages, dosage forms or dosing regimens of the present invention are adapted for administration by inhalation.

Topical administration includes application to the skin.

The compounds as described herein suitable for use in the present invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect.

Suitable dosing regimens for a compound as described herein suitable for use in the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated,

the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

METHODS OF TREATMENT

The present invention also relates to uses or methods for the treatment of respiratory or respiratory tract diseases, which comprises administering to a subject in need thereof an effective amount of a compound of Formulas (I) to (XVI), respectively, which are suitable for use in the present invention, as described herein.

As used herein, "patient" refers to a human or other mammal.

In one aspect, the present invention a use or a method for treatment of respiratory or respiratory tract diseases selected from asthma, allergen-induced asthmatic reactions, cystic fibrosis, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease (COPD), cough, adult respiratory distress syndrome (ARDS), chronic pulmonary inflammation, rhinitis and upper respiratory tract inflammatory disorders (URID), ventilator induced lung injury, silicosis, pulmonary sarcoidosis, idiopathic pulmonary fibrosis or bronchopulmonary dysplasia . Specific types of coughs which may be treated by compounds of the present invention, include, but are not limited to dry cough, wet cough, croupy cough, chest cough, post viral cough, viral cough or viral acute cough.

In one aspect of the present invention, also includes use of compounds for the manufacture of a medicament.

In one embodiment, the present invention relates to a use or a method for treating cough, which comprises administering an effective amount of a compound of Formulas (I) to (XVI), or a pharmaceutically acceptable salt thereof or pharmaceutical composition, respectively, suitable for use in the present invention, to a subject in need thereof. In another embodiment, the present invention relates to a use of a method for treating post viral cough, viral cough or viral acute cough, which comprises administering an effective amount of a compound of Formulas (I) to (XVI), or a pharmaceutically acceptable salt thereof or pharmaceutical composition, respectively suitable for use in the present invention, to a subject in need thereof. In another embodiment, the present invention relgates to a use or method for treating post viral

cough, viral cough or viral acute cough, which comprises administering an effective amount of a compound of Formula (IV), or a pharmaceutically acceptable salt thereof or pharmaceutical composition, respectively, suitable for use inthe present invention, to a subject in need thereof.

In one aspect, the present invention relates to a use or a method for treating chronic obstructive pulmonary diseases (COPD), which comprises administering an effective amount of a compound of Formulas (I) to (XVI), or pharmaceutical composition of the present invention, respectively, to a subject in need thereof.

In another aspect, the present invention relates to a use or a method for treating cough, which comprises administering to a subject in need thereof an effective amount of a compound of Formulas (I) to (XVI), respectively.

The compounds, pharmaceutical compositions, controlled release formulations or dosage forms prepared according to the present invention can be used to treat warm-blooded animals, such as mammals, which include humans.

In accordance with any of the methods or uses of administration of the present invention, the term a "therapeutically effective amount", as used herein, generally includes within its meaning a non-toxic but sufficient amount of the particular drug to which it is referring to provide the desired therapeutic effect. The exact amount required will vary from subject to subject depending on factors such as the patient's general health, the patient's age, etc.

Active drug or therapeutic agents or compounds, such as those described above may be prepared according to processes or methods taught by either the present disclosure or processes or methods known to those of skill in the art.

COMBINATION THERAPIES

Active drug or therapeutic agents, when employed in combination with the compounds, or pharmaceutical compositions of the present invention, may be used or administered, for example, in dosage amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

In the context of this specification, the term "simultaneously" when referring to simultaneous administration of the relevant drugs means at exactly the same time, as would be the case, for example in embodiments where the drugs are combined in a single preparation. In other embodiments, "simultaneously" can mean one drug taken a short duration after another, wherein "a short duration" means a duration which allows the drugs to have their intended synergistic effect.

In light of the foregoing, the present invention also relates to a combination

therapy, which may be a comprised of a simultaneous or co-administration, or serial administration of a combination of compounds or pharmaceutical compositions of the present invention with other active drug or therapeutic agents, such as described above, and where such administration also is determined by one of ordinary skill in the art.

In addition, the present invention also relates to a combination therapy for the treatment or prevention of repiratory tract or respiratory diseases as described herein, which is comprised of a composition, dosage form or formulation formed from a synergistic combination or mixture of compounds, controlled release compositions, dosage forms or formulations of the present invention and another active drug or therapeutic agent or agents as those described above and optionally which comprises pharmaceutically acceptable carrier, diluent or adjuvent. In such an aforementioned combination composition, dosage form or formulation of the present invention, each of the active drug components are contained in therapeutically effective and synergistic dosage amounts.

The Examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention.

EXAMPLES

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention.

While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention. Some of chemical compounds or pharmaceutically acceptable salts thereof of the present invention may be made by different chemical reaction methods or preparative procedures. Some examples of compounds prepared by different experimental procedures are found in, but not limited to representative Examples 225 and 474, 368 and 469, 365 and 468 , 407 and 471 and the like.

Biology and Biological Assays

Mechanism of Action of the Present Invention:

The cough reflex protects the airway from potential harm by aiding the clearance of luminal debris. Within the airway epithelium, irritant sensing vagal nerve endings transmit information arising from the presence of tussive stimuli to the brain stem evoking an urge to cough. Coughing is produced in a variety of airway diseases, which may enhance and intensify the cough response. Chronic cough, often thought as dry and unproductive, is associated with progressive irreversible lung damage such as occurs in chronic obstructive pulmonary disease (COPD). The persistence and intensity of this form of cough robs patients of quality of life.

Propagation of nerve impulses arising from tussive stimuli is mediated, at least in part, via voltage-gated Na^+ channels (NaV). Generation of the action potential is blocked by local anesthetics such as Lidocaine. Lidocaine reduces the inward sodium current which elicits neuronal impulses (Butterworth et al., 1990; Catterall, 1987; Hille, 1966; Taylor, 1959). Indeed, blockade of neuronal Na+ channels is one of the most powerful and well described analgesic principles (Catterall *et al.*, 2005). Lidocaine, a pan-NaV inhibitor, is used to minimize gagging and cough during bronchoconscopy (Reed, 1992) and to limit airway intubation-induced post operative cough and sore throat (Diachun et al., 2001). There is evidence suggesting that short-term administration of intravenous lidocaine may produce pain relief that far exceeds both the duration of infusion and the half-life of the drug (McCleane, 2007). Although widely investigated, the mechanism remains unknown. One possibility is that local anesthetics inhibit central sensitization, i.e., the long-term increase in the excitability of the central nervous system in response to on-going or repeated activation of nociceptors. Blockade of sensory nerve input even for a short time would allow restoration of normal nerve function, a similar long-lasting effect on intractable dry cough could be expected.

Biological Assays

The ability of the compounds of the invention to modulate the voltage-gated sodium channel subtype NaV 1.3 and NaV 1.7 may be determined by the following assay.

Cell biology

Stable cell lines expressing hNaV1.3 channels were created by transfecting CHO cells with the pCIN5-hNav1.3 vector using the lipofectamine (Invitrogen) transfection method. pCIN5 is a bicistronic vector for the creation of mammalian cell

lines that predisposes all neomycin resistant cells to express recombinant protein (see Rees S., Coote J., Stable J., Goodson S., Harris S. & Lee M.G. (1996) Biotechniques, 20, 102-112) by virtue of the recombinant cDNA being linked to the neomycin-selectable marker cDNA downstream of the CMV promoter (for full details see Chen YH, Dale TJ, Romanos MA, Whitaker WR, Xie XM, Clare JJ. Cloning, distribution and functional analysis of the type III sodium channel from human brain Eur J Neurosci, 2000 Dec;12, 4281-9). Cells were cultured in Iscove's Modified Dulbecco's Medium (Invitrogen, 21980-032) adding, 10% Dialized Fetal Bovine Serum (PAA, A15-107), 1% L-glutamine (Invitrogen, 25030-024), 1% Penicillin-Streptomycin (Invitrogen, 15140-122), 1% non-essential amino acids (Invitrogen, 11140-035), 2% HT supplement (Invitrogen, 41065-012) and 400ug/ml of G418 (PAA, P11-012). Cells were grown and maintained at 37°C in a humidified environment containing 5% CO2 in air. Cells were detached from the T175 culture flask for passage and harvesting using Versene (Invitrogen, 15040-033).

Cell preparation

Cells were grown to 60–95% confluence in a T175 flask. Cells were removed from the incubator and the media was aspirated. Cells were washed with 3 ml of warmed (37°C) Versene and then 1.5 ml of warmed (37°C) Versene was added to the flask for 6 min. The flask was tapped to dislodge cells and 10ml of warmed (37°C) DPBS (Invitrogen, 14040) was added to prepare a cell suspension. Cell suspension was then placed into a 15 ml centrifuge tube and centrifuged for 2 min at 1000 rpm. After centrifugation, the supernatant was removed and the cell pellet was resuspended in 5 ml of warmed (37°C) DPBS using a 5ml pipette to break up the pellet.

Electrophysiology

Currents were recorded at room temperature using the IonWorks Quattro™ planar array electrophysiology technology (Molecular Devices Corp.) with PatchPlate™ PPC for Ionworks Quattro (Molecular Devices, 9000-0902). Stimulation protocols and data acquisition were carried out using a microcomputer (Dell Pentium 4). In order to determine planar electrode hole resistances (Rp), a 10 mV voltage step was applied across each well. These measurements were performed before cell addition. After cell addition a seal test was performed by applying a voltage step from -100 mV to -90 mV for 80 ms prior to antibiotic amphotericin-B solution (Sigma, P11-012) circulation to achieve intracellular access. Leak subtraction was conducted in all

experiments by applying a 80 ms hyperpolarizing (10 mV) prepulse followed by a 80 ms at the holding potential before the test pulses, to measure leak current. Test pulses stepping from the holding potential of -90 mV to 0 mV were applied for 20 ms and repeated 10 times at a frequency of 10 Hz. In all experiments, the test pulse protocol was performed in the absence (pre-read) and presence (post-read) of a compound. Pre- and post-reads were separated by a compound addition followed by a 3 minute incubation.

Solutions and drugs

The intracellular solution contained the following (in m*M*): K-gluconate 100, KCl 40, MgCl2 3.2, EGTA 3, HEPES 5, adjusted to pH 7.5. Amphotericin-B solution was prepared as 50mg/ml stock solution in DMSO and diluted to a final working concentration of 0.1 mg/ml in intracellular solution. The external solution was Dulbecco's PBS (Invitrogen, 14040) and contained the following (in m*M*): CaCl2 0.90, KCl 2.67, KH2PO4 1.47, MgCl.6H2O 0.493, NaCl 136.9, Na3PO4 8.06, with a pH of 7.4. Compounds were prepared in DMSO as 10mM stock solutions and subsequent 1:3 serial dilutions was performed. Finally the compounds were diluted 1:100 in external solution containing 0.05% pluronic acid.

Data analysis

The recordings were analysed and filtered using both seal resistance (>40 MΩ) and peak current amplitude (>200pA) in the absence of compound to eliminate unsuitable cells from further analysis. Paired comparisons between pre-drug and post-drug additions were used to determine the inhibitory effect of each compound. Data were normalised to the high control (1% DMSO) and low control (0.3uM Tetrodotoxin from Tocris, 1069). The normalised data were analysed by using ActivityBase software. The concentrations of compounds required to inhibit current elicited by the 1st depolarising pulse by 50% (tonic pIC50) were determined by fitting of the four parameter logistic function to the concentration response data. In addition the use-dependent inhibitory properties of the compounds were determined by assessing the effect of compounds on the 10th versus 1st depolarising pulse. The ratio of the 10th over 1st pulse was calculated in the absence and presence of drug and the % use-dependent inhibition calculated. The data was fitted using the same equation as for the tonic pIC_{50} and the concentration producing 15% inhibition (use-dependent pUD_{15}) calculated.

The following compounds identified by Example numbers were tested and found to have pUD_{15} of 5.5 or greater against NaV1.3:

3-8, 10-11, 17, 19-20, 22-24, 27, 30, 38, 48, 51-52, 54-55, 58-61, 64, 67-68, 70, 72-74, 80, 86, 88, 90-91, 93-96, 98, 111-112, 114-119, 122-123, 125-128, 136, 139, 144, 148, 152, 169, 172-173, 175-176, 179-181, 183, 187, 188, 195, 197, 199, 203-204, 212, 220-223, 226, 228-229, 231-238, 244-245, 248, 250-251, 257, 258, 260-262, 264-266, 270-282, 285, 287, 289-291, 295-296, 298-299, 301, 303-307, 310-313, 316, 319, 322-328, 330-335, 347, 352, 357, 364-366, 368, 371, 373-377, 379-386, 389-395, 399-401, 403-404, 407, 409-412, 414, 417, 423, 428, 433, 436, 438, 442, 447, 449, 453, 455, 460, 463, 464, 466, 467, 468, 470, 471, 475, 476, 477, 478, 479, 482, 483, 485, 486, 488, 489, 490, 491, 492, 493, 494, 497, 498, 499, 500, 501, 502, 503, 504, 505, 508, 511, 513, 514, 515, 516, 517, 518, 520, 522, 523, 524, 527, 528, 542.

The following compounds were tested and found to have pUD_{15} of 5.5 or greater against NaV1.7:

4-8, 10-11, 14, 19-20, 23-24, 30, 38, 48, 51, 52, 54-55, 60-61, 64, 67-68, 70, 72-74, 81, 85-86, 88, 90-91, 93-95, 111, 115-118, 122-123, 125-128, 144, 152, 169, 173, 176-177, 181, 183, 190-191, 199, 204, 212, 216, 220-221, 226, 231-232, 234, 236-237, 244, 251, 256-257, 260-262, 265-266, 270-271, 274, 276-280, 282, 285, 287, 289, 291, 295, 298, 299, 303-306, 310-311, 313, 319, 322-325, 330, 332-333, 335, 357, 364, 365, 368, 373-375, 377, 379-384, 386-387, 389, 391-392, 394-395, 399, 409-410, 412, 414, 417, 419, 423, 425, 436-437, 442, 447, 449, 453, 460, 464, 467, 468, 470, 471, 472, 475, 476, 477, 479, 482, 488, 489, 490, 491, 492, 493, 497, 500, 501, 502, 508, 513, 514, 515, 516, 517, 518, 519, 520, 521, 523, 530, 532, 537, 542

The following compounds were tested and found to have pUD15 of 4-4.99 against NaV1.3:

12, 31, 34, 36-37, 43, 45-47, 49-50, 56, 62, 65-66, 69, 76-77, 83, 99-104, 106-110, 124, 129, 133, 143, 145-147, 150, 154-155, 158, 160, 162, 164, 166, 168, 170, 185-186, 189, 194,196, 200, 208, 210, 213, 215, 218, 2390-242, 246, 252, 254, 263, 268, 293, 300, 314-315, 318, 321, 329, 337, 339, 341, 344-345, 348, 355, 358, 361, 363, 370, 378, 406, 408, 416, 418, 420, 422, 427, 431-432, 437, 439, 441, 444-446, 450-451, 454, 456-457, 462,.473, 484, 510, 533-534, 538, 539, 540.

The following compounds were tested and found to have pUD15 of 5-5.99 against NaV1.3:

1-4, 8-10, 13-18, 21-22, 24-29, 32-33, 39-40, 42, 48, 53, 58-59, 61, 63-64, 71, 75, 78-82, 85, 87, 89, 93-94, 96-98, 105, 111-112, 114, 116, 119-123, 126, 130, 135-136, 138-139, 141, 144, 148- 149, 151-152, 156-157, 169, 171-184, 187-188,

190-191, 193, 195, 197, 199, 202-203, 205-207, 211-212, 214, 216, 219-230, 232-236, 238, 243-245, 247-248, 250-251, 253, 255-262, 264, 266-267, 269-279, 281-282, 284-288, 290-292, 294, 296-297, 301-303, 306-309, 312-313, 316-317, 319-320, 322-323, 325-328, 331, 333-334, 336, 340, 342, 346-347, 349-354, 356-357, 359-360, 362, 364-366, 368, 371-372, 374-377, 383, 385-405, 407, 409-414, 417, 419, 423, 425-426, 428-430, 433-436, 438, 440, 443, 447, 449, 453, 455, 459-461, 463, 464, 465, 466, 467, 468, 472, 474, 475, 479, 480, 481, 483, 485, 486, 487, 488, 489, 490, 492, 493, 494, 495, 496, 498, 499, 500, 502, 504, 506, 507, 509, 511, 512, 514, 516, 517, 518, 519, 521, 524, 525, 526, 528, 529-531, 537, 541.

The following compounds were tested and found to have pUD15 of 6-7.5 against NaV1.3:

5-7, 11, 19-20, 23, 30, 38, 51-52, 54-55, 60, 67-68, 70, 72-74, 86, 88, 90-91, 95, 115, 117-118, 125, 127-128, 204, 231, 237, 265, 280, 289, 295, 298-299, 304-305, 310-311, 324, 330, 332, 335, 373, 379-382, 384, 442, 447, 468, 470, 471, 476, 477, 478, 482, 491, 497, 501, 503, 505, 508, 513, 515, 520, 522, 523, 527, 542.

The following compounds were tested and found to be inactive with respect to use-dependent potency against NaV1.3:

35, 44, 84, 92, 113, 131-132, 134, 137, 140, 142, 153, 159, 161, 163, 165, 167, 192, 198, 201, 209, 217, 249, 283, 338, 343, 367, 369, 415, 421, 424, 448, 452, 458, 532, 535.

Examples 41 and 57 were not tested for potency against NaV1.3.

The following compounds were tested and found to have pUD15 of 4-4.99 against NaV1.7:

13, 21, 25-26, 29, 31, 35-36, 39, 47, 50, 53, 56, 65, 71, 75, 78-79, 87, 89, 97, 99-102, 107-110, 121, 124, 130, 133, 135-138, 142-143, 145, 147, 157, 168, 170, 172, 185, 198, 207-208, 210, 218-219, 240-242, 246, 252, 286, 308, 312, 314, 317-318, 327, 329, 331, 342-343, 346, 352, 354, 359, 362, 388, 398, 402, 406, 408, 427, 432-433, 440, 443, 456-457, 459, 480, 484, 495, 498, 503, 506, 512,

526, 529, 539, 540, 533-534.

The following compounds were tested and found to have pUD15 of 5-5.99 against NaV1.7:

1-4, 8-10, 12, 14-18, 20, 22, 24, 27-28, 30, 32-34, 38, 40, 42, 46, 48, 58-59, 61-64, 72-74, 80-81, 85, 90, 93-94, 96, 98, 103, 105, 111-112, 114-116, 118-120, 122-123, 126-127, 129, 139, 141, 144, 148-149, 151-152, 169, 171, 173-184, 188, 190, 195, 197, 199, 203, 206, 211-212, 214, 216, 220-239, 243-245, 247-248, 251, 253-262, 266, 270-272, 274-278, 282, 284-285, 287-288, 290-292, 298-299, 302-307, 309, 313, 316, 319-320, 322-323, 325-326, 328, 333-334, 340, 347, 350, 357, 360, 364-366, 368, 371, 373-378, 382-383, 385-387, 389-395, 397, 399-401, 403-405, 407, 409-410, 412, 414, 417, 419, 423, 425-426, 428-430, 434-439, 441, 446-447, 449, 451, 453, 455, 460, 463, 464, 465, 466, 467, 468, 472, 474, 475, 479, 481, 489, 490, 493, 494, 496, 497, 500, 504, 505, 507, 509, 511, 513, 514, 515, 516, 517, 518, 520, 521, 522, 523, 524, 525, 530, 532, 538, 537, 541, 542.

The following compounds were tested and found to have pUD15 of 6-7.5 against NaV1.7:

5-7, 11, 19, 23, 51-52, 54-55, 60, 67-68, 70, 86, 88, 91, 95, 117, 125, 128, 191, 204, 265, 279-280, 289, 295, 310-311, 324, 330, 332, 335, 379-381, 384, 442, 468, 470, 471, 476, 477, 482, 488, 491, 492, 501, 502, 508, 519.

The following compounds were tested and found to be inactive with respect to use-dependent potency against NaV1.7:

37, 44, 49, 66, 69, 76-77, 82-84, 92, 104, 106, 113, 131, 134, 140, 146, 150, 153-156, 158, 160, 162-167, 186-187, 189, 192-194, 196, 200-202, 205, 209, 213, 215, 217, 249-250, 283, 293, 296-297, 300-301, 315, 321, 336-339, 341, 344-345, 348-349, 351, 353, 355-356, 358, 361, 363, 367, 369-370, 372, 396, 411, 413, 416, 418, 420, 424, 431, 444-445, 448, 450, 452, 454, 458, 462, 473, 478, 483, 485, 486, 487, 499, 510, 527, 528, 535.

The following examples were not tested for potency against NaV1.7:

41, 43, 45, 57, 132, 159, 161, 263-264, 267-269, 273, 281, 294, 415, 421-422, 461 and 531.

Guinea Pig Cough Method

Male Hartley Guinea pigs (n=6-8/group), weight range 600-700gm were used in this study. After balancing transducers and air flow into the whole body plethysmograph chambers, the animals (after the appropriate pretreatment time) were placed into each of 4 chambers and allowed to acclimate to their new environment for approximately 5 minutes. Citric Acid (0.2M) was aerosolized into each chamber for 5 minutes and the animals remained in the chambers an additional 8 minutes. The number of coughs are counted by the computer software during the entire 13 minute time period. The software records each cough incident and records the time of the incident and totals the number of coughs for each animal during the test period (13 minutes). Results are summarized into a spread sheet.

Intratracheal Dosing in Guinea Pigs.

Dosing - Animals are anesthetized (with 5% isoflurane using 95%O2) and placed in the supine position. The drug/vehicle is then administered through the trachea. The trachea is intubated with a steel gavage needle (1.5 inch, 22 gauge, small ball) and 200μl of dosing solution or suspension is delivered. For intratracheal microspray applications (solutions only), the Penn-Century MicroSprayer® (19 gauge stainless steel tubing, see picture below) device is used to deliver 200μl. The animals are visually monitored during the recovery process, which typically occurs within two minutes.

COMPOUND EXAMPLES

Examples set forth in this section have been disclosed in complete detail in International Patent Appln. No. WO 2011/088201 ("WO '201 Appln."), International Publication Date: July 21, 2011, International Filing Date, which is hereby incorporated by reference in its entirety. Where not set forth below, compound Examples suitable for use in the present invention can be made or prepared by referring to complete descriptive experimental details as set forth in the WO '201 Appln. Such compound examples as exemplified in the WO '201 Appln. include, monomers, corresponding intermediates and compound examples as identified below.

General

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). Unless otherwise indicated, all reactions are conducted under an inert atmosphere at ambient temperature.

All temperatures are given in degrees Celsius, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon (Ar) or nitrogen (N_2) atmosphere where necessary.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. The CombiFlash system used for purification in this application was purchased from Isco, Inc. CombiFlash purification was carried out using prepacked silica gel columns, a detector with UV wavelength at 254 nm and a variety of solvents or solvent combinations.

Preparative HPLC was performed using a Gilson Preparative System with variable wavelength UV detection or an Agilent Mass Directed AutoPrep (MDAP) system with both mass and variable wavelength UV detection. A variety of reverse phase columns, e.g., Shimadzu 15 u m 250 *21.2 mm, Luna 5u C18(2) 100A, SunFire™ C18, XBridge™ C18 were used in the purification with the choice of column support dependent upon the conditions used in the purification. The compounds are eluted using a gradient of acetonitrile and water. Neutral conditions used an acetonitrile and water gradient with no additional modifier, acidic conditions used an acid modifier, usually 0.05 % or 0.1 % TFA (added to both the acetonitrile and water) and basic conditions used a basic modifier, usually 10 mmol/L NH_4HCO_3, 0.04 % NH_3H_2O or 0.1 % NH_4OH (added to the water).

Analytical HPLC was run using an Agilent system with variable wavelength UV detection using reverse phase chromatography with an acetonitrile and water gradient with a 0.05 or 0.1 % TFA modifier (added to each solvent). LC-MS was determined using Aglient 6110 quadrupole LC/MS, a PE Sciex Single Quadrupole LC/MS API-150 or a Waters. The compound is analyzed using a reverse phase column, e.g., Xbridge-C18, Sunfire-C18, Thermo Aquasil/Aquasil C18, Acquity UPLC C18, Thermo Hypersil Gold eluted using an acetonitrile and water gradient with a low percentage of an acid modifier such as 0.02% TFA or 0.1 % formic acid.

Nuclear magnetic resonance spectra were recorded at 400 MHz using a Bruker AVANCE3 400, Bruker AC 400 or Brucker DPX400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-D_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is

tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS) or calibrated to the residual proton signal in the NMR solvent (e.g., $CHCl_3$ in $CDCl_3$). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz.

Heating of reaction mixtures with microwave irradiations was carried out on a Smith Creator (purchased from Personal Chemistry, Forboro, MA, now owned by Biotage), an Emrys Optimizer (purchased from Personal Chemistry) or an Explorer (purchased from CEM, Matthews, NC) microwave.

Cartridges or columns containing polymer based functional groups (acid, base, metal chelators, etc) can be used as part of compound workup. The "amine" columns or cartridges are used to neutralize or basify acidic reaction mixtures or products. These include NH2 Aminopropyl SPE-ed SPE Cartridges available from Applied Separations and diethylamino SPE cartridges available from United Chemical Technologies, Inc.

In some cases, purifications and analyses of materials were carried out using the following instruments:

LC-MS analysis

The LC/MS of Intermediates and Examples were performed using the following equipment and conditions:

Liquid Chromatograph:

System: Shimadzu LC system with SCL-10A Controller and dual UV detector
Autosampler: Leap CTC with a Valco six port injector
Column: Aquasil/Aquasil (C18 40x1 mm)
Inj. Volume: 2.0 µL
Solvent A: H_2O, 0.02% TFA
Solvent B: MeCN, 0.018% TFA
Gradient: linear
Channel A: UV 214 nm
Channel B: ELS

Step	Time (min)	Dura.(min)	Flow (µL/min)	Sol.A	Sol.B
0	0.00	0.00	300.00	95.00	5.00
1	0.00	0.01	300.00	95.00	5.00
2	0.01	3.20	300.00	10.00	90.00
3	3.21	1.00	300.00	10.00	90.00
4	4.21	0.10	300.00	95.00	5.00
5	4.31	0.40	300.00	95.00	5.00

Mass Spectrometer:

Instrument:	PE Sciex Single Quadrupole LC/MS API-150
Polarity:	Positive
Acquisition mode:	Profile

Preparatory HPLC

Automated preparatory HPLC purifications were conducted using a Gilson® semi-preparative HPLC system under the following conditions:

- Column: 75 x 33mm I. D. , S-5um, 12nm
- Flow rate: 30mL/min
- Injection Volume: 0.800 mL
- Room temperature
- The eluent was a mixture composed of solvents A and B. Either one of three different solvent combinations were used:
  - TFA conditions
    - Solvent A: 0.1% trifluoroacetic acid in water
    - Solvent B: 0.1% trifluoroacetic acid in acetonitrile
  - NH_4OH conditions
    - Solvent A: 0.1% NH_4OH in water
    - Solvent B: 0.1% NH_4OH in acetonitrile
  - Neutral conditions
    - Solvent A: 0.1% NH_4OH in water
    - Solvent B: 0.1% NH_4OH in acetonitrile

Automated Flash Chromatography

The automated flash chromatography purifications were conducted with a CombiFlash® Companion® personal flash chromatography system under the following conditions:

- Silica cartridge:
  - Size, 4, 12, 40, 80 or 120 g depending on the amount of material to be purified
- Flow rate: Between 4 and 85 mL/min
- Room temperature
- The eluent was a mixture composed of solvents A and B:
  - Solvent A: Hexane
  - Solvent B: Ethyl acetate

Mass-Directed Auto Prep HPLC

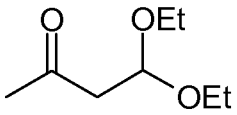
The Mass-Directed Auto Prep HPLC (MDAP) purifications were conducted with an Agilent preparatory HPLC-MS system under the following conditions:

- Column: ZORBAX Eclipse XDB-C18 (21.2 × 50 mm)
- Flow rate: 20 mL/min
- Injection volume: 900 uL
- Temperature: 30°C
- absorption wavelength: 230 nm
- The eluent was a mixture composed of solvents A and B:
  - Solvent A: 0.1% trifluoroacetic acid in water
  - Solvent B: 0.1% trifluoroacetic acid in acetonitrile

Monomers and Corresponding Intermediates

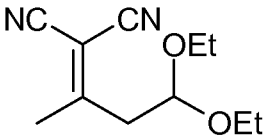
Intermediates

Intermediate 1: 4,4-bis(ethyloxy)-2-butanone



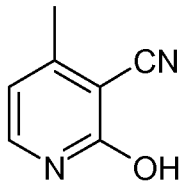
$BF_3{\cdot}Et_2O$ (53.8 g, 378.8 mmol) was added dropwise over 15 min to a cooled (- 40 °C) solution of $HC(OEt)_3$ (51.0 g, 344.4 mmol) in CH_2Cl_2 (200 mL). Stirring was continued for 10 min at -40 °C then the solution was transferred to an ice-water bath and stirred at 0 °C for 20 min. The mixture was cooled to -78 °C, and acetone (10.0 g, 172.2 mmol) added followed by dropwise addition of i-Pr_2NEt (66.7 g, 516.5 mmol) over 30 min. Stirring was continued for 1 h then the solution was poured onto a vigorously stirred mixture of saturated $NaHCO_3$ (200 mL) and CH_2Cl_2 (300 mL). The organic phase was separated, washed with ice-cold 1 N H_2SO_4 (200 mL×2) and brine (200 mL), dried over Na_2SO_4 and evaporated, the residue oil was purified by distillation under reduced pressure(1 mm Hg, 78-82 °C) to give the title compound. (19.5 g, 70.7%) as a colorless oil. This was used in the next step.

Intermediate 2: [3,3-bis(ethyloxy)-1-methylpropylidene]propanedinitrile



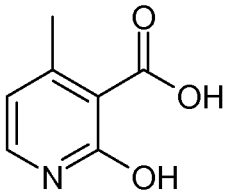
Malononitrile (22.78 g, 344.71 mmol) was added in portions over 15 min to a stirred solution of 4,4-bis(ethyloxy)-2-butanone (46.03 g, 287.31 mmol) in PhMe (250 mL) containing acetic acid (5.75 mL, 100.56 mmol) and piperidine (9.94 mL, 100.56 mmol). Stirring was continued at r.t. for overnight, and the resulting dark red solution was directly purified by distillation under reduced pressure(1 mm Hg, 108 ^{o}C) to give the crude product (45.3 g, 75.7%) as a colorless oil. This was used in the next step.

Intermediate 3: 4-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile



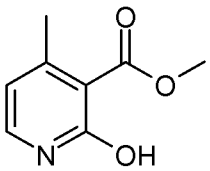
^{1}H NMR (400MHz, DMSO): δ 2.48 (s, 3 H), 6.28 (d, *J*=6.6 Hz, 1 H), 7.63 (d, *J*=6.6 Hz, 1 H), 12.32 (br, 1 H).

Intermediate 4: 4-methyl-2-oxo-1,2-dihydro-3-pyridinecarboxylic acid



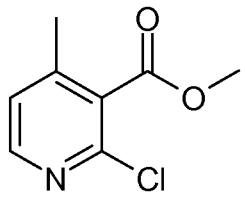
^{1}H NMR (400MHz, DMSO): δ 2.60 (s, 3 H), 6.55 (d, *J*=6.6 Hz, 1 H), 7.75 (d, *J*=6.6 Hz, 1 H), 13.05 (br, 1 H).

Intermediate 5: Methyl 4-methyl-2-oxo-1,2-dihydro-3-pyridinecarboxylate



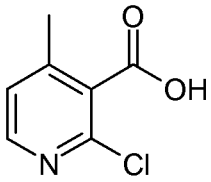
^{1}H NMR (400MHz, DMSO): δ 2.09 (s, 3 H), 3.75 (s, 3 H), 6.10 (d, *J*=6.4 Hz, 1 H), 7.36 (d, *J*=6.4 Hz, 1 H), 11.80 (br, 1 H).

Intermediate 6: Methyl 2-chloro-4-methyl-3-pyridinecarboxylate



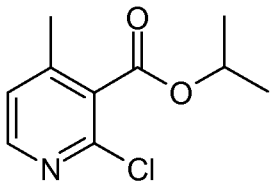
^{1}H NMR (400MHz, $CDCl_3$): δ 2.34 (s, 3 H), 3.97 (s, 3 H), 7.10 (d, *J*=5.2 Hz, 1 H), 8.28 (d, *J*=5.2 Hz, 1 H).

Intermediate 7: 2-chloro-4-methyl-3-pyridinecarboxylic acid



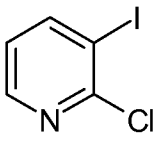
The compound Methyl 2-chloro-4-methyl-3-pyridinecarboxylate (1.3 g, 7.0 mmol) was added to 50 mL round bottom flask containing of 15 mL MeOH and followed by the addition of 20% NaOH (5 mL), and then the mixture was stirred at r.t. for 12 h. Adjust the value of pH to 4.0 and the solvent of MeOH and H_2O was remove under reduced pressure to give the crude product which was directly used in the next step.

Intermediate 8: 1-methylethyl 2-chloro-4-methyl-3-pyridinecarboxylate



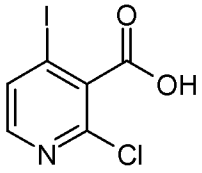
^{1}H NMR (400MHz, $CDCl_3$): δ 1.39 (d, *J*=6.4 Hz, 6 H), 2.35 (s, 3 H), 5.33 (m, 1 H), 7.09 (d, *J*=5.2 Hz, 1 H), 8.27 (d, *J*=5.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 21.8, 70.3, 124.3, 130.8, 147.6, 149.6, 165.5.

Intermediate 9: 2-chloro-3-iodopyridine



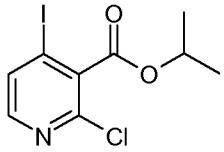
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94-6.97 (m, 1 H), 8.14-8.16 (m, 1 H), 8.36-8.37 (m, 1 H).

Intermediate 10: 2-chloro-4-iodo-3-pyridinecarboxylic acid



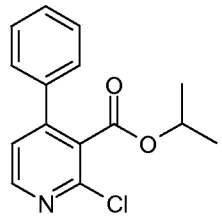
^{1}H NMR (400 MHz, DMSO): δ 7.98 (d, *J*=5.6 Hz, 1 H), 8.12 (d, *J*=5.6 Hz, 1 H).

Intermediate 11: 1-methylethyl 2-chloro-4-iodo-3-pyridinecarboxylate



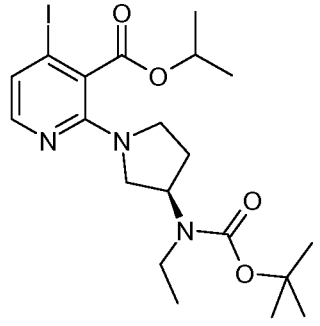
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, *J*=6.0 Hz, 6 H), 5.35 (q, *J*=6.0 Hz, 1 H), 7.70 (d, *J*=4.8 Hz, 1 H), 8.03 (d, *J*=4.8 Hz, 1 H).

Intermediate 12: 1-methylethyl 2-chloro-4-phenyl-3-pyridinecarboxylate



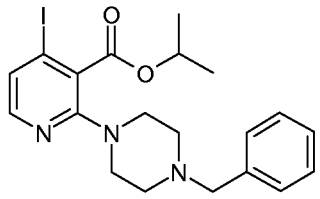
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, *J*= 6.4 Hz, 6 H), 5.05-5.14 (m, 1 H), 7.27 (d, *J*= 5.2 Hz, 1 H), 7.40-7.45 (m, 5 H), 8.45 (d, *J*= 5.2 Hz, 1 H) ^{13}C NMR (100MHz, $CDCl_3$): δ 21.5, 70.3, 123.4, 128.3, 128.9, 129.0, 129.5, 137.0, 148.1, 149.9, 150.6, 165.4.

Intermediate 13: 1-methylethyl 2-{(3R)-3-[{[(1,1-dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-4-iodo-3-pyridinecarboxylate



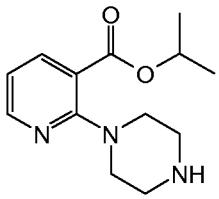
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, *J*=6.8 Hz, 3 H), 1.40 (d, *J*=5.2 Hz, 3 H),1.44(d, *J*=4.0 Hz, 3 H), 1.46 (s, 9 H), 2.04-2.10 (m, 2 H), 3.10-3.63 (m, 6 H), 4.51-4.66 (m, 1 H), 5.24-5.27 (m, 1 H), 7.05 (d, *J*=4.8 Hz, 1 H), 7.73 (d, *J*=4.8 Hz, 1 H). ^{13}C NMR (100MHz, $CDCl_3$): δ 15.7, 21.9, 28.7, 28.9, 38.6, 46.9, 50.3, 54.7, 70.6, 80.0, 106.4, 120.1, 122.7, 128.7, 148.4, 153.7, 168.4.

Intermediate 14: 1-methylethyl 4-iodo-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridine carboxylate



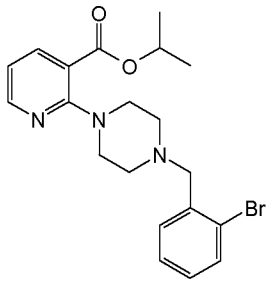
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (d, *J*=5.6 Hz, 6 H), 2.51 (t, *J*=5.2 Hz, 4 H), 3.39 (t, *J*=5.2 Hz, 4 H), 3.54 (s, 2 H), 5.22-5.28 (m, 1 H), 7.24-7.34 (m, 6 H), 7.80 (d, J=5.2 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl3) δ 21.9, 49.1, 53.1, 63.1, 70.2, 106.1, 126.0, 127.3, 128.4, 129.3, 138.0, 148.2, 158.3, 167.8.

Intermediate 15: 1-methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate



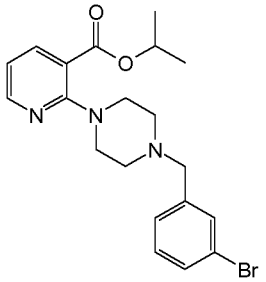
LC/MS: m/z= 249.9 $[M+H]^+$, Ret. Time: 0.59 min.

Intermediate 16: 1-methylethyl 2-{4-[(2-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



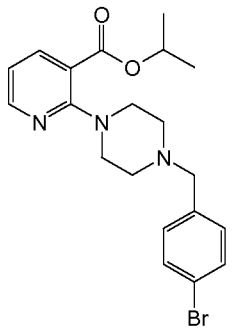
LC/MS: m/z= 418.2 $[M+H]^+$, Ret. Time: 0.88 min.

Intermediate 17: 1-methylethyl 2-{4-[(3-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



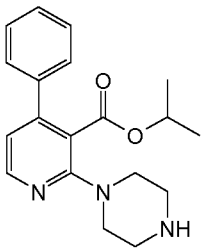
LC/MS: m/z= 418.2 $[M+H]^+$, Ret. Time: 0.88 min.

Intermediate 18: 1-methylethyl 2-{4-[(4-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



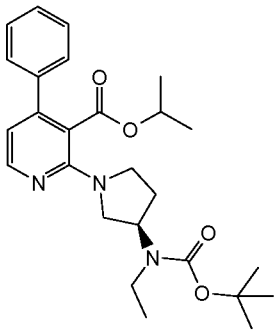
LC/MS: m/z= 418.2 $[M+H]^+$, Ret. Time: 0.91 min.

Intermediate 19: 1-methylethyl 4-phenyl-2-(1-piperazinyl)-3-pyridinecarboxylate



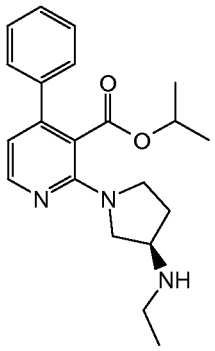
LC/MS: m/z= 326.0 $[M+H]^+$, Ret. Time: 0.83 min.

Intermediate 20: 1-methylethyl 2-{(3*R*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate



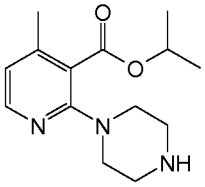
LC/MS: m/z= 454.1 $[M+H]^+$, Ret. Time: 1.15 min.

Intermediate 21: 1-methylethyl 2-[(3*R*)-3-(ethylamino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate



LC/MS: m/z= 354.0 $[M+H]^+$, Ret. Time: 0.81 min.

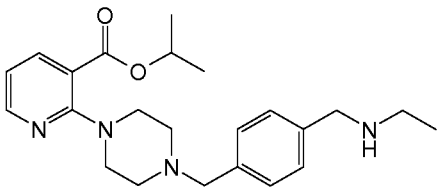
Intermediate 22: 1-methylethyl 4-methyl-2-(1-piperazinyl)-3-pyridinecarboxylate



LC/MS: m/z= 263.9 $[M+H]^+$, Ret. Time: 0.87 min.

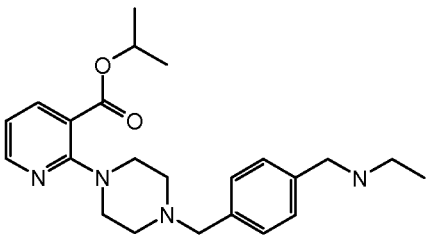
Intermediate 23: 1-methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate

Preparation 1



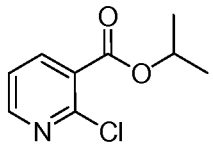
LC/MS: m/z= 397.1 $[M+H]^+$, Ret. Time: 0.73 min.

Preparation 2



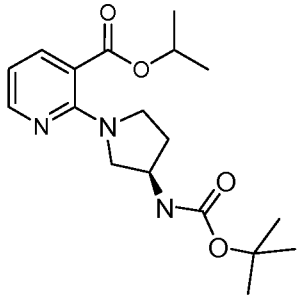
Lcms rt 0.70 [M+H] =397.1.

Intermediate 24: Isopropyl 2-chloronicotinate



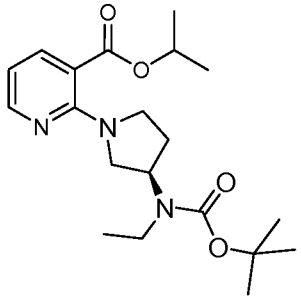
LC/MS: M/z=200.1 (M+H), Ret. Time: 1.42 min.

Intermediate 25: (R)- Isopropyl 2-[3-(ter-butoxycarbonylamino)pyrrolidine-1-yl]nicotinate



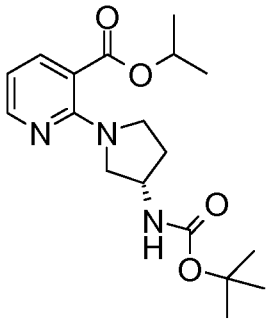
LC/MS: M/z=350.2 (M+H), Ret. Time: 1.48 min.

Intermediate 26: (R)- Isopropyl 2-{3-[tert-butoxycarbonyl(ethyl)amino]pyrrolidin-1-yl}nicotinate



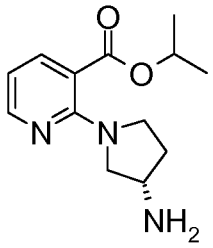
LC/MS: M/z=378.0 (M+H), Ret. Time: 1.89 min.

Intermediate 27: 1-Methylethyl 2-[(3*S*)-3-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate



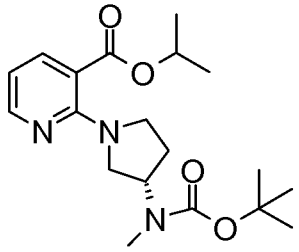
LC-MS *m/z* 350 $(M+H)^+$, 1.75 min (ret time)

Intermediate 28: 1-Methylethyl 2-[(3*S*)-3-amino-1-pyrrolidinyl]-3-pyridinecarboxylate



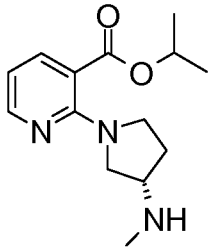
LC-MS *m/z* 250 $(M+H)^+$, 1.37 min (ret time)

Intermediate 29: 1-Methylethyl 2-{(3*S*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



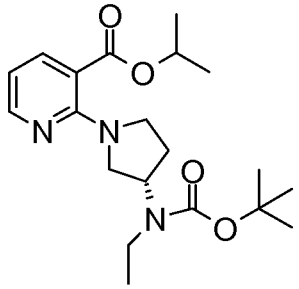
LC-MS *m/z* 364$(M+H)^+$, 1.83 min (ret time)

Intermediate 30: 1-Methylethyl 2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-3-pyridinecarboxylate



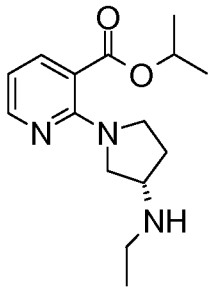
LC-MS *m/z* 264 $(M+H)^+$, 1.42 min (ret time)

Intermediate 31: 1-Methylethyl 2-{(3*S*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl} (ethyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



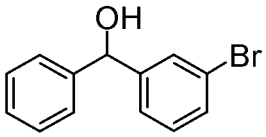
LC-MS *m/z* 378 $(M+H)^+$, 1.88 min (ret time)

Intermediate 32: 1-Methylethyl 2-[(3*S*)-3-(ethylamino)-1-pyrrolidinyl]-3-pyridinecarboxylate



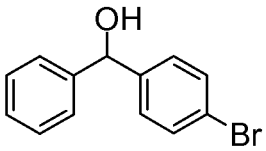
LC-MS *m/z* 278 $(M+H)^+$, 1.48 min (ret time)

Intermediate 33: (3-Bromophenyl)(phenyl)methanol



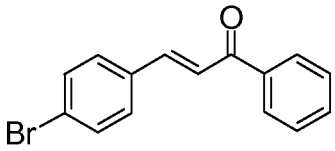
LC-MS *m/z* 246.9 $(M-18+H)^+$, 1.55 min (ret time)

Intermediate 34: (4-Bromophenyl)(phenyl)methanol



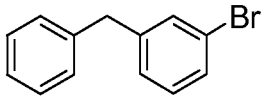
LC-MS *m/z* 244.9 $(M-18+H)^+$, 1.59 min (ret time)

Intermediate 35: (2*E*)-3-(4-Bromophenyl)-1-phenyl-2-propen-1-one



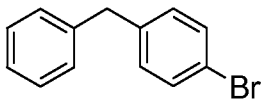
LC-MS *m/z* 286.9 $(M+H)^+$, 1.73 min (ret time).

Intermediate 36: 1-Bromo-3-(phenylmethyl)benzene



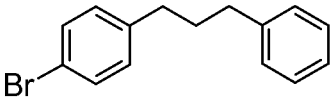
To a solution of (3-bromophenyl)(phenyl)methanol (10 g, 38 mmol) in diethyl ether was added TFA (2 mL) and the resulting solution was stirred at room temperature for 24 h. 10 % NaOH (20 mL) was added, the mixture was extracted with EtOAc (3 x 20 mL). The combined organics were dried, concentrated to give the desired product (9.4 g, 100 %) as yellow oil.

Intermediate 37: 1-Bromo-4-(phenylmethyl)benzene



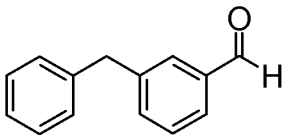
To a solution of (4-bromophenyl)(phenyl)methanol (2.5 g, 9.5 mmol) in DCM (5 mL) was added TFA (4.6 g, 47.5 mmol), followed by Et_3SiH (3.3 g, 28.5 mmol), the resulting mixture was stirred at room temperature for 2 h. Solvent was evaporated to dryness to give the title compound (2.35 g, 100 %) as yellow oil.

Intermediate 38: 1-Bromo-4-(3-phenylpropyl)benzene



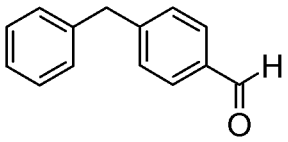
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2 H), 7.31-7.28 (m, 2 H), 7.22-7.19 (m, 3 H), 7.08 (d, *J* = 4.0 Hz, 2 H), 2.69-2.61 (m, 4 H, 1.98-1.95 (m, 2 H).

Intermediate 39: 3-(Phenylmethyl)benzaldehyde



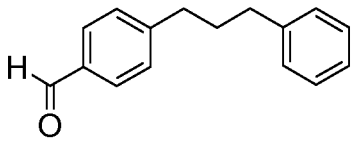
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 7.76-7.21 (m, 9 H), 4.09 (s, 2 H).

Intermediate 40: 4-(Phenylmethyl)benzaldehyde



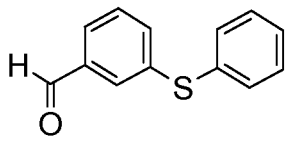
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.84-7.20 (m, 9 H), 4.09 (s, 2 H).

Intermediate 41: 4-(3-Phenylpropyl)benzaldehyde



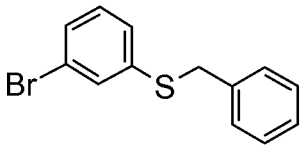
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 7.84-7.82 (m, 2 H), 7.36-7.20 (m, 7 H), 2.78-2.68 (m, 4 H), 2.05-2.00 (m, 2 H).

Intermediate 42: 3-(Phenylthio)benzaldehyde



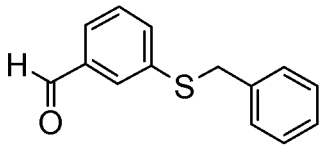
Cu(I)I (16.5 mg, 0.086 mmol), potassium carbonate (475 mg, 3.44 mmol) and 3-iodobenzaldehyde (400 mg, 1.72 mmol) were added to a screw-capped test tube. The tube was evacuated and backfilled with argon (3 cycles). 2-Propanol (2 mL), ethylene glycol (3.44 mmol, 200 mg) and thiophenol (190 mg, 1.72 mmol) were added via syringe at room temperature. The resulting mixture was heated at 80 °C for 20 h. The reaction was quenched by addition of water (10 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (2 x 30 mL), dried and concentrated to give the crude product (302 mg, 82 %) as yellow oil.

Intermediate 43: 3-Bromophenyl phenylmethyl sulfide



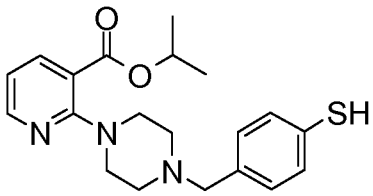
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (s, 1 H), 7.51-7.21 (m, 8 H), 4.29(s, 1 H).

Intermediate 44: 3-[(Phenylmethyl)thio]benzaldehyde



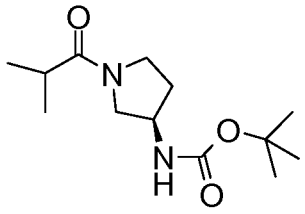
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1 H), 7.81-7.22 (m, 9 H), 4.20 (s, 2 H).

Intermediate 45: 1-Methylethyl 2-{4-[(4-mercaptophenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate



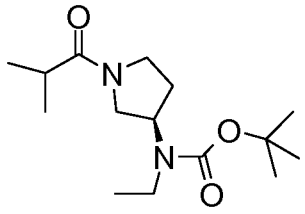
LC-MS *m/z* 372.0 $(M+H)^+$, 1.085 min (ret time).

Intermediate 46: 1,1-Dimethylethyl [(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl] carbamate



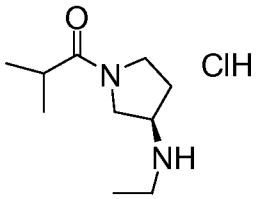
LC-MS *m/z* 257.1 $(M+H)^+$, 1.25 min (ret time).

Intermediate 47: 1,1-Dimethylethyl ethyl[(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl] carbamate



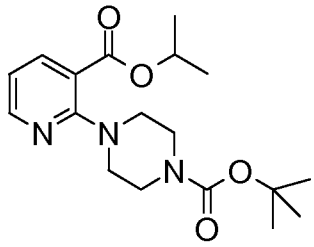
LC-MS *m/z* 285.1 $(M+H)^+$, 1.41 min (ret time)

Intermediate 48:(3*R*)-*N*-Ethyl-1-(2-methylpropanoyl)-3-pyrrolidinamine hydrochloride



LC-MS *m/z* 185.1 $(M+H)^+$, 0.34 min (ret time).

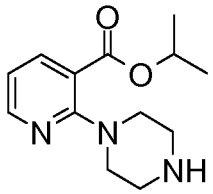
Intermediate 49: 1,1-Dimethylethyl 4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazine carboxylate



LC-MS *m/z* 350.2 $(M+H)^+$, 1.80 min (ret time)

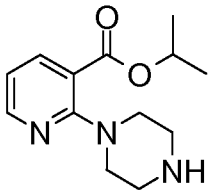
Intermediate 50:1-Methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate

(Preparation 1)



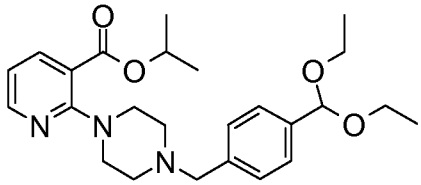
LC-MS *m/z* 250.0 $(M+H)^+$, 0.89 min (ret time)

(Preparation 2)



1-Methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate hydrochloride (800 mg) was suspended in EtOAc (75 mL) and shaken with 1N aq NaOH (25 mL) and the solid dissolved. The EtOAc was washed again with 1 N aq NaOH (25 mL) and then with water (25 mL) and then satd aq NaCl (25 mL), dried (Na_2SO_4) and concentrated to afford 1-methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate free base as a clear oil.

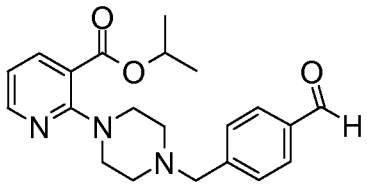
Intermediate 51: 1-Methylethyl 2-[4-({4-[bis(ethyloxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate



LC-MS *m/z* 442.3 $(M+H)^+$, 1.93 min (ret time)

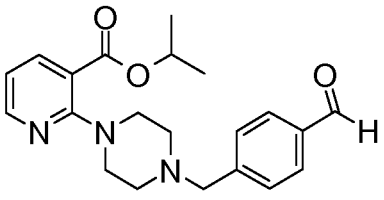
Intermediate 52: 1-Methylethyl 2-{4-[(4-formylphenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate

(Preparation 1)



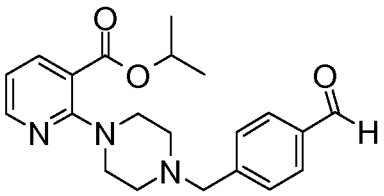
LC-MS *m/z* 368.1 $(M+H)^+$, 1.73 min (ret time)

(Preparation 2)



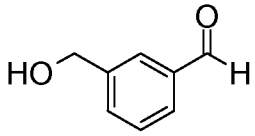
Lcms rt 0.78 [M+H] =368.3.

(Preparation 3)



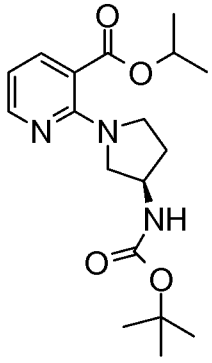
LC-MS m/z = 368 (M+H), 1.10 minutes (retention time).

Intermediate 53: 3-(Hydroxymethyl)benzaldehyde



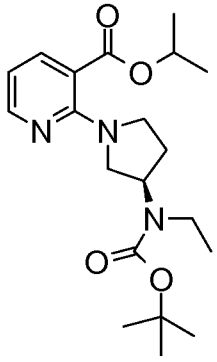
LC-MS *m/z* 137.1 $(M+H)^+$, 1.01 min (ret time).

Intermediate 54: 1-Methylethyl 2-[(3*R*)-3-({[(1,1-dimethylethyl)oxy]carbonyl} amino)-1-pyrrolidinyl] -3-pyridinecarboxylate



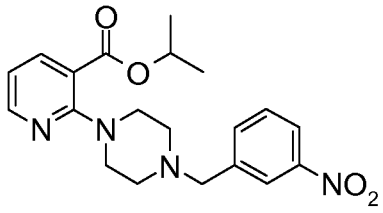
LC-MS *m/z* 350.1 $(M+H)^+$, 1.26 min (ret time)

Intermediate 55: 1-Methylethyl 2-{(3*R*)-3-[{[(1,1-dimethylethyl)oxy]carbonyl} (ethyl) amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



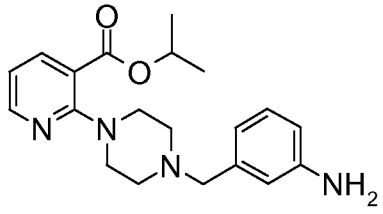
LC-MS *m/z* 378.1 $(M+H)^+$, 1.43 min (ret time)

Intermediate 56:1-Methylethyl 2-{4-[(3-nitrophenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate



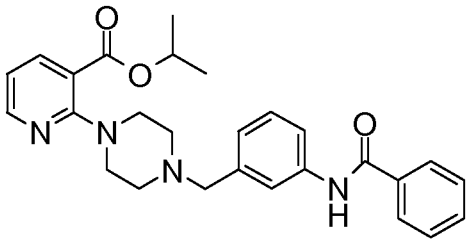
LC-MS *m/z* 385.0 $(M+H)^+$, 1.84 min (ret time)

Intermediate 57:1-Methylethyl 2-{4-[(3-aminophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



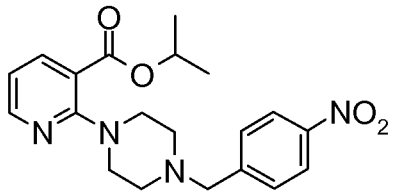
LC-MS *m/z* 355.1 $(M+H)^+$, 1.03 min (ret time)

Intermediate 58:1-Methylethyl 2-[4-({3-[(phenylcarbonyl)amino]phenyl} methyl) -1-piperazinyl]-3-pyridinecarboxylate



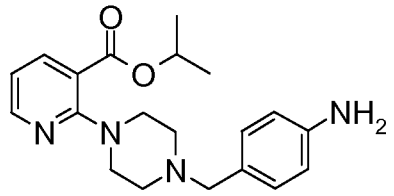
LC-MS *m/z* 459.1 $(M+H)^+$, 1.77 min (ret time)

Intermediate 59: 1-Methylethyl2-{4-[(4-nitrophenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate



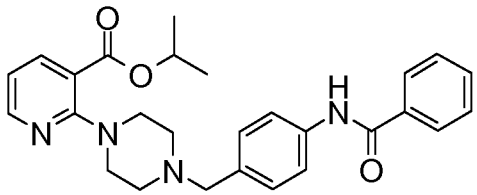
LC-MS *m/z* 385.1 $(M+H)^+$, 1.13 min (ret time)

Intermediate 60:1-Methylethyl 2-{4-[(4-aminophenyl)methyl]-1-piperazinyl} -3-pyridine carboxylate



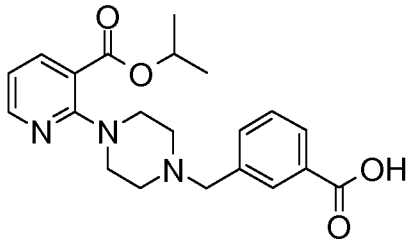
LC-MS *m/z* 365.1 $(M+H)^+$, 1.61 min (ret time)

Intermediate 61:1-Methylethyl 2-[4-({4-[(phenylcarbonyl)amino]phenyl}methyl) -1-piperazinyl]-3-pyridinecarboxylate



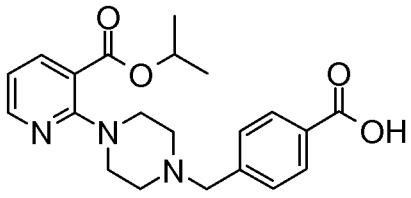
LC-MS *m/z* 459.1 $(M+H)^+$, 1.76 min (ret time)

Intermediate 62: 3-{[4-(3-{[(1-Methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl} benzoic acid



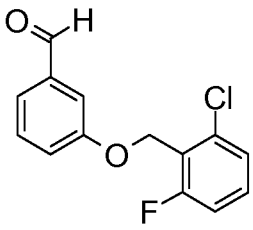
LC-MS *m/z* 384.0 $(M+H)^+$, 1.30 min (ret time)

Intermediate 63: 4-{[4-(3-{[(1-Methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl}benzoic acid



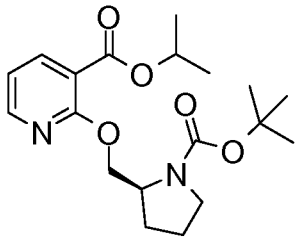
LC-MS *m/z* 384.1 $(M+H)^+$, 1.30 min (ret time)

Intermediate 64: 3-{[(2-Chloro-6-fluorophenyl)methyl]oxy}benzaldehyde



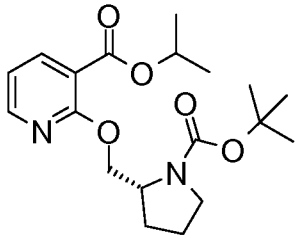
LC-MS *m/z* 264.9 $(M+H)^+$, 1.59 min (ret time)

Intermediate 65:1-Methylethyl2-{[((2*S*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-pyrrolidinyl) methyl] oxy}-3-pyridinecarboxylate



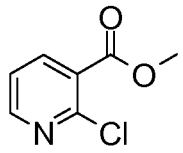
LC-MS *m/z* 365.0 $(M+H)^+$, 1.72 min (ret time); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 - 1.30 (d, 6 H) 1.40 (s, 9 H) 1.62 - 1.66 (m, 2 H) 1.84 - 1.90 (m, 2 H) 3.37 - 3.50 (m, 2 H) 3.50 - 3.52 (m, 2 H) 5.10 - 5.13 (m, 1 H) 5.37 - 5.39 (m, 1 H) 7.06 - 7.09 (m, 1 H) 8.07 - 8.09 (m,1 H) 8.32 - 8.34 (m, 1 H).

Intermediate 66:1-Methylethyl 2-{[((2*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-pyrrolidinyl) methyl] oxy}-3-pyridinecarboxylate



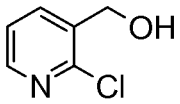
LC-MS *m/z* 365.2 $(M+H)^+$, 1.90 min (ret time).

Intermediate 67:Methyl 2-chloro-3-pyridinecarboxylate



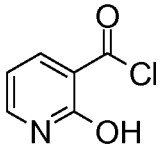
LC-MS *m/z* 172 $(M+H)^+$, 1.36 min (ret time)

Intermediate 68:(2-Chloro-3-pyridinyl)methanol



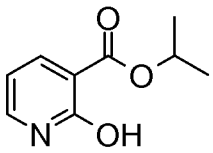
LC-MS *m/z* 144 $(M+H)^+$, 0.87 min (ret time)

Intermediate 69: 2-Oxo-1,2-dihydro-3-pyridinecarbonyl chloride



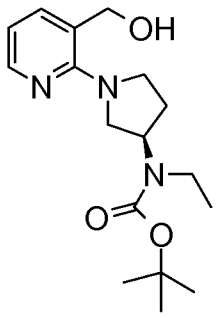
To a suspension of 2-hydroxynicotinic acid (50 g, 0.36 mol) and oxalyl chloride (54.7 g, 0.43 mol) in dichloromethane (250 mL) was added DMF (1 mL) dropwise. The mixture was stirred at room temperature for 30 min. Solvent was removed to obtain the title compound (56.6 g, 100 %) as yellow solid.

Intermediate 70:1-Methylethyl 2-oxo-1,2-dihydro-3-pyridinecarboxylate



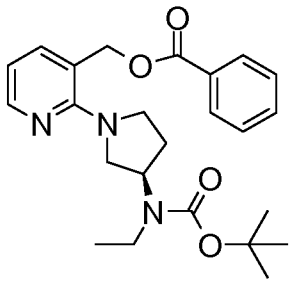
LC-MS *m/z* 182$(M+H)^+$, 1.02 min (ret time)

Intermediate 71:1,1-Dimethylethyl ethyl{(3*R*)-1-[3-(hydroxymethyl)-2-pyridinyl]-3-pyrrolidinyl} carbamate



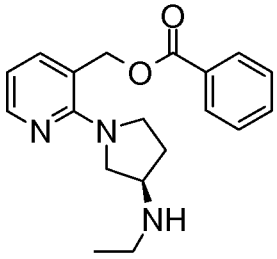
LC-MS *m/z* 322.1 $(M+H)^+$, 0.99 min (ret time)

Intermediate 72:(2-{(3*R*)-3-[{[(1,1-Dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinyl) methyl benzoate



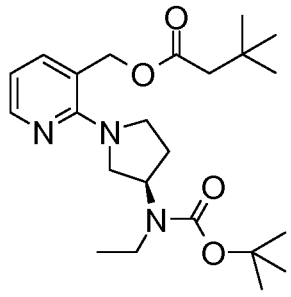
LC-MS *m/z* 426.2 $(M+H)^+$, 1.45 min (ret time)

Intermediate 73:{2-[(3*R*)-3-(Ethylamino)-1-pyrrolidinyl]-3-pyridinyl}methyl benzoate



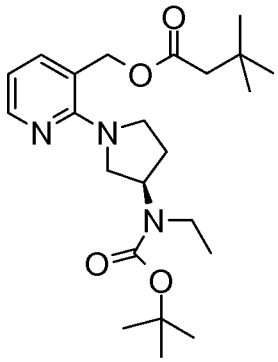
LC-MS *m/z* 326.1 $(M+H)^+$, 0.93 min (ret time)

Intermediate 74: (2-{(3*R*)-3-[{[(1,1-Dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinyl)methyl 3,3-dimethylbutanoate



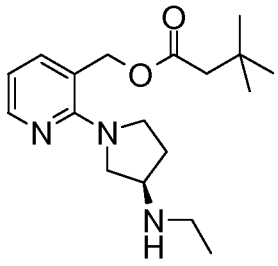
LC-MS *m/z* 420.2 $(M+H)^+$, 1.29 min (ret time)

Intermediate 75: (2-{(3*R*)-3-[{[(1,1-Dimethylethyl)oxy]carbonyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinyl)methyl 3,3-dimethylbutanoate



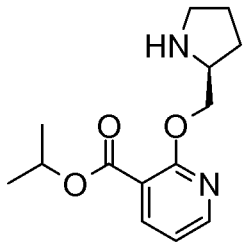
LC-MS *m/z* 420.3 $(M+H)^+$, 1.50 min (ret time)

Intermediate 76:{2-[(3*R*)-3-(Ethylamino)-1-pyrrolidinyl]-3-pyridinyl}methyl 3,3-dimethylbutanoate



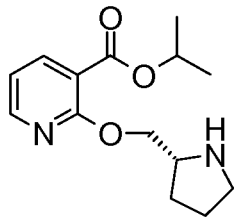
LC-MS *m/z* 320.2 $(M+H)^+$, 1.16 min (ret time)

Intermediate 77: 1-Methylethyl 2-{[(2*S*)-2-pyrrolidinylmethyl]oxy}-3-pyridinecarboxylate



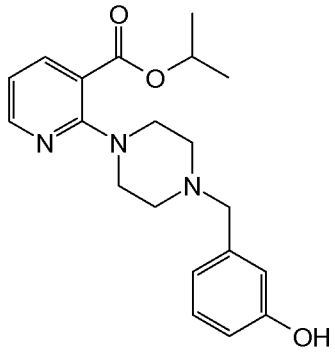
LC-MS *m/z* 265.0 $(M+H)^+$, 1.47 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, *J* = 6.4 Hz, 6 H), 1.84-2.13 (m, 4 H), 3.23 (m, 2 H), 3.96 (m, 1 H), 4.43 (m, 1 H), 4.54 (m, 1 H), 5.12 (m, 1 H), 7.16 (m, 1 H), 8.15 (m, 1 H), 8.38 (m, 1 H).

Intermediate 78: 1-Methylethyl 2-{[(2*R*)-2-pyrrolidinylmethyl]oxy}-3-pyridinecarboxylate



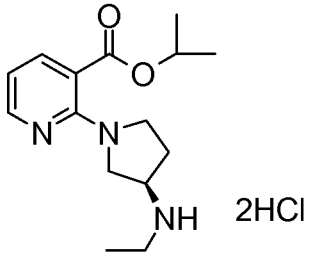
LC-MS *m/z* 265.1 $(M+H)^+$, 1.46 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 1.31 (d, *J* = 5.2 Hz, 6 H), 1.81-1.86 (m, 2 H), 1.98-2.10 (m, 2 H), 3.16-3.19 (m, 2 H), 4.02-4.03 (m, 1 H), 4.38-4.42 (m,1 H), 4.50-4.53 (m, 1 H), 5.10-5.12 (m, 1 H), 7.14-7.17 (m, 1 H), 8.14-8.16 (m, 1 H), 8.36-8.38 (m, 1 H).

Intermediate 79 1-Methylethyl 2-{4-[(3-hydroxyphenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



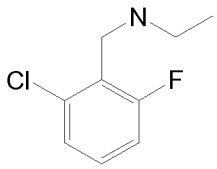
Lcms rt = 0.66 [M+H]= 356.2. Purity by LCMS 87%.

Intermediate 80: 1-Methylethyl 2-[(3*R*)-3-(ethylamino)-1-pyrrolidinyl] -3-pyridine carboxylate dihydrochloride



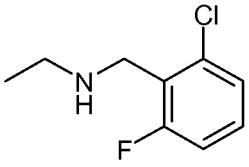
LC-MS m/z 277.9 (M+H)+, 0.67 min (ret time)

Intermediate 81: [(2-chloro-6-fluorophenyl)methyl]ethylaminePreparation 1



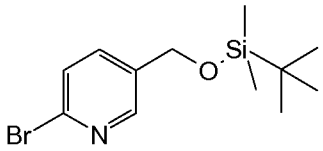
^{1}H NMR (400 MHz, DMSO-d_6) d 7.32 - 7.51 (m, 2H), 7.17 - 7.33 (m, 1H), 3.79 - 3.94 (m, 2H), 2.68(m, 2), 0.99 - 1.14 (m,3H).

Preparation 2: Intermediate: [(2-chloro-6-fluorophenyl)methyl]ethylamine



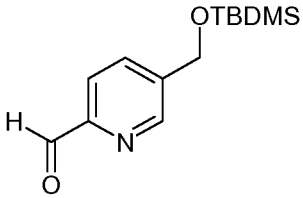
LC-MS m/z = 188 (M+H), 0.46 minutes (retention time).

Intermediate 82 2-bromo-5-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy} methyl) pyridine



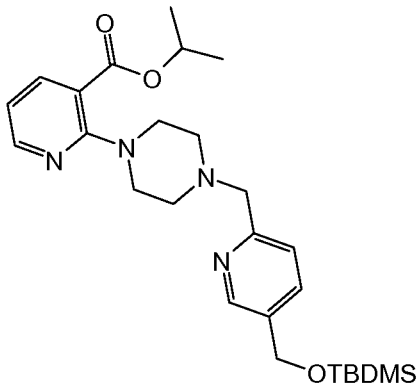
(LC-MS *m/z* 302/304 $(M+H)^+$ 1.42 (ret time)

Intermediate 83 : 5-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-pyridine carbaldehyde



LC-MS *m/z* 252.2 $(M+H)^+$ 1.16 (ret time)

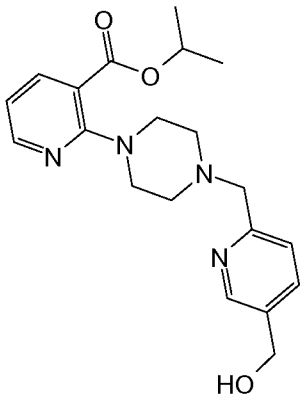
Intermediate 84: 1-methylethyl 2-(4-{[5-({[(1,1-dimethylethyl)(dimethyl) silyl]oxy} methyl)-



2-pyridinyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate

LC-MS *m/z* 485.5 $(M+H)^+$ 1.14 (ret time)

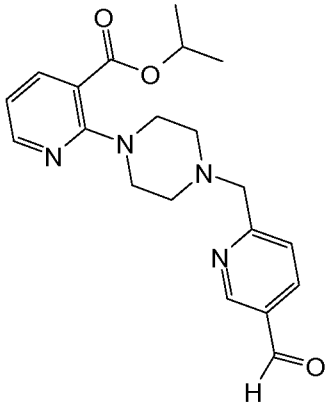
Intermediate 85: 1-methylethyl 2-(4-{[5-(hydroxymethyl)-2-pyridinyl]methyl}-1-piperazinyl)-



3-pyridinecarboxylate

LC-MS *m/z* 371.1 $(M+H)^+$ 0.73 (ret time)

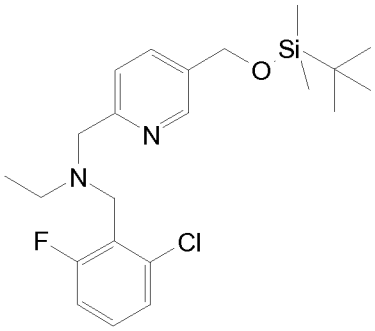
Intermediate 86: 1-methylethyl 2-(4-{[5-(hydroxymethyl)-2-pyridinyl]methyl}-1-piperazinyl)-



3-pyridinecarboxylate

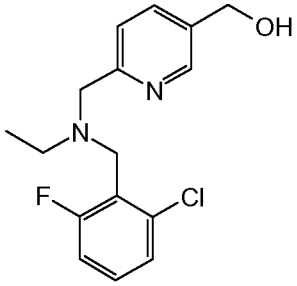
LC-MS m/z 369 $(M+H)^+$ 0.78 (ret time)

Intermediate 87: N-[(2-chloro-6-fluorophenyl)methyl]-N-{[5-({[(1,1-dimethylethyl) (dimethyl) silyl]oxy} methyl)-2-pyridinyl]methyl}ethanamine



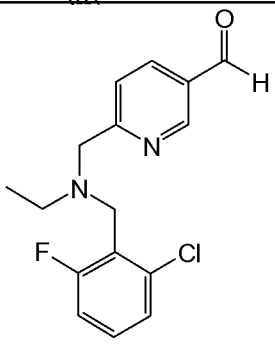
LC-MS *m/z* 423.0 $(M+H)^+$ 0.78 (ret time)

Intermediate 88: (6-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-3-pyridinyl) methanol



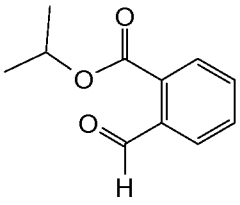
LC-MS *m/z* 308.9 $(M+H)^+$ 0.65 (ret time)

Intermediate 89: 6-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-3-pyridine carbaldehyde



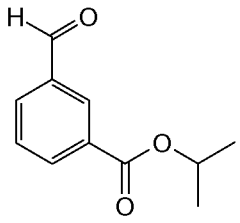
LC-MS *m/z* 307.1 $(M+H)^+$ 0.57 (ret time) within an impure mixture.

Intermediate 90: Intermediate ester1 1-methylethyl 2-formylbenzoate



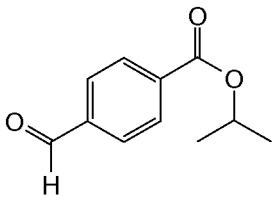
LC-MS *m/z* 193.1 $(M+H)^+$ 0.94 (ret time).

Intermediate 91: 2 1-methylethyl 3-formylbenzoate



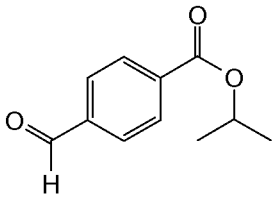
LC-MS *m/z* 193.1 $(M+H)^+$ 0.94 (ret time).

Intermediate 92: 3 1-methylethyl 4-formylbenzoate



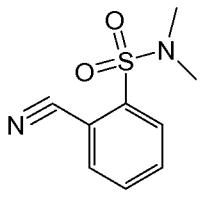
LC-MS *m/z* 193.1 $(M+H)^+$ 0.94 (ret time).

Intermediate 93: 1-methylethyl 4-formylbenzoate



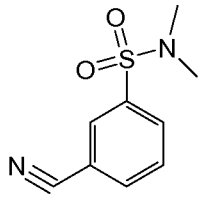
LC-MS *m/z* 193.1 $(M+H)^+$ 0.94 (ret time).

Intermediate 94: 2-cyano-N,N-dimethylbenzenesulfonamide



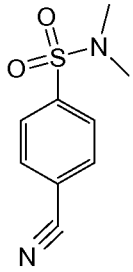
LC-MS *m/z* 211.1 $(M+H)^+$ 0.61 (ret time).

Intermediate 95: 3-cyano-N,N-dimethylbenzenesulfonamide



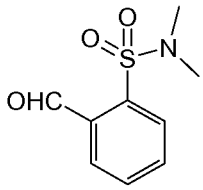
LC-MS *m/z* 211.0 $(M+H)^+$ 0.79 (ret time).

Intermediate 96: 4-cyano-N,N-dimethylbenzenesulfonamide



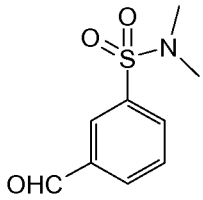
LC-MS *m/z* 211.0 $(M+H)^+$ 0.79 (ret time).

Intermediate 97: 2-Formyl-N,N-dimethylbenzenesulfonamide



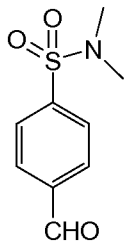
LC-MS *m/z* 214.1 $(M+H)^+$ 0.66 (ret time) (70% purity)

Intermediate 98: 3-Formyl-N,N-dimethylbenzenesulfonamide



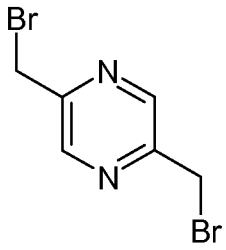
LC-MS *m/z* 214.1 $(M+H)^+$ 0.65 (ret time) (77% purity)

Intermediate 99: 4-Formyl-N,N-dimethylbenzenesulfonamide



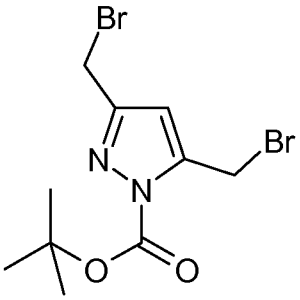
LC-MS *m/z* 214.1 $(M+H)^+$ 0.74 (ret time) (77% purity)

Intermediate 100: 2,5-bis(bromomethyl)pyrazine



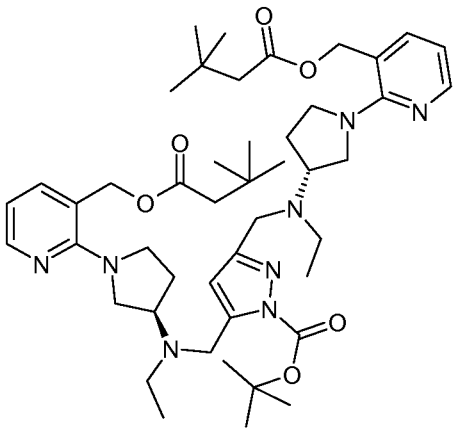
LC-MS m/z = 266 (M+H), 0.67 minutes (retention time).

Intermediate 101: 1,1-dimethylethyl 3,5-bis(bromomethyl)-1H-pyrazole-1-carboxylate



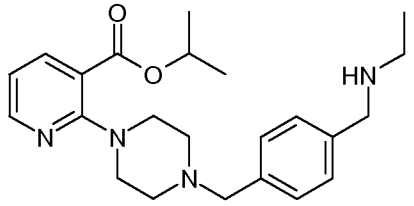
LC-MS m/z = 355 (M+H), 1.12 minutes (retention time).

Intermediate 102: 1,1-dimethylethyl 3,5-bis{[[(3R)-1-(3-{[(3,3-dimethylbutanoyl)oxy]methyl}-2-pyridinyl)-3-pyrrolidinyl](ethyl)amino]methyl}-1H-pyrazole-1-carboxylate



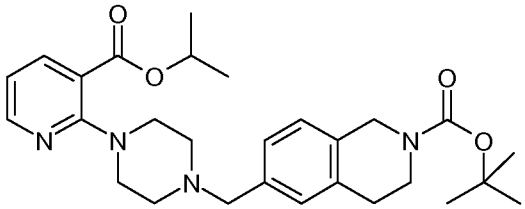
LC-MS m/z = 832 (M+H), 1.02 minutes (retention time).

Intermediate 103: 1-methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate



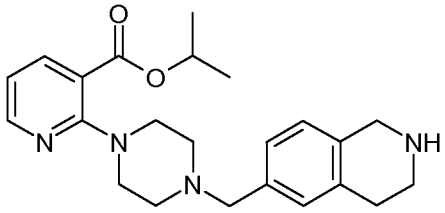
LC-MS m/z = 397 (M+H), 0.44 minutes (retention time).

Intermediate 104: 1,1-dimethylethyl 6-{[4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl}-3,4-dihydro-2(1H)-isoquinolinecarboxylate



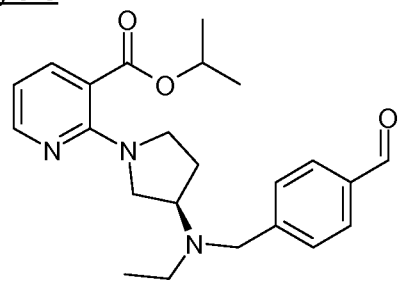
LC-MS m/z = 495 (M+H), 0.99 minutes (retention time).

Intermediate 105: 1-methylethyl 2-[4-(1,2,3,4-tetrahydro-6-isoquinolinylmethyl)-1-piperazinyl]-3-pyridine carboxylate -7hydrochloride



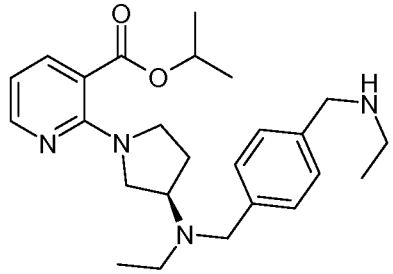
LC-MS m/z = 395 (M+H), 0.48 minutes (retention time).

Intermediate 106: 1-methylethyl 2-((3R)-3-{ethyl[(4-formylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



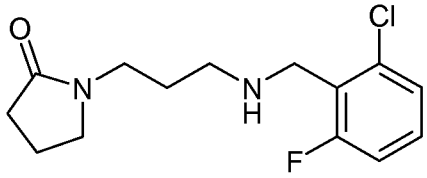
LC-MS m/z = 396 (M+H), 0.73 minutes (retention time).

Intermediate 107: 1-methylethyl 2-{(3R)-3-[ethyl({4-[(ethylamino)methyl]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



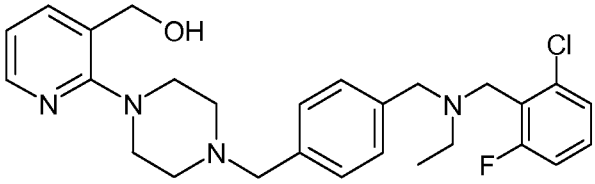
LC-MS m/z = 425 (M+H), 0.60 minutes (retention time).

Intermediate 108: 1-(3-{[(2-chloro-6-fluorophenyl)methyl]amino}propyl)-2-pyrrolidinone



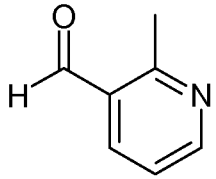
LC-MS m/z = 285 (M+H), 0.59 minutes (retention time) which was used without further purification.

Intermediate 109: (2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methanol



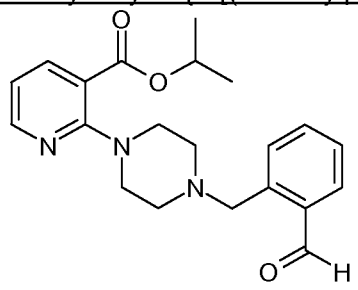
LC-MS m/z = 483 (M+H), 0.55 minutes (retention time).

Intermediate 110: 2-methyl-3-pyridinecarbaldehyde



^{1}H NMR (400 MHz, DMSO-d_6) d ppm 2.80 (s, 3 H) 7.47 (dd, *J*=7.65, 4.89 Hz, 1 H) 8.18 (dd, *J*=7.78, 1.76 Hz, 1 H) 8.68 (dd, *J*=4.77, 1.76 Hz, 1 H) 10.29 (s, 1 H)

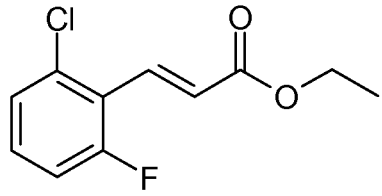
Intermediate 111: 1-methylethyl 2-{4-[(2-formylphenyl)methyl]-1-piperazinyl}-3-



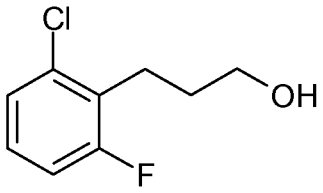
pyridinecarboxylate

LC-MS m/z = 368 (M+H), 0.71 minutes (retention time).

Intermediate 112: Ethyl (2E)-3-(2-chloro-6-fluorophenyl)-2-propenoate

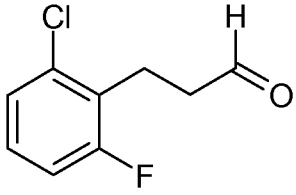


LC-MS m/z = 229 (M+H), 1.18 minutes (retention time). Title compound was carried on crude for the preparation of 3-(2-chloro-6-fluorophenyl)-1-propanol.



Intermediate 113: 3-(2-chloro-6-fluorophenyl)-1-propanol

LC-MS m/z = 189 (M+H), 0.84 minutes (retention time).



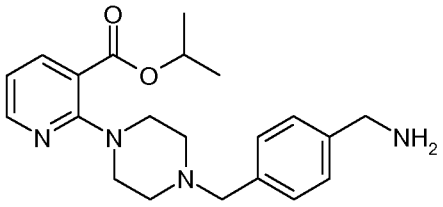
Intermediate 114: 3-(2-chloro-6-fluorophenyl)propanal

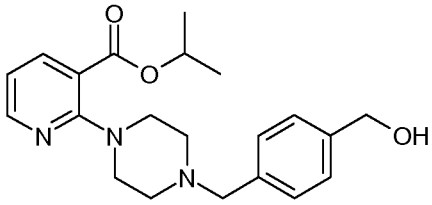
LC-MS m/z = 187 (M+H), 0.91 minutes (retention time). The title compound was carried on crude for the preparation of 1-methylethyl 2-{4-[(4-{[[3-(2-chloro-6-

fluorophenyl)propyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate.

Intermediate 115: 1-Methylethyl2-(4-{[4-(aminomethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate

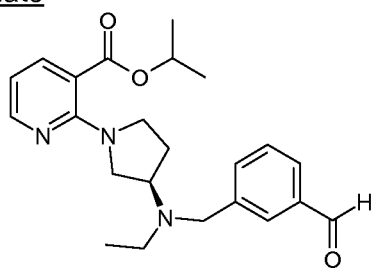
Intermediate: 116: Methylethyl2-(4-{[4-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate





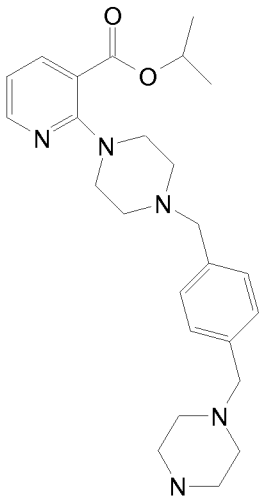
LC-MS m/z = 369 (M+H), 0.53 minutes (retention time) and 1-methylethyl 2-(4-{[4-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate (0.185g, 17%). LC-MS m/z = 370 (M+H), 0.67 minutes (retention time).

Intermediate 117: 1-methylethyl 2-((3R)-3-{ethyl[(3-formylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



LC-MS m/z = 396 (M+H), 0.72 minutes (retention time).

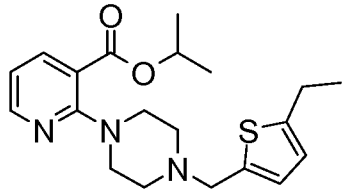
Intermediate 118: 1-methylethyl 2-(4-{[4-(1-piperazinylmethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



LC/MS: m/z= 438.1 $[M+H]^+$, Ret. Time: 0.57 min

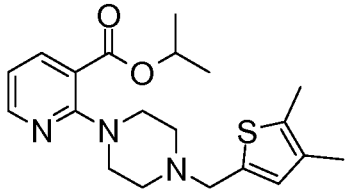
Compound Examples

Example 1
1-Methylethyl 2-{4-[(5-ethyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



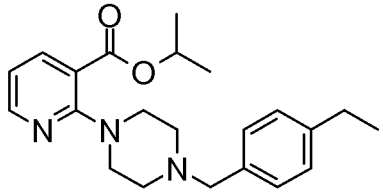
LC-MS *m/z* 374.2 $(M+H)^+$, 1.94 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 1 H), 7.94-7.91 (m, 1 H), 6.74-6.61 (m, 3 H), 5.19-5.16 (m, 1 H), 3.72 (s, 2 H), 3.48-3.46 (m, 4 H), 2.82 (q, *J* = 7.6, 14.8 Hz, 2 H), 2.64-2.63 (m, 4 H), 1.35 (d, *J* = 6.4 Hz, 6 H), 1.30 (t, *J* = 7.6 Hz, 3 H).

Example 2
1-Methylethyl 2-{4-[(4,5-dimethyl-2-thienyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate



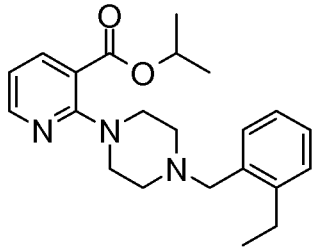
LC-MS *m/z* 374.2 $(M+H)^+$, 1.93 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 1 H), 7.94-7.91 (m, 1 H), 6.72-6.69 (m, 1 H), 6.60 (s, 1 H), 5.19-5.16 (m, 1 H), 3.64 (s, 2 H), 3.46 (t, *J* = 5.2 Hz, 4 H), 2.59 (t, *J* = 5.2 Hz, 4 H), 2.30 (s, 3 H), 2.08 (s, 3 H), 1.34 (d, *J* = 6.4 Hz, 6 H).

Example 3
1-Methylethyl 2-{4-[(4-ethylphenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate



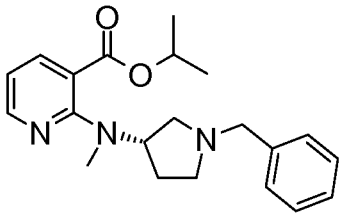
LC-MS *m/z* 368.2 $(M+H)^+$, 2.23 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27-8.24 (m, 1 H), 7.93-7.90 (m, 1 H), 7.27-7.15 (m, 4 H), 6.72-6.69 (m, 1 H), 5.19-5.16 (m, 1 H), 3.55 (s, 2 H), 3.45 (t, *J* = 4.8 Hz, 4 H), 2.67-2.61 (q, *J* = 7.6, 14.8 Hz, 2 H), 2.58 (t, *J* = 4.8 Hz, 4 H), 1.33 (d, *J* = 6.4 Hz, 6 H), 1.23 (t, *J* = 7.6 Hz, 3 H).

Example 4
1-Methylethyl 2-{4-[(2-ethylphenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



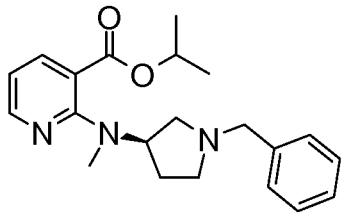
LC-MS *m/z* 368.2 $(M+H)^+$, 2.31 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 1 H), 7.92-7.90 (m, 1 H), 7.30-7.20 (m, 4 H), 6.72-6.69 (m, 1 H), 5.20-5.14 (m, 1 H), 3.53 (s, 2 H), 3.43 (t, *J* = 4.8 Hz, 4 H), 2.75 (q, *J* = 7.6, 14.8 Hz, 2 H), 2.56 (t, *J* = 4.8 Hz, 4 H), 1.35 (d, *J* = 6.4 Hz, 6 H), 1.23 (t, *J* = 7.6 Hz, 3 H).

Example 5
1-Methylethyl 2-{methyl[(3*S*)-1-(phenylmethyl)-3-pyrrolidinyl]amino} -3-pyridine carboxylate hydrochloride



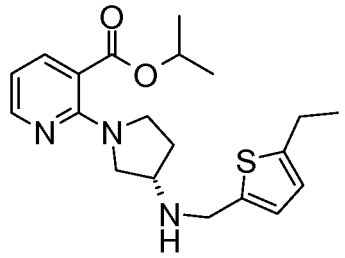
LC-MS *m/z* 354 $(M+H)^+$, 1.15 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 13.11 (s, 1 H), 8.35-8.33 (d, *J* = 5.6Hz, 1 H), 8.25-8.23 (d, *J* = 7.2Hz, 1 H), 7.75-7.74 (d, *J* = 6.0Hz, 2 H), 7.44-7.42 (m, 3 H), 7.071(t, *J* = 8.9 Hz, 1 H), 5.70-5.66(m, 1 H), 5.25-5.22 (m, 1 H), 4.46-4.32 (m, 3 H), 3.73-3.70 (m, 1 H), 3.61-3.58 (m, 1 H), 3.19 (s, 3 H), 3.10-3.07 (m, 1 H), 2.80-2.76 (m, 1 H), 2.53-2.50 (m, 1 H), 1.40-1.30 (dd, *J* = 8.4Hz, 6 H)

Example 6
1-Methylethyl2-{methyl[(3*R*)-1-(phenylmethyl)-3-pyrrolidinyl]amino}-3-pyridine carboxylate hydrochloride



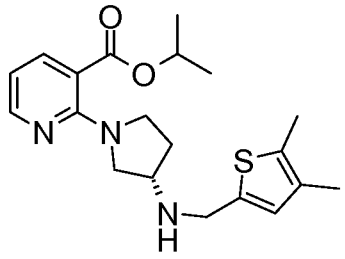
LC-MS *m/z* 354 $(M+H)^+$, 1.15 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 13.11 (s, 1 H), 8.34-8.32 (d, J = 5.6 Hz, 1 H), 8.23-8.21 (d, J = 6 Hz, 1 H), 7.75-7.73 (d, J = 6.0 Hz, 2 H), 7.44-7.42 (m, 3 H), 7.06-7.03 (m, 1 H), 5.71-5.63 (m, 1 H), 5.25-5.21 (m, 1 H), 4.45-4.32 (m, 3 H), 3.74-3.70 (m, 1 H), 3.62-3.57 (m, 1 H), 3.18 (s, 3 H), 3.08-3.03 (m, 1 H), 2.79-2.75 (m, 1 H), 2.52-2.48 (m, 1 H), 1.39-1.35 (dd, J = 6 Hz, 6 H).

Example 7
1-Methylethyl 2-((3*S*)-3-{[(5-ethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



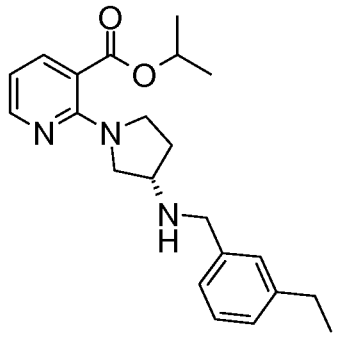
LC-MS *m/z* 374 $(M+H)^+$, 2.09 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.22 (m, 1 H), 7.84-7.81 (m, 1 H), 6.71-6.70 (m, 1 H), 6.61-6.58 (m, 2 H), 5.22-5.16 (m, 1 H), 3.94 (s, 2 H), 3.60-3.45 (m, 4 H), 3.28-3.24 (m, 1 H), 2.82-2.76 (m, 2 H), 2.18-2.10 (m, 1 H), 1.87-1.79 (m, 1 H), 1.67 (s, 1 H), 1.36-1.35 (d, *J* = 6.4 Hz, 6 H), 1.27 (t, *J* = 7.6 Hz, 3 H).

Example 8
1-Methylethyl 2-((3*S*)-3-{[(4,5-dimethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



LC-MS *m/z* 374 $(M+H)^+$, 2.08 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.243-8.22 (m, 1 H), 7.83-7.81 (m, 1 H), 6.60-6.6.57 (m, 2 H), 5.22-5.16 (m, 1 H), 3.88 (s, 2 H), 3.59-3.44 (m, 4 H), 3.27-3.23 (m, 1 H), 2.28 (s, 3 H), 2.17-2.10 (m, 1 H), 2.06 (s, 3 H), 1.86-1.77 (m, 1 H), 1.62 (s, 1 H), 1.36-1.34 (dd, *J* = 1.2 Hz, 1.6 Hz, 6 H).

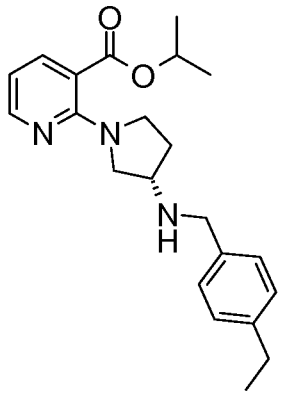
Example 9
1-Methylethyl 2-((3*S*)-3-{[(3-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridine carboxylate



LC-MS *m/z* 368 $(M+H)^+$, 2.09 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 1 H), 7.84-7.82 (m, 1 H), 7.26-7.21 (m, 1 H), 7.15-7.07 (m, 3 H), 6.61-6.58 (m, 1 H), 5.24-5.15 (m, 1 H), 3.80 (s, 2 H), 3.61-3.41 (m, 4 H), 3.31-3.27 (m, 1 H), 2.66-2.60 (m, 2 H), 2.19-2.11 (m, 1 H), 1.88-1.80 (m, 1 H), 1.54 (s, 1 H), 1.36-1.35 (d, *J* = 6 Hz, 6 H), 1.22 (t, *J* = 8 Hz, 3 H).

Example 10

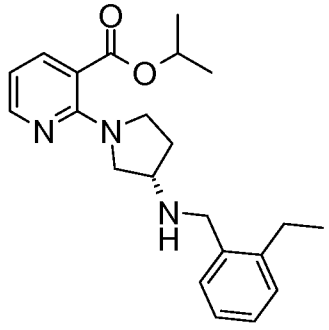
1-Methylethyl 2-((3*S*)-3-{[(4-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridine carboxylate



LC-MS *m/z* 368 $(M+H)^+$, 2.10 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23-8.21 (m, 1 H), 7.84-7.82 (m, 1 H), 7.30-7.26 (m, 2 H), 7.17-7.15 (m, 2 H), 6.62-6.59 (m, 1 H), 5.21-5.15 (m, 1 H), 3.90-3.82 (m, 2 H), 3.65-3.61 (m, 1 H), 3.52-3.41 (m, 4 H), 2.98 (s, 1 H), 2.65-2.59 (m, 2 H), 2.23-2.15 (m, 1 H), 2.02-1.93 (m, 1 H), 1.36-1.34 (d, *J* = 6 Hz, 6 H), 1.21 (t, *J* = 8 Hz, 3 H).

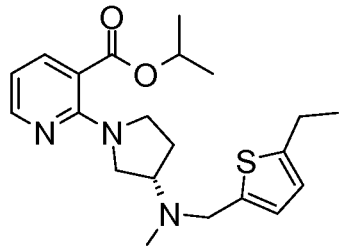
Example 11

1-Methylethyl 2-((3*S*)-3-{[(2-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



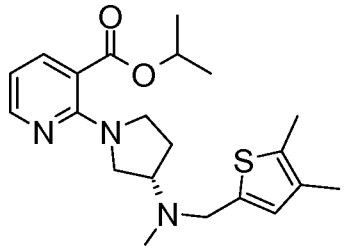
LC-MS *m/z* 368 $(M+H)^+$, 2.12 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1 H), 7.84-7.82 (m, 1 H), 7.30-7.12 (m, 4 H), 6.61-6.58 (m, 1 H), 5.23-5.16 (m, 1 H), 3.81 (s, 2 H), 3.63-3.44 (m, 4 H), 3.30-3.26 (m, 1 H), 2.70-2.64 (m, 2 H), 2.20-2.13 (m, 1 H), 1.90-1.82 (m, 1 H), 1.52 (m, 1 H), 1.36-1.35 (d, *J* = 6 Hz, 6 H), 1.20 (t, *J* = 7.6 Hz, 3 H).

Example 12
1-Methylethyl 2-{(3*S*)-3-[[(5-ethyl-2-thienyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



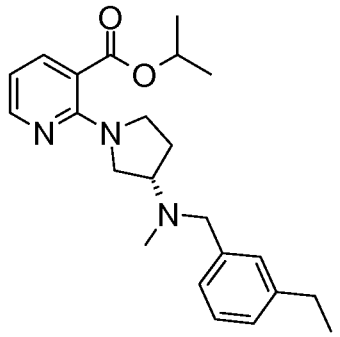
LC-MS *m/z* 388 $(M+H)^+$, 2.23 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 1 H), 7.83-7.81 (m, 1 H), 6.69-6.69 (m, 1 H), 6.61-6.58 (m, 2 H), 5.23-5.16 (m, 1 H), 3.77 (s, 2 H), 3.66-3.36 (m, 4 H), 3.13-3.05 (m, 1 H), 2.82-2.77 (m, 2 H), 2.28 (s, 3 H), 2.21-2.15 (m, 1 H), 1.97-1.89 (m, 1 H), 1.38-1.34 (dd, *J* = 6.4 Hz, 6 H), 1.28 (m, *J* = 7.6 Hz, 3 H).

Example 13
1-Methylethyl 2-{(3*S*)-3-[[(4,5-dimethyl-2-thienyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



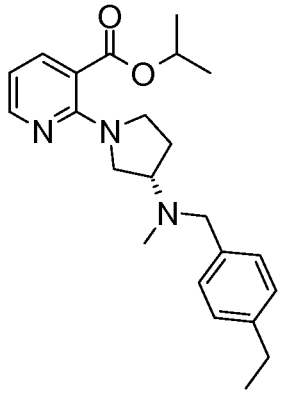
LC-MS *m/z* 388 $(M+H)^+$, 2.22 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 1 H), 7.83-7.81 (m, 1 H), 6.61-6.57 (m, 2 H), 5.23-5.16 (m, 1 H), 3.72 (s, 2 H), 3.66-3.35 (m, 4 H), 3.12-3.04 (m, 1 H), 2.28 (s, 6 H), 2.20-2.14 (m, 1 H), 2.07 (s, 3 H), 1.96-1.85 (m, 1 H), 1.37-1.34 (dd, *J* = 6.4 Hz, 6 H).

Example 14
1-Methylethyl 2-{(3*S*)-3-[[(3-ethylphenyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



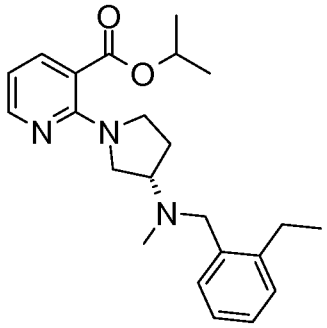
LC-MS *m/z* 382 $(M+H)^+$, 2.28 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.24 (m, 1 H), 7.84-7.82 (m, 1 H), 7.26-7.07 (m, 4 H), 6.61-6.58 (m, 1 H), 5.22-5.17 (m, 1 H), 3.68-3.40 (m, 6 H), 3.11-3.04 (m, 1 H), 3.66-2.60 (m, 2 H), 2.18-2.17 (m, 4 H), 2.00-1.90 (m, 1 H), 1.37-1.33 (m, 6 H), 1.25-1.21 (m, 3 H).

Example 15
1-Methylethyl 2-{(3*S*)-3-[[(4-ethylphenyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



LC-MS *m/z* 382 $(M+H)^+$, 2.28 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25-8.24 (m, 1 H), 7.84-7.81 (m, 1 H), 7.26-7.13 (m, 4 H), 6.62-6.59 (m, 1 H), 5.22-5.16 (m, 1 H), 3.67-3.39 (m, 6 H), 3.11-3.03 (m, 1 H), 2.66-2.60 (m, 2 H), 2.22-2.17 (m, 4 H), 1.99-1.79 (m, 1 H), 1.37-1.33 (dd, *J* = 6.4 Hz, 6 H), 1.22 (t, *J* = 8 Hz, 3 H).

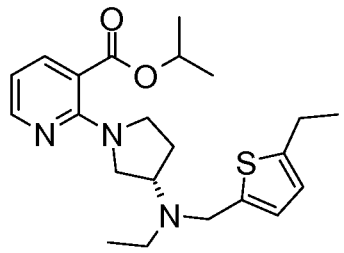
Example 16
1-Methylethyl 2-{(3*S*)-3-[[(2-ethylphenyl)methyl](methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



LC-MS *m/z* 382 $(M+H)^+$, 2.33 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17-8.16

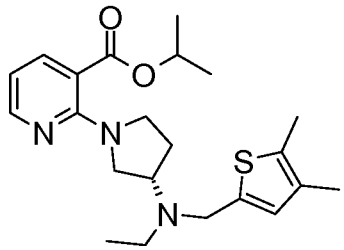
(m, 1 H), 7.76-7.74 (m, 1 H), 7.22-7.03 (m, 4 H), 6.53-6.50 (m, 1 H), 5.19-5.08 (m, 1 H), 3.61-3.35 (m, 6 H), 3.03-2.96 (m, 1 H), 2.68-2.63 (m, 2 H), 2.15-2.09 (m, 1 H), 2.04 (s, 3 H), 1.95-1.85 (m, 1 H), 1.28-1.24 (dd, *J* = 6.4 Hz, 6 H), 1.12 (t, *J* = 8 Hz, 3 H).

Example 17
1-Methylethyl 2-((3*S*)-3-{ethyl[(5-ethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



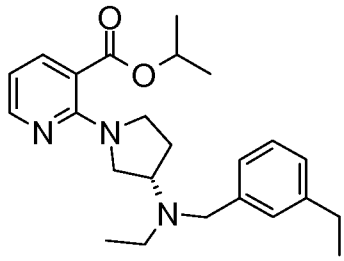
LC-MS *m/z* 402 $(M+H)^+$, 2.33 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1 H), 7.82-7.80 (m, 1 H), 6.69-6.68 (m, 1 H), 6.60-6.57 (m, 2 H), 5.22-5.16 (m, 1 H), 3.87 (s, 2 H), 3.64-3.32 (m, 5 H), 2.82-2.76 (m, 2 H), 2.69-2.62 (m, 2 H), 2.19-2.13 (m, 1 H), 1.95-1.85 (m, 1 H), 1.37-1.33 (dd, *J* = 6.4 Hz, 6 H), 1.28 (t, *J* = 7.6 Hz, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H).

Example 18
1-Methylethyl 2-{(3*S*)-3-[[(4,5-dimethyl-2-thienyl)methyl](ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



LC-MS *m/z* 402 $(M+H)^+$, 2.31 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.22 (m, 1 H), 7.82-7.80 (m, 1 H), 6.60-6.56 (m, 2 H), 5.22-5.16 (m, 1 H), 3.82 (s, 2 H), 3.64-3.30 (m, 5 H), 2.70-2.60 (m, 2 H), 2.28 (s, 3 H), 2.18-2.12 (m, 1 H), 2.06 (s, 3 H), 1.94-1.84 (m, 1 H), 1.37-1.33 (dd, *J* = 6.4 Hz, 6 H), 1.07 (t, *J* = 7.2 Hz, 3 H).

Example 19
1-Methylethyl 2-((3*S*)-3-{ethyl[(3-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate

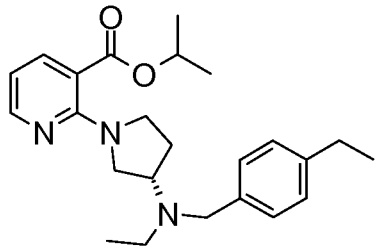


LC-MS *m/z* 396 $(M+H)^+$, 2.38 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1 H), 7.82-7.80 (m, 1 H), 7.25-7.14 (m, 3 H), 7.07-7.05 (m, 1 H), 6.60-6.57 (m, 1 H), 5.21-5.14 (m, 1 H), 2.70-3.36 (m, 7 H), 2.66-2.60 (m, 4 H), 2.10-2.09 (m, 1 H),

1.97-1.86 (m, 1 H), 1.36-1.32 (m, 6 H), 1.24-1.21 (m, 3 H), 1.00 (t, *J* = 6.8 Hz, 3 H).

Example 20

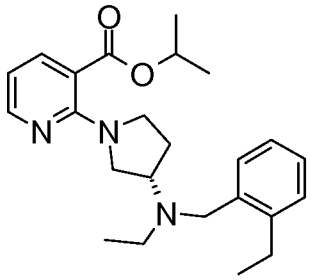
1-Methylethyl 2-((3*S*)-3-{ethyl[(4-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



LC-MS *m/z* 396 $(M+H)^+$, 2.38 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1 H), 7.82-7.80 (m, 1 H), 7.26-7.24 (m, 2 H), 7.13-7.11 (m, 2 H), 6.60-6.57 (m, 1 H), 5.21-5.14 (m, 1 H), 3.69-3.35 (m, 7 H), 2.65-2.60 (m, 4 H), 2.13-2.09 (m, 1 H), 2.08-1.85 (m, 1 H), 1.36-1.32 (dd, *J* = 6.4 Hz, 6 H), 1.22 (t, *J* = 7.6 Hz, 3 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

Example 21

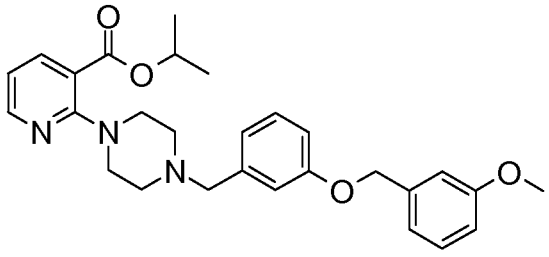
1-Methylethyl 2-((3*S*)-3-{ethyl[(2-ethylphenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



LC-MS *m/z* 396 $(M+H)^+$, 2.42 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.23 (m, 1 H), 7.82-7.80 (m, 1 H), 7.41-7.39 (m, 1 H), 7.25-7.10 (m, 3 H), 6.60-6.57 (m, 1 H), 5.21-5.14 (m, 1 H), 3.75-3.36 (m, 7 H), 2.75-2.70 (m, 2 H), 2.62-2.59 (m, 2 H), 2.12-2.07 (m, 1 H), 1.98-1.88 (m, 1 H), 1.36-1.32 (dd, *J* = 6.4 Hz, 6 H), 1.20 (t, *J* = 7.6 Hz, 3 H), 0.97 (t, *J* = 6.8 Hz, 3 H).

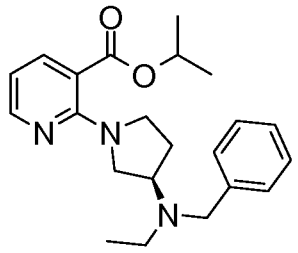
Example 22

1-Methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride



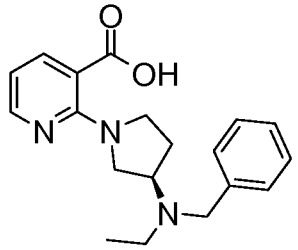
LC-MS *m/z* 476.3 $(M+H)^+$, 1.27 min (ret time); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (d, *J* = 6 Hz, 6 H), 3.06-3.07 (m, 2 H), 3.31-3.52 (m, 4 H), 3.83 (d, *J* = 14 Hz, 2 H), 4.31 (d, *J* = 4.4 Hz), 5.18-5.12 (m, 2 H), 6.88-7.47 (m, 9 H), 8.04-8.06 (m, 1 H), 8.34-8.35 (m, 1 H).

Example 23
1-Methylethyl 2-{(3*R*)-3-[ethyl(phenylmethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



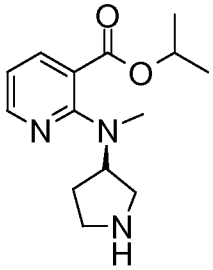
LC-MS *m/z* 368.0 $(M+H)^+$, 1.99 min (ret time)

Example 24
2-{(3*R*)-3-[Ethyl(phenylmethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylic acid



LC-MS *m/z* 326$(M+H)^+$, 1.28 min (ret time); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1 H), 8.27-8.25 (m, 1 H), 8.09-8.06 (m, 1 H), 7.74-7.73 (m, 2 H), 7.46-7.45 (m, 3 H), 6.91-6.88 (m, 1 H), 4.57-3.44 (m, 7 H), 3.07-2.945 (m, 2 H), 2.57-2.51 (m, 1 H), 2.50-2.39 (m, 1 H), 1.27-1.22 (m, 3 H).

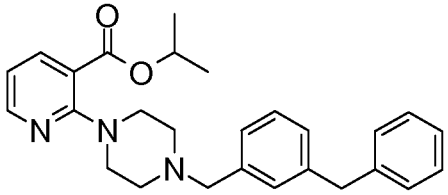
Example 25
1-Methylethyl 2-{methyl[(3*R*)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 264.2 $(M+H)^+$, 0.94 min (ret time); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (d, *J*=3.2 Hz, 6 H), 2.21-2.04 (m, 4 H), 2.78 (s, 3 H), 3.53-3.13 (m, 4 H), 5.12-4.90 (m, 2 H), 6.87-6.84 (m, 1 H), 7.93-7.91 (m, 1 H), 8.30-8.28 (m, 1 H), 9.21 (d, *J* = 10.2 Hz, 2 H).

Example 26
1-methylethyl2-(4-{[3-(Phenylmethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine

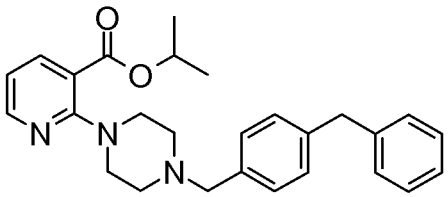
carboxylate hydrochloride



LC-MS *m/z* 430.1 $(M+H)^+$, 2.28 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, br, 1 H), 8.35 (d, *J* = 3.2 Hz, 1 H), 8.07 (d, *J* = 7.2 Hz, 1 H), 7.57-6.98 (m, 10 H), 5.11-5.08 (m, 1 H), 4.33 (d, *J* = 3.6 Hz, 2 H), 3.96 (s, 2 H), 3.85-3.04 (m, 8 H), 1.29 (d, *J* = 6.4 Hz, 6 H).

Example 27

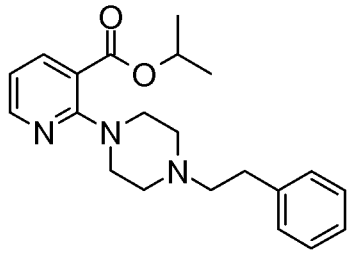
1-Methylethyl 2-(4-{[4-(phenylmethyl)phenyl]methyl}-1-piperazinyl) -3 pyridinecarboxylate hydrochloride



LC-MS *m/z* 430.1 $(M+H)^+$, 2.29 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, br, 1 H), 8.34 (s, 1 H), 8.06 (d, *J* = 6.8 Hz, 1 H), 7.59-6.99 (m, 10 H), 5.11-5.08 (m, 1 H), 4.30 (s, 2 H), 3.96 (s, 2 H), 3.84-3.03 (m, 8 H), 1.28 (d, *J* = 5.6 Hz, 6 H).

Example 28

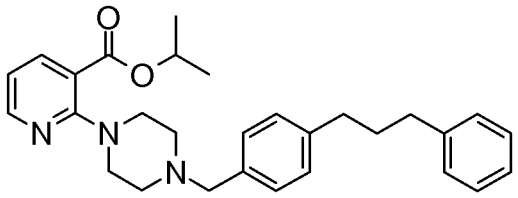
1-Methylethyl 2-[4-(2-phenylethyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 354.1 $(M+H)^+$, 2.06 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.49 (m, 6 H), 3.33 (s, 4 H), 3.46-4.45 (m, 8 H), 5.28 (s, 1 H), 7.28-7.31 (d, 8 H), 8.46 (s, 2 H), 13.54 (s, 1 H).

Example 29

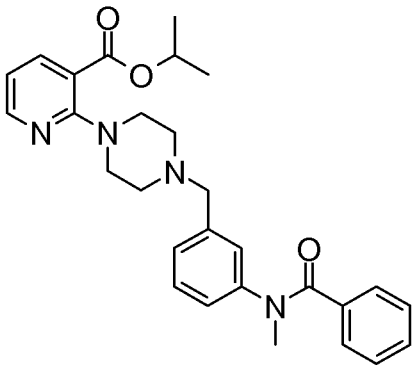
1-Methylethyl2-(4-{[4-(3-phenylpropyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride



LC-MS *m/z* 458.1 $(M+H)^+$, 2.43 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, br, 1 H), 9.19 (s, br, 2 H), 8.34 (d, *J* = 3.2 Hz, 1 H), 8.08-8.06 (m, 1 H), 7.59 (d, *J* = 7.6 Hz, 2 H), 7.28-6.98 (m, 8 H), 5.11-5.08 (m, 1 H), 4.32 (d, *J* = 4.0 Hz, 2 H), 3.83 (d, *J* = 13.6 Hz, 2 H), 3.56-3.53 (m, 2 H), 3.53-3.36 (m, 2 H), 3.07-3.06 (m, 2 H), 2.64-2.58 (m, 4 H), 1.97-1.87 (m, 2 H), 1.28 (d, *J* = 6.0 Hz, 6 H).

Example 30

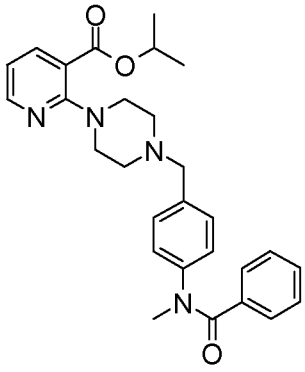
1-Methylethyl 2-[4-({3-[methyl(phenylcarbonyl)amino]phenyl}methyl) -1-piperazinyl]-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 473.1 $(M+H)^+$, 1.95 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 1.06-1.35 (m, 10 H), 3.11 (s, 2 H), 3.45 (d, 3 H), 4.11 (s, 4 H), 5.21 (s, 1 H), 7.10-7.52 (m, 12 H), 13.12 (s, 1 H).

Example 31

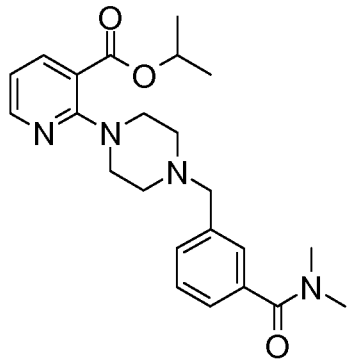
1-Methylethyl 2-[4-({4-[methyl(phenylcarbonyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 473.2 $(M+H)^+$, 1.19 min (ret time); ^1H NMR (400 MHz, Methanol-d_4) δ 3.31-3.33 (m, 6 H), 3.40-3.68 (m, 9 H), 3.98 (s, 2 H), 4.44 (s, 2 H), 5.25-5.28 (t, 1 H), 7.23-7.33 (m, 8 H), 7.55-7.57 (d, 2 H), 8.38-8.38 (d, 1 H), 8.58-8.60 (d, 1 H).

Example 32

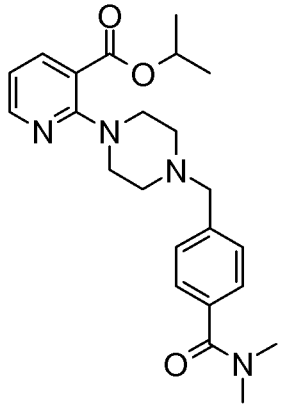
1-methylethyl 2-[4-({3-[(dimethylamino)carbonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 411.1 $(M+H)^+$, 1.79 min (ret time); ^{1}H NMR (400 MHz, DMSO-d_6&D_2O) δ 1.25-1.26 (d, 6 H), 2.89-3.42 (m, 12 H), 3.80 (s, 2 H), 4.39 (s, 2 H), 5.03-5.09 (m, 1 H), 6.98-7.01 (m, 1 H), 7.47-7.62 (m, 4 H), 8.03-8.05 (d, 1 H), 8.30-8.31(d, 1 H).

Example 33

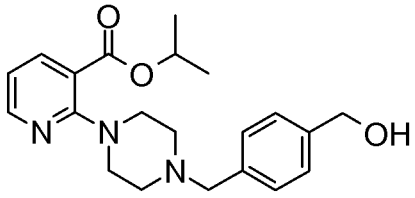
1-Methylethyl 2-[4-({4-[(dimethylamino)carbonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 411.1 $(M+H)^+$, 1.78 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 6 H), 3.13 (s, 6 H), 3.47-3.75 (m, 4 H), 4.10-4.43 (m, 6 H), 5.26 (s, 1 H), 7.54 (s, 3 H), 7.83 (s, 2 H), 8.46 (s, 2 H),13.25 (s, 1 H).

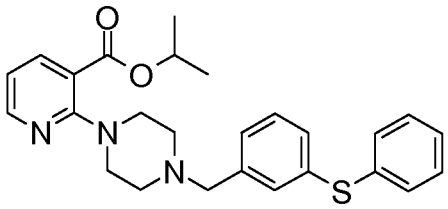
Example 34

1-Methylethyl2-(4-{[4-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate hydrochloride



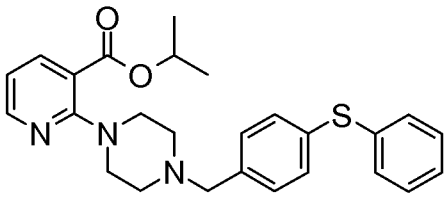
LC-MS *m/z* 370.2 $(M+H)^+$, 1.73 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) 1.38-1.39 (d, *J*=4.4 Hz, 6 H) 3.41 (s, 4 H) 4.03 (s, 2 H) 4.28 (s, 4 H) 4.70 (s, 2 H) 5.23 (s, 1 H) 7.17 (s, 1 H) 7.41(s, 2 H) 7.63(s, 2 H) 8.37(s, 2 H) 13.03 (s, 1 H)

Example 35
1-Methylethyl 2-(4-{[3-(phenylthio)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride



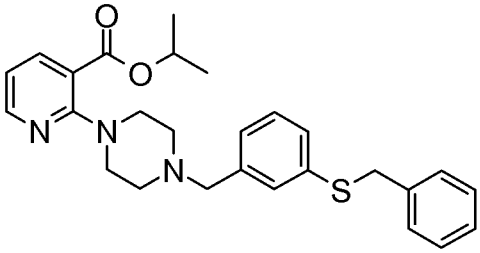
LC-MS *m/z* 448.1 $(M+H)^+$, 1.22 min (ret time); ^{1}H NMR (400 MHz, MEOD) δ 8.64 (d, *J* = 4.8 Hz, 1 H), 8.39 (s, 1 H), 7.60-7.36 (m, 10 H), 5.29 (s, 1 H), 4.47 (s, 2 H), 3.99-3.45 (m, 8 H), 1.42 (d, *J* = 4.8 Hz, 6 H).

Example 36
1-Methylethyl 2-(4-{[4-(phenylthio)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride



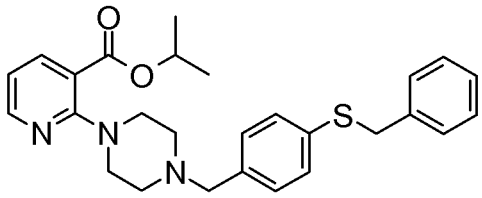
LC-MS *m/z* 448.1 $(M+H)^+$, 1.40 min (ret time); ^{1}H NMR (400 MHz, MEOD) δ 8.54 (d, *J* = 5.6 Hz, 1 H), 8.38 (s, 1 H), 7.55-7.28 (m, 10 H), 5.27 (s, 1 H), 4.44 (s, 2 H), 3.98 (s, 2 H), 3.61-3.42 (m, 6 H), 1.41 (d, *J* = 5.2 Hz, 6 H).

Example 37
1-Methylethyl 2-[4-({3-[(phenylmethyl)thio]phenyl}methyl)-1-piperazinyl] -3-pyridine carboxylate hydrochloride



LC-MS *m/z* 462.1 $(M+H)^+$, 1.42 min (ret time); ^{1}H NMR (400 MHz, MEOD) δ 8.70 (d, *J* = 6.8 Hz, 1 H), 8.40 (d, *J* = 4.0 Hz, 1 H), 7.65 (s, 1 H), 7.48-7.22 (m, 9 H), 5.30-5.28 (m, 1 H), 4.54 (s, 2H), 4.28 (s, 2 H), 3.99-3.32 (m, 8 H), 1.43 (d, *J* = 6.0 Hz, 6 H).

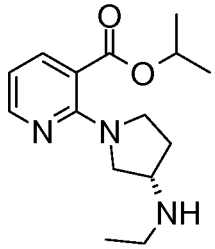
Example 38
1-Methylethyl 2-[4-({4-[(phenylmethyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate hydrochloride



LC-MS *m/z* 462.1 $(M+H)^+$, 1.42 min (ret time); ^1H NMR (400 MHz, MEOD) δ 8.68 (s, 1 H), 8.39 (s, 1 H), 7.57-7.22 (m, 10 H), 5.29 (s, 1 H), 4.46 (s, 2 H), 4.23 (s, 2 H), 4.01-3.47 (m, 8 H), 1.43 (s, 6 H).

Example 39

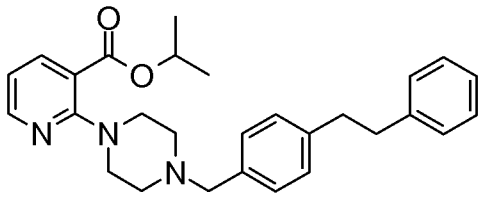
1-Methylethyl 2-[(3*S*)-3-(ethylamino)-1-pyrrolidinyl] -3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 278.3 $(M+H)^+$, 0.95 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, 3 H), 1.35 (t, 6 H), 2.28-2.37 (m, 2 H), 2.50 (s, 2 H), 2.90-3.02 (m, 2 H), 3.16 (s, 1 H), 3.58-3.72 (m, 4 H), 3.86 (m, 1 H), 5.10 (m, 1 H), 6.92 (m, 1 H), 8.08 (d, 1 H), 8.26 (d, 1 H), 9.56 (s, 1 H), 9.73 (s, 1 H).

Example 40

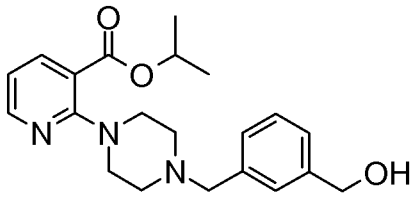
1-Methylethyl2-(4-{[4-(2-phenylethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride



LC-MS *m/z* 444.1 $(M+H)^+$, 1.40 min (ret time); ^1H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 6 H), 2.50 (s, 3 H),2.89 (s, 4 H), 3.00-3.08 (m, 2 H), 3.34 (d, 2 H), 3.48 (t, 2 H), 3.82 (d, 2 H), 4.31(d, 1 H), 5.10 (m, 1 H), 6.98 (m, 1 H), 7.16-7.30 (m, 7 H), 7.55 (m, 2 H), 8.04 (dd, 1 H), 8.34 (dd, 1 H), 11.64 (s, 1 H).

Example 41

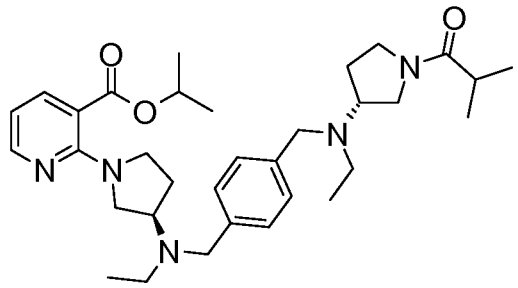
1-Methylethyl 2-(4-{[3-(hydroxymethyl)phenyl]methyl}-1-piperazinyl) -3-pyridine carboxylate



LC-MS *m/z* 370.1 $(M+H)^+$, 1.08 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 1.33-1.34 (d, *J*=6.0 Hz, 6 H) 2.02 (s, 1 H) 2.63 (s, 4 H) 3.46-3.49 (m, 4 H) 3.62 (s, 2 H) 4.70 (s, 2 H) 5.15-5.21 (m, 1 H) 6.71-6.74 (m, 1 H) 7.26-7.39 (m, 4 H) 7.92-7.95 (m, 1 H) 8.24-8.26 (m, 1 H)

Example 42

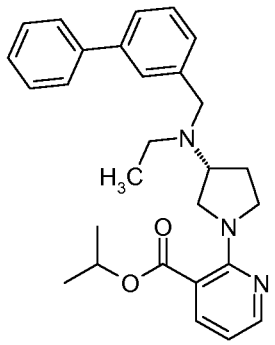
1-Methylethyl2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl] amino}methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate



LC-MS m/z 564.4 $(M+H)^+$, 2.21min (ret time); ^1H NMR (400MHz, $CDCl_3$) δ 8.26-8.24 (m, 1H), 7.84-7.82 (m,1H), 7.83-7.28(m, 4H), 6.65-6.7- (m, 1H), 5.20-5.17 (m, 1H), 3.70-3.28(m,14H), 2.66-2.59 (m,5H), 2.10-1.90(m, 4H), 1.38-1.34 (m,6H), 1.14-0.99 (m, 12H).

Example 43

1-methylethyl 2-{(3R)-3-[(3-biphenylylmethyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridine carboxylate



In an A-vial, acetaldehyde (5.30 mg, 0.120 mmol) and 1-methylethyl 2-[(3R)-3-amino-1-pyrrolidinyl]-3-pyridinecarboxylate (30.0 mg, 0.120 mmol) were added to the solution of dimethyl sulfoxide (DMSO) (1.5 ml) with acetic acid (7.23 mg, 0.120 mmol). The solution was stirred for 1h at room temperature. Then MP-$B(OAc)_3H$ (282 mg, 1.203 mmol) was added. The resulted mixture was stirred at room temperature for 12 hours after which time sodium cyanoborohydride (76 mg, 1.203 mmol) was added and the contents were stirred for another 12 h. To the resulting mixture 3-biphenyl benzylaldehyde (37.9 mg, 0.361 mmol) was added and the solution was stirred for 3

hr. The polymer was filtered and the crude product was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x100mm 5 preparatory column), eluting with acetonitrille and 0.1% aqueous NH_4OH. The desired fractions were concentrated under a stream of nitrogen at 50 °C, giving 7.67 mg (%) of the title compound. LC-MS m/z 444.4 $(M+H)^+$, 1.05 min (ret time).

Following the procedure as described above in the preparation of 1-methylethyl 2-{(3R)-3-[(3-biphenylylmethyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate, 1-methylethyl 2-[(3R)-3-amino-1-pyrrolidinyl]-3-pyridinecarboxylate (30.0 mg, 0.120 mmol) was reacted with the appropriate aldehyde to yield the examples listed in Table I.

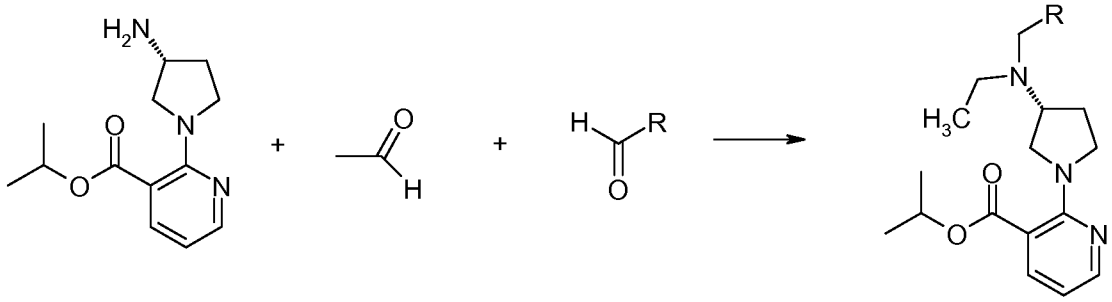
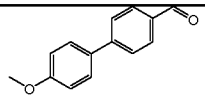
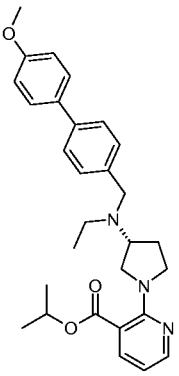
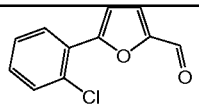
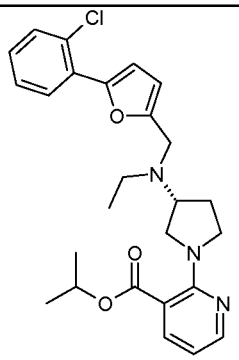
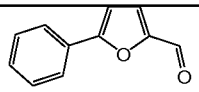
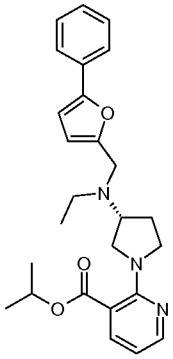
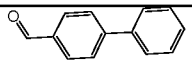
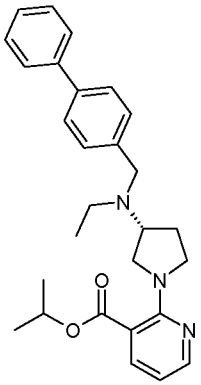


Table I.

Example	Aldehyde or Ketone	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 44		 1-methylethyl 2-[(3R)-3-(ethyl{[4'-(methyloxy)-4-biphenylyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	474.3	1.0

Example 45		 1-methylethyl 2-{(3R)-3-[{[5-(2-chlorophenyl)-2-furanyl]methyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	468.3	1.1
Example 46		 1-methylethyl 2-((3R)-3-{ethyl[(5-phenyl-2-furanyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	435.2	0.8
Example 47		 1-methylethyl 2-{(3R)-3-[(4-biphenylyl methyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridine carboxylate	444.4	1.0

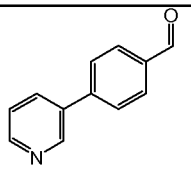
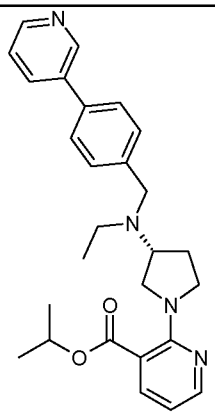
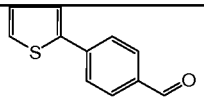
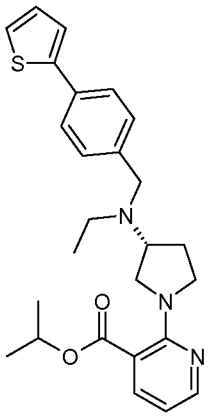
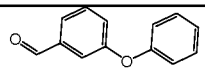
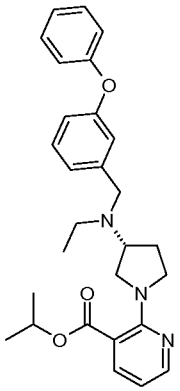
Example 48		 1-methylethyl 2-[(3R)-3-(ethyl{[4-(3-pyridinyl) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridine carboxylate	445.5	0.8
Example 49		 1-methylethyl 2-[(3R)-3-(ethyl{[4-(2-thienyl)phenyl] methyl} amino)-1-pyrrolidinyl]-3-pyridine carboxylate	450.2	1.0
Example 50		 1-methylethyl 2-[(3R)-3-(ethyl{[3-(phenyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridine carboxylate	460.3	1.0

Table 2

Following the procedure as described above in the preparation of 1-methylethyl 2-{methyl[(3R)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate,

1-methylethyl 2-{ethyl[(2R)-2-(ethylamino)propyl]amino}-3-pyridine carboxylate (25 mg, 0.09 mmol) was reacted with the appropriate aldehyde or ketone to yield the examples listed in Table II.

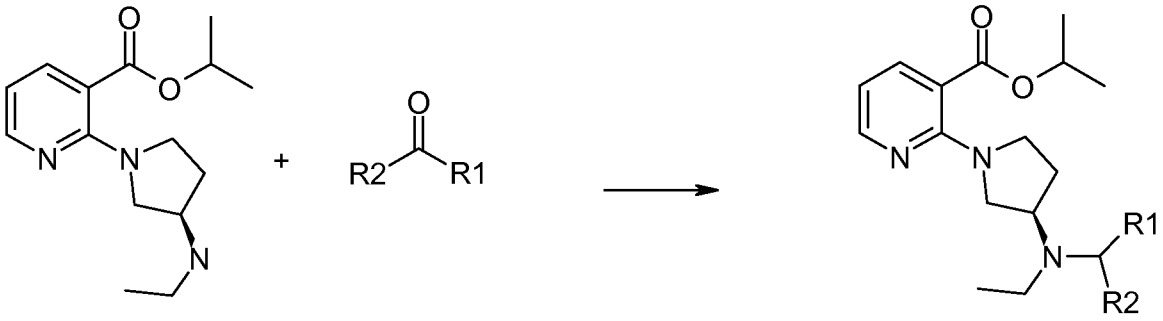
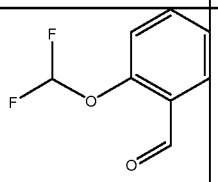
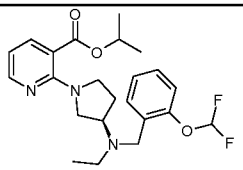
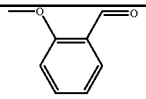
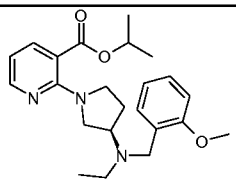
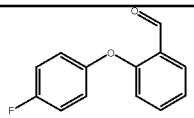
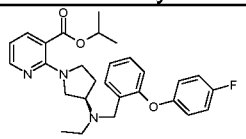
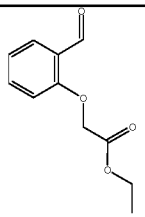
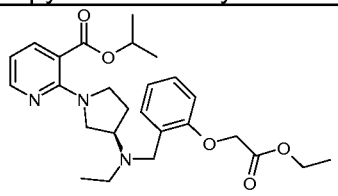
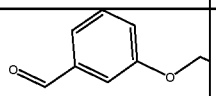
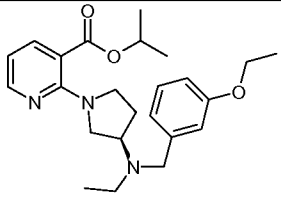
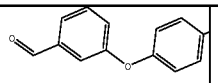
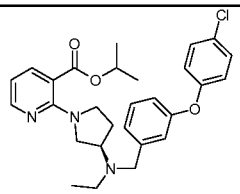
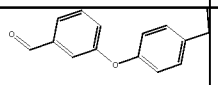
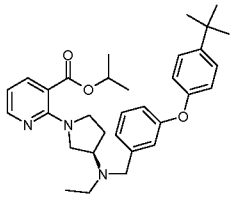
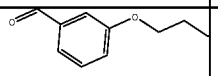
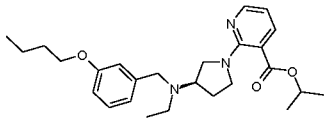
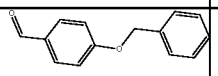
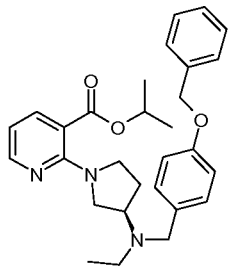
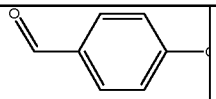
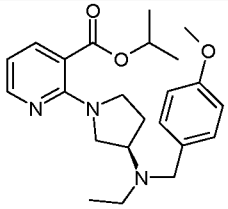
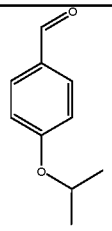
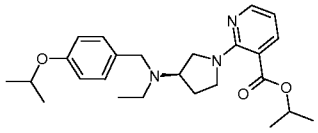
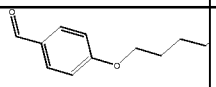
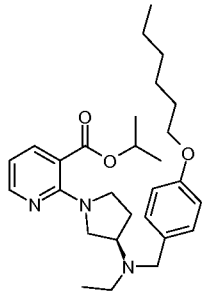
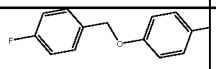
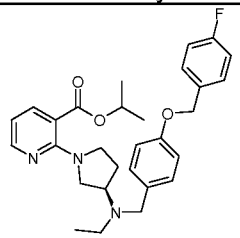


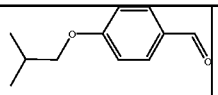
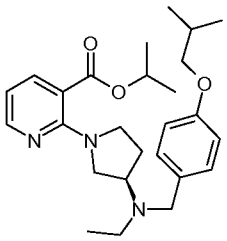
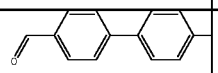
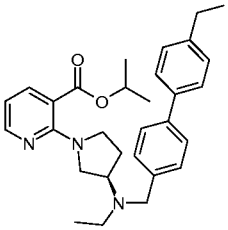
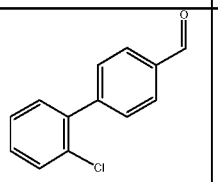
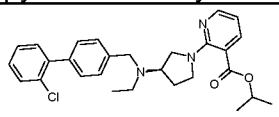
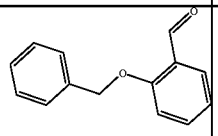
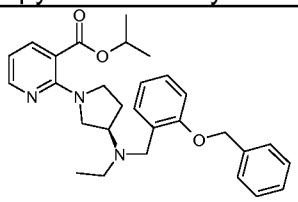
Table II.

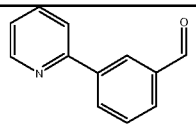
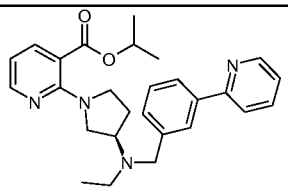
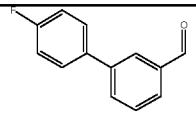
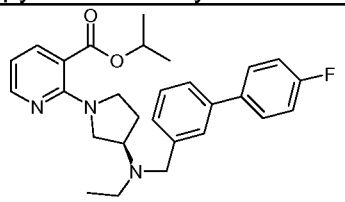
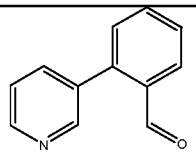
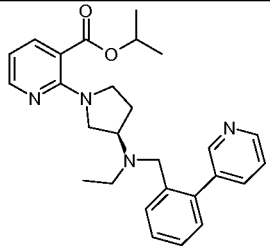
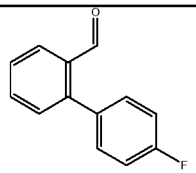
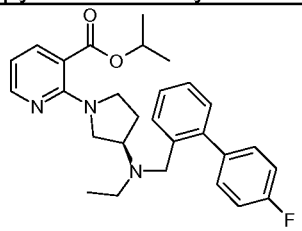
Example	Aldehyde or Ketone	Product	LC-MS	
			m/z (M+H)+	RT (min)
Example 51		 1-methylethyl 2-{(3R)-3-[({2-[(difluoromethyl) oxy] phenyl}methyl) (ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	434.2 1	0.9

Example 52		 1-methylethyl 2-[(3R)-3-(ethyl{[2-(methyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	398.15	0.8
Example 53		 1-methylethyl 2-{(3R)-3-[ethyl({2-[(4-fluoro phenyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	478.18	1.0
Example 54		 1-methylethyl 2-((3R)-3-{ethyl[(2-{[2-(ethyloxy)-2-oxoethyl]oxy} phenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	470.36	1.0
Example 55		 1-methylethyl 2-[(3R)-3-(ethyl{[3-(ethyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	412.13	0.9

Example 56		 1-methylethyl 2-{(3R)-3-[({3-[(4-chlorophenyl) oxy]phenyl}methyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	494.23	1.1
Example 57		 1-methylethyl 2-{(3R)-3-[[(3-{[4-(1,1-dimethyl ethyl)phenyl]oxy}phenyl)methyl](ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	516.39	1.2
Example 58		 1-methylethyl 2-{(3R)-3-[{[3-(butyloxy)phenyl] methyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	440.27	1.0
Example 59		 1-methylethyl 2-{(3R)-3-[ethyl({4-[(phenyl methyl)oxy]phenyl}meth yl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	474.3	1.0

Example 60		 1-methylethyl 2-[(3R)-3-(ethyl{[4-(methyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	398.15	0.8
Example 61		 1-methylethyl 2-{(3R)-3-[ethyl({4-[(1-methyl ethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	426.27	1.2
Example 62		 1-methylethyl 2-[(3R)-3-(ethyl{[4-(hexyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	468.46	1.2
Example 63		 1-methylethyl 2-((3R)-3-{ethyl[(4-{[(4-fluoro phenyl)methyl]oxy}phen yl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	492.32	1.0

Example 64		 1-methylethyl 2-{(3R)-3-[ethyl({4-[(2-methylpropyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	440.29	1.0
Example 65		 1-methylethyl 2-((3R)-3-{ethyl[(4'-ethyl-4-biphenylyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	472.32	1.1
Example 66		 1-methylethyl 2-{(3R)-3-[[(2'-chloro-4-biphenylyl)methyl](ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	478.25	1.0
Example 67		 1-methylethyl 2-{(3R)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	474.27	1.0

Example 68		 1-methylethyl 2-[(3R)-3-(ethyl{[3-(2-pyridinyl) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	445.29	0.8
Example 69		 1-methylethyl 2-((3R)-3-{ethyl[(4'-fluoro-3-biphenylyl)methyl]amino }-1-pyrrolidinyl)-3-pyridinecarboxylate	462.28	1.0
Example 70		 1-methylethyl 2-[(3R)-3-(ethyl{[2-(3-pyridinyl) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	445.29	0.7
Example 71		 1-methylethyl 2-((3R)-3-{ethyl[(4'-fluoro-2-biphenylyl)methyl]amino }-1-pyrrolidinyl)-3-pyridinecarboxylate	462.29	1.0

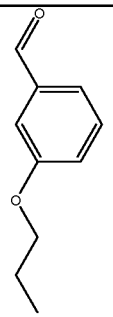
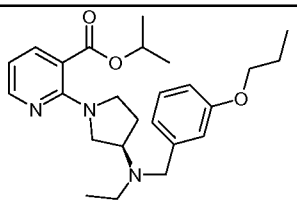
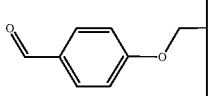
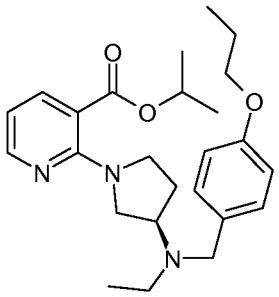
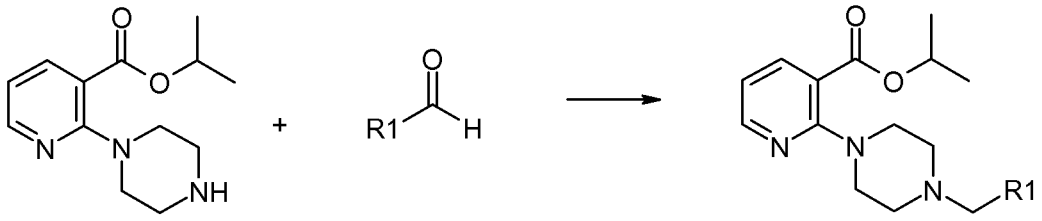
Example 72		 1-methylethyl 2-[(3R)-3-(ethyl{[3-(propyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	426.27	1.0
Example 73		 1-methylethyl 2-[(3R)-3-(ethyl{[4-(propyloxy) phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	426.28	1.0

Table III

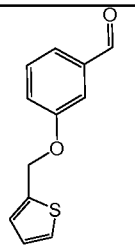
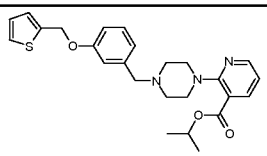
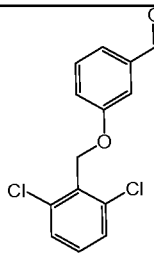
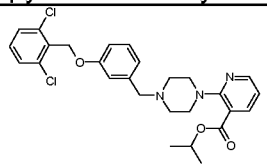
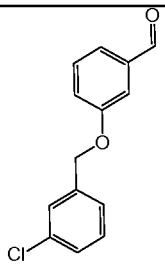
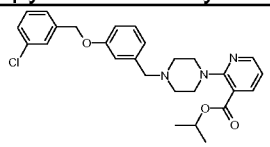
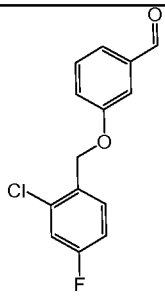
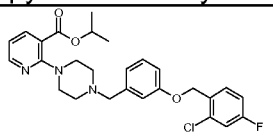


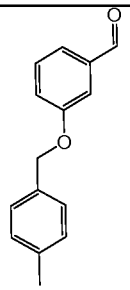
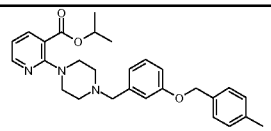
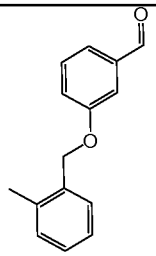
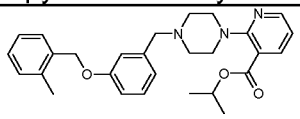
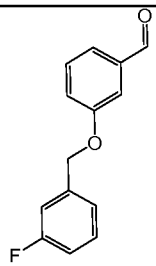
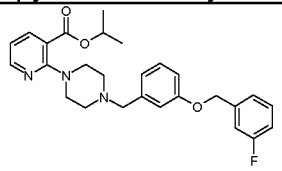
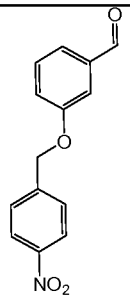
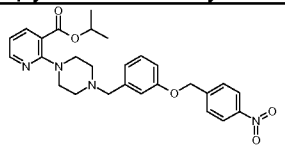
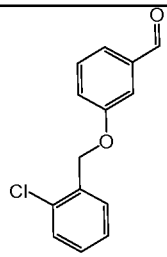
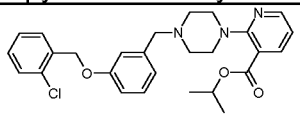
A solution of 1-methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate (625 mg, 2.5 mmol) in dimethyl sulfoxide (DMSO) (37.5 ml) was dispensed into 25 A-vials containing benzaldehydes (0.2 mmol, purchased from Sigma Aldrich) followed by addition of acetic acid (5 L, 0.087 mmol). The reaction was stirred for 4h in a VX-2500 Multi-Tube Vortexer. MP-$B(OAc)_3$ (83 mg, 0.201 mmol) was then added and the reaction was stirred overnight in a VX-2500 Multi-Tube Vortexer. Starting material remained so sodium triacetoxyborohydride (50.0 mg, 0.236 mmol) was added to all the reaction mixtures. These were stirred over a weekend in a VX-2500 Multi-Tube Vortexer.

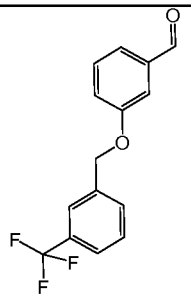
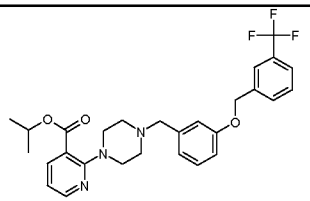
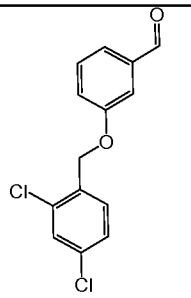
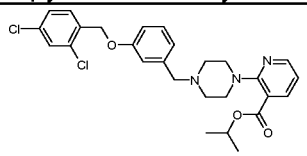
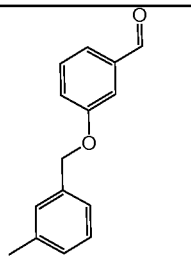
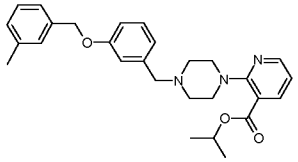
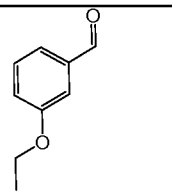
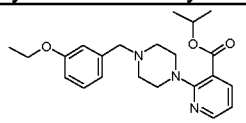
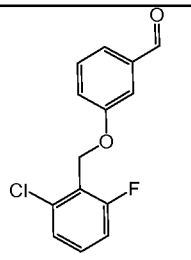
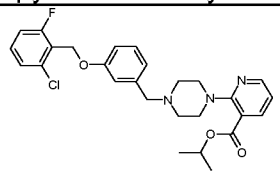
The reaction mixtures were filtered using a Bohdan miniblock, concentrated then

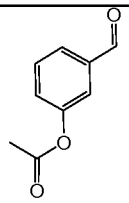
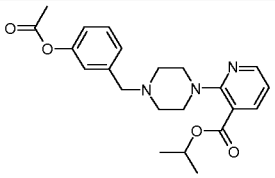
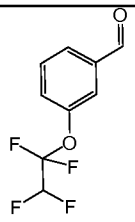
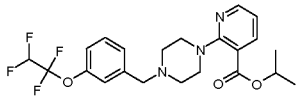
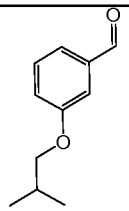
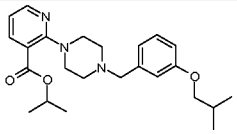
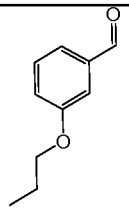
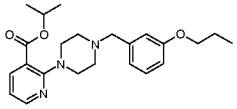
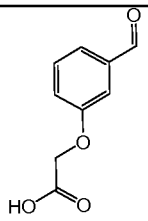
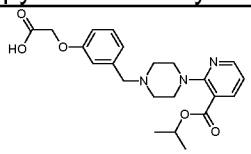
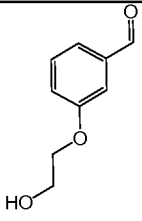
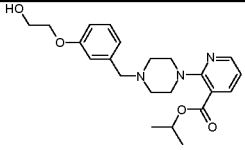
purified via preparative HPLC (Column: X-Bridge 19x100 mm 5 , Mobile phase: Acetonitrile : Water 0.1% NH_4OH, Flow rate: 15 ml/min). These are shown in Table III.

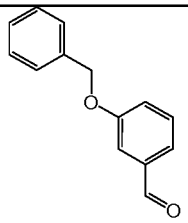
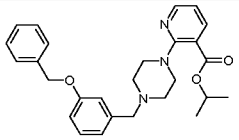
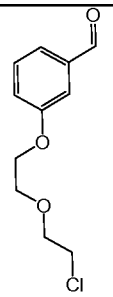
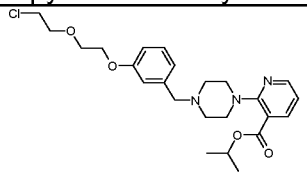
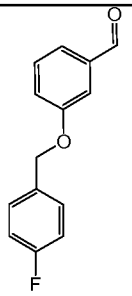
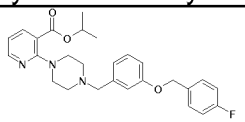
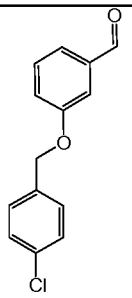
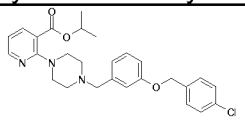
Table III.

Example	Aldehyde (ketone)	Product Name	LC-MS	
			m/z (M+H)$^+$	RT (min)
Example 74		 1-methylethyl 2-[4-({3-[(2-thienylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	452.18	1.0
Example 75		 1-methylethyl 2-{4-[(3-{[(2,6-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.32	1.1
Example 76		 1-methylethyl 2-{4-[(3-{[(3-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	480.13	1.1
Example 77		 1-methylethyl 2-{4-[(3-{[(2-chloro-4-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	498.42	1.1

Example 78		 1-methylethyl 2-{4-[(3-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.28	1.053
Example 79		 1-methylethyl 2-{4-[(3-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.29	1.0
Example 80		 1-methylethyl 2-{4-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	464.31	1.0
Example 81		 1-methylethyl 2-{4-[(3-{[(4-nitrophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	491.31	1.0
Example 82		 1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	480.15	1.0

Example 83		 1-methylethyl 2-(4-{[3-({[3-(trifluoromethyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	514.44	1.1
Example 84		 1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	515.1	0.9
Example 85		 1-methylethyl 2-{4-[(3-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	461.1	0.9
Example 86		 1-methylethyl 2-(4-{[3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	385	0.8
Example 87		 1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	499.1	0.8

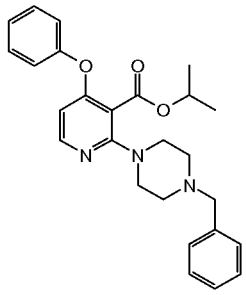
Example 88		 1-methylethyl 2-(4-{[3-(acetyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	399	0.7
Example 89		 1-methylethyl 2-[4-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	457	0.8
Example 90		 1-methylethyl 2-[4-({3-[(2-methylpropyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	413	0.8
Example 91		 1-methylethyl 2-(4-{[3-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	399	0.8
Example 92		 [(3-{[4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl]methyl}phenyl)oxy]acetic acid	415	0.6
Example 93		 1-methylethyl 2-[4-({3-[(2-hydroxyethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	401	0.6

Example 94		 1-methylethyl 2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	447.1	0.8
Example 95		 1-methylethyl 2-(4-{[3-({2-[(2-chloroethyl)oxy]ethyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	463.1	0.8
Example 96		 1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	465.1	0.8
Example 97		 1-methylethyl 2-{4-[(3-{[(4-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	481.1	0.9

5

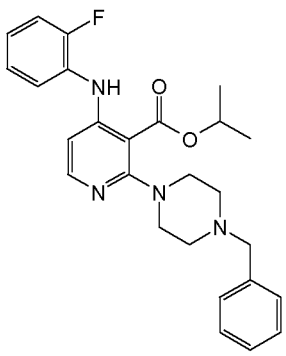
Table 4

Example 98
1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenyloxy)-3-pyridinecarboxylate



LC/MS: m/z= 432.1 $[M+H]^+$, Ret. Time: 1.00 min.

Example 99
1-methylethyl4-[(2-fluorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3- pyridinecarboxylate



Added the 1-methylethyl 4-iodo-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridine carboxylate (30.0 mg, 0.064 mmol), Anilines (0.148 mmol), Xantphos (6.2 mg, 0.013 mmol), Potassium phosphate (41.1 mg, 0.193 mmol) and Palladium(II) acetate (1.45 mg, 10 mol%) in 3.0 mL Toluene in a 5 mL reaction vial, and then stirred the mixture for 30min at room temperature under nitrogen atmosphere. The stirring was kept for overnight at 102 °C. Pretreated a StratoSpheres PL-Thiol MP SPE column with methanol, filtered reaction mixture through column, washed with methanol. Concentrated to give the crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (Sunfire 30 x 150 mm, 5 um preparatory column), eluting at 40 mL/min with linear gradient running from 30% to 100% acetonitrile and 0.1% aqueous NH_4OH over 25 min. The desired fractions were concentrated under a stream of nitrogen at 50 ºC, giving the desired product (6.47 mg, 22.37%). LC/MS: m/z= 449.1 $[M+H]^+$, Ret. Time: 0.84 min.

Following the procedure as described above in the preparation of 1-methylethyl 4-[(2-fluorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate, 1-methylethyl 4-iodo-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate (30.0 mg, 0.064 mmol) was reacted with the appropriate aryl anilines (0.148 mmol) to yield the examples listed in Table IV.

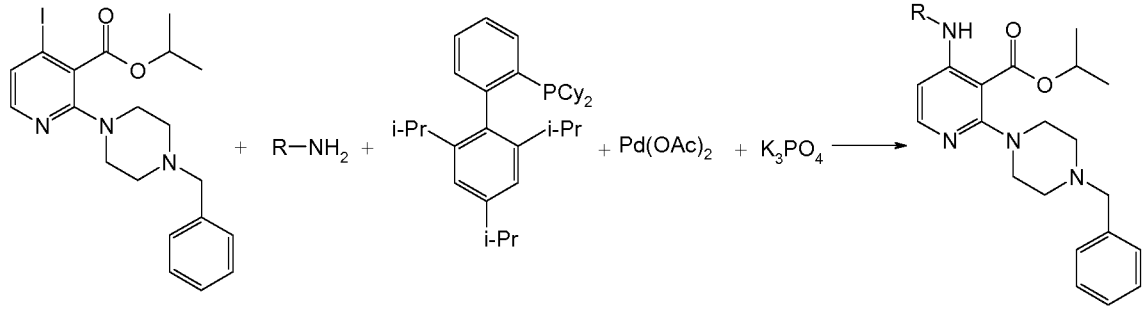
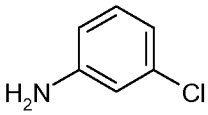
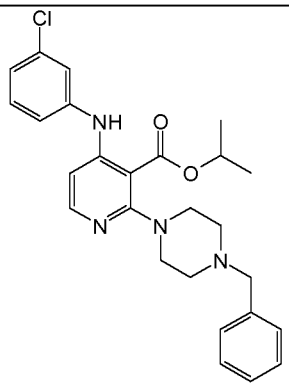
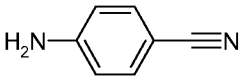
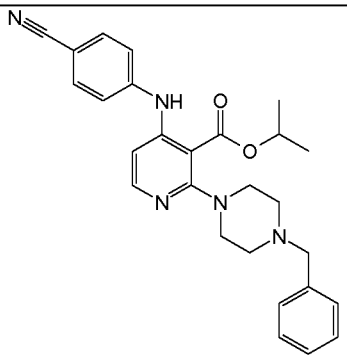
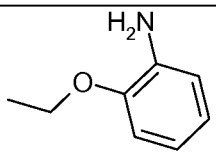
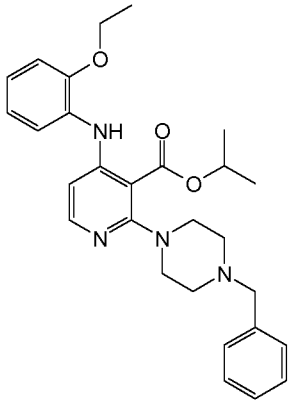
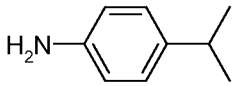
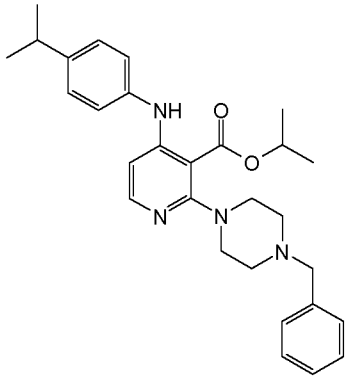
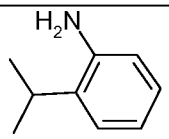
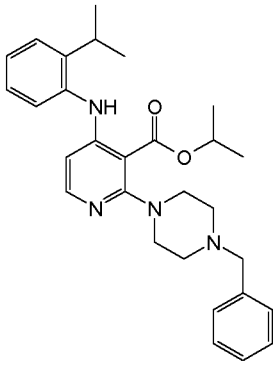
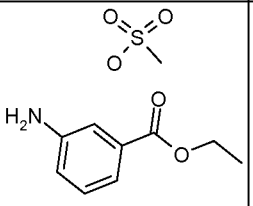
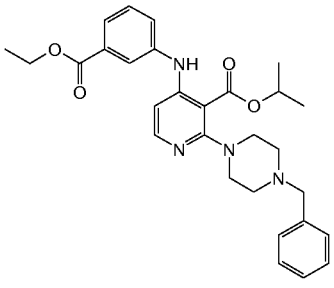


Table IV.

Example	Aniline	Product	LC-MS	
			m/z (M+H)+	RT (min)
Example 100		 1-methylethyl 4-[(3-chlorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	465.1	0.9

Example 101		 1-methylethyl 4-[(4-cyanophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	456.1	0.8
Example 102		 1-methylethyl 4-{[2-(ethyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	475.1	0.8

Example 103		 1-methylethyl 4-{[4-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	473.2	0.9
Example 104		 1-methylethyl 4-{[2-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	473.2	0.9
Example 105		 1-methylethyl 4-({3-[(ethyloxy)carbonyl]phenyl}amino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	503.2	0.9

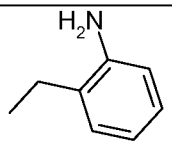
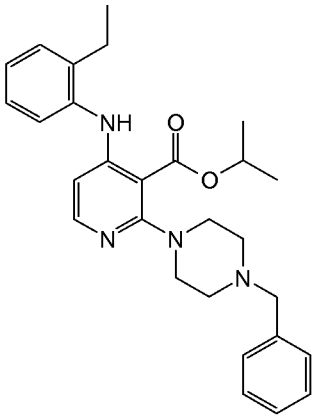
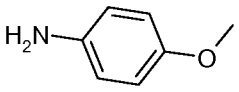
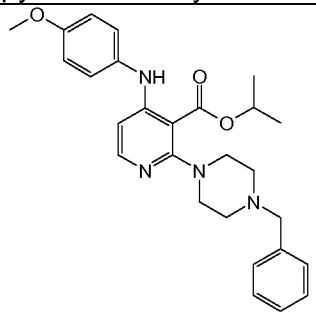
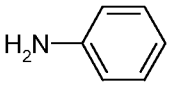
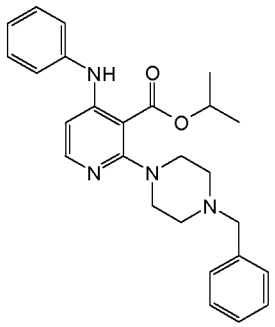
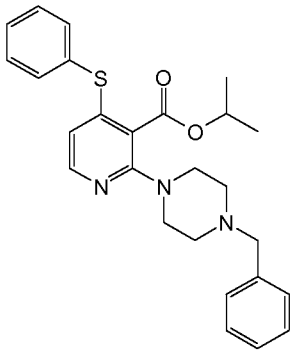
Example 106		 1-methylethyl 4-[(2-ethylphenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	459.1	0.9
Example 107		 1-methylethyl 4-{[4-(methyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	461.1	0.8
Example 108		 1-methylethyl 4-(phenylamino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	431.1	0.8

Table 5

Example 109

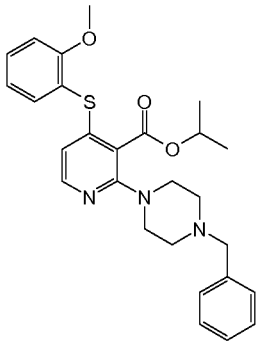
1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenylthio)-3-pyridinecarboxylate



LC/MS: m/z= 448.1 $[M+H]^+$, Ret. Time: 1.03 min.

Example 110

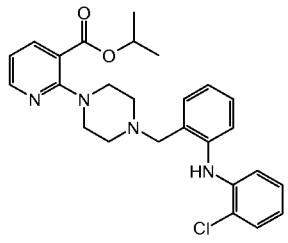
1-methylethyl 4-{[2-(methyloxy)phenyl]thio}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridine carboxylate



LC/MS: m/z= 478.1 $[M+H]^+$, Ret. Time: 1.08 min.

Example 111

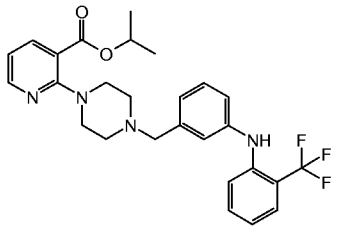
1-methylethyl 2-[4-({2-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate



LC/MS: m/z= 465.0 $[M+H]^+$, Ret. Time: 1.08 min.

Example 112

1-methylethyl 2-{4-[(3-{[2-(trifluoromethyl)phenyl]amino}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



Added the 1-methylethyl 2-{4-[(3-bromophenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate (25.0 mg, 0.060 mmol), [2-(trifluoromethyl)phenyl]amine (0.120 mmol), XPhos (5.7 mg, 0.012 mmol), potassium phosphate (38.1 mg, 0.179 mmol) and palladium(II) acetate (1.34 mg, 10 mol%) in 3.0 mL Toluene in a 5 mL reaction vial, and then stirred the mixture for 30min at room temperature under nitrogen atmosphere. The stirring was kept for 12 hr at 105 °C. Pretreated a StratoSpheres PL-Thiol MP SPE column with methanol, filtered reaction mixture through column, washed with Methanol. Concentrated to give the crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 20% to 95% acetonitrile and 0.1% aqueous NH_4OH over 18 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (11.48 mg, 38.5%). LC/MS: m/z= 499.0 $[M+H]^+$, Ret. Time: 1.07 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-{4-[(3-{[2-(trifluoromethyl)phenyl]amino}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate, aryl anilines (0.12 mmol) was reacted with the appropriate boronic acid to yield the examples listed in Table V.

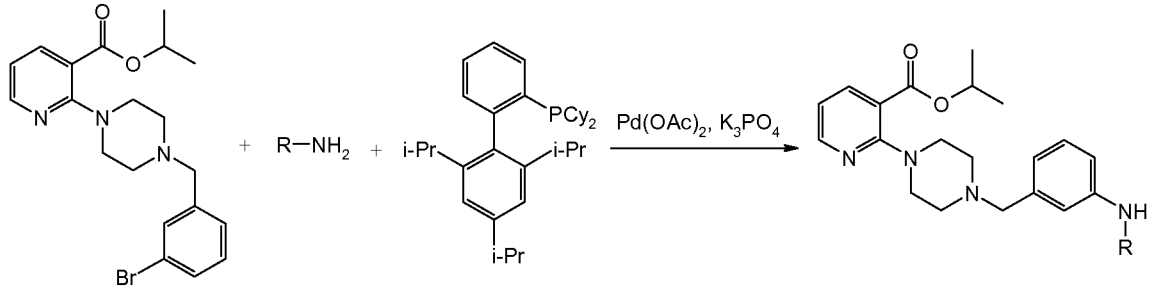
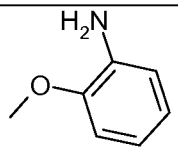
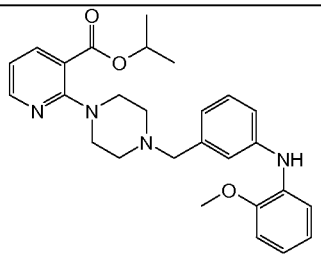
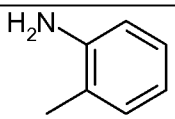
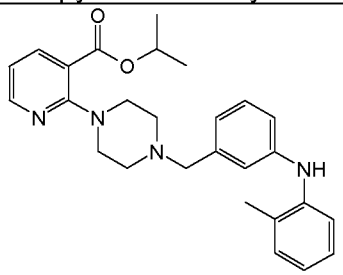
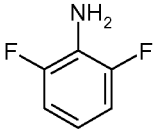
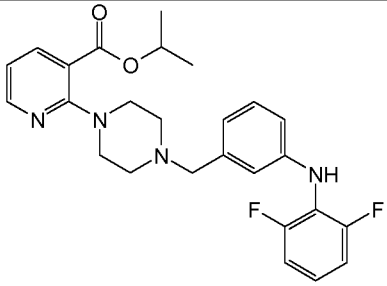


Table V.

Example	Aniline	Product	LC-MS	
			m/z (M+H)+	RT (min)
Example 113		 1-methylethyl 2-{4-[(3-{[2-(methyloxy)phenyl]amino}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	461	1.0
Example 114		 1-methylethyl 2-[4-({3-[(2-methylphenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	445	1.1
Example 115		 1-methylethyl 2-[4-({3-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	467	1.0

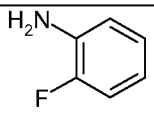
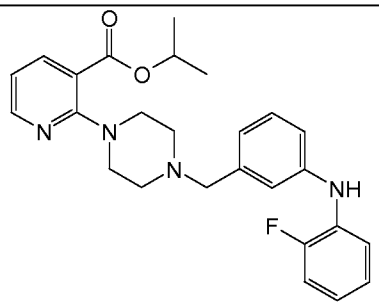
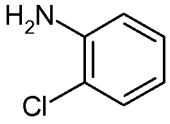
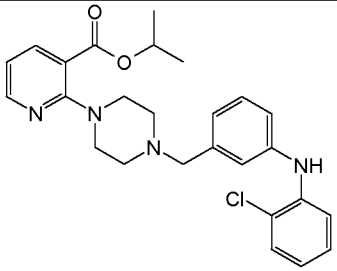
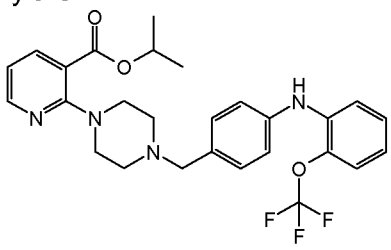
Example 116		 1-methylethyl 2-[4-({3-[(2-fluorophenyl)amino]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate	449	1.0
Example 117		 1-methylethyl 2-[4-({3-[(2-chlorophenyl)amino]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate	465	1.1

Table 6

Example 118

1-methylethyl 2-(4-{[4-({2-[(trifluoromethyl)oxy]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



Added the 1-methylethyl 2-{4-[(4-bromophenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate (25.0 mg, 0.060 mmol), Anilines (0.120 mmol), Xphos (5.7 mg, 0.012 mmol), potassium phosphate (38.1 mg, 0.179 mmol) and palladium(II) acetate (1.34 mg, 10 mol%) in 3.0 mL Toluene in a 5 mL reaction vial, and then stirred the mixture for 30min at room temperature under nitrogen atmosphere. The stirring was kept for 12 hr at 105 °C. Pretreated a StratoSpheres PL-Thiol MP SPE column with methanol, filtered reaction mixture through column, washed with Methanol. Concentrated to give the crude product, which was dissolved in DMSO, and purified on a Gilson HPLC

(XBridge 19 x 100mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 20% to 95% acetonitrile and 0.1% aqueous NH_4OH over 18 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (12.83 mg, 41.7%).

LC/MS: m/z= 515.0 $[M+H]^+$, Ret. Time: 1.16 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-(4-{[4-({2-[(trifluoromethyl)oxy]phenyl}amino)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate, 1-methylethyl 2-{4-[(4-bromophenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate (25.0 mg, 0.060 mmol) was reacted with the appropriate aryl anilines (0.12 mmol) to yield the examples listed in Table VI.

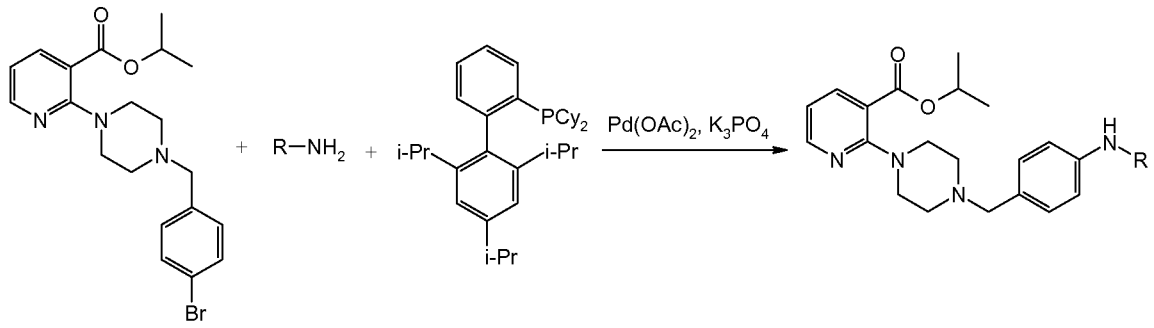
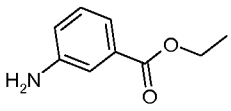
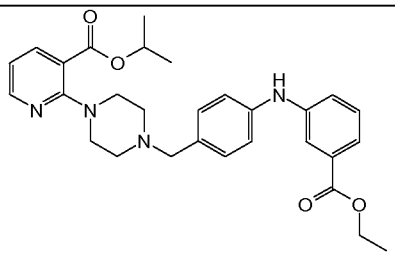
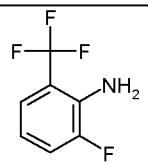
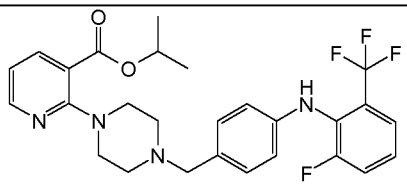
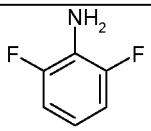
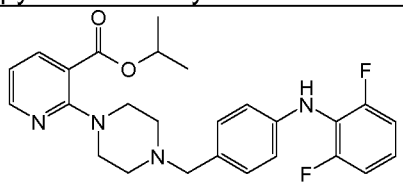
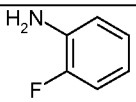
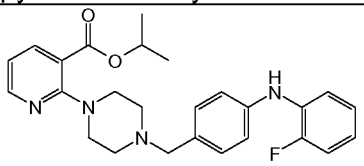
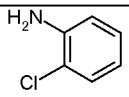
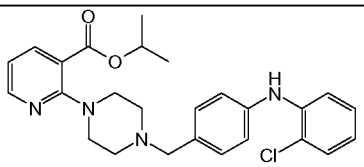


Table VI.

Example	Aryl aniline	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 119		 1-methylethyl 2-(4-{[4-({3-(ethyloxy)carbonyl]phenyl}amino)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate	503	1.1

Example 120		 1-methylethyl 2-{4-[(4-{[2-fluoro-6-(trifluoromethyl) phenyl]amino}phenyl)meth yl]-1-piperazinyl}-3-pyridinecarboxylate	516.9	1.1
Example 121		 1-methylethyl 2-[4-({4-[(2,6-difluorophenyl)amino]phen yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	467.0	1.1
Example 122		 1-methylethyl 2-[4-({4-[(2-fluorophenyl)amino]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate	449.0	1.1
Example 123		 1-methylethyl 2-[4-({4-[(2-chlorophenyl)amino]phenyl }methyl)-1-piperazinyl]-3-pyridinecarboxylate	465	1.1

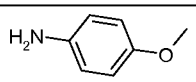
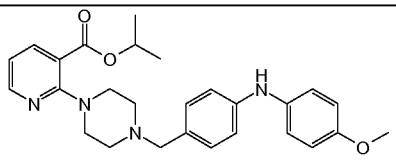
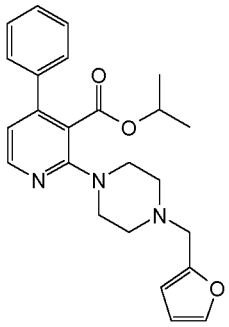
Example 124		 1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]amino} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate	461.1	1.0

Table 7

Example 125
1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate



Dissolved 1-methylethyl 4-phenyl-2-(1-piperazinyl)-3-pyridinecarboxylate (30.0 mg, 0.092 mmol) and furan-2-carbaldehyde (0.24 mmol) in THF (2.5 mL) and DMSO (0.5 mL) with acetic acid (5.54 mg, 0.092 mmol). The solution was stirred for 1h at room temperature. Then added MP-cyanoborohydride (0.277 mmol) and stirred at room temperature for 12 hr. The polymer was filtered and got the crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100 mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 30% to 95% acetonitrile and 0.1% aqueous NH_4OH over 18 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (3.66 mg, 9.79%). LC/MS: m/z= 406.1 $[M+H]^+$, Ret. Time: 0.97 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate,
1-methylethyl 4-phenyl-2-(1-piperazinyl)-3-pyridinecarboxylate (30.0 mg, 0.092 mmol) was reacted with the appropriate aldehydes (0.24mmol) to yield the examples listed in Table VII.

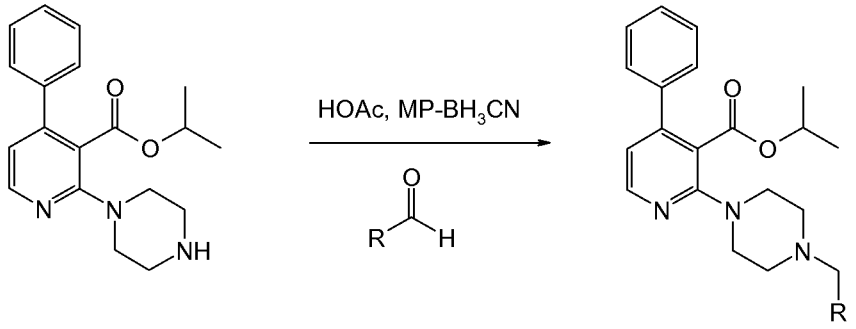
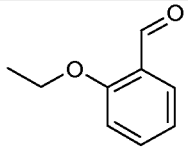
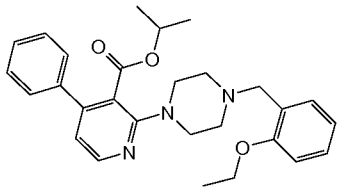
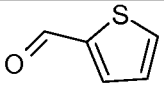
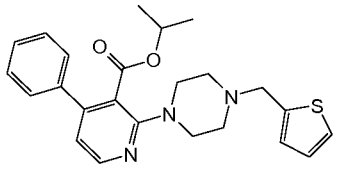
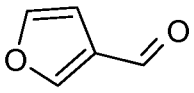
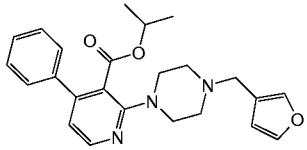
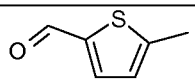
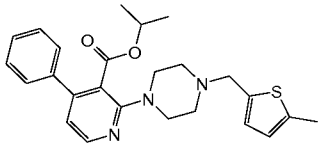
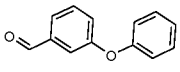
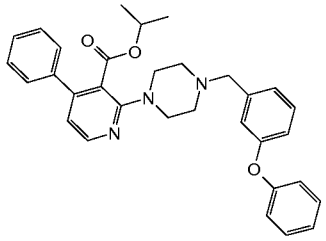
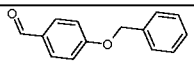
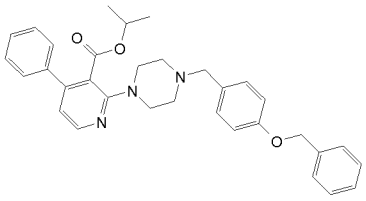
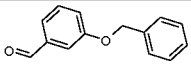
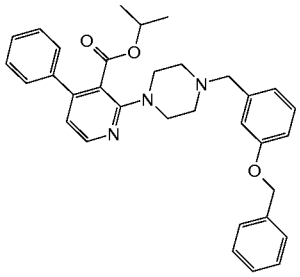
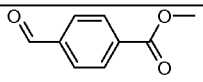
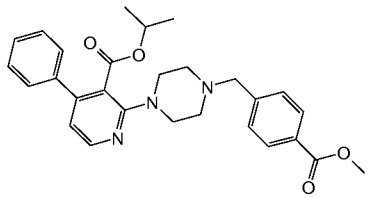
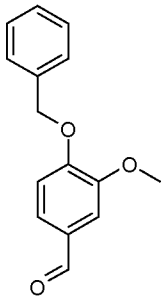
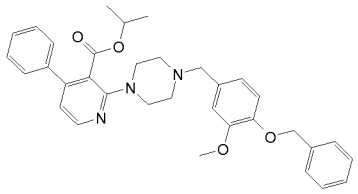
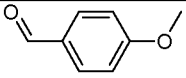
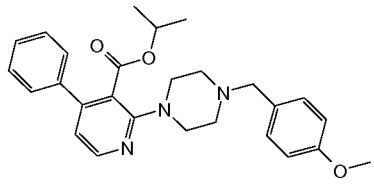
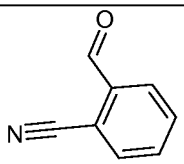
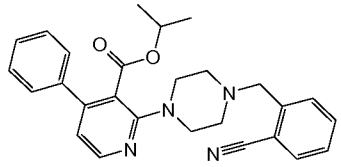
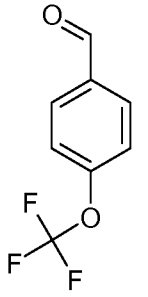
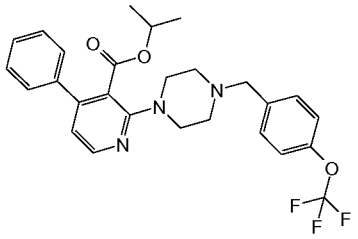
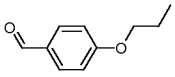
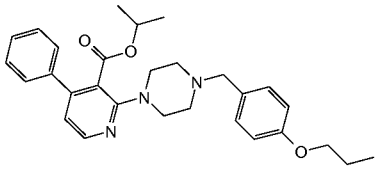
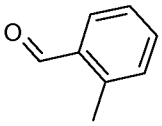
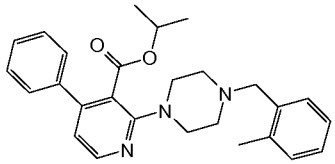
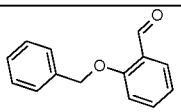
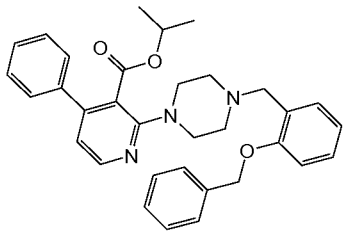


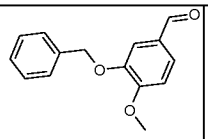
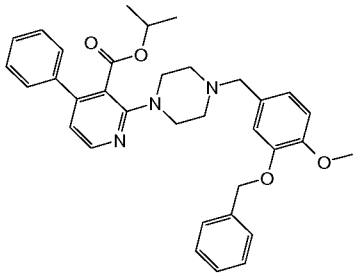
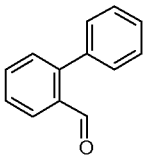
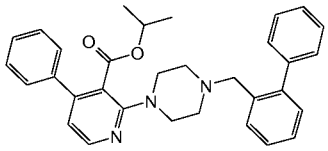
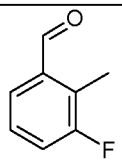
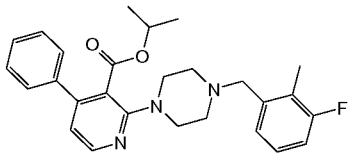
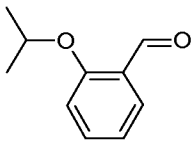
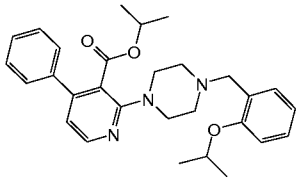
Table VII.

Example	Aldehyde	Product	LC-MS	
			m/z (M+H)+	RT (min)
Example 126		 1-methylethyl 2-(4-{[2-(ethyloxy)phenyl]methyl}-1-piperazinyl)-4-phenyl-3-pyridinecarboxylate	460.0	1.2
Example 127		 1-methylethyl 4-phenyl-2-[4-(2-thienylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	422.0	1.0
Example 128		 1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	406.0	1.0

Example 129		 1-methylethyl 2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate	436.0	1.0
Example 130		 1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	508.0	1.2
Example 131		 1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	522.0	1.2
Example 132		 1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	522.0	1.2

Example 133		 1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	474.0	1.0
Example 134		 1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	552.0	1.2
Example 135		 1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	446.1	1.0
Example 136		 1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate	441.0	1.0

Example 137		 1-methylethyl 4-phenyl-2-[4-({4-[(trifluoromethyl) oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	500.0	1.1
Example 138		 1-methylethyl 4-phenyl-2-(4-{[4-(propyloxy)phenyl]methyl }-1-piperazinyl)-3-pyridinecarboxylate	474.0	1.1
Example 139		 1-methylethyl 2-{4-[(2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate	430.0	1.0
Example 140		 1-methylethyl 4-phenyl-2-[4-({2-[(phenylmethyl)oxy]phen yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	522.0	1.2

Example 141		 1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	552.0	1.2
Example 142		 1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	492.0	1.2
Example 143		 1-methylethyl 2-{4-[(3-fluoro-2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate	448.1	1.1
Example 144		 1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	474.1	1.1

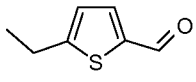
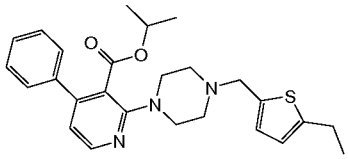
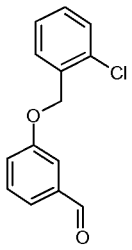
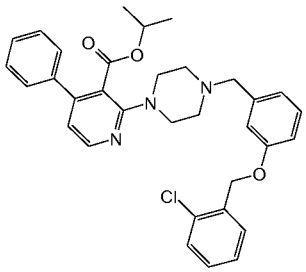
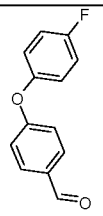
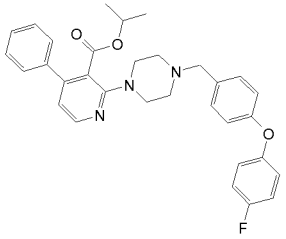
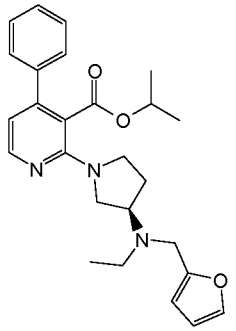
Example 145		 1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	450.0	1.1
Example 146		 1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate	556	1.2
Example 147		 1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate	526.0	1.2

Table 8

Example 148
1-methylethyl 2-{(3*R*)-3-[ethyl(2-furanylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate



Dissolved 1-methylethyl 2-[(3R)-3-(ethylamino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate (25.0 mg, 0.071 mmol) and furan-2-carbaldehyde (0.212 mmol) in methanol (2.5 mL) with acetic acid (1 mg, 0.014 mmol). The solution was stirred for 1h at room temperature. Then added sodiumcyanoborohydride (15.56 mg, 0.248 mmol) and stirred at room temperature for 12 hr. The polymer was filtered and concentrated the filtrate to give crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 30% to 90% acetonitrile and 0.1% aqueous NH_4OH over 15 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (3.34 mg, 10.89%). LC/MS: m/z= 434.1 $[M+H]^+$, Ret. Time: 0.96 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-{(3*R*)-3-[ethyl(2-furanylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate, 1-methylethyl 2-[(3R)-3-(ethylamino)-1-pyrrolidinyl]-4-phenyl-3-pyridine carboxylate (25.0 mg, 0.071 mmol) was reacted with the appropriate aldehydes (0.212 mmol) yield the examples listed in Table VIII.

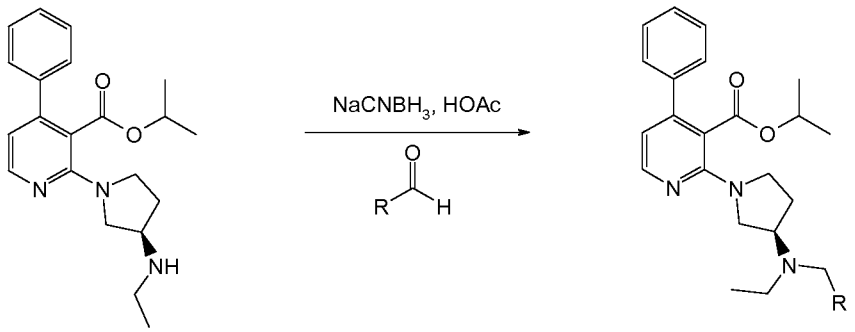
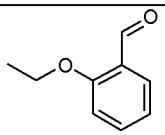
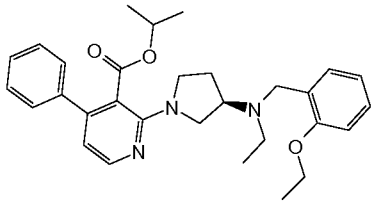
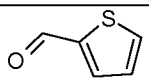
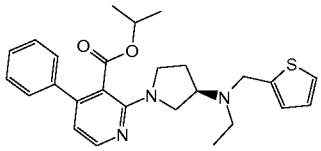
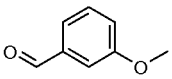
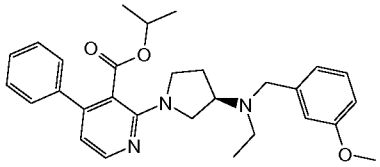
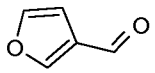
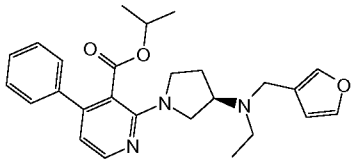
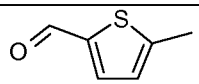
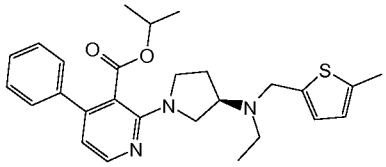
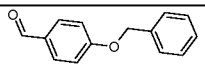
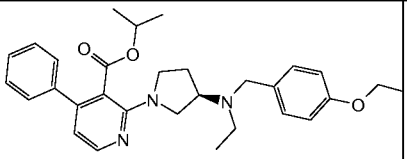
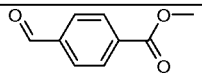
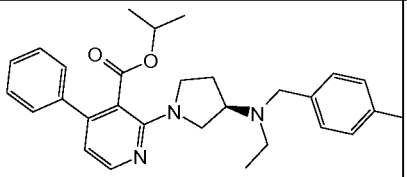
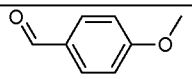
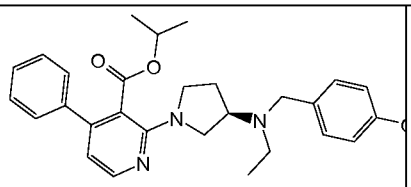
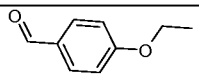
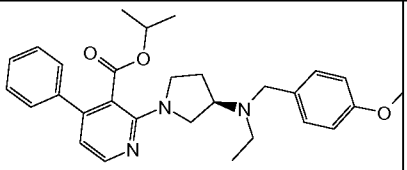
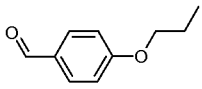
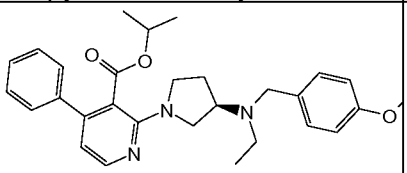
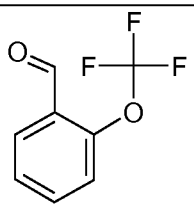
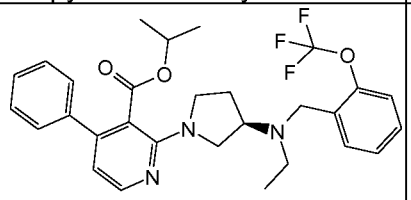
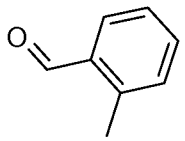
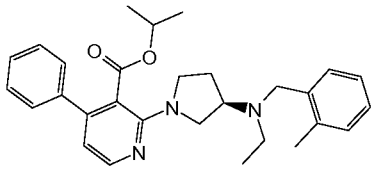
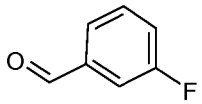
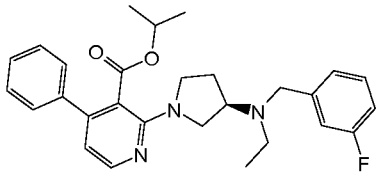
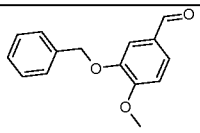
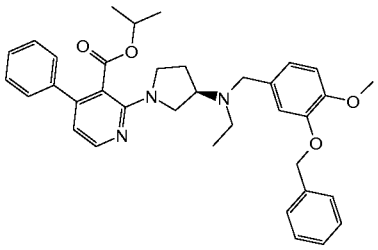
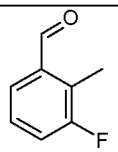
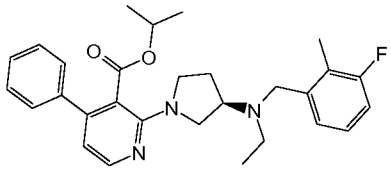


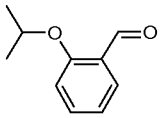
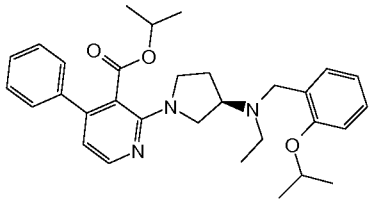
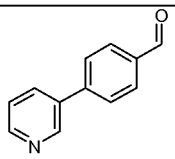
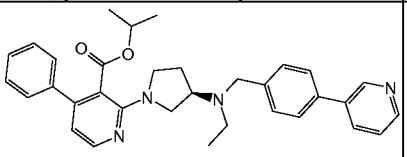
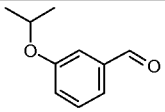
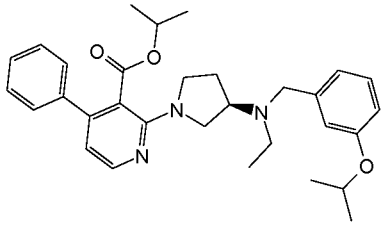
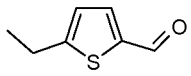
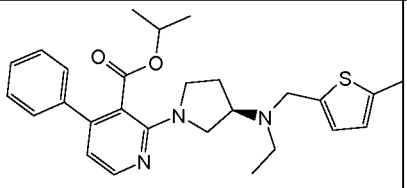
Table VIII.

Example	Aldehyde	Product	LC-MS	
			m/z (M+H)$^+$	RT (min)
Example 149		 1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	488.1	1.1
Example 150		 1-methylethyl 2-{(3*R*)-3-[ethyl(2-thienylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	450.0	0.99
Example 151		 1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	474.1	1.0

Example 152		 1-methylethyl 2-{(3*R*)-3-[ethyl(3-furanylmethyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	434.1	1.0
Example 153		 1-methylethyl 2-((3*R*)-3-{ethyl[(5-methyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate	464.0	1.1
Example 154		 1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	550.1	1.2
Example 155		 1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(methyloxy)carbonyl]phenyl}methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	502.1	1.0

Example 156		 1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	474.1	1.0
Example 157		 1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	488.1	1.1
Example 158		 1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	502.1	1.2
Example 159		 1-methylethyl 2-{(3*R*)-3-[ethyl({2-[(trifluoromethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	528.0	1.1

Example 160		 1-methylethyl 2-((3*R*)-3-{ethyl[(2-methylphenyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate	458.1	1.0
Example 161		 1-methylethyl 2-((3*R*)-3-{ethyl[(3-fluorophenyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate	462.1	1.0
Example 162		 1-methylethyl 2-{(3*R*)-3-[ethyl({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	580.1	1.2
Example 163		 1-methylethyl 2-((3*R*)-3-{ethyl[(3-fluoro-2-methylphenyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate	476.1	1.1

Example 164		 1-methylethyl 2-{(3*R*)-3-[ethyl({2-[(1-methylethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	502.1	1.1
Example 165		 1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(3-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	521.1	0.9
Example 166		 1-methylethyl 2-{(3*R*)-3-[ethyl({3-[(1-methylethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-phenyl-3-pyridinecarboxylate	502.1	1.1
Example 167		 1-methylethyl 2-((3*R*)-3-{ethyl[(5-ethyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-4-phenyl-3-pyridinecarboxylate	478.0	1.1

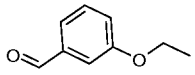
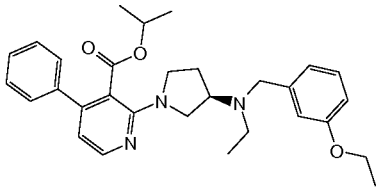
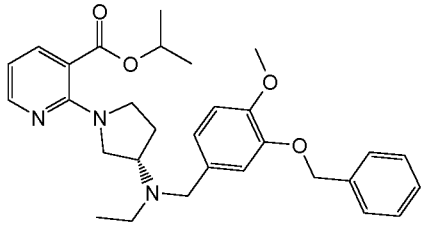
Example 168		 1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-phenyl-3-pyridinecarboxylate	488.1	1.1

Table 9

Example 169

1-methylethyl 2-{(3*S*)-3-[ethyl({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridine carboxylate



Dissolved 1-methylethyl 2-[(3S)-3-(ethylamino)-1-pyrrolidinyl]-3-pyridine carboxylate (30.0 mg, 0.108 mmol) and furan-2-carbaldehyde (0.27 mmol) in methanol (2.5 mL) with acetic acid (1.3 mg, 0.022 mmol). The solution was stirred for 1h at room temperature. Then added sodium cyanoborohydride (23.79 mg, 0.379 mmol) and stirred at room temperature for 12 hr. The polymer was filtered and concentrated the filtrate to give crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 40% to 95% acetonitrile and 0.1% aqueous NH_4OH over 15 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (27.4 mg, 50.3%). LC/MS: m/z= 504.1 $[M+H]^+$, Ret. Time: 1.02 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-{(3*S*)-3-[ethyl({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate,

1-methylethyl 2-[(3S)-3-(ethylamino)-1-pyrrolidinyl]-3-pyridine carboxylate (30.0 mg,

0.108 mmol) was reacted with the appropriate aldehydes (0.27 mmol) to yield the examples listed in Table IX.

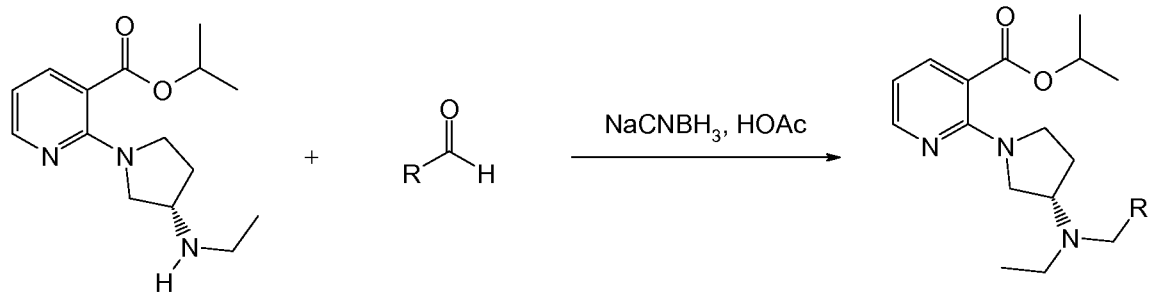
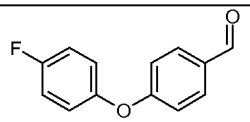
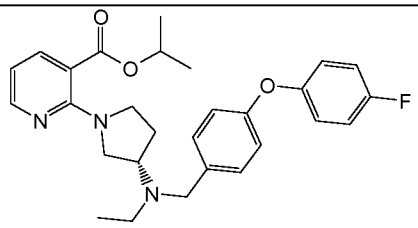
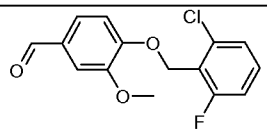
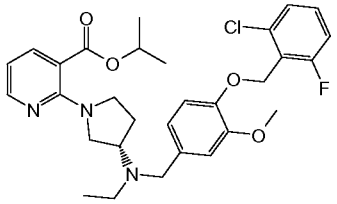
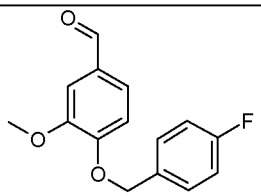
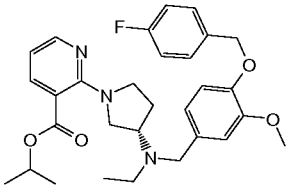
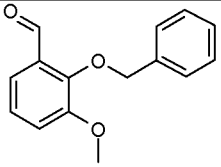
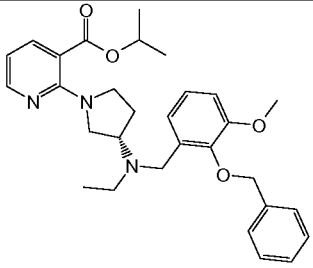
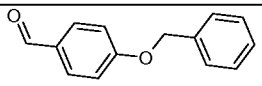
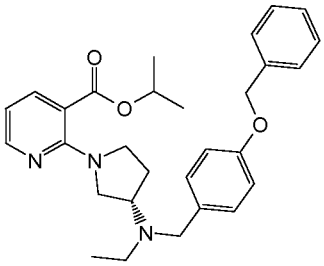
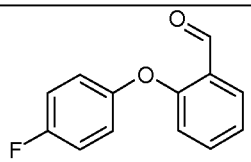
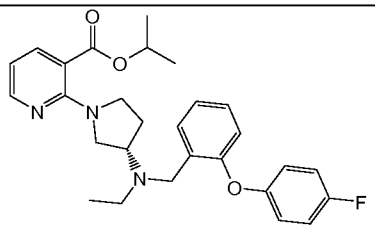
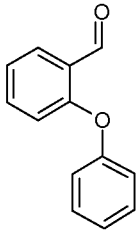
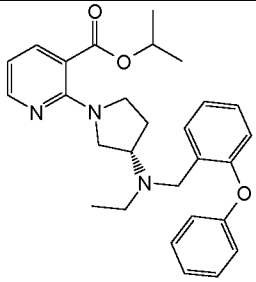
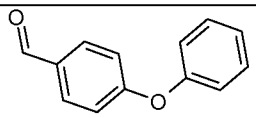
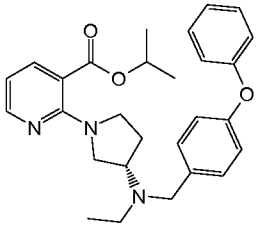
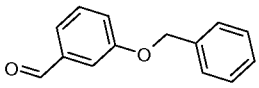
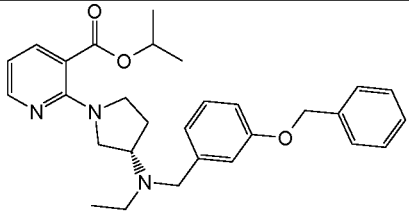
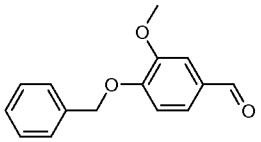
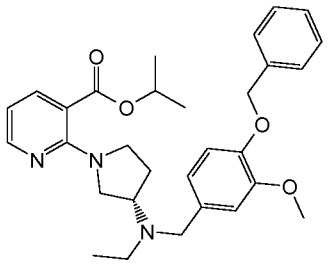
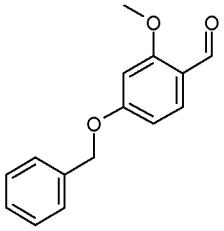
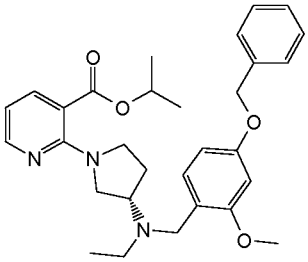
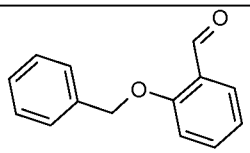
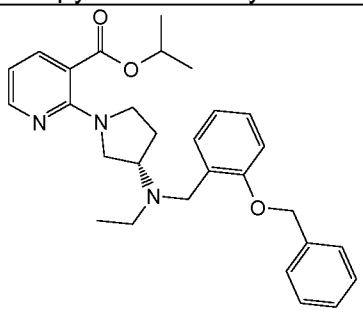


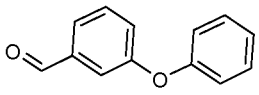
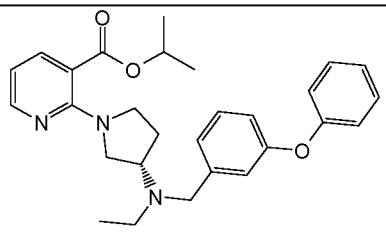
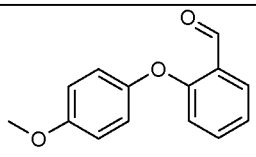
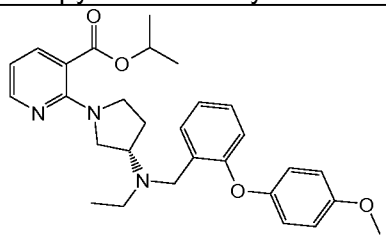
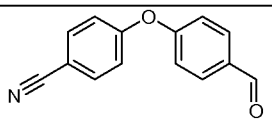
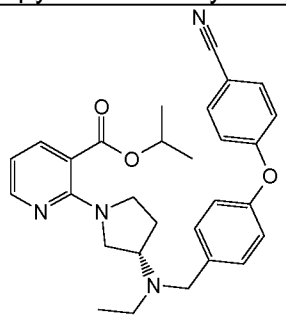
Table IX.

Example	Aldehyde	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 170		 1-methylethyl 2-{(3*S*)-3-[ethyl({4-[(4-fluorophenyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	478.1	1.1
Example 171		 1-methylethyl 2-{(3*S*)-3-[{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	556.0	1.1

Example 172		 1-methylethyl 2-[(3*S*)-3-(ethyl{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	522.1	1.1
Example 173		 1-methylethyl 2-{(3*S*)-3-[ethyl({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	504.1	1.1
Example 174		 1-methylethyl 2-{(3*S*)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	474.1	1.1

Example 175		 1-methylethyl 2-{(3*S*)-3-[ethyl({2-[(4-fluorophenyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	478.1	1.1
Example 176		 1-methylethyl 2-[(3*S*)-3-(ethyl{[2-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	460.1	1.1
Example 177		 1-methylethyl 2-[(3*S*)-3-(ethyl{[4-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	460.1	1.1
Example 178		 1-methylethyl 2-{(3*S*)-3-[ethyl({3-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	474.1	1.1

Example 179		 1-methylethyl 2-{(3*S*)-3-[ethyl({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	504.1	1.1
Example 180		 1-methylethyl 2-{(3*S*)-3-[ethyl({2-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	504.1	1.1
Example 181		 1-methylethyl 2-{(3*S*)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	474.1	1.1

Example 182		 1-methylethyl 2-[(3*S*)-3-(ethyl{[3-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate	460.1	1.1
Example 183		 1-methylethyl 2-((3*S*)-3-{ethyl[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	490.1	1.1
Example 184		 1-methylethyl 2-{(3*S*)-3-[({4-[(4-cyanophenyl)oxy]phenyl}methyl)(ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate	485.1	1.0

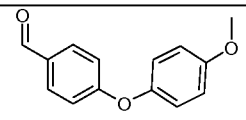
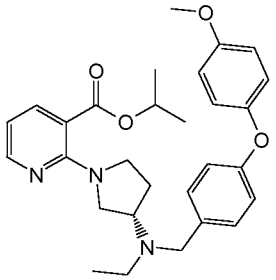
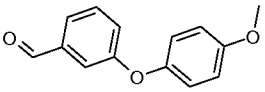
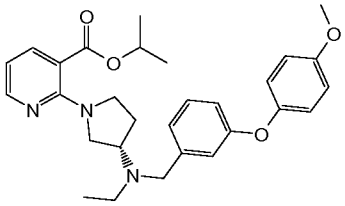
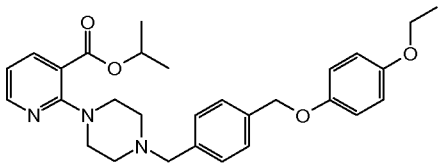
Example 185		 1-methylethyl 2-((3*S*)-3-{ethyl[(4-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	490.1	1.1
Example 186		 1-methylethyl 2-((3*S*)-3-{ethyl[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate	490.1	1.1

Table X

Example 187

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



To a solution of bis(1-methylethyl) (E)-1,2-diazenedicarboxylate (24.63 mg, 0.122 mmol) in anhydrous THF (1 mL) added Triphenyl phosphine (31.9 mg, 0.122 mmol), the mixture was stirred for 10 min at room temperature. 1-methylethyl 2-(4-{[4-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate (30 mg, 0.081 mmol) and 4-(ethyloxy)phenol (0.089 mmol) was added to the mixture, and then kept stirring for 12 h at room temperature. Concentrated to give crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100 mm 5 u

preparatory column), eluting at 18 mL/min with a linear gradient running from 35% to 90% acetonitrile and 0.1% aqueous NH_4OH over 15 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (4.31 mg, 10.84%). LC/MS: m/z= 490.2 $[M+H]^+$, Ret. Time: 1.10 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate,

1-methylethyl 2-(4-{[4-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate (30 mg, 0.081 mmol) was reacted with the appropriate phenols (0.089 mmol) to yield the examples listed in Table X.

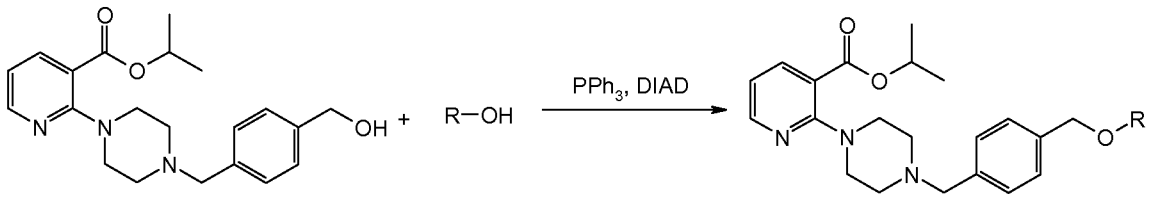
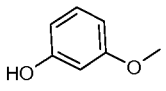
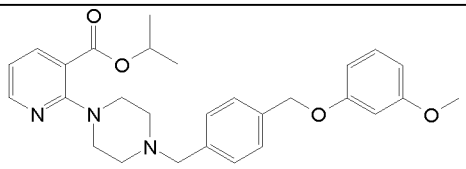
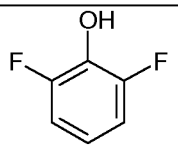
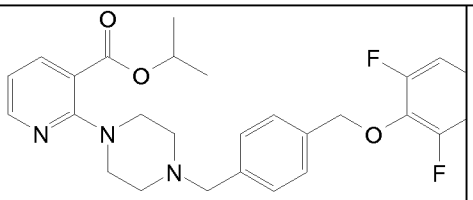
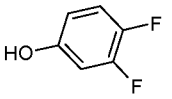
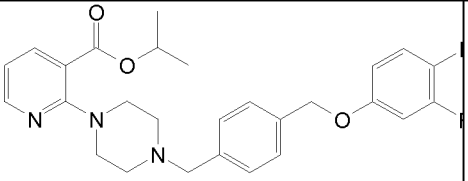
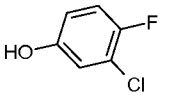
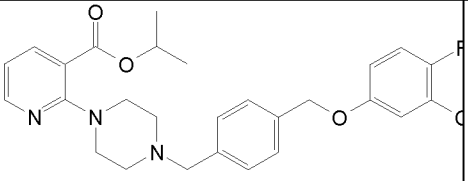
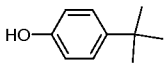
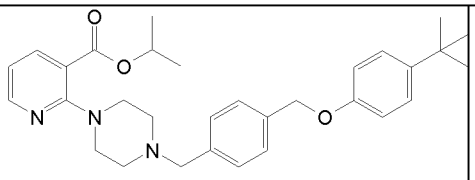
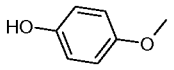
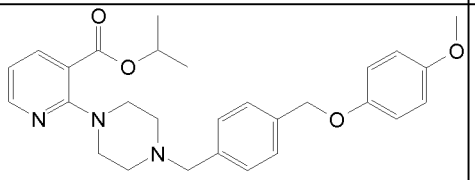
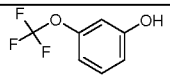
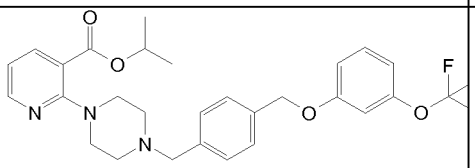
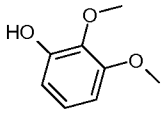
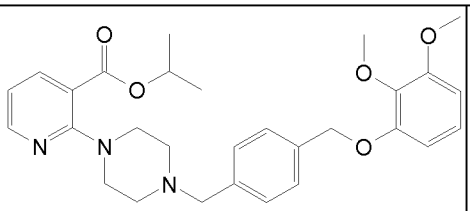
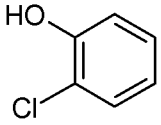
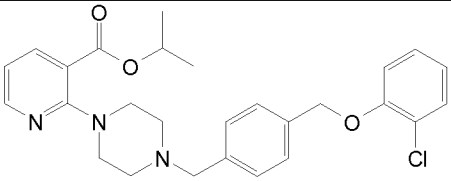
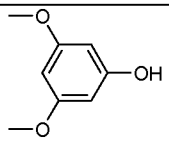
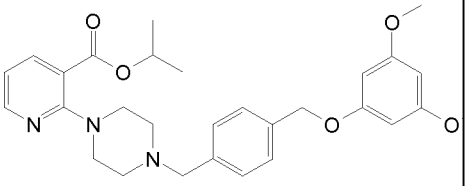


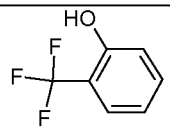
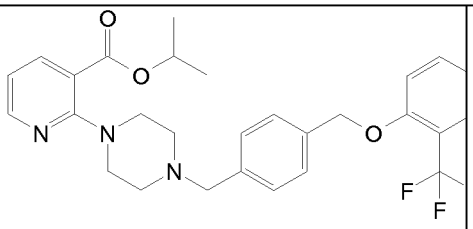
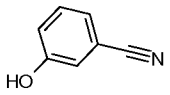
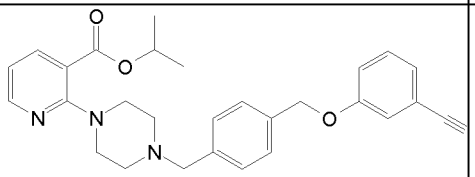
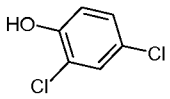
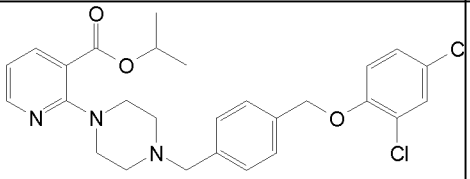
Table X.

EXAMPLE	Aldehyde	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 188		 1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.2	1.1

Example 189		 1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482.1	1.1
Example 190		 1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482.1	1.1
Example 191		 1-methylethyl 2-{4-[(4-{[(3-chloro-4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	498.1	1.2

Example 192		 1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	502.2	1.3
Example 193		 1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.2	1.0
Example 194		 1-methylethyl 2-[4-({4-[({3-[(trifluoromethyl)oxy]phenyl}oxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	530.1	1.2

Example 195		 1-methylethyl 2-(4-{[4-({[2,3-bis(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.2	1.0
Example 196		 1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	480.1	1.1
Example 197		 1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.2	1.1

Example 198		 1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	514.1	1.2
Example 199		 1-methylethyl 2-{4-[(4-{[(3-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	471.2	1.0
Example 200		 1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.1	1.2

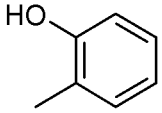
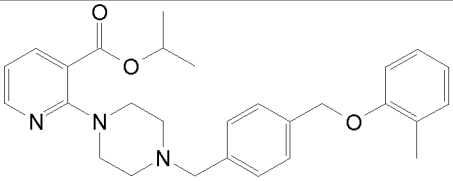
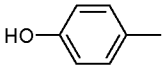
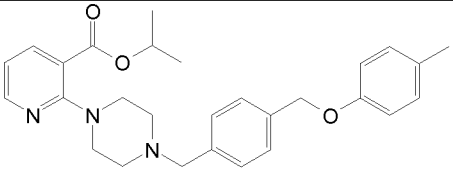
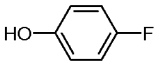
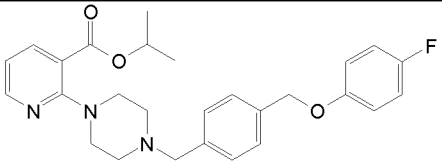
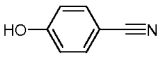
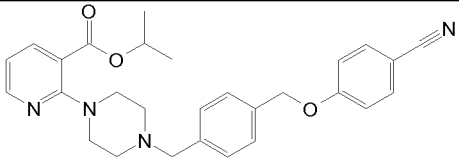
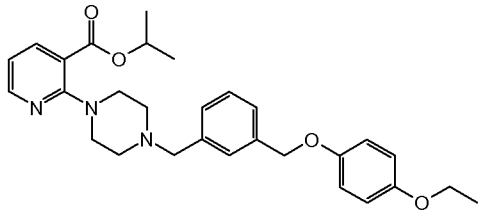
Example 201		 1-methylethyl 2-{4-[(4-{[(2-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.2	1.1
Example 202		 1-methylethyl 2-{4-[(4-{[(4-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.2	1.1
Example 203		 1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	464.2	1.1
Example 204		 1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	471.2	1.0

Table 11

Example 205

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



To a solution of bis(1-methylethyl) (E)-1,2-diazenedicarboxylate (41.0 mg, 0.203 mmol) in anhydrous THF (1 mL) added Triphenyl phosphine (53.2 mg, 0.203 mmol), the mixture was stirred for 10 min at room temperature. 1-methylethyl 2-(4-{[3-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate (30 mg, 0.081 mmol) and 4-(ethyloxy)phenol (0.081 mmol) was added to the mixture, and then kept stirring for 18 h at room temperature. Concentrated to give crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100 mm 5 u preparatory column), eluting at 18 mL/min with a linear gradient running from 40% to 90% acetonitrile and 0.1% aqueous NH_4OH over 15 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (4.82 mg, 12.12%). LC/MS: m/z= 490.1 $[M+H]^+$, Ret. Time: 1.00 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate,

1-methylethyl 2-(4-{[3-(hydroxymethyl)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate (30 mg, 0.081 mmol) was reacted with the appropriate phenols (0.081 mmol) to yield the examples listed in Table XI.

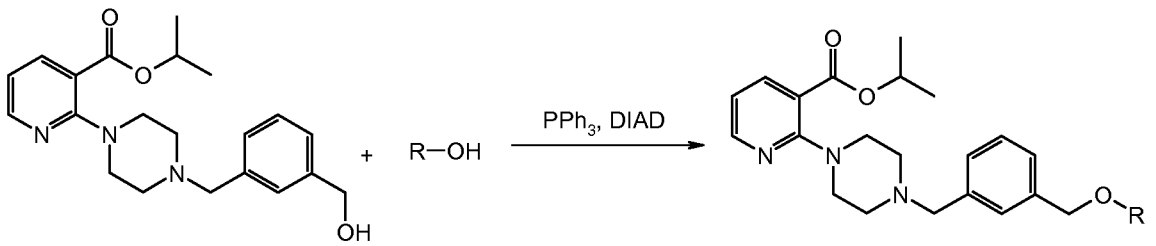
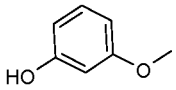
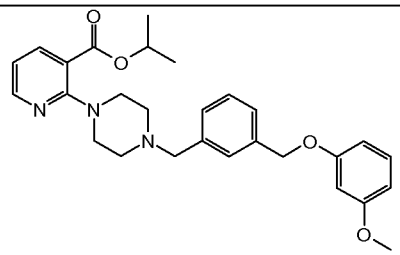
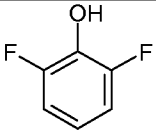
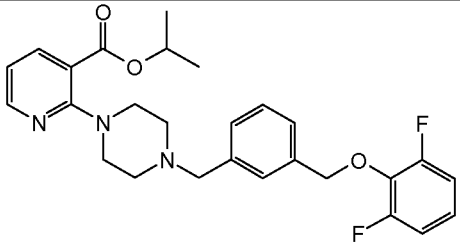
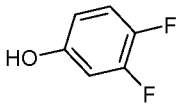
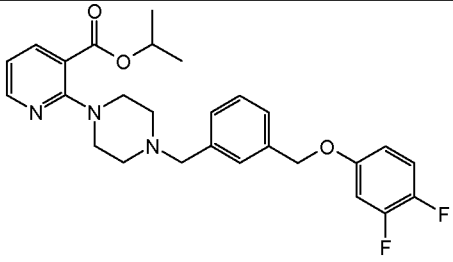
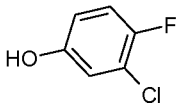
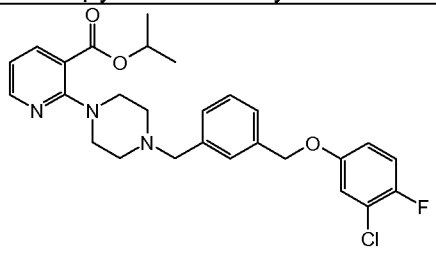
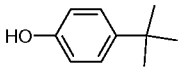
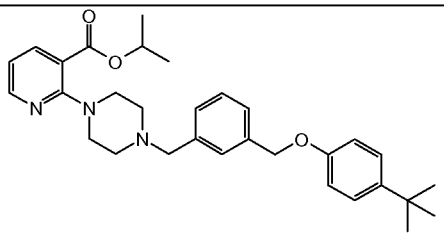
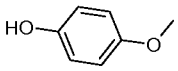
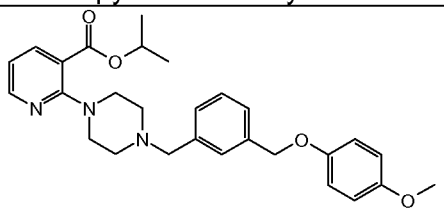
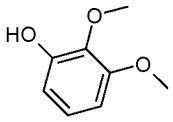
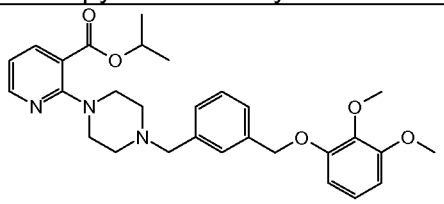
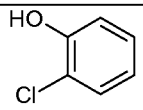
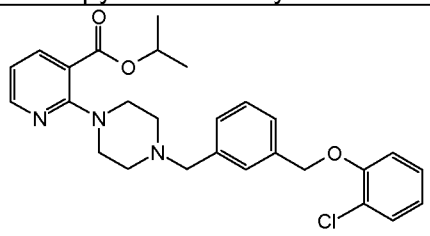
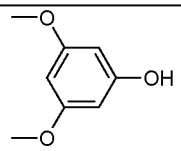
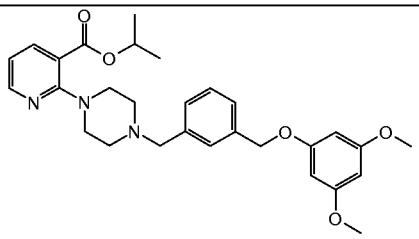
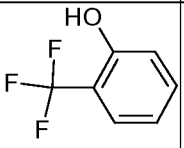
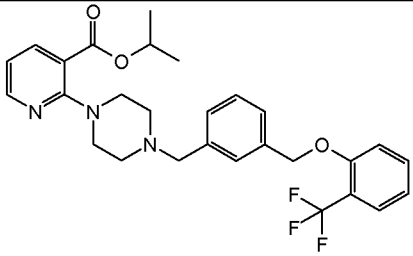
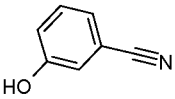
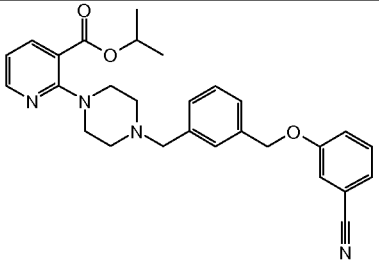
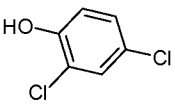
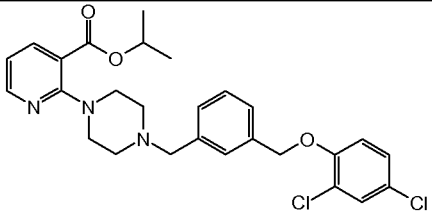


Table XI.

Example	Aldehyde	Product	LC-MS

	or Ketone		m/z $(M+H)^+$	RT (min)
Example 206		 1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.1	1.1
Example 207		 1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482.1	1.0
Example 208		 1-methylethyl 2-{4-[(3-{[(3,4-difluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482.1	1.0
Example 209		 1-methylethyl 2-{4-[(3-{[(3-chloro-4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	498.0	1.1

Example 210		 1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	502.2	1.2
Example 211		 1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.1	1.0
Example 212		 1-methylethyl 2-(4-{[3-({[2,3-bis(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.1	0.9
Example 213		 1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	480.1	0.9

Example 214		 1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.1	1.0
Example 215		 1-methylethyl 2-(4-{[3-({[2-(trifluoromethyl)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	514.1	1.1
Example 216		 1-methylethyl 2-{4-[(3-{[(3-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	471.1	0.9
Example 217		 1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.0	1.1

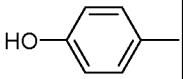
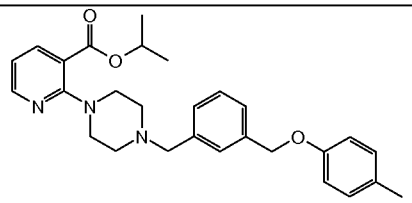
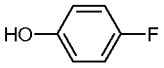
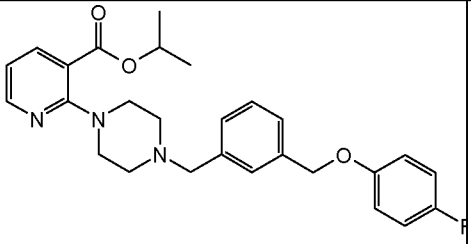
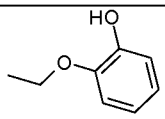
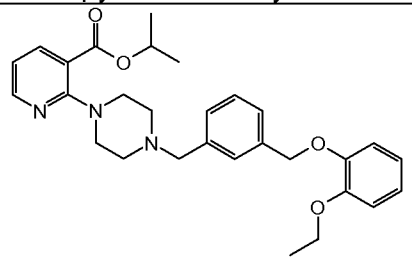
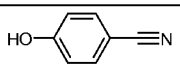
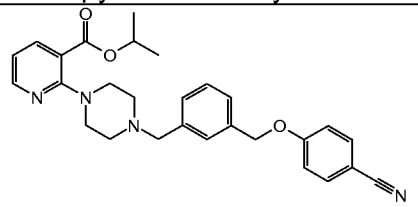
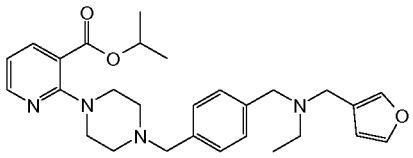
Example 218		 1-methylethyl 2-{4-[(3-{[(4-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.1	1.0
Example 219		 1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	464.1	1.0
Example 220		 1-methylethyl 2-(4-{[3-({[2-(ethyloxy)phenyl]oxy}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	490.1	1.0
Example 221		 1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	471.1	0.9

Table 12

Example 222

1-methylethyl 2-{4-[(4-{[ethyl(3-furanylmethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



Dissolved 1-methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate (20.0 mg, 0.05 mmol) and furan-3-carbaldehyde (0.126 mmol) in methanol (3.5 mL) with acetic acid (3.1 mg, 0.050 mmol). The solution was stirred for 1h at room temperature. Then added sodium cyanoborohydride (11.1 mg, 0.177 mmol) and stirred at room temperature for 12 hr. The polymer was filtered and concentrated the filtrate to give crude product, which was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 40% to 90% acetonitrile and 0.1% aqueous NH_4OH over 15 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (12.73 mg, 53%). LC/MS: m/z= 477.1 $[M+H]^+$, Ret. Time: 0.64 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-{4-[(4-{[ethyl(3-furanylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate,

1-methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate (20.0 mg, 0.05 mmol) was reacted with the appropriate aldehydes (0.126 mmol) to yield the examples listed in Table XII.

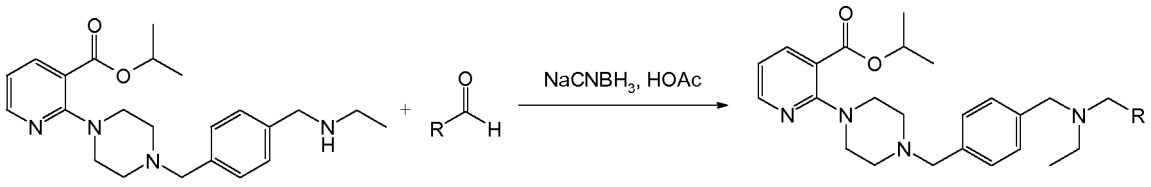
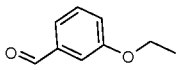
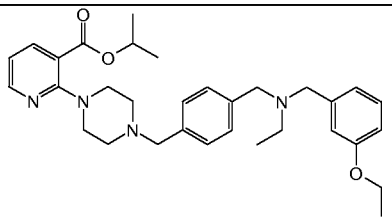
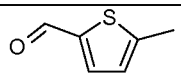
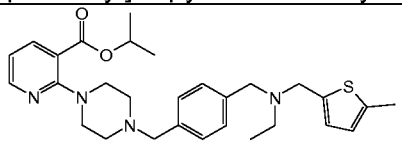
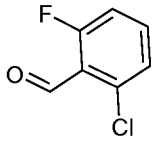
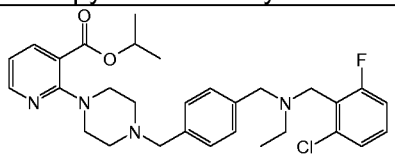
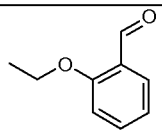
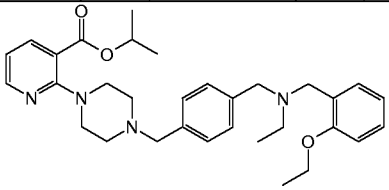


Table XII.

Example	Aldehyde	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 223		 1-methylethyl 2-[4-({4-[(ethyl{[3-(ethyloxy)phenyl]methyl}amino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	531.1	0.8
Example 224		 1-methylethyl 2-(4-{[4-({ethyl[(5-methyl-2-thienyl)methyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	507.1	0.7
Example 225		 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate ^{1}H NMR (400 MHz, CHLOROFORM-d) d 8.27 (dd, *J* = 1.88, 4.64 Hz, 1H), 7.94 (dd, *J* = 1.76, 7.53 Hz, 1H),7.22 - 7.38 (m, 5H), 7.06 - 7.22 (m, 2H), 6.89 - 7.03 (m, 1H), 6.73 (dd, *J* = 4.77, 7.53 Hz, 1H), 5.21 (spt, *J* =6.23 Hz, 1H), 3.70 - 3.86 (m, 2H), 3.61 (s, 2H), 3.55 (s, 2H), 3.38 - 3.51 (m, 4H), 2.47 - 2.68 (m, 4H), 1.29 - 1.45 (m, 6H), 1.03 - 1.17 (m, 3H)	539.1	0.7
Example 226		 1-methylethyl 2-[4-({4-[(ethyl{[2-(ethyloxy)phenyl]methyl}amino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	531.1	0.8

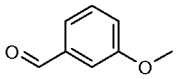
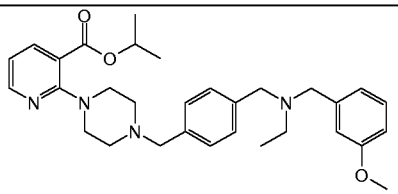
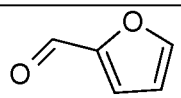
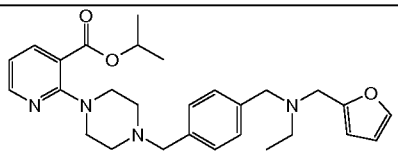
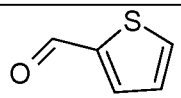
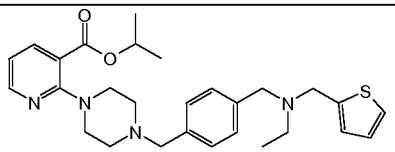
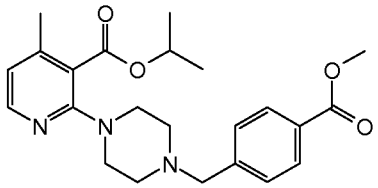
Example 227		 1-methylethyl 2-[4-({4-[(ethyl{[3-(methyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	517.1	0.8
Example 228		 1-methylethyl 2-{4-[(4-{[ethyl(2-furanylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	477.1	0.6
Example 229		 1-methylethyl 2-{4-[(4-{[ethyl(2-thienylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	493.1	0.7

Table 13

Example 230

1-methylethyl 4-methyl-2-[4-({4-[(methyloxy)carbonyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate



Dissolved 1-methylethyl 4-methyl-2-(1-piperazinyl)-3-pyridinecarboxylate (25.0 mg, 0.095 mmol) and methyl 4-formylbenzoate (0.252 mmol) in methanol (2.5 mL) with acetic acid (5.7 mg, 0.095 mmol). The solution was stirred for 4h at room temperature. Then added sodium cyanoborohydride (20.88 mg, 0.335 mmol) and stirred at room temperature for 12 hr. The polymer was filtered and got the crude products, which was

dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x 100mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 25% to 80% acetonitrile and 0.1% aqueous NH_4OH over 15 min. The desired fractions were concentrated under a stream of nitrogen at 45 °C, giving the desired product (16.46 mg, 42.1%). LC/MS: m/z= 412.2 $[M+H]^+$, Ret. Time: 0.77 min.

Following the procedure as described above in the preparation of 1-methylethyl 4-methyl-2-[4-({4-[(methyloxy)carbonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate, 1-methylethyl 4-methyl-2-(1-piperazinyl)-3-pyridinecarboxylate (25.0 mg, 0.095 mmol) was reacted with the appropriate aldehydes (0.252 mmol) to yield the examples listed in Table XIII.

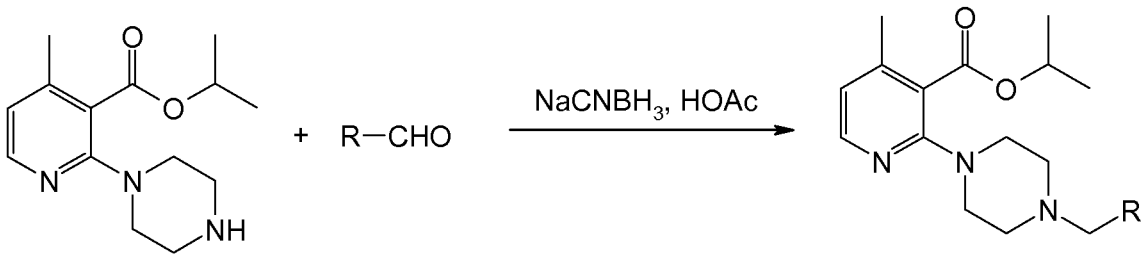
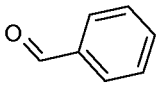
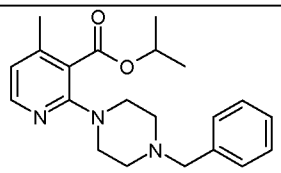
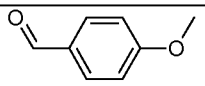
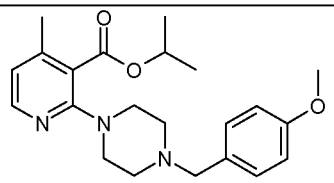
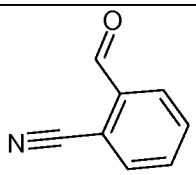
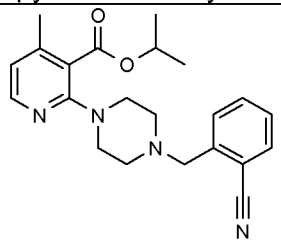
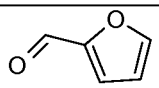
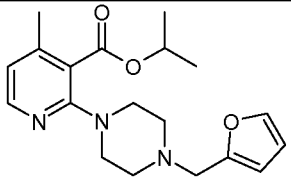
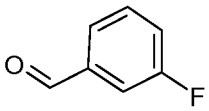
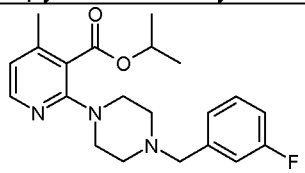
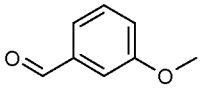
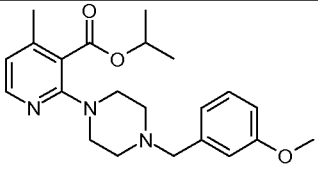
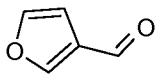
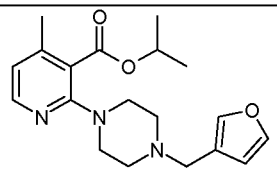
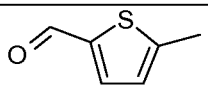
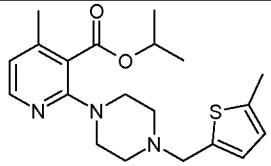
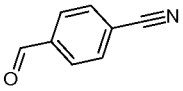
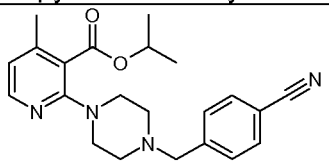
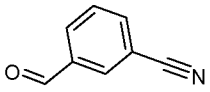
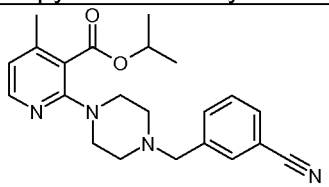
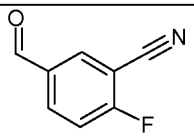
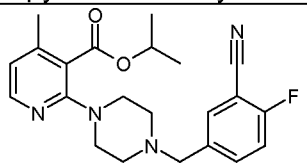
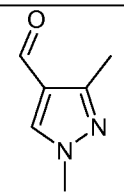
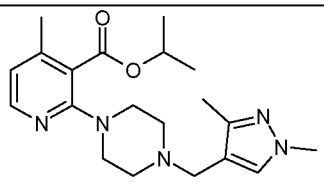
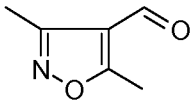
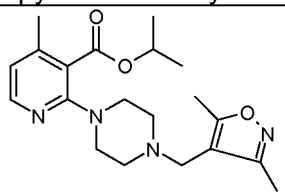
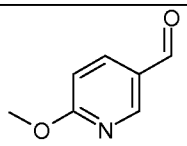
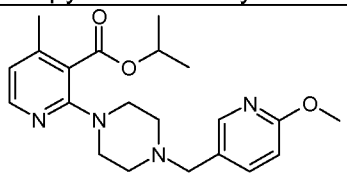
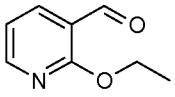
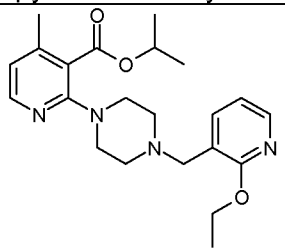


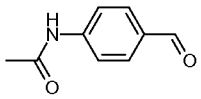
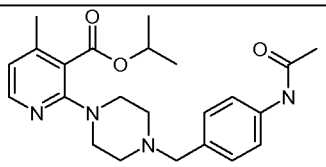
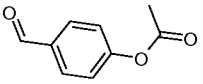
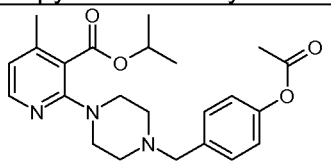
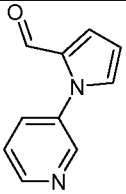
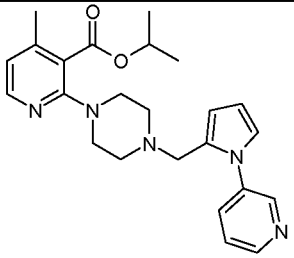
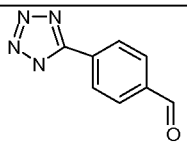
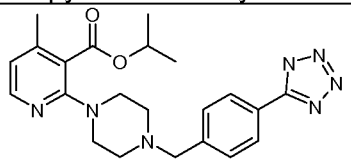
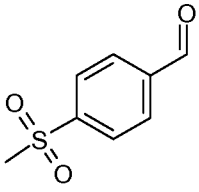
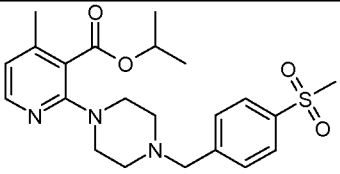
Table XIII.

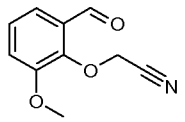
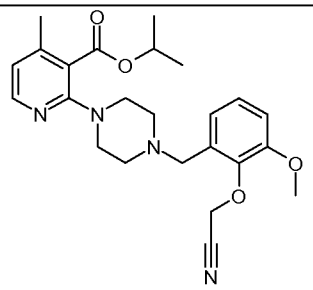
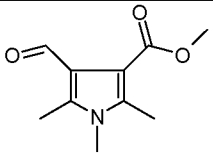
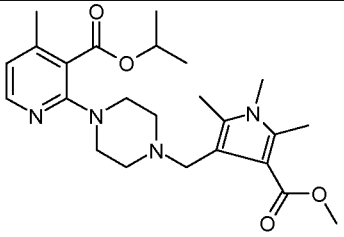
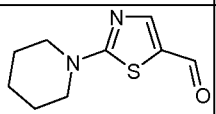
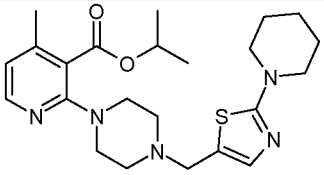
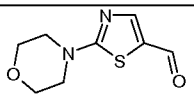
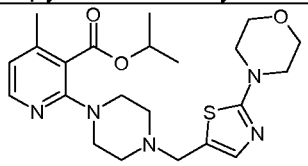
Example	Aldehyde or Ketone	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 231		 1-methylethyl 4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	354.18	0.8

Example 232		 1-methylethyl 4-methyl-2-(4-{[4-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	384.17	0.9
Example 233		 1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	379.16	0.7
Example 234		 1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate	344.17	0.7
Example 235		 1-methylethyl 2-{4-[(3-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	372.14	0.8
Example 236		 1-methylethyl 4-methyl-2-(4-{[3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	384.2	0.8

Example 237		 1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate	344.16	0.7
Example 238		 1-methylethyl 4-methyl-2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	374.14	0.8
Example 239		 1-methylethyl 2-{4-[(4-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	379.17	0.7
Example 240		 1-methylethyl 2-{4-[(3-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	379.17	0.7
Example 241		 1-methylethyl 2-{4-[(3-cyano-4-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	397.14	0.8

Example 242		 1-methylethyl 2-{4-[(1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	372.21	0.8
Example 243		 1-methylethyl 2-{4-[(3,5-dimethyl-4-isoxazolyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate	373.16	0.7
Example 244		 1-methylethyl 4-methyl-2-(4-{[6-(methyloxy)-3-pyridinyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	385.17	0.7
Example 245		 1-methylethyl 2-(4-{[2-(ethyloxy)-3-pyridinyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate	399.21	0.8

Example 246		 1-methylethyl 2-(4-{[4-(acetylamino)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate	411.18	0.7
Example 247		 1-methylethyl 2-(4-{[4-(acetyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate	412.2	0.8
Example 248		 1-methylethyl 4-methyl-2-(4-{[1-(3-pyridinyl)-1*H*-pyrrol-2-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	420.21	0.7
Example 249		 1-methylethyl 4-methyl-2-(4-{[4-(1*H*-tetrazol-5-yl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	582.8	0.7
Example 250		 1-methylethyl 4-methyl-2-(4-{[4-(methylsulfonyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	432.15	0.8

Example 251		 1-methylethyl 2-(4-{[2-[(cyanomethyl)oxy]-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate	439.19	0.8
Example 252		 1-methylethyl 4-methyl-2-[4-({1,2,5-trimethyl-4-[(methyloxy)carbonyl]-1*H*-pyrrol-3-yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	443.21	0.8
Example 253		 1-methylethyl 4-methyl-2-(4-{[2-(1-piperidinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	444.2	0.8
Example 254		 1-methylethyl 4-methyl-2-(4-{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	446.17	0.7

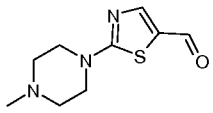
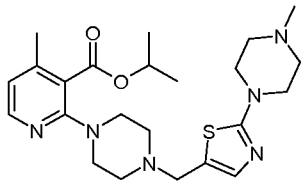
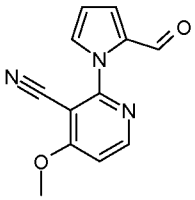
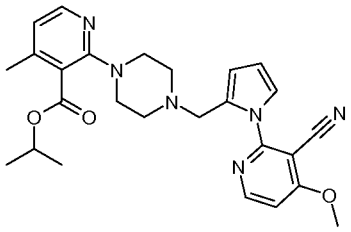
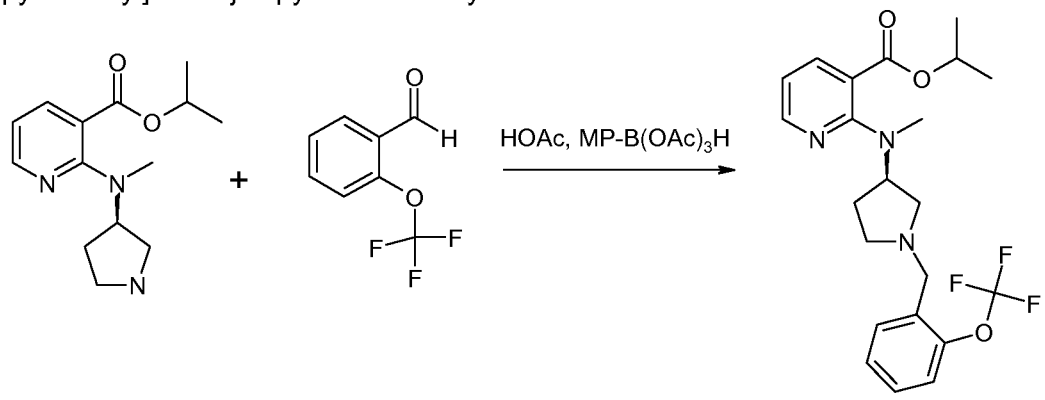
Example 255		 1-methylethyl 4-methyl-2-(4-{[2-(4-methyl-1-piperazinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	459.2	0.6
Example 256		 1-methylethyl 2-[4-({1-[3-cyano-4-(methyloxy)-2-pyridinyl]-1*H*-pyrrol-2-yl}methyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate	475.17	0.8

Table 14

Example 257

1-methylethyl 2-{methyl[(3*R*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate



In an A-vial, 2-[(trifluoromethyl)oxy]benzaldehyde (45.1 mg, 0.237 mmol) and 1-methylethyl 2-{methyl[(3R)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate (25 mg, 0.095 mmol) were added to the solution of with acetic acid (5.7 mg, 0.095 mmol) in dimethyl sulfoxide (DMSO) (1.5 ml). The solution was stirred for 1h at room temperature. Then MP-$B(OAc)_3H$ (111 mg, 0.475 mmol) was added. The resulted solution was stirred at

room temperature for 12 hours. The polymer was filtered and the crude product was dissolved in DMSO, and purified on a Gilson HPLC (XBridge 19 x100mm 5u preparatory column), eluting with acetonitrile, water 0.1%NH4OH. The desired fractions were concentrated under a stream of nitrogen at 50 ºC, giving 4.09 mg (10.9%) of the titled compound. LC-MS m/z 438.17 (M+H)+, 1.0 min (ret time).

Following the procedure as described above in the preparation of 1-methylethyl 2-{methyl[(3*R*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate,
1-methylethyl 2-{methyl[(3*R*)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate (25 mg, 0.095 mmol) was reacted with the appropriate aldehyde to yield the examples listed in Table XIV.

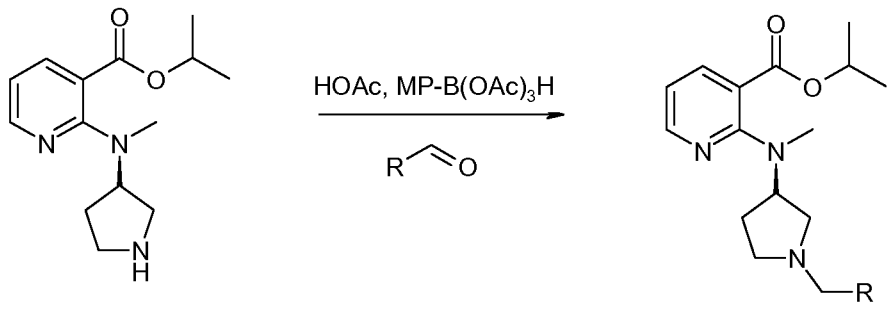
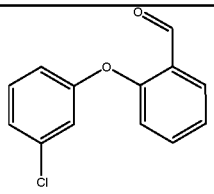
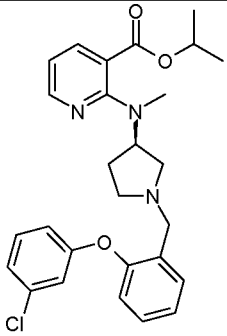
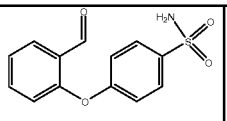
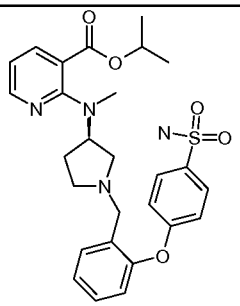
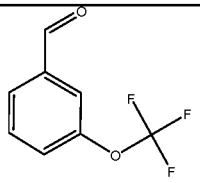
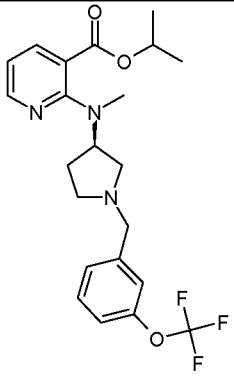
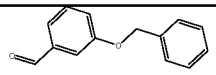
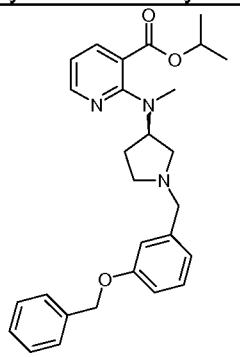
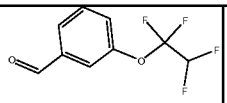
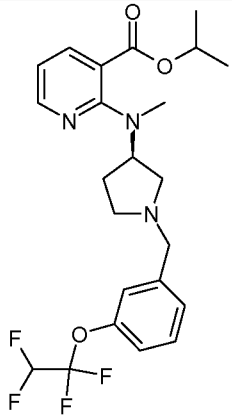
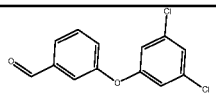
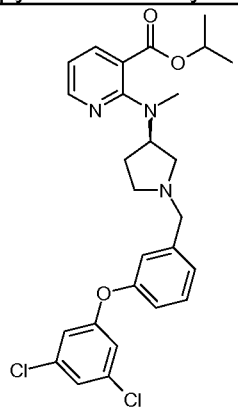
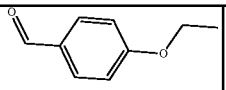
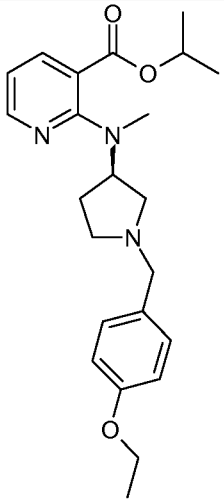
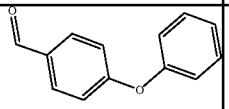
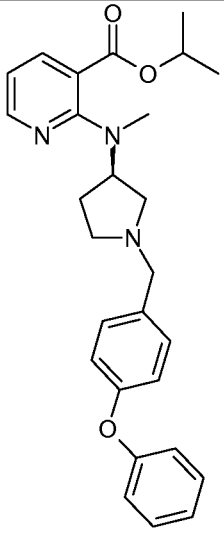


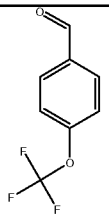
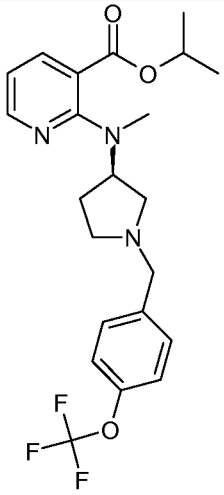
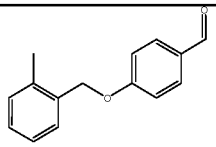
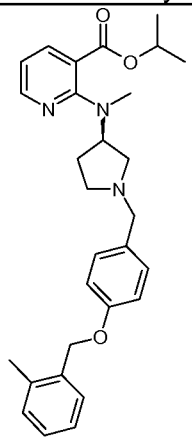
Table XIV.

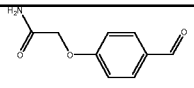
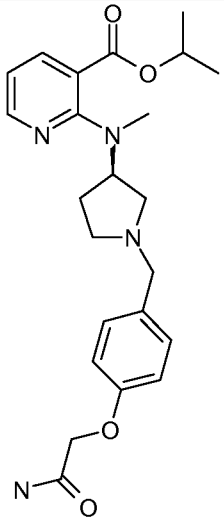
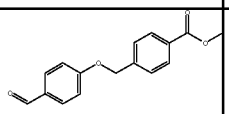
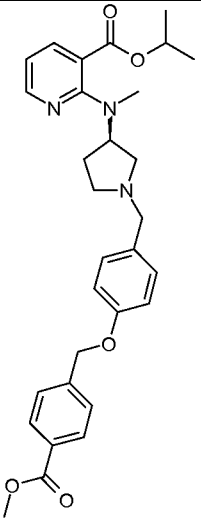
Example	Aldehyde	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 258		 1-methylethyl 2-[[(3*R*)-1-({2-[(3-chlorophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	480.19	1.2

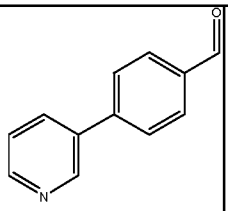
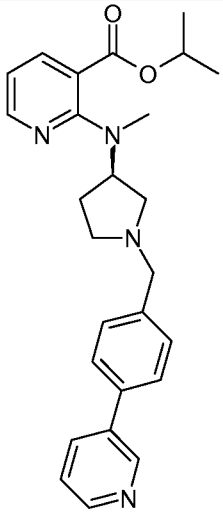
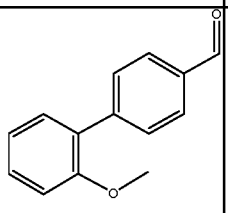
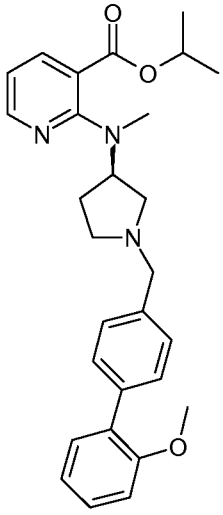
Example 259		 1-methylethyl 2-[{(3*R*)-1-[(2-{[4-(aminosulfonyl)phenyl]oxy}phenyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	525.2	0.9
Example 260		 1-methylethyl 2-{methyl[(3*R*)-1-({3-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	438.17	1.0
Example 261		 1-methylethyl 2-{methyl[(3*R*)-1-({3-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	460.24	1.1

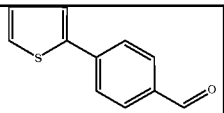
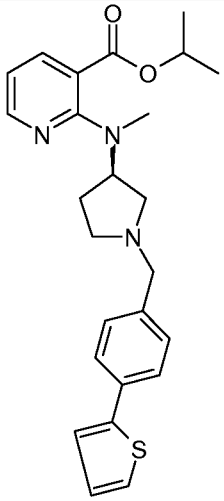
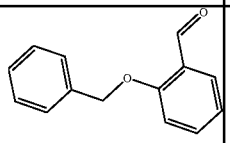
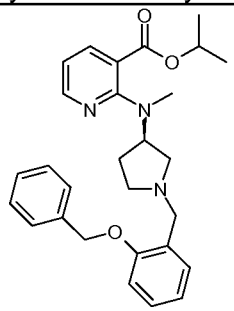
Example 262		 1-methylethyl 2-{methyl[(3*R*)-1-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	470.19	1.0
Example 263		 1-methylethyl 2-[[(3*R*)-1-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	514.15	1.3

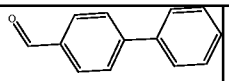
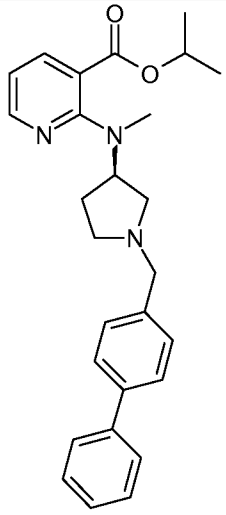
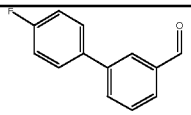
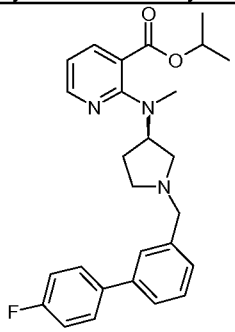
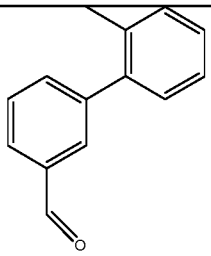
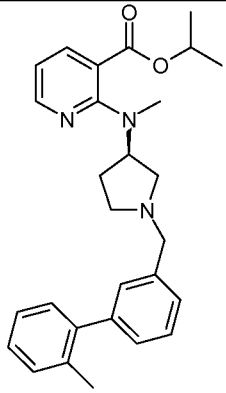
Example 264		 1-methylethyl 2-[((3*R*)-1-{[4-(ethyloxy)phenyl]methyl}-3-pyrrolidinyl)(methyl)amino]-3-pyridinecarboxylate	398.22	1.0
Example 265		 1-methylethyl 2-[methyl((3*R*)-1-{[4-(phenyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	446.23	1.1

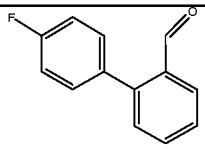
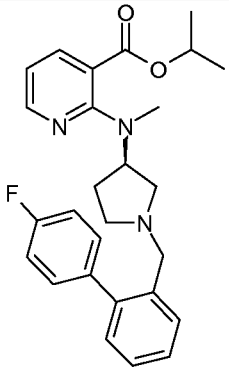
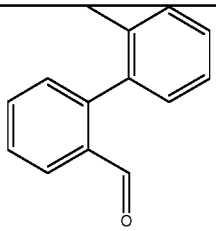
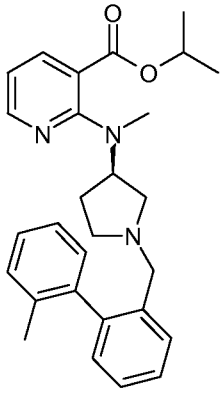
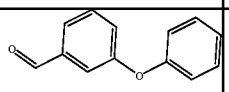
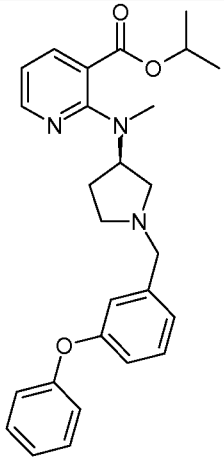
Example 266		 1-methylethyl 2-{methyl[(3*R*)-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	438.17	1.0
Example 267		 1-methylethyl 2-(methyl{(3*R*)-1-[(4-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate	474.26	1.1

Example 268		 1-methylethyl 2-[[(3*R*)-1-({4-[(2-amino-2-oxoethyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	427.24	0.7
Example 269		 1-methylethyl 2-{methyl[(3*R*)-1-({4-[({4-[(methyloxy)carbonyl]phenyl}methyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	518.24	1.1

Example 270		 1-methylethyl 2-[methyl((3*R*)-1-{[4-(3-pyridinyl)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	431.24	0.7
Example 271		 1-methylethyl 2-[methyl((3*R*)-1-{[2'-(methyloxy)-4-biphenylyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	460.22	1.0

Example 272		 1-methylethyl 2-[methyl((3*R*)-1-{[4-(2-thienyl)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	436.18	1.0
Example 273		 1-methylethyl 2-{methyl[(3*R*)-1-({2-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	460.23	1.1

Example 274		 1-methylethyl 2-[[(3*R*)-1-(4-biphenylylmethyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	430.23	1.1
Example 275		 1-methylethyl 2-[{(3*R*)-1-[(4'-fluoro-3-biphenylyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	448.24	1.1
Example 276		 1-methylethyl 2-(methyl{(3*R*)-1-[(2'-methyl-3-biphenylyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate	444.24	1.1

Example 277		 1-methylethyl 2-[{(3*R*)-1-[(4'-fluoro-2-biphenylyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	448.24	1.0
Example 278		 1-methylethyl 2-(methyl{(3*R*)-1-[(2'-methyl-2-biphenylyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate	444.25	1.1
Example 279		 1-methylethyl 2-[methyl((3*R*)-1-{[3-(phenyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	446.21	1.1

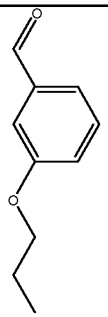
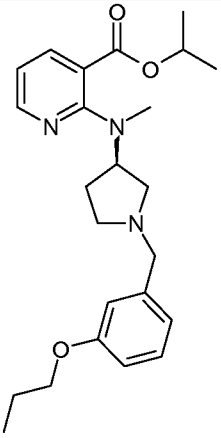
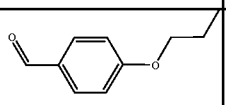
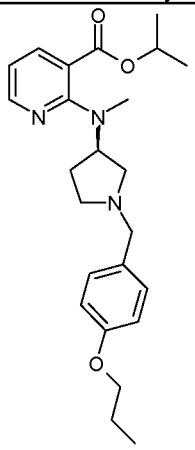
Example 280		 1-methylethyl 2-[methyl((3*R*)-1-{[3-(propyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	412.22	1.0
Example 281		 1-methylethyl 2-[methyl((3*R*)-1-{[4-(propyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	412.23	1.1

Table 15

Following the procedure as described above in the preparation of 1-methylethyl 2-{methyl[(3R)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate,

1-methylethyl 2-[(3*R*)-3-(ethylamino)-1-pyrrolidinyl]-4-methyl-3-pyridine carboxylate (30 mg, 0.103 mmol) was reacted with the appropriate aldehyde or ketone to yield the examples listed in Table XV.

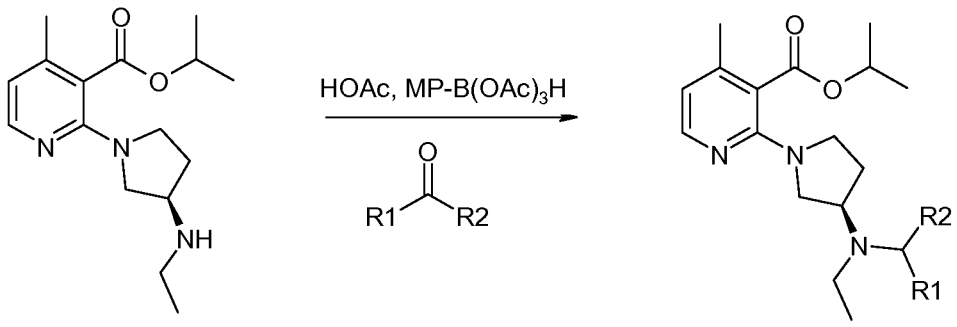
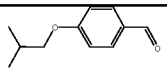
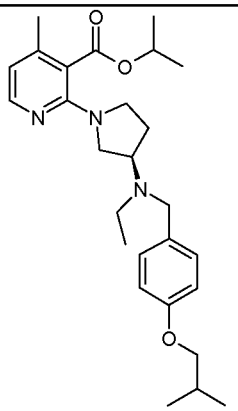
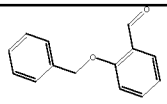
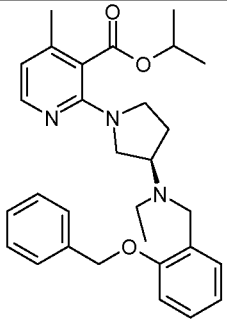
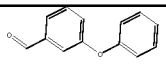
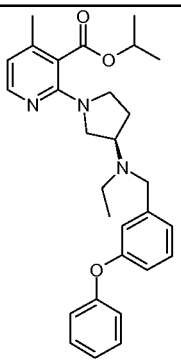
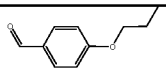
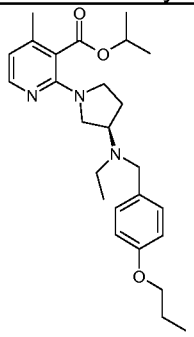
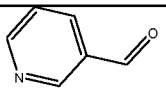
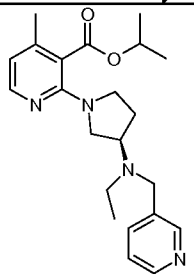
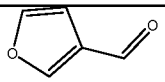
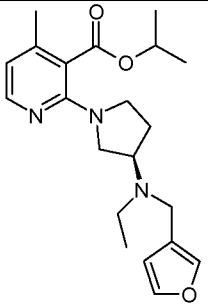
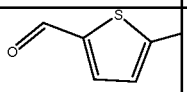
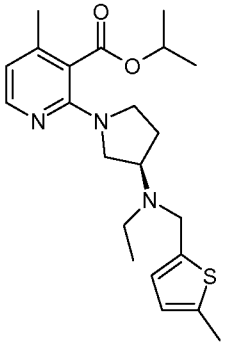
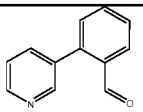
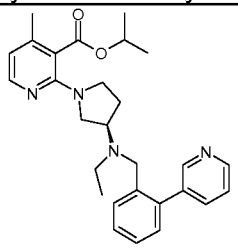
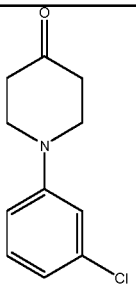
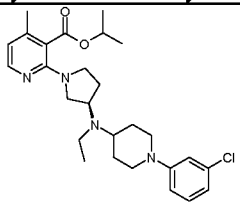
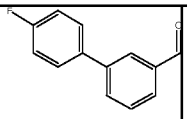
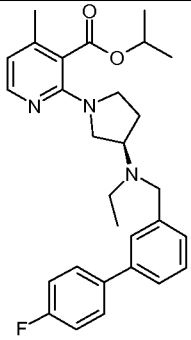
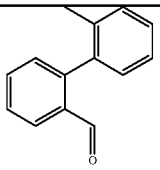
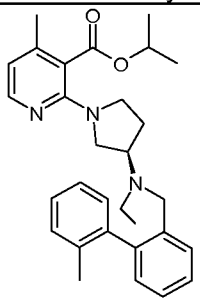
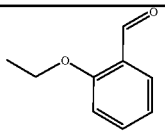
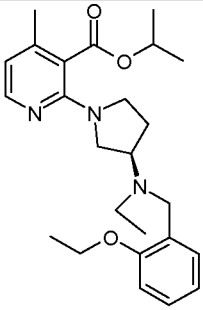


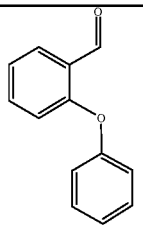
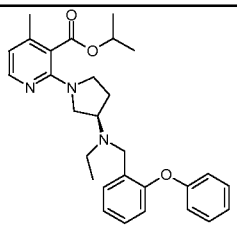
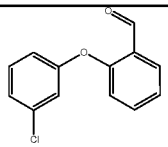
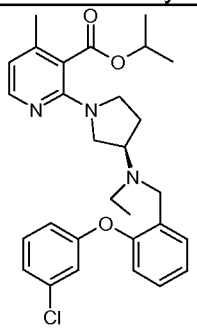
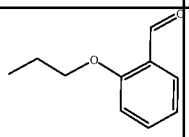
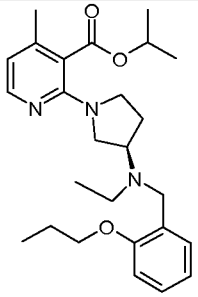
Table XV.

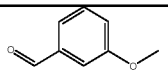
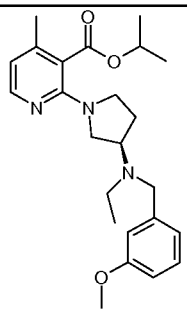
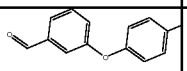
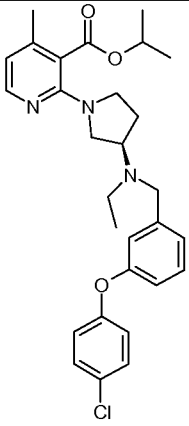
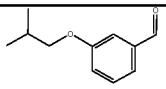
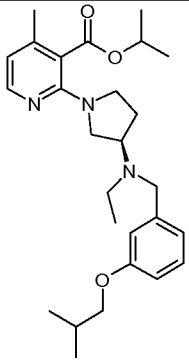
Example	Aldehyde (ketone)	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 282		 1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(2-methylpropyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	454.2	1.0
Example 283		 1-methylethyl 2-{(3*R*)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	488.17	0.9

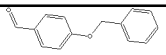
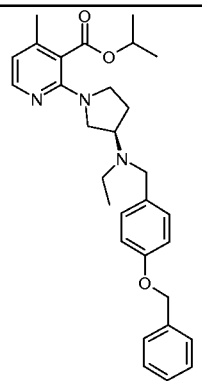
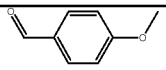
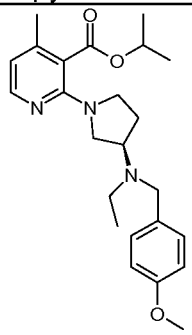
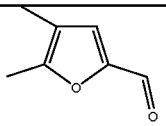
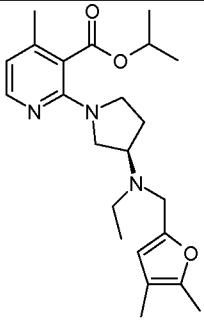
Example 284		 1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	474.15	0.9
Example 285		 1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	440.17	0.9
Example 286		 1-methylethyl 2-{(3*R*)-3-[ethyl(3-pyridinylmethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	383.11	0.6

Example 287		 1-methylethyl 2-{(3*R*)-3-[ethyl(3-furanylmethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	372.09	0.7
Example 288		 1-methylethyl 2-((3*R*)-3-{ethyl[(5-methyl-2-thienyl)methyl]amino}-1-pyrrolidinyl)-4-methyl-3-pyridinecarboxylate	402.1	0.8
Example 289		 1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(3-pyridinyl)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	459.1	0.7
Example 290		 1-methylethyl 2-{(3*R*)-3-[[1-(3-chlorophenyl)-4-piperidinyl](ethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	485.1	1.0

Example 291		 1-methylethyl 2-((3*R*)-3-{ethyl[(4'-fluoro-3-biphenylyl)methyl]amino}-1-pyrrolidinyl)-4-methyl-3-pyridinecarboxylate	476.1	1.0
Example 292		 1-methylethyl 2-((3*R*)-3-{ethyl[(2'-methyl-2-biphenylyl)methyl]amino}-1-pyrrolidinyl)-4-methyl-3-pyridinecarboxylate	472.14	1.0
Example 293		 1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(ethyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	426.15	0.9

Example 294		 1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(phenyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	474.16	0.9
Example 295		 1-methylethyl 2-{(3*R*)-3-[({2-[(3-chlorophenyl)oxy]phenyl}methyl)(ethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	508	1.0
Example 296		 1-methylethyl 2-[(3*R*)-3-(ethyl{[2-(propyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	440.17	0.9

Example 297		 1-methylethyl 2-[(3*R*)-3-(ethyl{[3-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	412.14	0.8
Example 298		 1-methylethyl 2-{(3*R*)-3-[({3-[(4-chlorophenyl)oxy]phenyl}methyl)(ethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	508	1.1
Example 299		 1-methylethyl 2-{(3*R*)-3-[ethyl({3-[(2-methylpropyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	454.19	1.0

Example 300		 1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	488.17	1.0
Example 301		 1-methylethyl 2-[(3*R*)-3-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-1-pyrrolidinyl]-4-methyl-3-pyridinecarboxylate	412.14	0.8
Example 302		 1-methylethyl 2-{(3*R*)-3-[[(4,5-dimethyl-2-furanyl)methyl](ethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	400.12	0.8

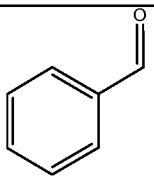
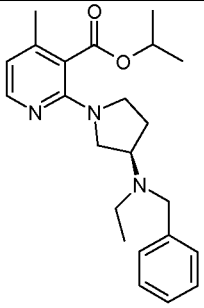
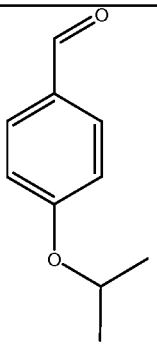
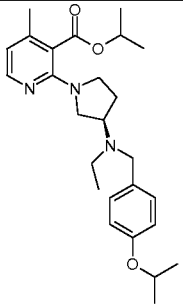
Example 303		 1-methylethyl 2-{(3*R*)-3-[ethyl(phenylmethyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	382.15	0.8
Example 304		 1-methylethyl 2-{(3*R*)-3-[ethyl({4-[(1-methylethyl)oxy]phenyl}methyl)amino]-1-pyrrolidinyl}-4-methyl-3-pyridinecarboxylate	440.17	0.9

Table 16

Following the procedure as described above in the preparation of 1-methylethyl 2-{methyl[(3*R*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate,

1-methylethyl 2-{methyl[(3*R*)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate (25 mg, 0.095 mmol) was reacted with the appropriate aldehyde or ketone to yield the examples listed in Table XVI.

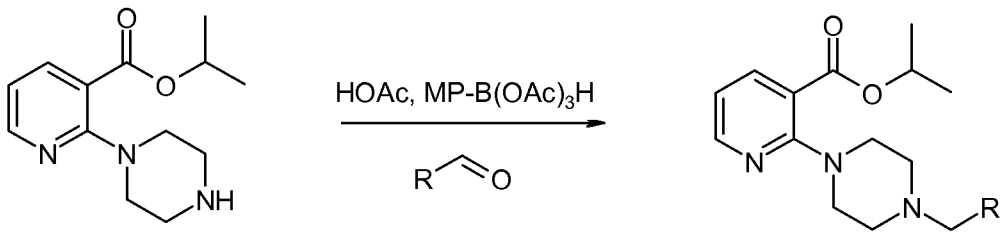
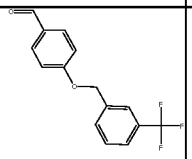
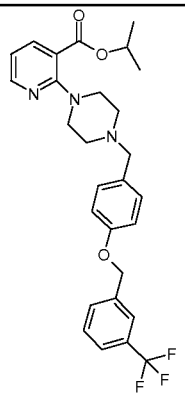
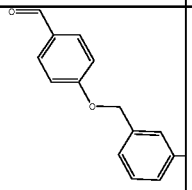
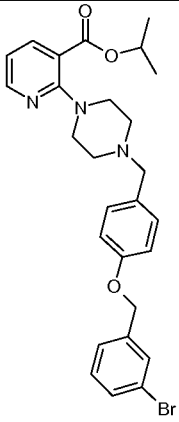
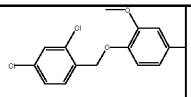
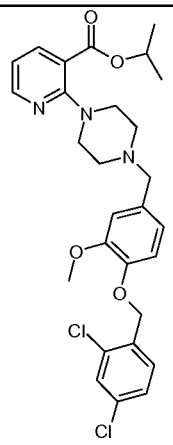
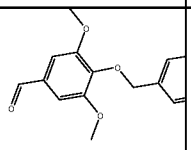
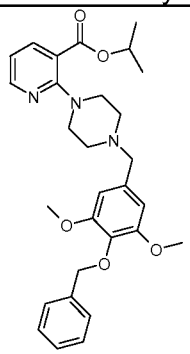
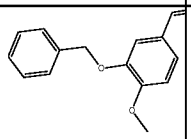
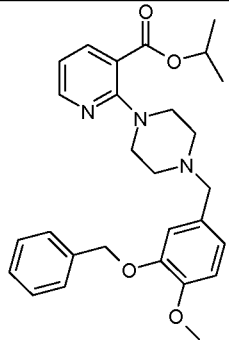
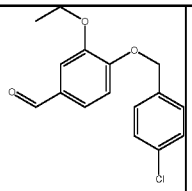
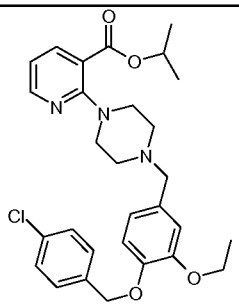
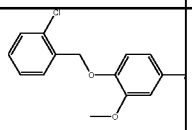
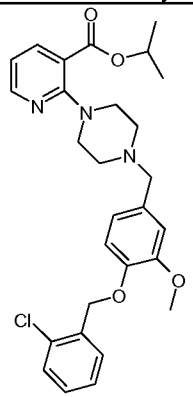
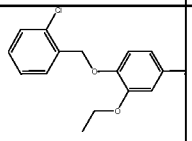
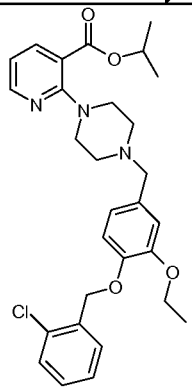
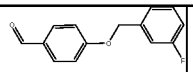
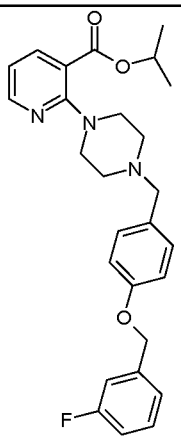
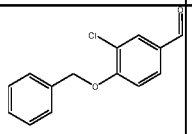
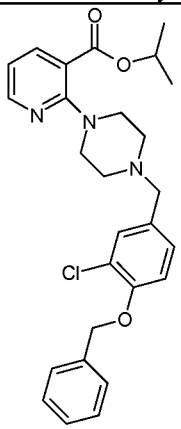
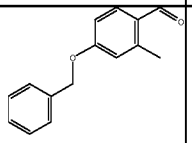
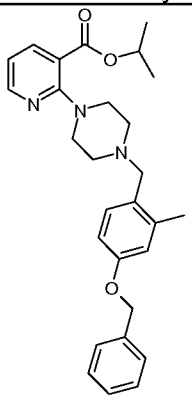


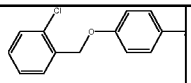
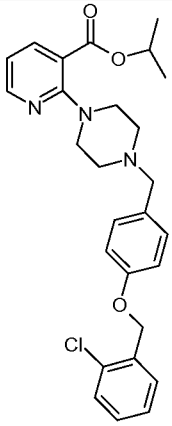
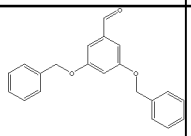
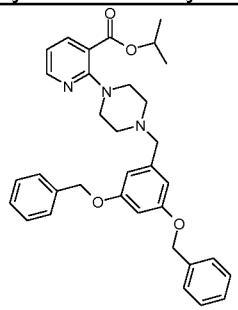
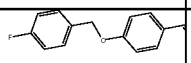
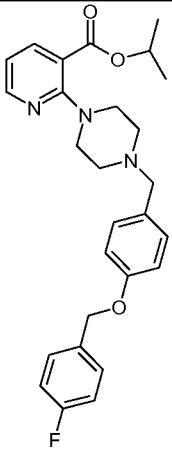
Table XVI.

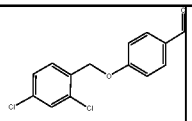
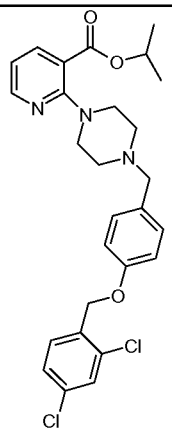
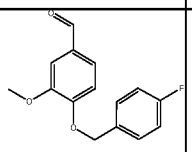
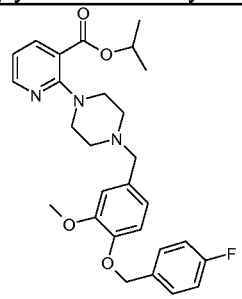
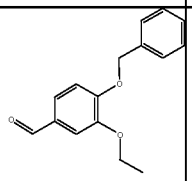
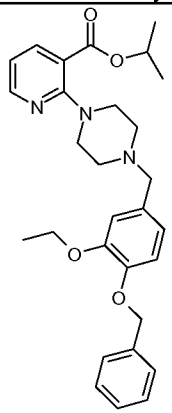
Example	Aldehyde (ketone)	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 305		 1-methylethyl 2-(4-{[4-({[3-(trifluoromethyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	514.3	1.13
Example 306		 1-methylethyl 2-{4-[(4-{[(3-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	524.3	1.1

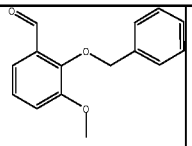
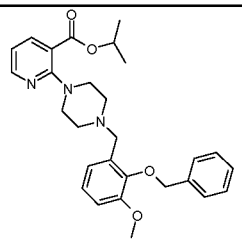
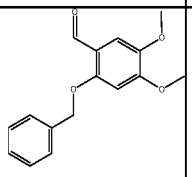
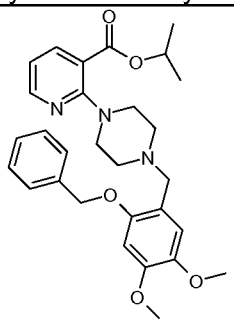
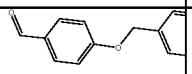
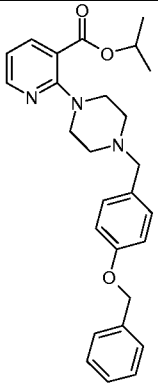
Example 307		 1-methylethyl 2-(4-{[4-{[(2,4-dichlorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	544.2	1.2
Example 308		 1-methylethyl 2-[4-({3,5-bis(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	506.3	1.2
Example 309		 1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	476.3	1.0

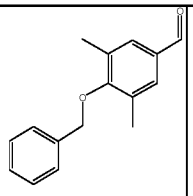
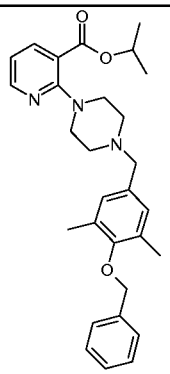
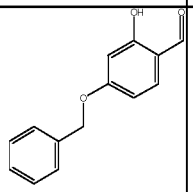
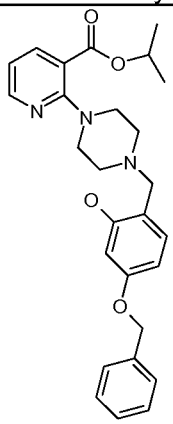
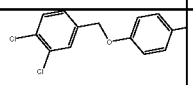
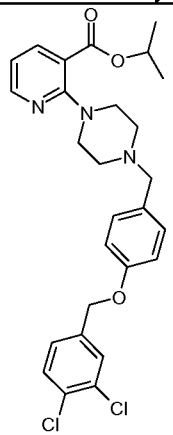
Example 310		 1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	524.3	1.1
Example 311		 1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	510.1	1.1
Example 312		 1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	524.3	1.1

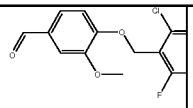
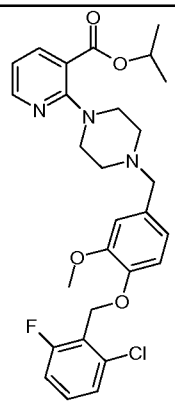
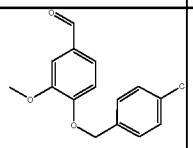
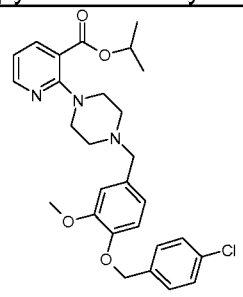
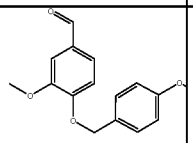
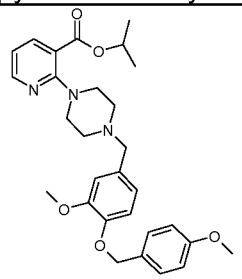
Example 313		 1-methylethyl 2-{4-[(4-{[(3-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate	464.5	1.1
Example 314		 1-methylethyl 2-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	480.1	1.1
Example 315		 1-methylethyl 2-[4-({2-methyl-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	460.2	1.1

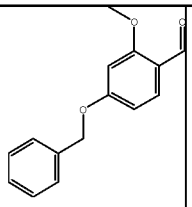
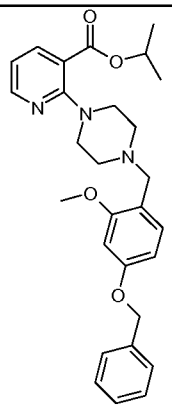
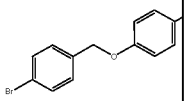
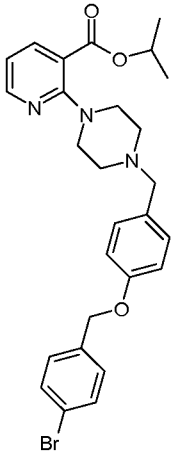
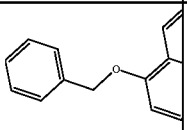
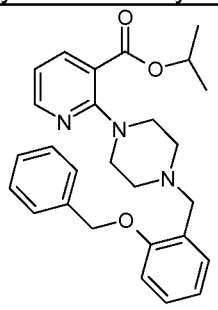
Example 316		 1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate	480.1	1.1
Example 317		 1-methylethyl 2-[4-({3,5-bis[(phenylmethyl)oxy]phenyl}me thyl)-1-piperazinyl]-3-pyridinecarboxylate	552.6	1.2
Example 318		 1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate	464.2	1.1

Example 319		 1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.3	1.2
Example 320		 1-methylethyl 2-(4-{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	494.2	1.1
Example 321		 1-methylethyl 2-[4-({3-(ethyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	490.3	1.1

Example 322		 1-methylethyl 2-[4-({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	476.2	1.1
Example 323		 1-methylethyl 2-[4-({4,5-bis(methyloxy)-2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	506.2	1.1
Example 324		 1-methylethyl 2-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	446.5	1.1

Example 325		 1-methylethyl 2-[4-({3,5-dimethyl-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	474.3	1.1
Example 326		 1-methylethyl 2-[4-({2-hydroxy-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	462.1	1.0
Example 327		 1-methylethyl 2-{4-[(4-{[(3,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.3	1.2

Example 328		 1-methylethyl 2-(4-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	528.3	1.1
Example 329		 1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	510.1	1.1
Example 330		 1-methylethyl 2-(4-{[3-(methyloxy)-4-({[4-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.3	1.0

Example 331		 1-methylethyl 2-[4-({2-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	476.1	1.1
Example 332		 1-methylethyl 2-{4-[(4-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	524.2	1.1
Example 333		 1-methylethyl 2-[4-({2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	446.5	1.1

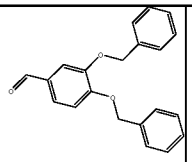
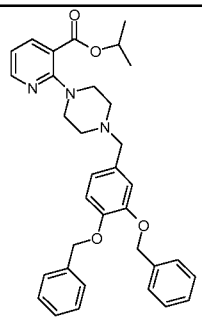
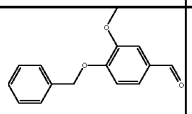
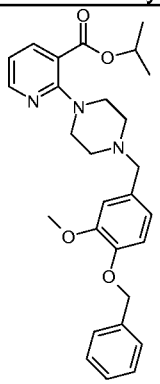
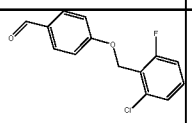
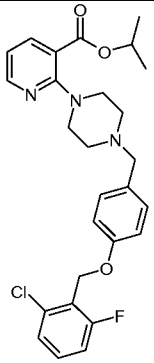
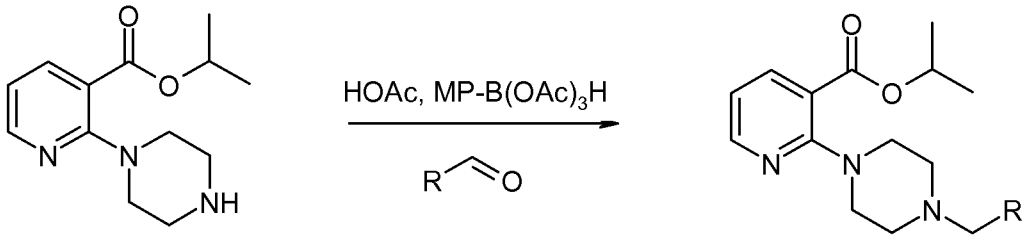
Example 334		 1-methylethyl 2-[4-({3,4-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	552.6	1.2
Example 335		 1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	476.1	1.1
Example 336		 1-methylethyl 2-{4-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	498.4	1.1

Table 17

Following the procedure as described above in the preparation of 1-methylethyl 2-{methyl[(3*R*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-

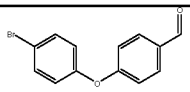
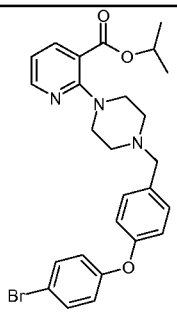
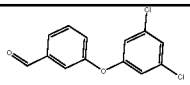
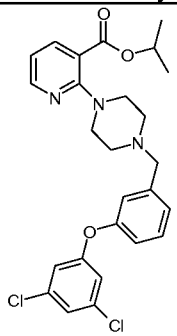
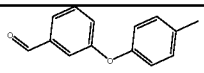
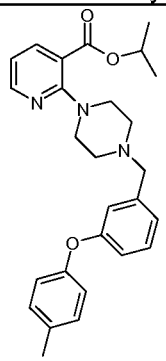
pyridinecarboxylate,

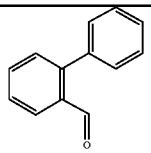
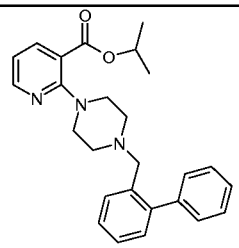
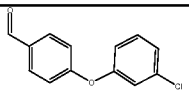
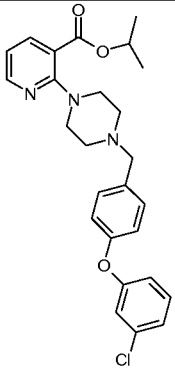
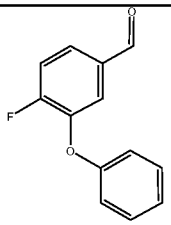
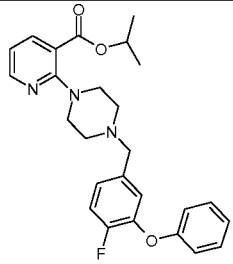
1-methylethyl 2-(1-piperazinyl)-3-pyridinecarboxylate (30 mg, 0.12 mmol) was reacted with the appropriate aldehyde or ketone to yield the examples listed in Table XVII.

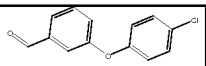
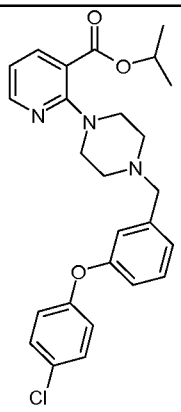
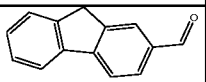
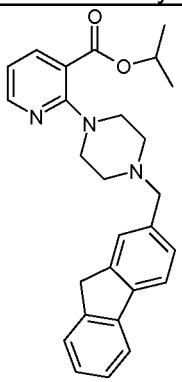
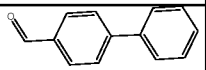
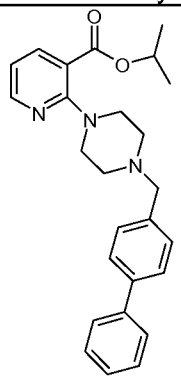


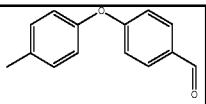
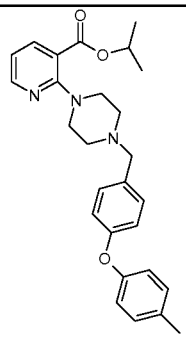
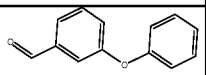
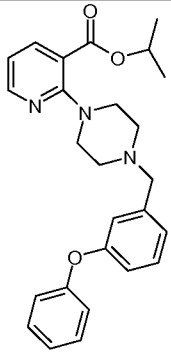
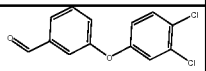
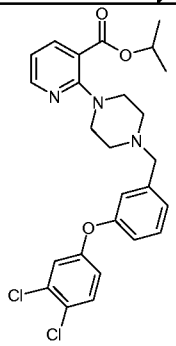
5

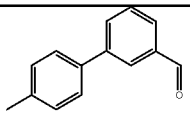
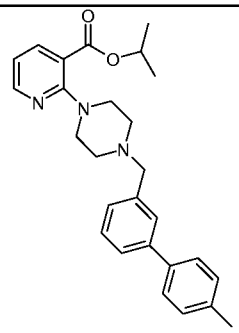
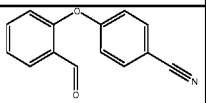
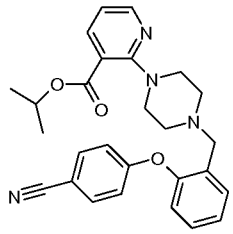
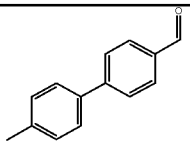
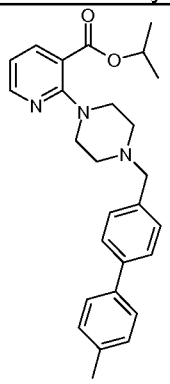
Table XVII.

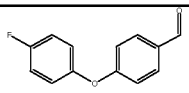
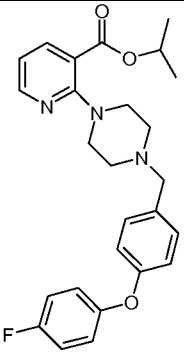
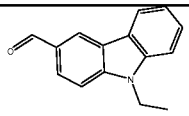
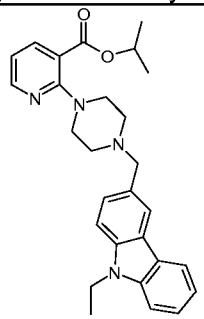
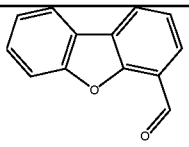
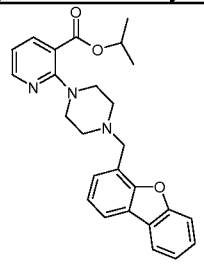
Example	Aldehyde (ketone)	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 337		 1-methylethyl 2-[4-({4-[(4-bromophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	512.2	1.1
Example 338		 1-methylethyl 2-[4-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	500.3	1.1
Example 339		 1-methylethyl 2-[4-({3-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	446.5	1.1

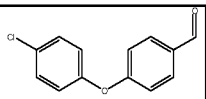
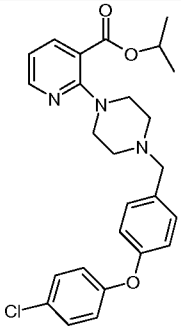
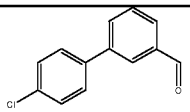
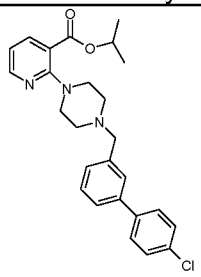
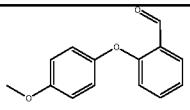
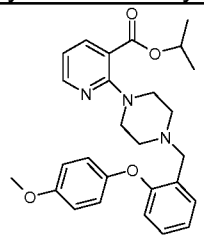
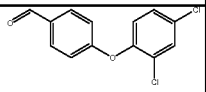
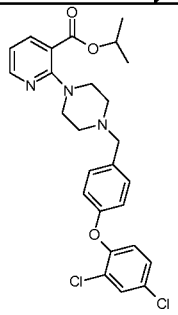
Example 340		 1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	416.2	1.0
Example 341		 1-methylethyl 2-[4-({4-[(3-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	466.2	1.1
Example 342		 1-methylethyl 2-(4-{[4-fluoro-3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	450.0	1.0

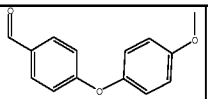
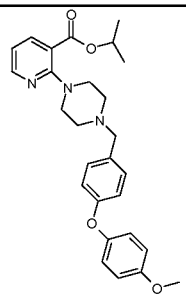
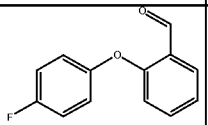
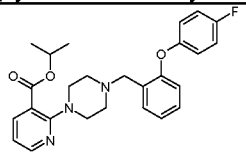
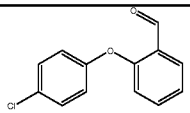
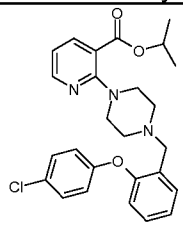
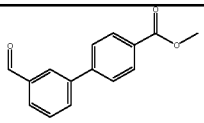
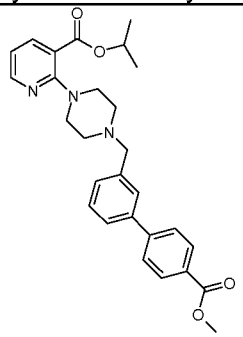
Example 343		 1-methylethyl 2-[4-({3-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	466.0	1.1
Example 344		 1-methylethyl 2-[4-(9*H*-fluoren-2-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	427.9	1.0
Example 345		 1-methylethyl 2-[4-(4-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	416.2	1.0

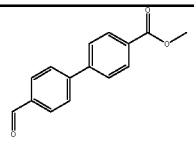
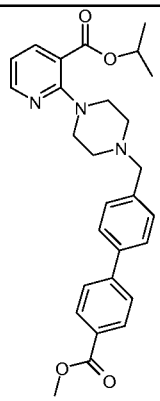
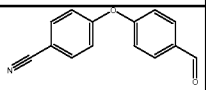
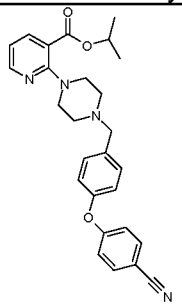
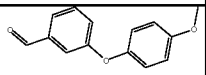
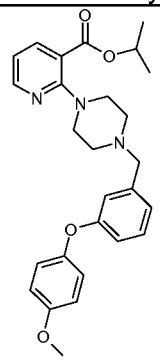
Example 346		 1-methylethyl 2-[4-({4-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	446.4	1.1
Example 347		 1-methylethyl 2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	432.0	1.0
Example 348		 1-methylethyl 2-[4-({3-[(3,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	500.3	1.1

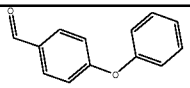
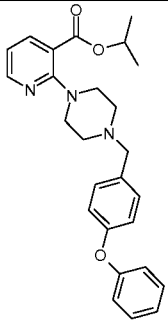
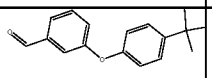
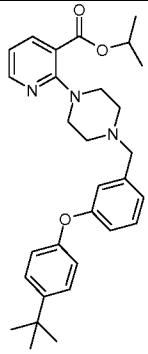
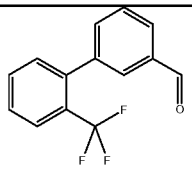
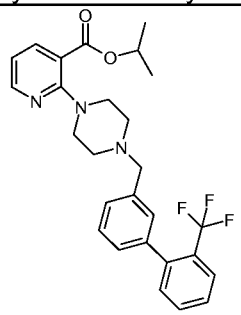
Example 349		 1-methylethyl 2-{4-[(4'-methyl-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	430.0	1.1
Example 350		 1-methylethyl 2-[4-({2-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	456.9	1.0
Example 351		 1-methylethyl 2-{4-[(4'-methyl-4-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	430.0	1.1

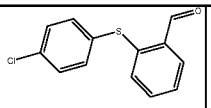
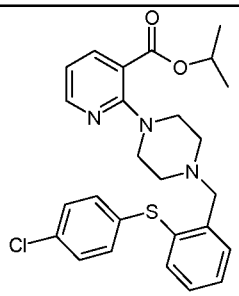
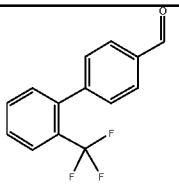
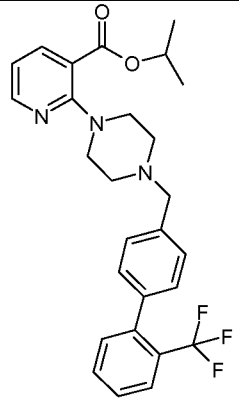
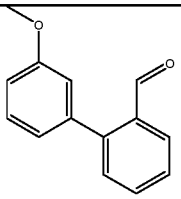
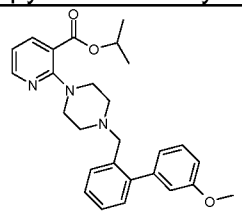
Example 352		 1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	450.0	1.0
Example 353		 1-methylethyl 2-{4-[(9-ethyl-9*H*-carbazol-3-yl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	457.0	1.1
Example 354		 1-methylethyl 2-[4-(dibenzo[*b*,*d*]furan-4-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate	429.9	1.0

Example 355		 1-methylethyl 2-[4-({4-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	466.1	1.1
Example 356		 1-methylethyl 2-{4-[(4'-chloro-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	450.0	1.1
Example 357		 1-methylethyl 2-{4-[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	462.1	1.0
Example 358		 1-methylethyl 2-[4-({4-[(2,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	500.3	1.1

Example 359		 1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	462.1	1.0
Example 360		 1-methylethyl 2-[4-({2-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	449.9	1.0
Example 361		 1-methylethyl 2-[4-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	466.2	1.1
Example 362		 1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-3-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	474.3	1.0

Example 363		 1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-4-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	474.3	1.0
Example 364		 1-methylethyl 2-[4-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	456.9	1.0
Example 365		 1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	462.0	1.0

Example 366		 1-methylethyl 2-(4-{[4-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	432.0	1.0
Example 367		 1-methylethyl 2-{4-[(3-{[4-(1,1-dimethylethyl)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	488.2	1.2
Example 368		 1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	483.9	1.1

Example 369		 1-methylethyl 2-[4-({2-[(4-chlorophenyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	481.9	1.1
Example 370		 1-methylethyl 2-(4-{[2'-(trifluoromethyl)-4-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	484.0	1.1
Example 371		 1-methylethyl 2-(4-{[3'-(methyloxy)-2-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	446.4	1.0

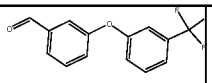
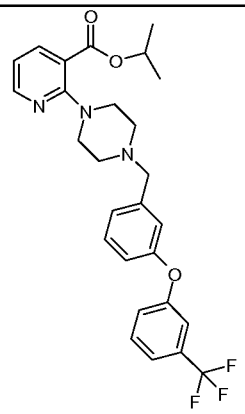
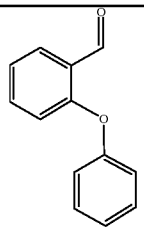
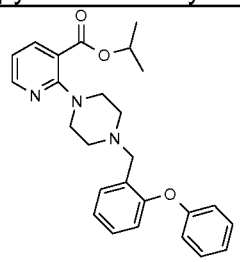
Example 372		 1-methylethyl 2-{4-[(3-{[3-(trifluoromethyl)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	500.3	1.1
Example 373		 1-methylethyl 2-(4-{[2-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	432.0	1.0

Table 18

Following the procedure as described above in the preparation of 1-methylethyl 2-{methyl[(3*R*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate, 1-methylethyl 2-{methyl[(3*S*)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate (20 mg, 0.076 mmol) was reacted with the appropriate aldehyde or ketone to yield the examples listed in Table XVIII.

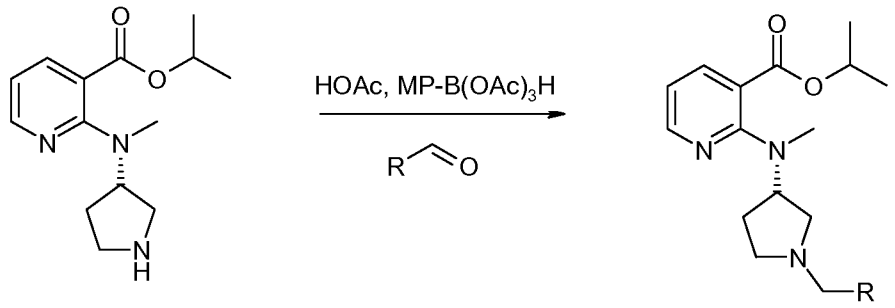
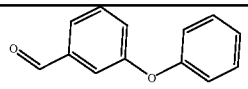
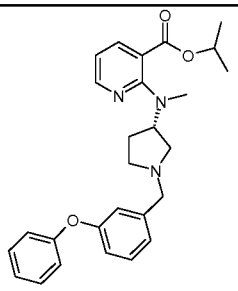
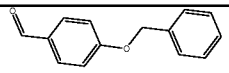
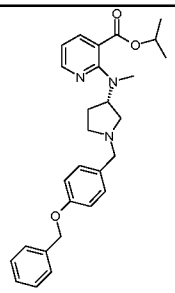
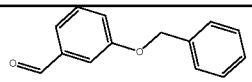
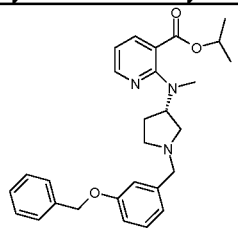
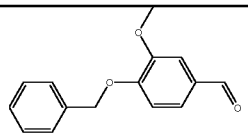
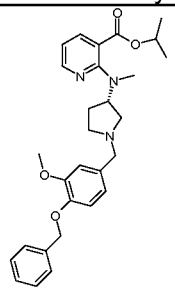
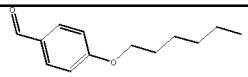
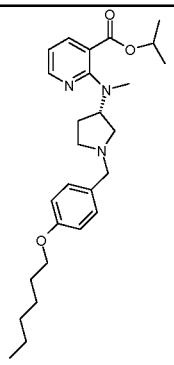
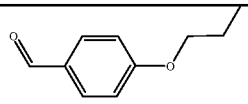
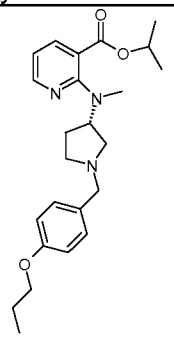
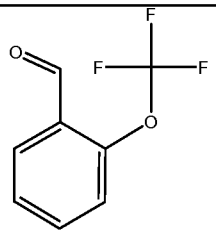
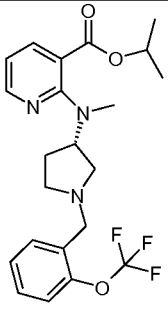
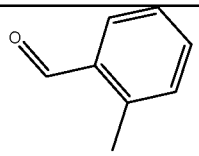
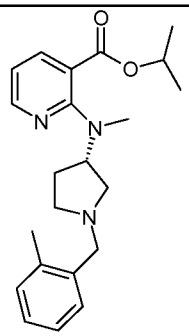
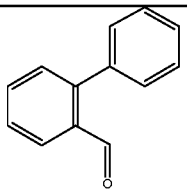
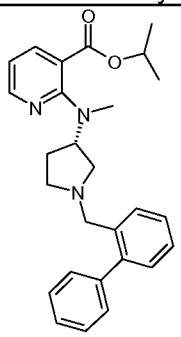
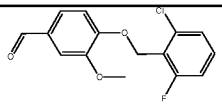
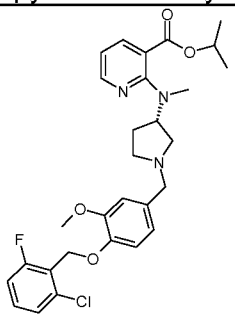


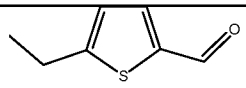
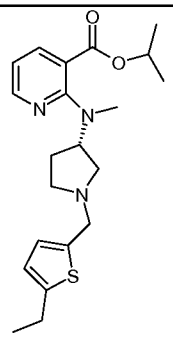
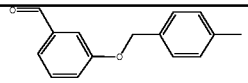
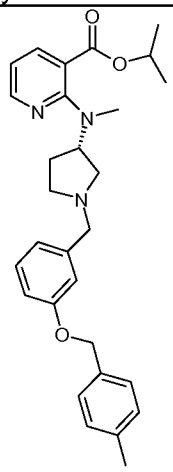
Table XVIII.

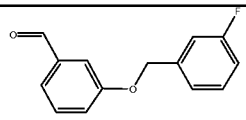
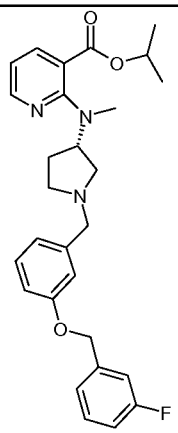
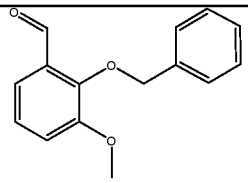
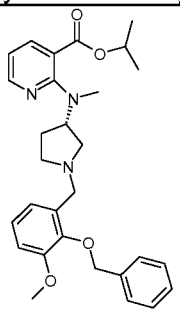
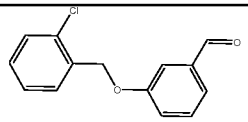
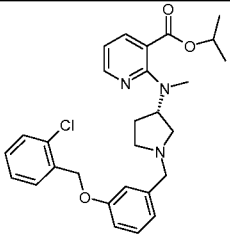
Example	Aldehyde	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 374		 1-methylethyl 2-[methyl((3*S*)-1-{[3-(phenyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	446.11	1.1

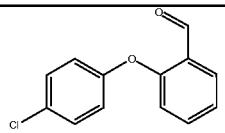
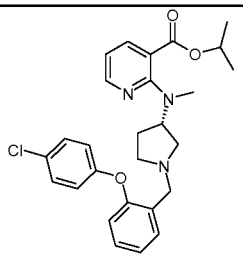
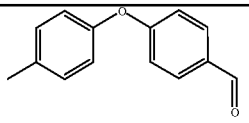
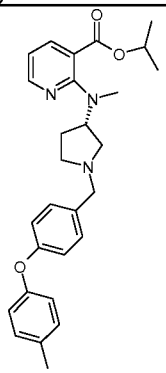
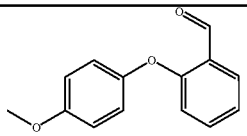
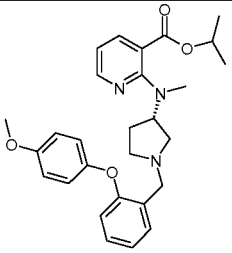
Example 375		 1-methylethyl 2-{methyl[(3*S*)-1-({4-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	460	1.1
Example 376		 1-methylethyl 2-{methyl[(3*S*)-1-({3-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	460.1	1.1
Example 377		 1-methylethyl 2-{methyl[(3*S*)-1-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	490.1	1.1

Example 378		 1-methylethyl 2-[((3*S*)-1-{[4-(hexyloxy)phenyl]methyl}-3-pyrrolidinyl)(methyl)amino]-3-pyridinecarboxylate	454.17	1.2
Example 379		 1-methylethyl 2-[methyl((3*S*)-1-{[4-(propyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-3-pyridinecarboxylate	412.13	1.0
Example 380		 1-methylethyl 2-{methyl[(3*S*)-1-({2-[(trifluoromethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	438.04	1.0

Example 381		 1-methylethyl 2-(methyl{(3*S*)-1-[(2-methylphenyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate	368.13	1.0
Example 382		 1-methylethyl 2-[[(3*S*)-1-(2-biphenylylmethyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	430.08	1.1
Example 383		 1-methylethyl 2-[((3*S*)-1-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)(methyl)amino]-3-pyridinecarboxylate	542	1.1

Example 384		 1-methylethyl 2-[{(3*S*)-1-[(5-ethyl-2-thienyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	388.07	1.0
Example 385		 1-methylethyl 2-(methyl{(3*S*)-1-[(3-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate	474.15	1.2

Example 386		 1-methylethyl 2-[{(3*S*)-1-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	478.1	1.1
Example 387		 1-methylethyl 2-{methyl[(3*S*)-1-({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	476.1	1.1
Example 388		 1-methylethyl 2-[{(3*S*)-1-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	494	1.2

Example 389		 1-methylethyl 2-[[(3*S*)-1-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	480	1.2
Example 390		 1-methylethyl 2-{methyl[(3*S*)-1-({4-[(4-methylphenyl)oxy]phenyl}methyl)-3-pyrrolidinyl]amino}-3-pyridinecarboxylate	461.1	1.2
Example 391		 1-methylethyl 2-(methyl{(3*S*)-1-[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-3-pyrrolidinyl}amino)-3-pyridinecarboxylate	476	1.1

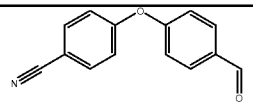
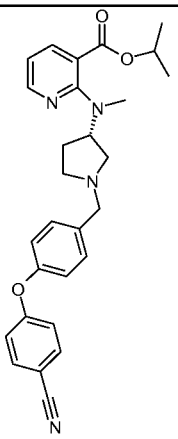
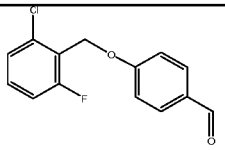
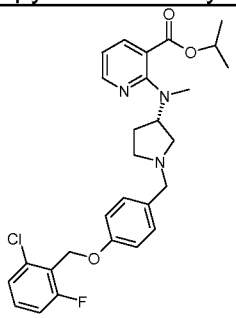
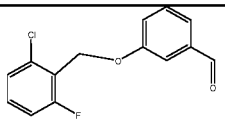
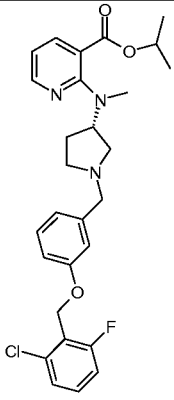
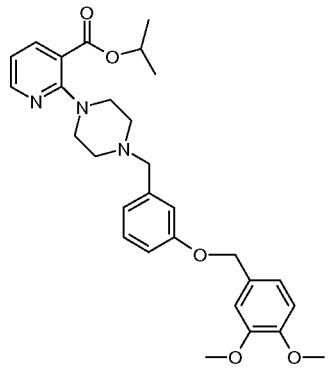
Example 392		 1-methylethyl 2-[[(3*S*)-1-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-3-pyrrolidinyl](methyl)amino]-3-pyridinecarboxylate	471.1	1.0
Example 393		 1-methylethyl 2-[{(3*S*)-1-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	512	1.1
Example 394		 1-methylethyl 2-[{(3*S*)-1-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl)methyl]-3-pyrrolidinyl}(methyl)amino]-3-pyridinecarboxylate	512	1.1

Table 19

Example 395

1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



In a vial, 1-methylethyl 2-{4-[(3-hydroxyphenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate (30 mg, 0.084 mmol) and [3,4-bis(methyloxy)phenyl] methanol (0.127 mmol) were dissovled in DCM (1.5 ml) with Ph_3P (44.3 mg, 0.169 mmol). The solution was stirred for 15 min with ice-bath. Then DEAD (26.7 µl, 0.169 mmol) was added. The resulted solution was stirred at room temperature for 12 hours. The polymer was filtered and the resulting solution was purified by preparotory HPLC (basic condition) to afford 4.32 mg of the title compound. LC-MS m/z 506.3 $(M+H)^+$, 0.96 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate, 1-methylethyl 2-{4-[(3-hydroxyphenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate (30 mg, 0.084 mmol) was reacted with the appropriate alcohol to yield the examples listed in Table XIX.

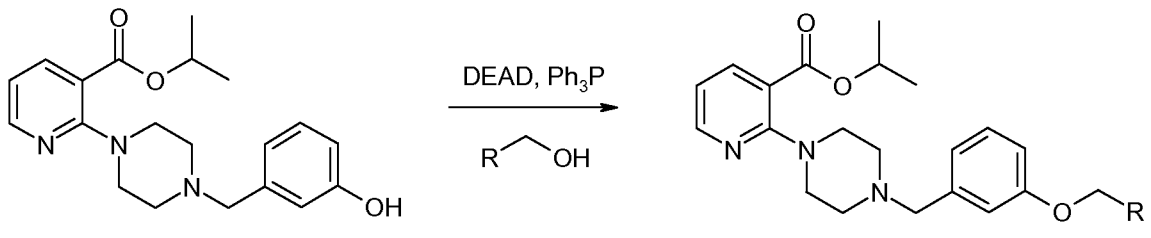
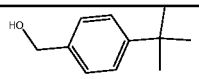
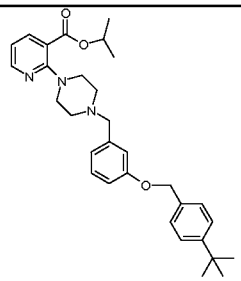
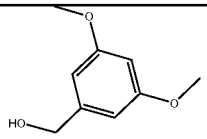
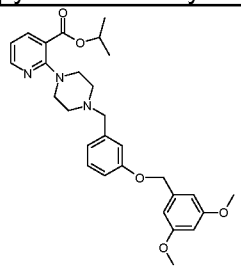
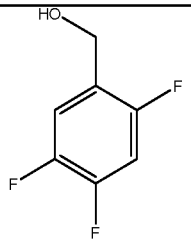
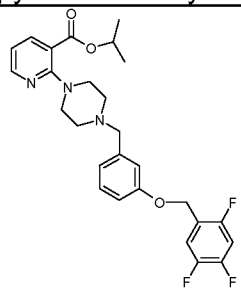
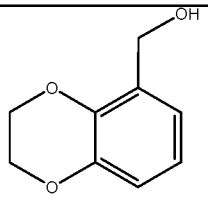
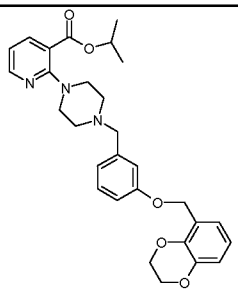
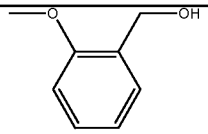
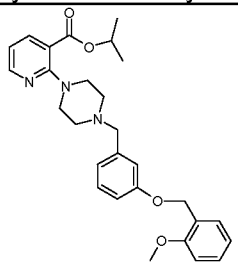
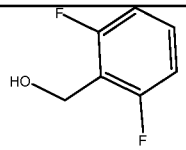
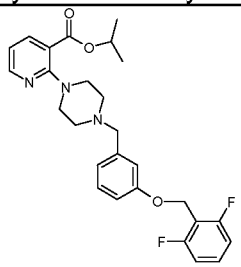
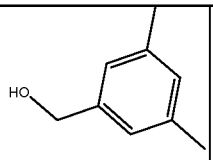
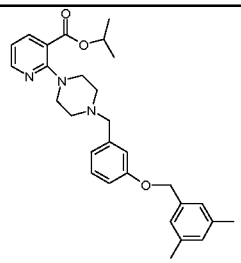
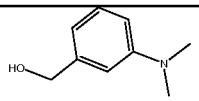
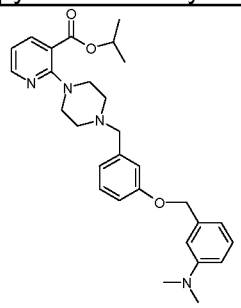
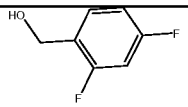
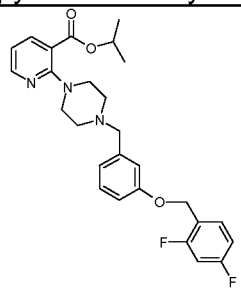
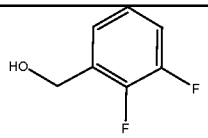
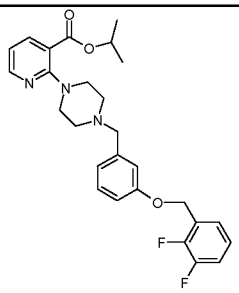
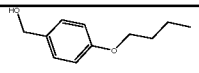
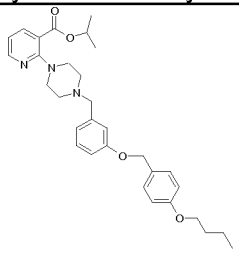
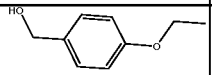
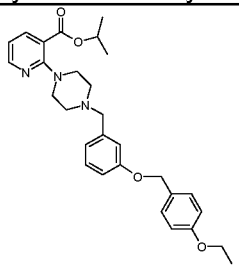


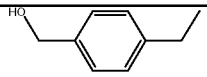
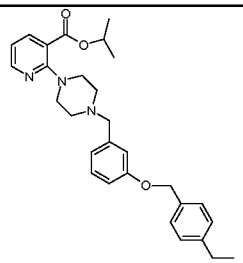
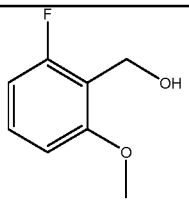
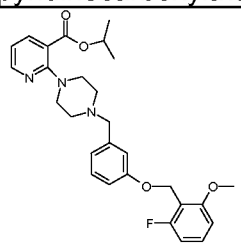
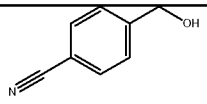
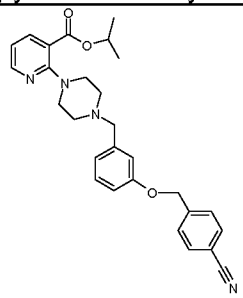
Table XIX.

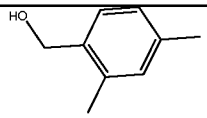
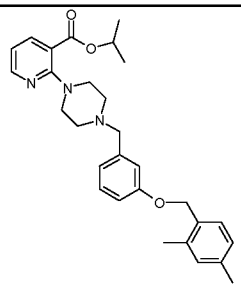
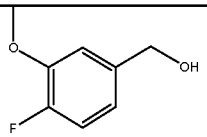
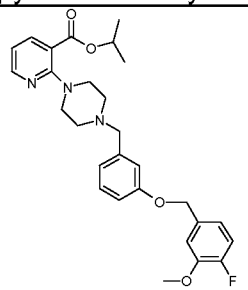
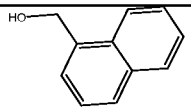
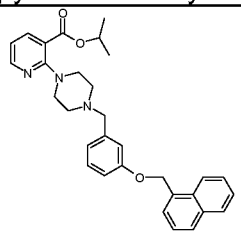
Example	Aldehyde (ketone)	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 396		 1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	502.3	1.2
Example 397		 1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.3	1.0
Example 398		 1-methylethyl 2-{4-[(3-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	500.4	1.1

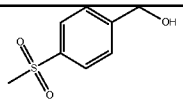
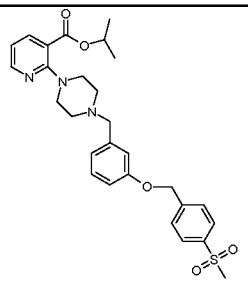
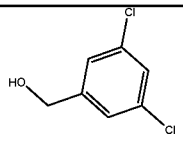
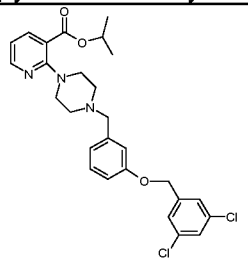
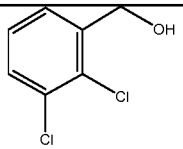
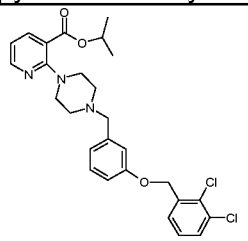
Example 399		 1-methylethyl 2-[4-({3-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	504.2	1.0
Example 400		 1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.1	1.0
Example 401		 1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	481.9	1.0

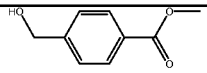
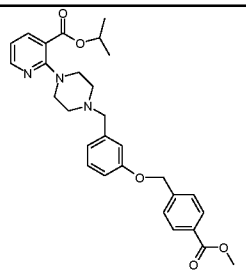
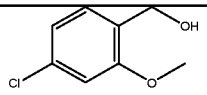
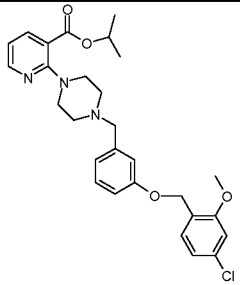
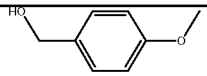
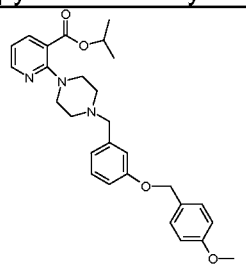
Example 402		 1-methylethyl 2-{4-[(3-{[(3,5-dimethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474.3	1.1
Example 403		 1-methylethyl 2-(4-{[3-({[3-(dimethylamino)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	489.3	0.9
Example 404		 1-methylethyl 2-{4-[(3-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482.0	1.0

Example 405		 1-methylethyl 2-{4-[(3-{[(2,3-difluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482.0	1.0
Example 406		 1-methylethyl 2-(4-{[3-({[4-(butyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	518.4	1.2
Example 407		 1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	490.2	1.1

Example 408		 1-methylethyl 2-{4-[(3-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474.4	1.1
Example 409		 1-methylethyl 2-(4-{[3-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	494.2	1.0
Example 410		 1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	471.3	1.0

Example 411		 1-methylethyl 2-{4-[(3-{[(2,4-dimethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474.3	1.1
Example 412		 1-methylethyl 2-(4-{[3-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	494.1	1.0
Example 413		 1-methylethyl 2-[4-({3-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	496.3	1.1

Example 414		 1-methylethyl 2-(4-{[3-({[4-(methylsulfonyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	524.3	0.9
Example 415		 1-methylethyl 2-{4-[(3-{[(3,5-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.2	1.1
Example 416		 1-methylethyl 2-{4-[(3-{[(2,3-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	514.2	1.1

Example 417		 1-methylethyl 2-[4-({3-[({4-[(methyloxy)carbonyl]phenyl}methyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	504.1	1.0
Example 418		 1-methylethyl 2-(4-{[3-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	510.1	1.1
Example 419		 1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.1	1.0

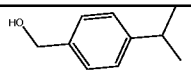
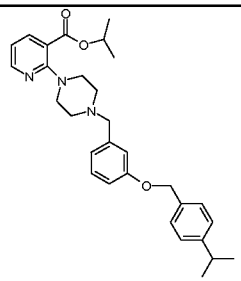
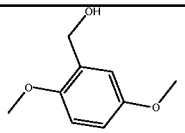
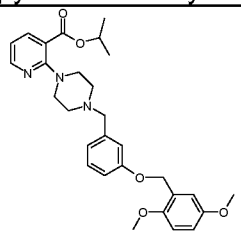
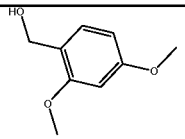
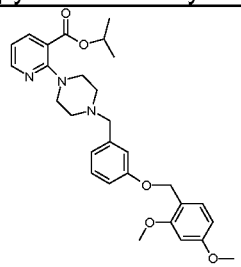
Example 420		 1-methylethyl 2-(4-{[3-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	488.2	1.2
Example 421		 1-methylethyl 2-(4-{[3-({[2,5-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.3	1.0
Example 422		 1-methylethyl 2-(4-{[3-({[2,4-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506.2	1.0

Table 20

Following the procedure as described above in the preparation of 1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate, 1-methylethyl 2-{4-[(4-hydroxyphenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate (30 mg, 0.084 mmol) was reacted with the appropriate alcohol to yield the

examples listed in Table XX.

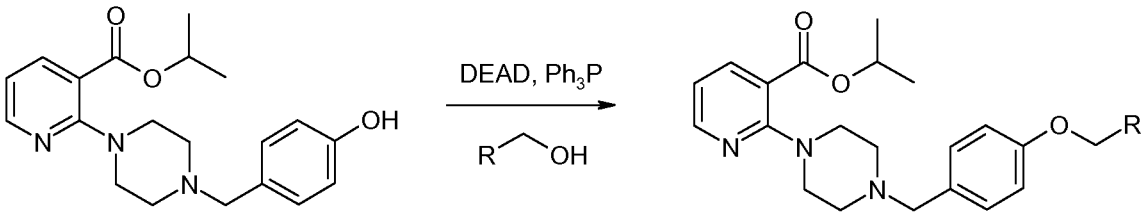
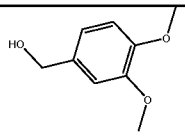
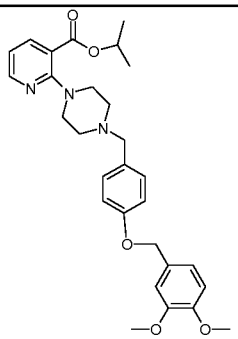
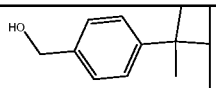
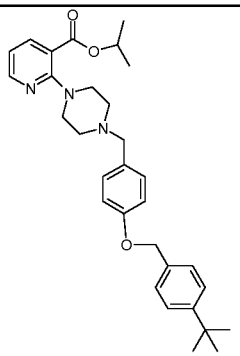
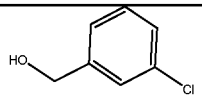
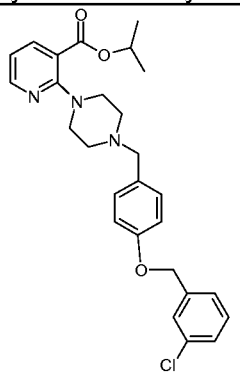
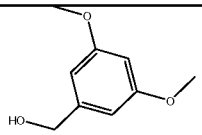
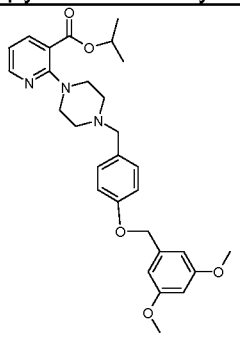
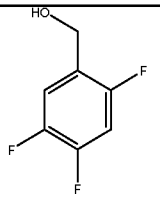
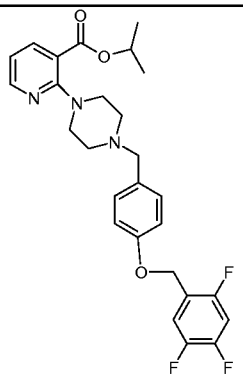
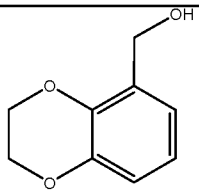
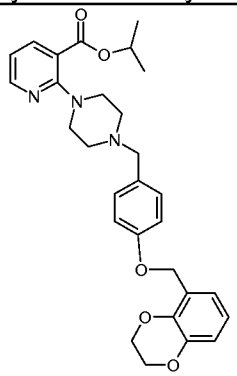
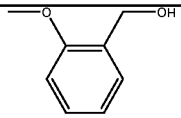
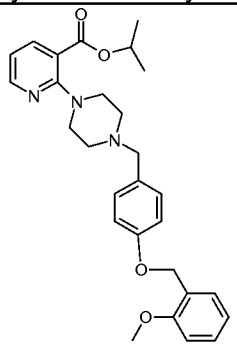
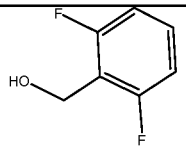
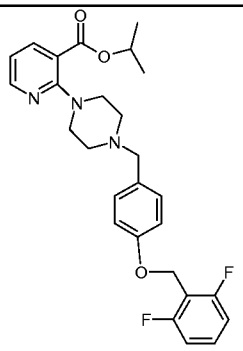
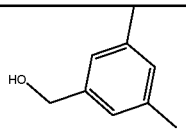
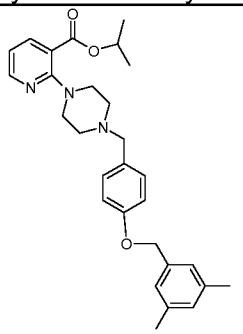
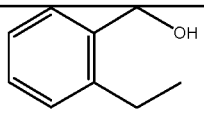
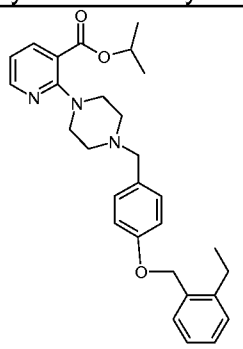


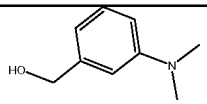
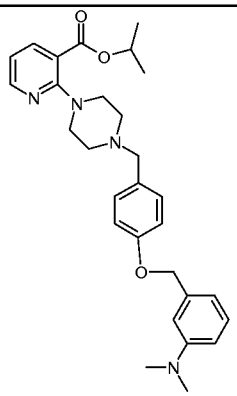
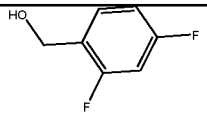
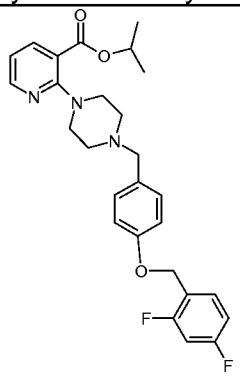
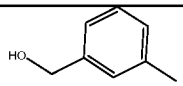
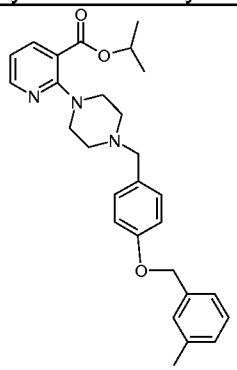
Table XX.

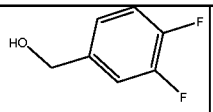
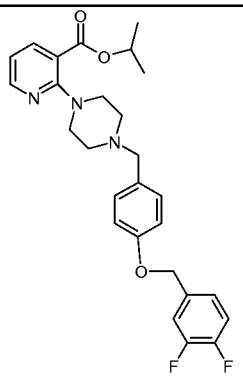
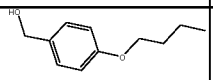
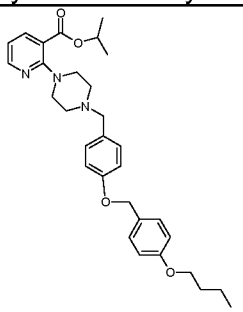
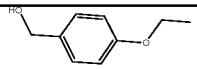
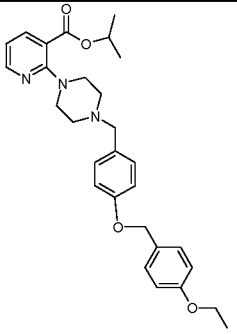
Example	Aldehyde (ketone)	Product Name	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 423		 1-methylethyl 2-(4-{[4-({[3,4-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506	1.2

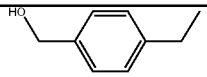
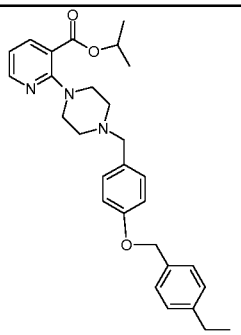
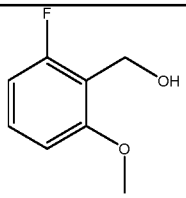
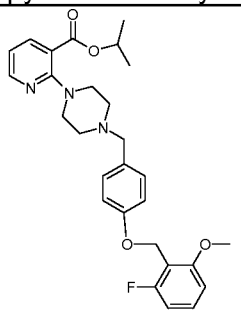
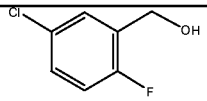
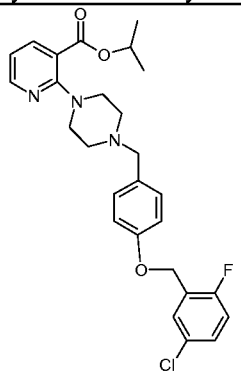
Example 424		 1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	502.1	1.3
Example 425		 1-methylethyl 2-{4-[(4-{[(3-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	480	1.0
Example 426		 1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506	1.1

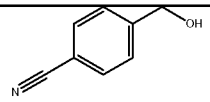
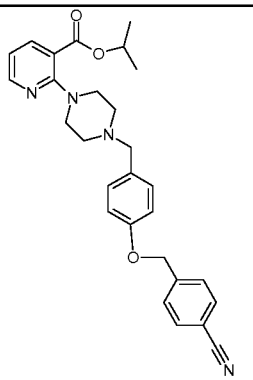
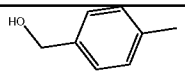
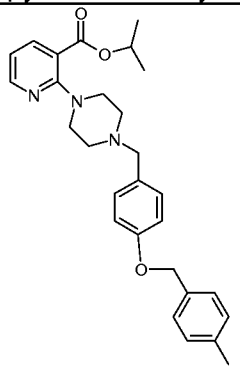
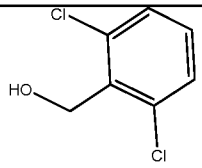
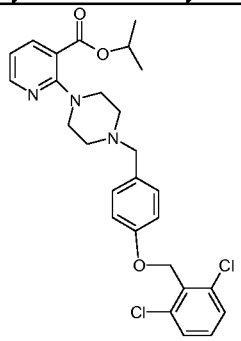
Example 427		 1-methylethyl 2-{4-[(4-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	500	1.1
Example 428		 1-methylethyl 2-[4-({4-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	504.06	1.0
Example 429		 1-methylethyl 2-(4-{[4-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476	1.1

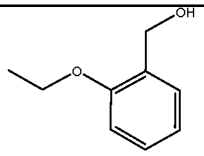
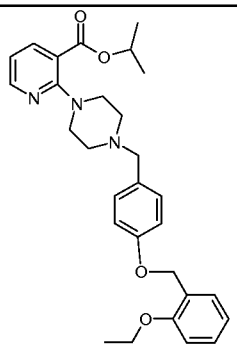
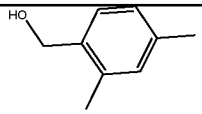
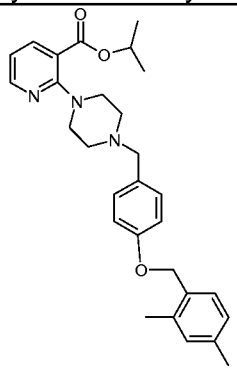
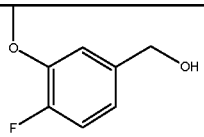
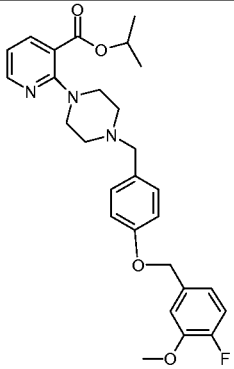
Example 430		 1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482	1.1
Example 431		 1-methylethyl 2-{4-[(4-{[(3,5-dimethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474	1.2
Example 432		 1-methylethyl 2-{4-[(4-{[(2-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474	1.1

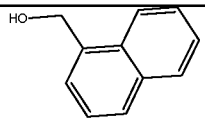
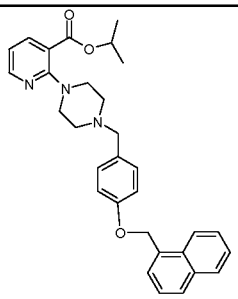
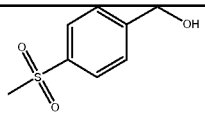
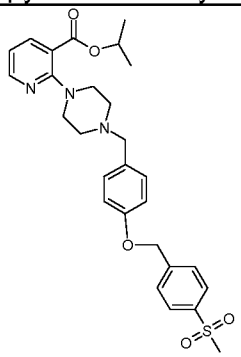
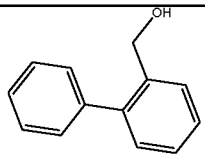
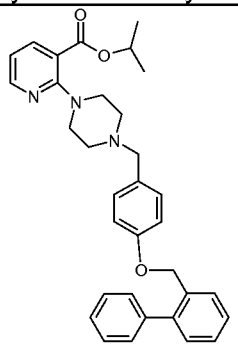
Example 433		 1-methylethyl 2-(4-{[4-({[3-(dimethylamino)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	1	0.9
Example 434		 1-methylethyl 2-{4-[(4-{[(2,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	489	1.1
Example 435		 1-methylethyl 2-{4-[(4-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.1	1.1

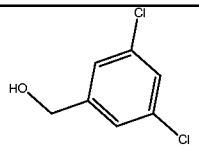
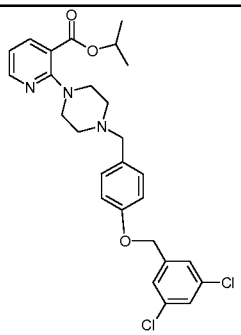
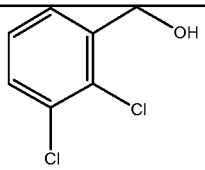
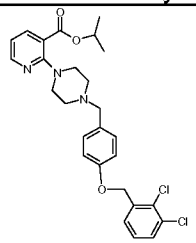
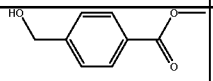
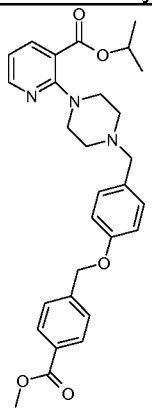
Example 436		 1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	482	1.1
Example 437		 1-methylethyl 2-(4-{[4-({[4-(butyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	518	1.2
Example 438		 1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	490	1.1

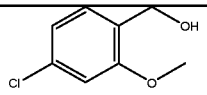
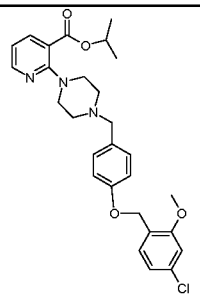
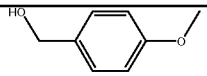
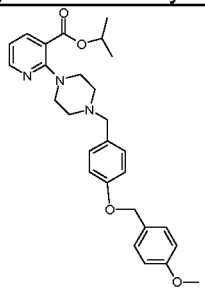
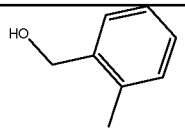
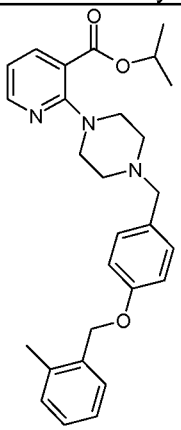
Example 439		 1-methylethyl 2-{4-[(4-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474	1.2
Example 440		 1-methylethyl 2-(4-{[4-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	494	1.1
Example 441		 1-methylethyl 2-{4-[(4-{[(5-chloro-2-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	498	1.1

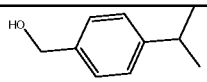
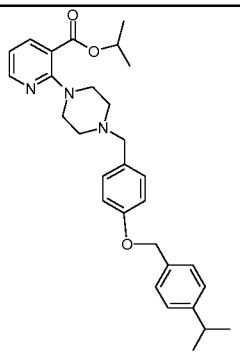
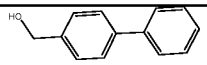
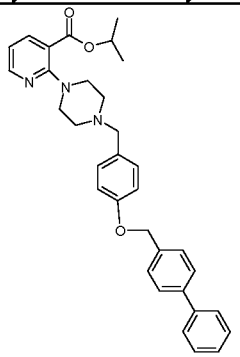
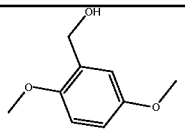
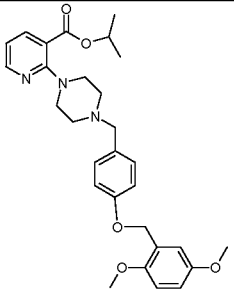
Example 442		 1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	471	1.0
Example 443		 1-methylethyl 2-{4-[(4-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.1	1.1
Example 444		 1-methylethyl 2-{4-[(4-{[(2,6-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	513.9	1.1

Example 445		 1-methylethyl 2-(4-{[4-({[2-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	490	1.1
Example 446		 1-methylethyl 2-{4-[(4-{[(2,4-dimethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	474	1.2
Example 447		 1-methylethyl 2-(4-{[4-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	494	1.1

Example 448		 1-methylethyl 2-[4-({4-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	496	1.1
Example 449		 1-methylethyl 2-(4-{[4-({[4-(methylsulfonyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	524.04	0.9
Example 450		 1-methylethyl 2-[4-({4-[(2-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	522	1.2

Example 451		 1-methylethyl 2-{4-[(4-{[(3,5-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	513.9	1.2
Example 452		 1-methylethyl 2-{4-[(4-{[(2,3-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	522	1.2
Example 453		 1-methylethyl 2-[4-({4-[({4-[(methyloxy)carbonyl]phenyl}methyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	504.06	1.0

Example 454		 1-methylethyl 2-(4-{[4-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	510	1.1
Example 455		 1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.06	1.0
Example 456		 1-methylethyl 2-{4-[(4-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	460.09	1.1

Example 457		 1-methylethyl 2-(4-{[4-({[4-(1-methylethyl)phenyl]methyl} oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate	488	1.2
Example 458		 1-methylethyl 2-[4-({4-[(4-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate	522	1.2
Example 459		 1-methylethyl 2-(4-{[4-({[2,5-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506	1.0

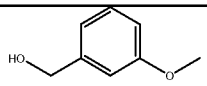
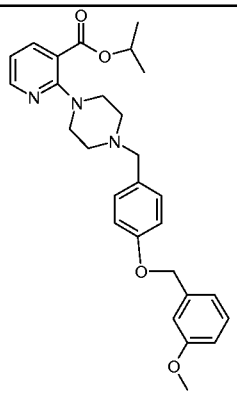
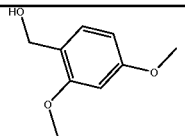
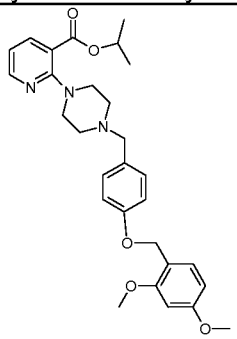
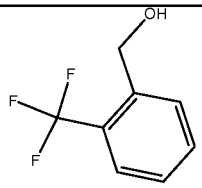
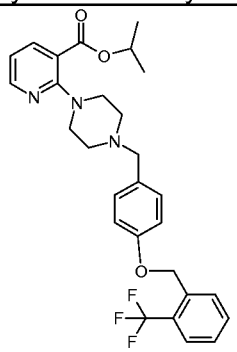
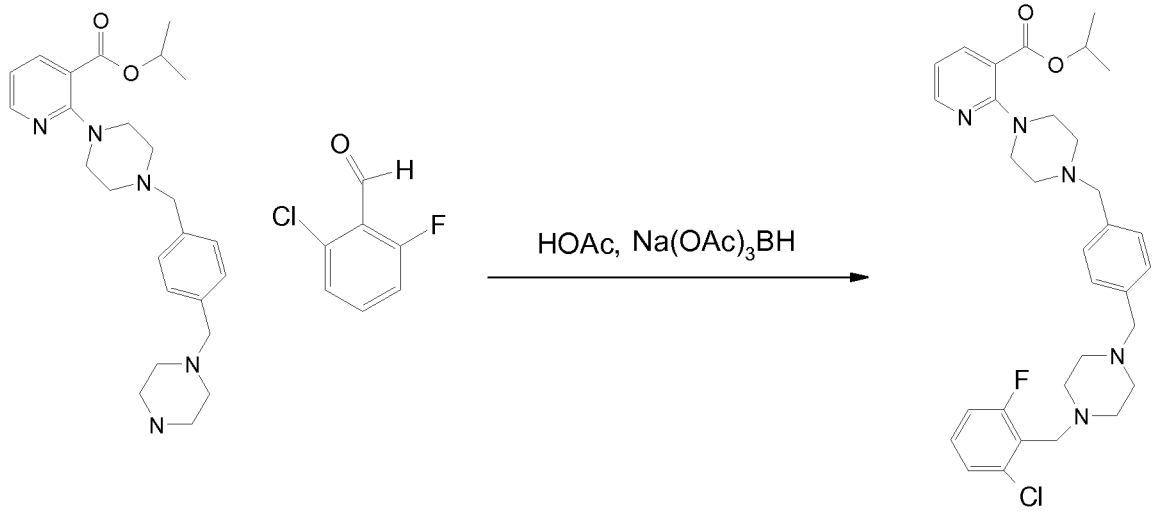
Example 460		 1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	476.06	1.0
Example 461		 1-methylethyl 2-(4-{[4-({[2,4-bis(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	506	1
Example 462		 1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate	514.04	1.1

Table 21

Example 463
1-methylethyl 2-(4-{[4-({4-[(2-chloro-6-fluorophenyl)methyl]-1-piperazinyl} methyl)phenyl]methyl} -1-piperazinyl)-3-pyridinecarboxylate



To a vial with 1-methylethyl 2-(4-{[4-(1-piperazinylmethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate (130 mg, 0.297 mmol) in Dichloromethane (DCM) (5 mL) with 2-chloro-6-fluorobenzaldehyde (56.5 mg, 0.357 mmol) was added HOAc (17.84 mg, 0.297 mmol) . The result solution was stirred for 2 hr. $Na(OAc)_3BH$ (127 mg, 0.594 mmol) was added into the solution and stirred for another 12hr. H_2O (10 mL) and DCM (10 mL) were added and the result solution was seperated by Phase Seperator. The water layer was washed with DCM (10 mL). Combined the organic layer and removed the solvent. The product was purified by prepared HPLC (Gilson, basic) to afford 88 mg (46.0%) of the desired product. LC/MS: m/z= 580.3 $[M+H]^+$, Ret. Time: 0.74 min.

Following the procedure as described above in the preparation of 1-methylethyl 2-(4-{[4-({4-[(2-chloro-6-fluorophenyl)methyl]-1-piperazinyl}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate, 1-methylethyl 2-(4-{[4-(1-piperazinylmethyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate (40.0 mg, 0.091 mmol) was reacted with the appropriate benzyl aldehyde (0.137 mmol) to yield the examples listed in Table 1.

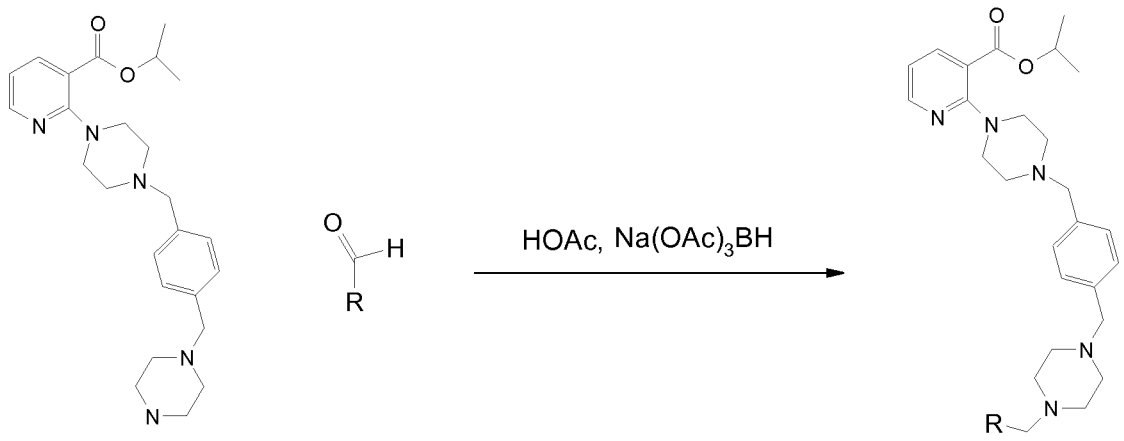
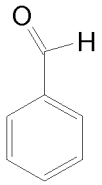
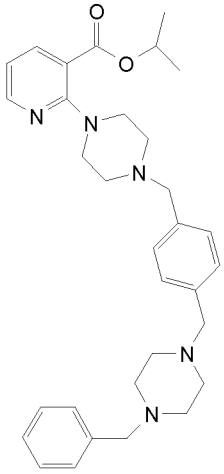
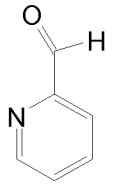
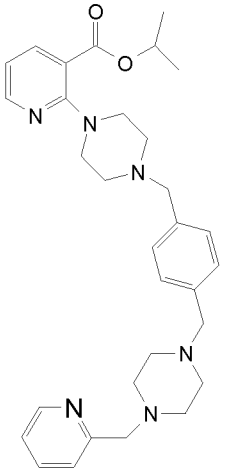
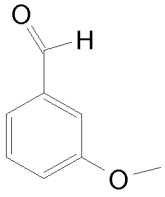
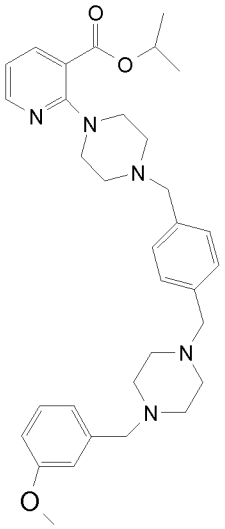
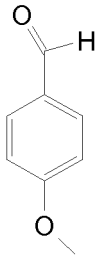
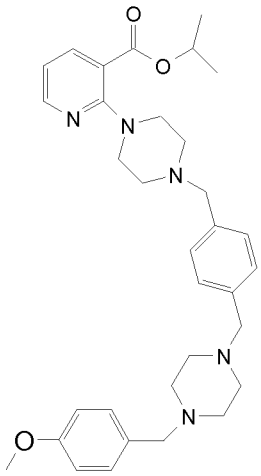


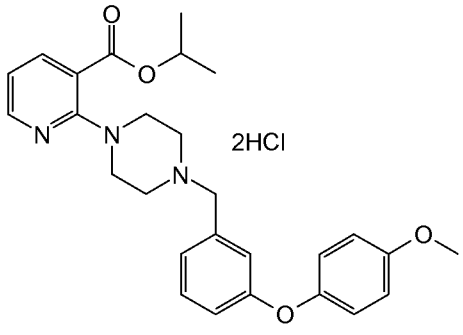
Table XXI

Example	Aldehyde	Product	LC-MS	
			m/z $(M+H)^+$	RT (min)
Example 464		 1-methylethyl 2-{4-[(4-{[4-(phenylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	525.8	0.65

Example 465		 1-methylethyl 2-{4-[(4-{[4-(2-pyridinylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate	529.5	0.55
Example 466		 1-methylethyl 2-[4-({4-[(4-{[3-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate	558.5	0.70

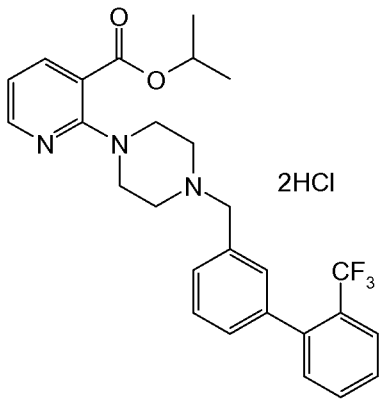
Example 467		 1-methylethyl 2-[4-({4-[(4-{[4-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate	558.5	0.67

Example 468
1-Methylethyl-2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride



Lcms rt 0.98 [M+H]=462.3

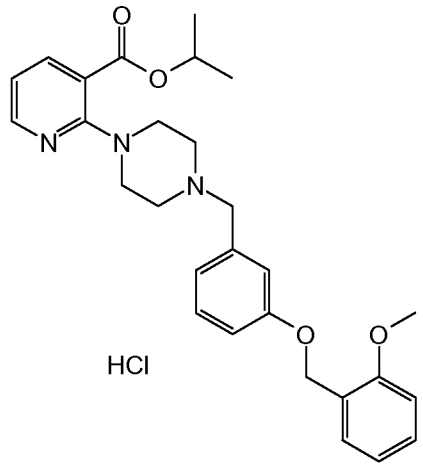
Example 469
1-Methylethyl-2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridine



carboxylate

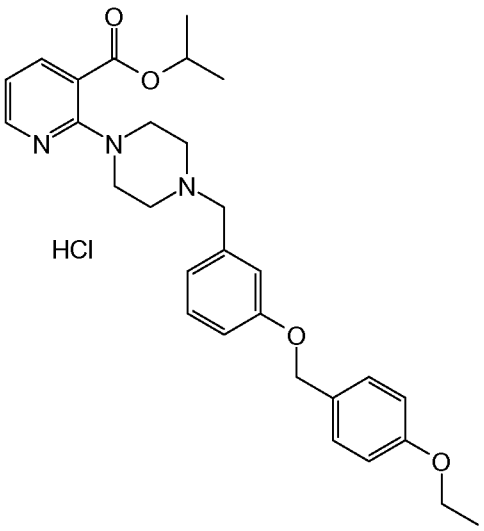
Lcms rt=1.04 [M+H] =484.3

Example 470
1-Methylethyl-2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride



Lcms rt 1.02 [M+H] = 476.4.

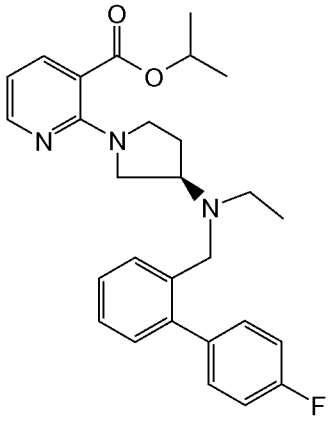
Example 471
1-Methylethyl-2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



Lcms rt 1.08 [M+H] =490.3.

Example 472

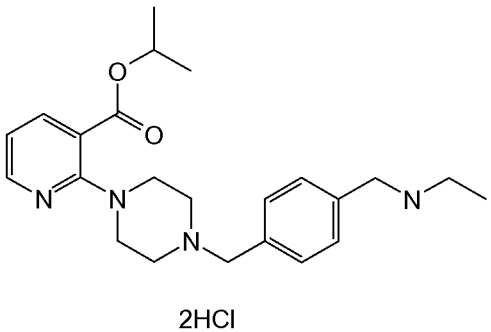
1-Methylethyl-2-((3R)-3-{ethyl[(4'-fluoro-2-biphenylyl)methyl]amino}-1-pyrrolidinyl)-3-pyridinecarboxylate



Lcms rt 0.95 [M+H] = 462.3.

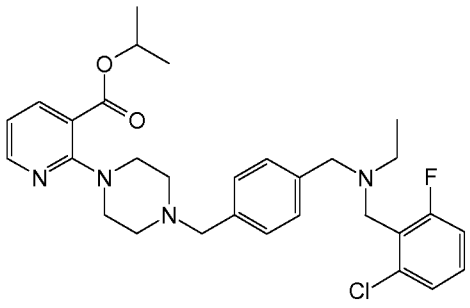
Example 473

1-Methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate dihydrochloride



Lcms rt 0.70 [M+H] =397.1

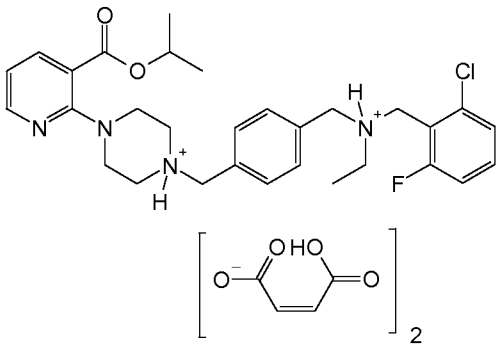
Example 474
1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)



methyl]-1-piperazinyl}-3-pyridinecarboxylate

1-Methylethyl 2-{4-[(4-formylphenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate (1.64 g, 4.46 mmol), [(2-chloro-6-fluorophenyl)methyl]ethylamine (1.005 g, 5.36 mmol), and acetic acid (0.383 ml, 6.69 mmol) were combined in 1,2-Dichloroethane (DCE) (17.47 ml) and stirred 5 min and then sodium triacetoxyborohydride (1.419 g, 6.69 mmol) was added. Stirred 16h and diluted with dichloromethane (200 mL) and washed with 1M aq NaOH (35 mL), water (2 x 35 mL) and satd aq NaCl (2 x 35 mL), dried (Na_2SO_4) and concentrated to afford 2.53g of a yellow oil.
Another batch of material was prepared with same reactants and reagents under similar reaction conditions as above, the product of which, was combined with above-identified 2.53 g of a yellow oil product. The combined crude material was purified.
Purification was by preparative hplc (The crude product was dissolved in DMSO (1 mL), filtered through a 0.45 µm acrodisc syringe filter, and purified on a Gilson HPLC (XBridge C18 30x150 mm 5µ preparatory column), eluting at 40 mL/min with a linear gradient running from 50% CH_3CN in H_2O (0.1% NH_4OH) to 100% CH_3CN over 20 min.) The desired fractions were concentrated under a stream of nitrogen at 50 °C to afford 1.66 (69%) of the free base as a yellow oil. LC-MS m/z = 539.1 (M+H), 0.64 minutes (retention time). ^{1}H NMR (400 MHz, DMSO-d6) d 8.25 (dd, *J* = 2.01, 4.77 Hz, 1H), 7.74 - 7.93 (m, 1H), 7.11 - 7.41 (m, 7H),6.81 (dd, *J* = 4.52, 7.53 Hz, 1H), 5.07 (spt, *J* = 6.23 Hz, 1H), 4.08 (q, *J* = 5.27 Hz, 2H), 3.71 (d, *J* = 1.25 Hz,2H), 3.55 (s, 2H), 3.46 (s, 2H), 3.05 - 3.24 (m, 4H), 2.30 - 2.45 (m, 4H), 1.29 (d, *J* = 6.27Hz, 6H), 0.87 - 1.13 (m, 3H).

Example 475
1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate

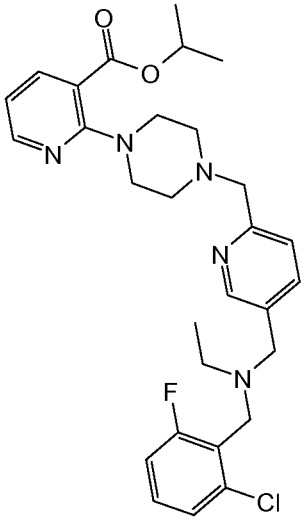


A solution of 0.1 M in ether 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate (2.2 mL, 0.22 mmol) and 1.0 M in methanol maleic acid (441 µl, 0.441 mmol) were combined and diluted to 11 mL with ether and allowed to stand in the sealed vial for 3 days. Filtered to afford 1-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl} phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium dimaleate (72 mg, 0.093 mmol, 42.2 % yield) as light tan crystals. Microscopy with polarized light indicates the particles are birefringent. Nmr integration indicates the di-maleate. LC-MS m/z = 539.4 (M+H), 0.75 minutes (retention time).

^{1}H NMR (400 MHz, DMSO-d_6) d 8.35 (dd, *J* = 1.76, 4.77 Hz, 1H), 7.99 - 8.08 (m, 1H), 7.26 - 7.49 (m, 6H), 7.17 - 7.25 (m, 1H), 6.91 - 7.02 (m, 1H), 6.15 (s, 4H), 5.05 - 5.16 (m, 1H), 2.87 - 4.41 (m, 26H), 1.30 (d, *J* = 6.27 Hz, 6H), 1.09 (d, *J* = 7.03 Hz, 3H).

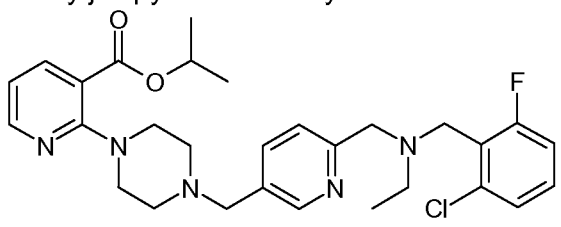
Example 476

1-methylethyl 2-{4-[(5-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-2-pyridinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



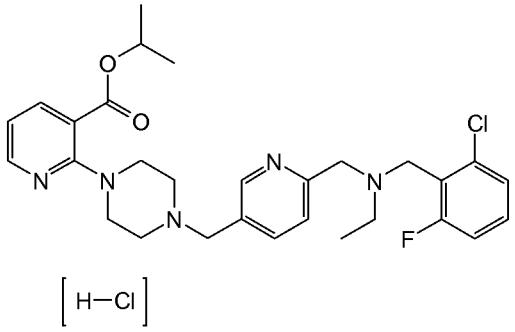
LC-MS *m/z* 540.8 $(M+H)^+$ 0.69 (ret time)

Example 477
1-methylethyl 2-{4-[(6-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-3-pyridinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS *m/z* 540.1 $(M+H)^+$ 0.67 (ret time)

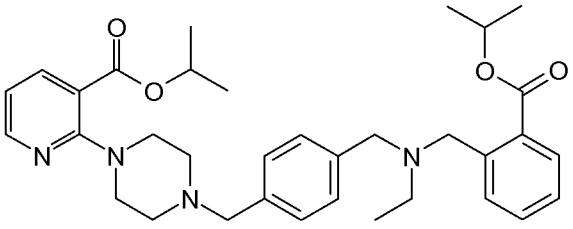
Example 478
1-methylethyl 2-{4-[(6-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-3-pyridinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate trihydrochloride



3

LC-MS *m/z* 540.3 $(M+H)^+$ 0.74 (ret time)

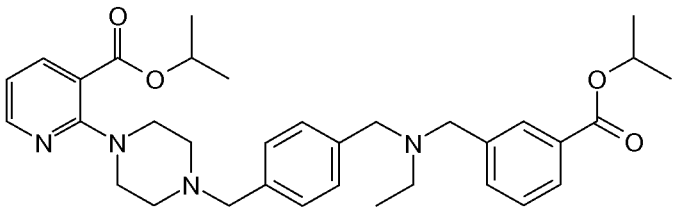
Example 479
1-methylethyl 2-(4-{[4-({ethyl[(2-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride



2 HCl

LC-MS *m/z* 573.6 $(M+H)^+$ 0.80 (ret time).

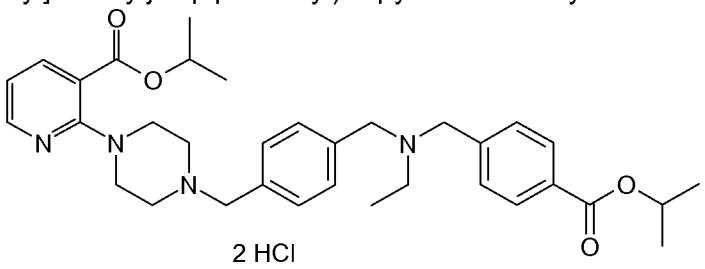
Example 480
1-methylethyl 2-(4-{[4-({ethyl[(3-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride



2 HCl

LC-MS *m/z* 573.6 $(M+H)^+$ 0.81 (ret time).

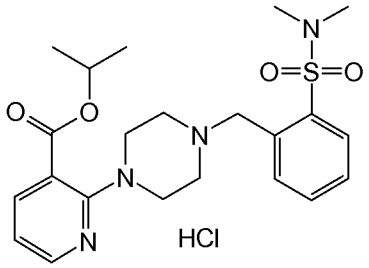
Example 481
1-methylethyl 2-(4-{[4-({ethyl[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



2 HCl

LC-MS *m/z* 573.6 $(M+H)^+$ 0.84 (ret time).

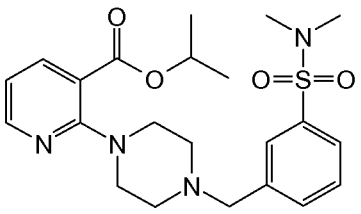
Example 482
1-methylethyl 2-[4-({2-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate hydrochloroide



HCl

LC-MS *m/z* 447.3 $(M+H)^+$ 0.85 (ret time).

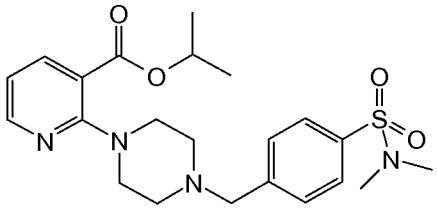
Example 483
1-Methylethyl 2-[4-({3-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate



HCl

LC-MS *m/z* 447.2 $(M+H)^+$ 0.76 (ret time).

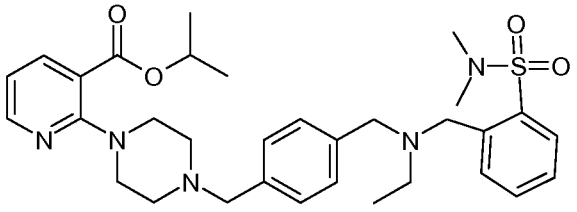
Example 484
1-methylethyl 2-[4-({4-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate



HCl

LC-MS *m/z* 447.3 $(M+H)^+$ 0.83 (ret time).

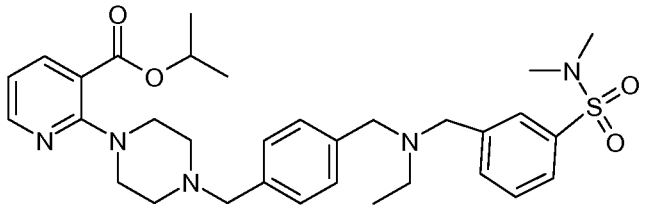
Example 485
1-methylethyl 2-{4-[(4-{[({2-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl) amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS m/z = 594 (M+H), 0.67 minutes (retention time).

Example 486

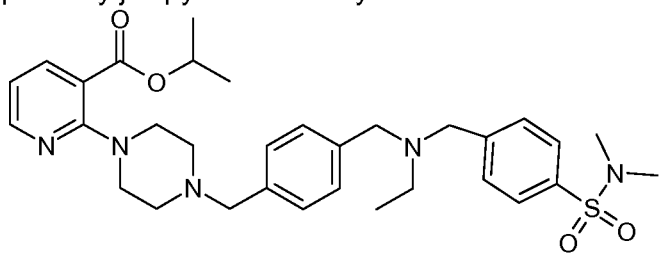
1-methylethyl 2-{4-[(4-{[({3-[(dimethylamino)sulfonyl]phenyl}methyl) (ethyl) amino] methyl} phenyl)methyl]-1-piperazinyl}-3-



pyridinecarboxylate

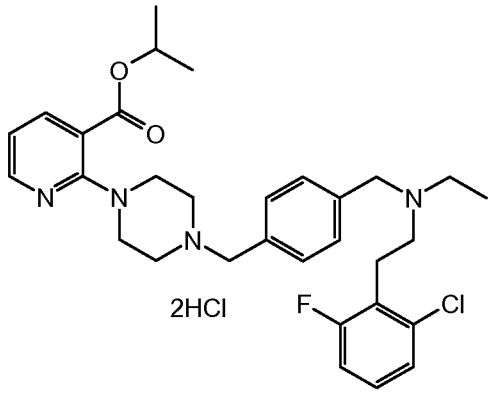
LC-MS m/z = 594 (M+H), 0.68 minutes (retention time).

Example 487
1-methylethyl 2-{4-[(4-{[({4 [(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



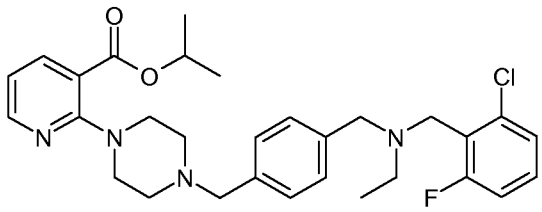
LC-MS m/z = 594 (M+H), 0.69 minutes (retention time).

Example 488
1 1-Methylethyl 2-{4-[(4-{[[2-(2-chloro-6-fluorophenyl)ethyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride



LC-MS *m/z* 553.0 $(M+H)^+$ 0.84 (ret time). 1H NMR (400 MHz, DMSO-d6) d 11.75 - 11.94 (m, 1H), 11.51 - 11.70 (m, 1H), 8.29 - 8.43 (m, 1H), 8.00 -8.12 (m, 1H), 7.81 (d, J = 16.06 Hz, 4H), 7.34 (s, 2H), 7.19 - 7.29 (m, 1H), 6.92 - 7.04 (m,1H), 5.00 - 5.17 (m,1H), 4.32 - 4.61 (m, 4H), 3.77 - 3.96 (m, 2H), 2.98 - 3.42 (m, 11H), 1.17 - 1.46 (m, 9H).

Example 489
1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-



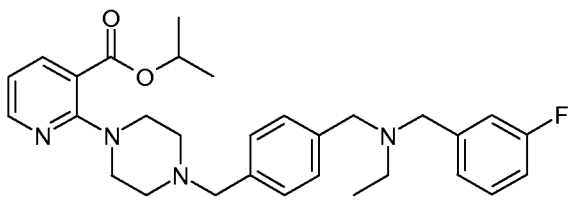
piperazinyl}-3-pyridinecarboxylate dihydrochloride

To a solution of 1-methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate (0.876 g, 2.209 mmol) in dry Methanol (15 mL) was added 2-chloro-6-fluorobenzaldehyde (0.876 g, 5.52 mmol) and acetic acid (0.025 mL, 0.442 mmol) and stirred at ambient temperature for 6 hours. Sodium cyanoborohydride (0.486 g, 7.73 mmol) was added and stirred at ambient termperature for 18 hours. Additional sodium cyanoborohydride (0.139 g, 2.209 mmol) was added and stirred for 4 hours. After which time, 2-chloro-6-fluorobenzaldehyde (0.438 g, 2.76 mmol) was added and the resulting mixture was stirred over night.

Additional 2-chloro-6-fluorobenzaldehyde (0.438 g, 2.76 mmol) and acetic acid (0.100 mL, 1.747 mmol) was added and stirred for 4 hours. Additional acetic acid (0.100 mL, 1.747 mmol) was added and stirred for approximately 4 hours. The solvent was then concentrated and the residue was dissolved in EtOAc, washed with water, and back extracted aqueous with EtOAc(2X). The combined extracts were washed with water (2X), saturated $NaHCO_3$, brine, dried $MgSO_4$, and concentrated. The resulting mixture was purified Gilson HPLC (Xbridge 30X 150 mm 5u preparatory column), eluting at 40 mL/min with a linear gradient running from 80 % to 100 % with acetonitrile and 0.1 % aqueous NH_4OH over 10 minutes to give the freebase of the title compound (739mg). The compound was dissolved in diethyl ether (15 mL), and 2M HCl in diethyl ether (1.326 mL, 2.65 mmol) (1.9eq) was added and stirred for 2 hours, concentrated and dried under vacuum pump. The solid was then dissolved in 2ml water and lyophilized to give the title compound (771 mg, 55 %) as white solid. LC-MS m/z = 540 (M+H), 0.69 minutes (retention time). ^{1}H NMR (400 MHz, DMSO-d6) d 11.97 (br. s., 1H), 10.38 (br. s., 1H), 8.35 (dd, *J* = 1.51, 4.52 Hz, 1H), 8.05(dd, *J* = 1.25, 7.53 Hz, 1H), 7.80 (s, 4H), 7.48 - 7.63 (m, 1H), 7.22 - 7.47 (m, 3H), 6.99 (dd, *J* = 4.77, 7.53 Hz,1H), 5.10 (dt, *J* = 6.24, 12.36 Hz, 1H), 4.59 (br. s., 1H), 4.42 (br. s., 4H), 4.27 (br. s., 1H), 3.75 - 3.96 (m, 2H),2.85 - 3.39 (m, 7H), 1.15 - 1.56 (m, 9H)

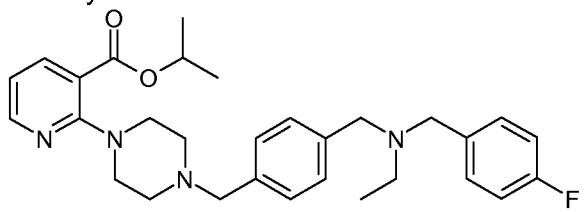
Example 490

1-methylethyl 2-(4-{[4-({ethyl[(3-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



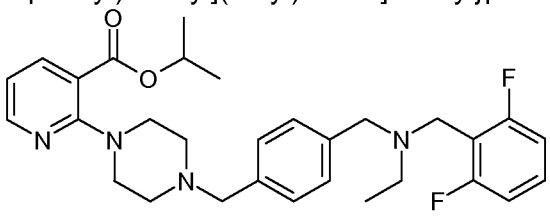
LC-MS m/z = 505 (M+H), 0.76 minutes (retention time).

Example 491
1-methylethyl 2-(4-{[4-({ethyl[(4-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



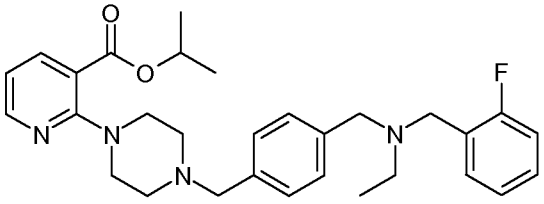
LC-MS m/z = 505 (M+H), 0.75 minutes (retention time).

Example 492
1-methylethyl 2-{4-[(4-{[[(2,6-difluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



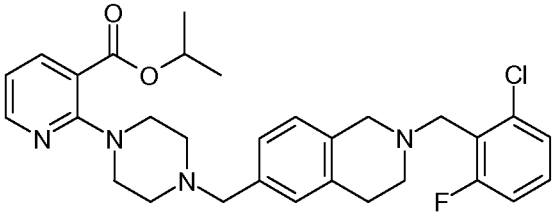
LC-MS m/z = 523 (M+H), 0.73 minutes (retention time).

Example 493
1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



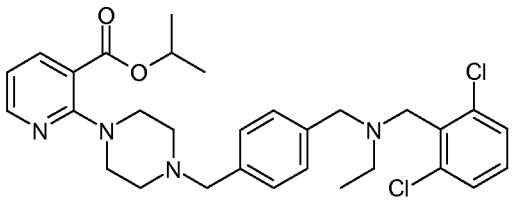
LC-MS m/z = 505 (M+H), 0.72 minutes (retention time).

Example 494
1-methylethyl 2-[4-({2-[(2-chloro-6-fluorophenyl)methyl]-1,2,3,4-tetrahydro-6-isoquinolinyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate



LC-MS m/z = 538 (M+H), 0.65 minutes (retention time).

Example 495
1-methylethyl 2-{4-[(4-{[[(2,6-dichlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-

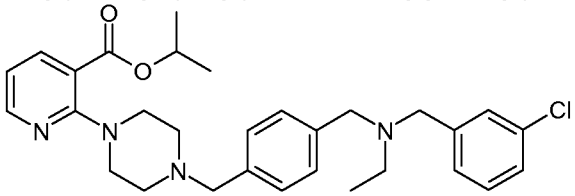


1-piperazinyl}-3-pyridinecarboxylate

LC-MS m/z = 556 (M+H), 0.70 minutes (retention time).

Example 496

1-methylethyl 2-{4-[(4-{[[(3-chlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-

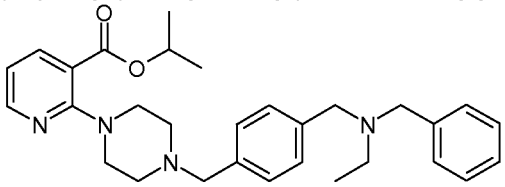


piperazinyl}-3-pyridinecarboxylate

LC-MS m/z = 522 (M+H), 0.72 minutes (retention time).

Example 497

1-methylethyl 2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-

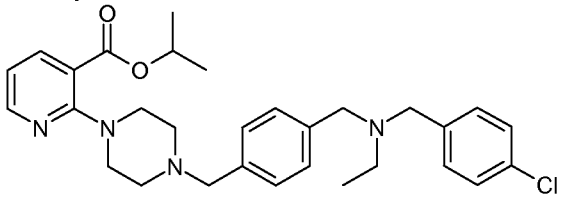


pyridinecarboxylate

LC-MS m/z = 487 (M+H), 0.66 minutes (retention time).

Example 498

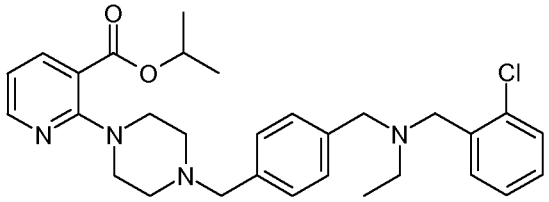
1-methylethyl 2-{4-[(4-{[[(4-chlorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS m/z = 522 (M+H), 0.73 minutes (retention time).

Example 499

1-methylethyl 2-{4-[(4-{[[(2-chlorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]

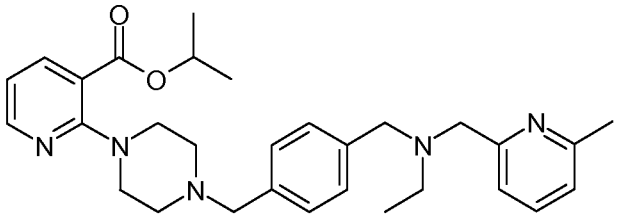


-1-piperazinyl}-3-pyridinecarboxylate

LC-MS m/z = 522 (M+H), 0.68 minutes (retention time).

Example 500

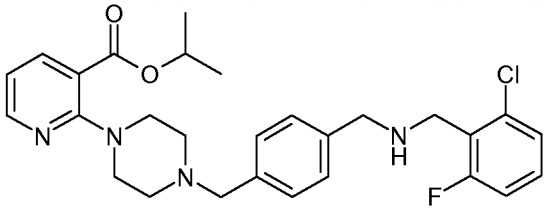
1-methylethyl 2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



LC-MS m/z = 501 (M+H), 0.78 minutes (retention time).

Example 501

1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-

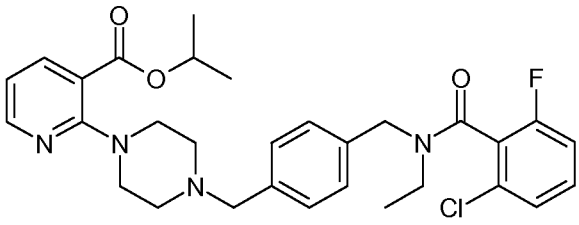


piperazinyl)-3-pyridinecarboxylate

LC-MS m/z = 511 (M+H), 0.76 minutes (retention time).

Example 502

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



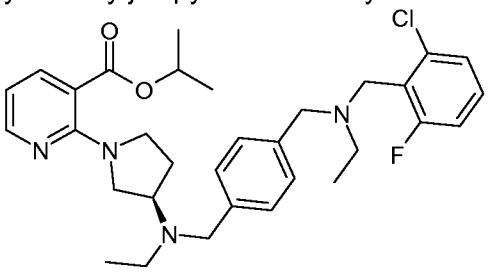
The freebase of the title compound which was an inseparable mixture of cis and trans amide isomers. Isomer A had LC-MS m/z = 553 (M+H), 0.87 minutes (retention time).

Isomer B LC-MS m/z = 553 (M+H), 0.90 minutes (retention time).

Example 503

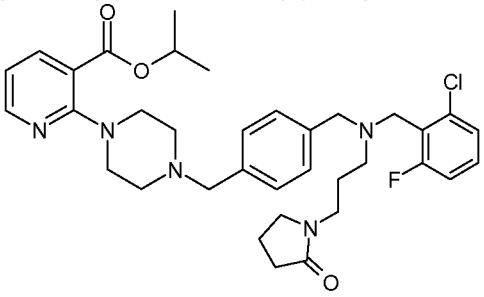
1-methylethyl 2-{(3R)-3-[[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl)

methyl] (ethyl) amino] -1-pyrrolidinyl}-3-pyridinecarboxylate



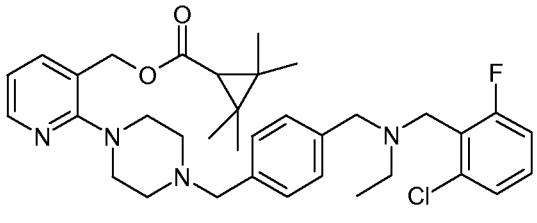
LC-MS m/z = 568 (M+H), 0.71 minutes (retention time).

Example 504
1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl][3-(2-oxo-1-pyrrolidinyl) propyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



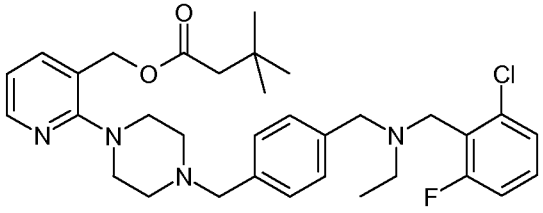
LC-MS m/z = 637 (M+H), 0.70 minutes (retention time).

Example 505
(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl 2,2,3,3-tetramethylcyclopropanecarboxylate



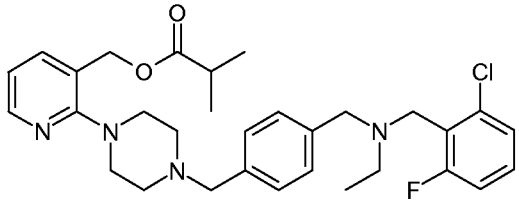
LC-MS m/z = 607 (M+H), 0.64 minutes (retention time).

Example 506
(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl 3,3-dimethylbutanoate



LC-MS m/z = 581 (M+H), 0.82 minutes (retention time).

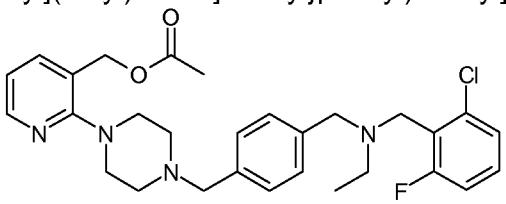
Example 507
(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl 2-



methylpropanoate

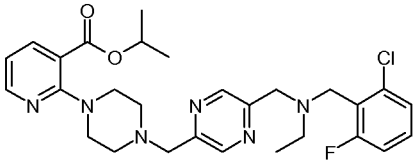
LC-MS m/z = 553 (M+H), 0.69 minutes (retention time).

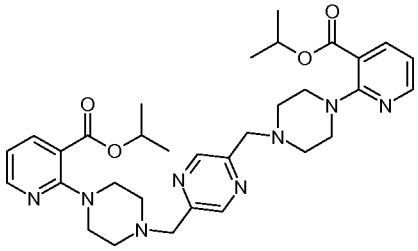
Example 508
(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl acetate



LC-MS m/z = 525 (M+H), 0.62 minutes (retention time).

Example 509
1-methylethyl 2-{4-[(5-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-2-pyrazinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate
Example 510: bis(1-methylethyl) 2,2'-[2,5-pyrazinediylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridine carboxylate)



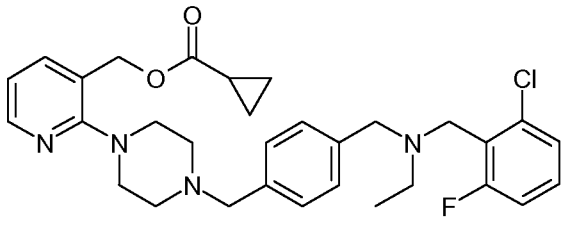


The resulting mixture was purified to give the freebase of:

- 1-methylethyl 2-{4-[(5-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-2-pyrazinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate. LC-MS m/z = 541 (M+H), 0.69 minutes (retention time).
- bis(1-methylethyl) 2,2'-[2,5-pyrazinediylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridinecarboxylate). LC-MS m/z = 602 (M+H), 0.74 minutes (retention time).

Example 511

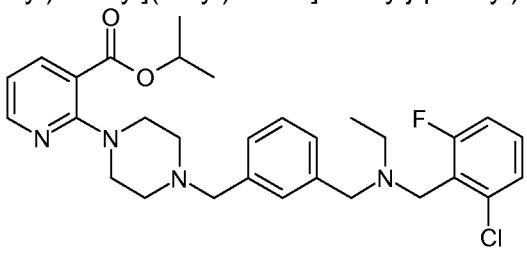
(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl cyclopropanecarboxylate



LC-MS m/z = 551 (M+H), 0.67 minutes (retention time).

Example 512

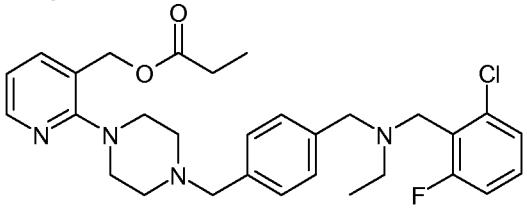
1-methylethyl 2-{4-[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS m/z = 539 (M+H), 0.67 minutes (retention time).

Example 513

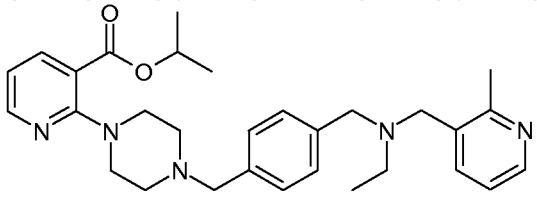
(2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinyl)methyl propanoate



LC-MS m/z = 539 (M+H), 0.66 minutes (retention time).

Example 514

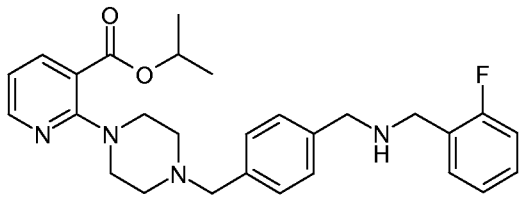
1-methylethyl 2-(4-{[4-({ethyl[(2-methyl-3-pyridinyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



LC-MS m/z = 502 (M+H), 0.61 minutes (retention time).

Example 515

1-methylethyl2-(4-{[4-({[(2-fluorophenyl)methyl]amino}methyl)phenyl]methyl}-1-

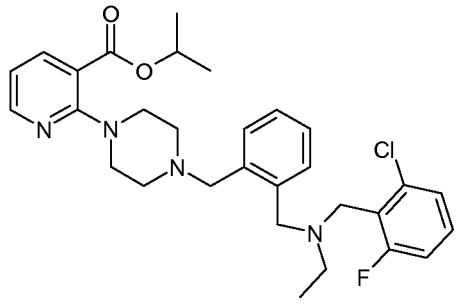


piperazinyl)-3-pyridinecarboxylate

LC-MS m/z = 477 (M+H), 0.64 minutes (retention time).

Example 516

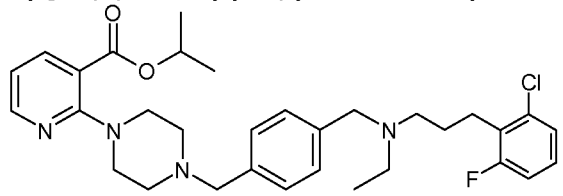
1-methylethyl 2-{4-[(2-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS m/z = 539 (M+H), 0.96 minutes (retention time).

Example 517

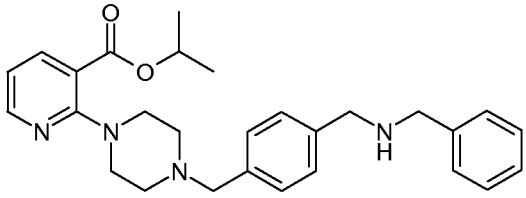
1-methylethyl2-{4-[(4-{[[3-(2-chloro-6-fluorophenyl)propyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS m/z = 567 (M+H), 0.82 minutes (retention time).

Example 518

1-methylethyl 2-{4-[(4-{[(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}

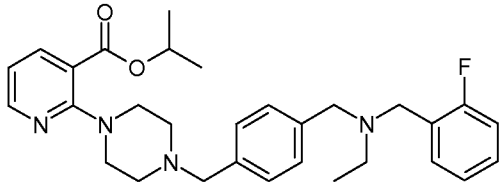


-3-pyridinecarboxylate

LC-MS m/z = 459 (M+H), 0.66 minutes (retention time).

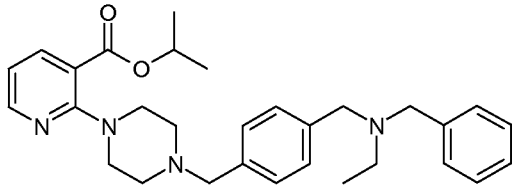
Example 519

1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}



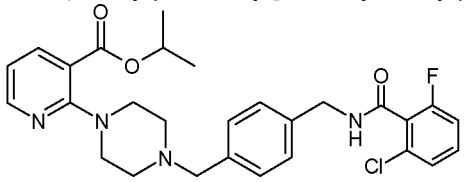
-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride LC-MS m/z = 505 (M+H), 0.68 minutes (retention time).

Example 520
1-methylethyl 2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-



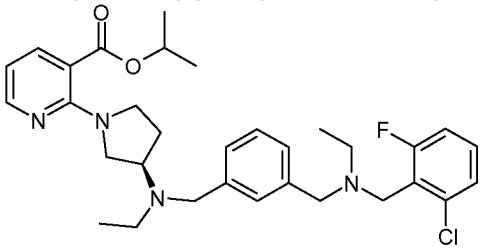
pyridinecarboxylate dihydrochloride
LC-MS m/z = 486 (M+H), 0.68 minutes (retention time).

Example 521
1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)carbonyl]amino}methyl)phenyl] methyl}-



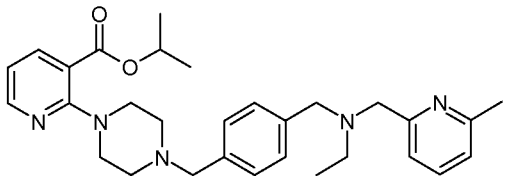
1-piperazinyl)-3-pyridinecarboxylate
LC-MS m/z = 526 (M+H), 0.86 minutes (retention time).

Example 522
1-methylethyl 2-{(3R)-3-[[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] methyl} phenyl)methyl](ethyl)amino]-1-pyrrolidinyl}-3-pyridinecarboxylate



LC-MS m/z = 568 (M+H), 0.68 minutes (retention time).

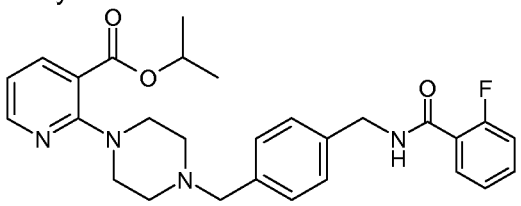
Example 523
1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate quaternary hydrochloride



LC-MS m/z = 502 (M+H), 0.69 minutes (retention time).

Example 524

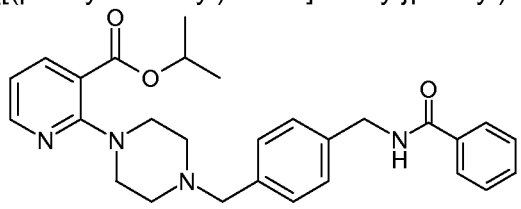
1-methylethyl 2-(4-{[4-({[(2-fluorophenyl)carbonyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate



LC-MS m/z = 491 (M+H), 0.80 minutes (retention time).

Example 525

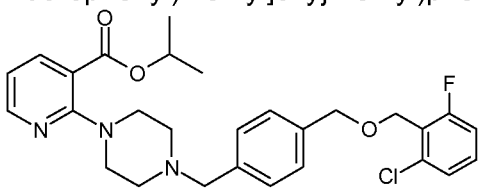
1-methylethyl 2-{4-[(4-{[(phenylcarbonyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate



LC-MS m/z = 473 (M+H), 0.80 minutes (retention time).

Example 526

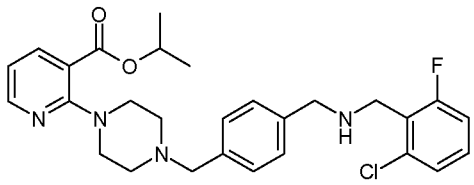
1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate



LC-MS m/z = 512 (M+H), 1.00 minutes (retention time).

Example 527

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-

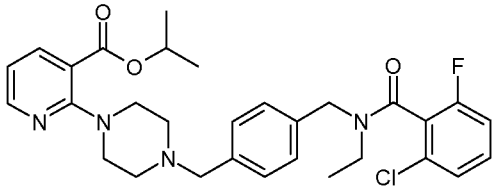


piperazinyl)-3-pyridinecarboxylate trihydrochloride

LC-MS m/z = 539 (M+H), 0.71 minutes (retention time).

Example 528

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride

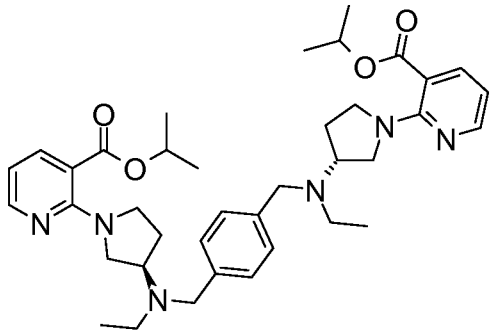


Title compound which was an inseparable mixture of cis and trans amide isomers. Isomer A had LC-MS m/z = 554 (M+H), 0.96 minutes (retention time). Isomer B had LC-MS m/z = 554 (M+H), 0.99 minutes (retention time).

DImer Compounds and Corresponding Precursors/Intermediates

Example 529

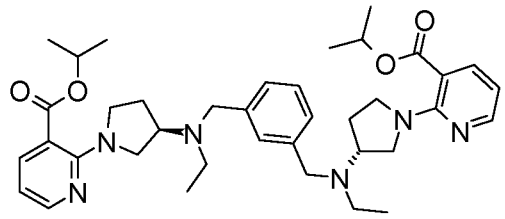
Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate)



LC-MS *m/z* 657.4 $(M+H)^+$, 2.33 min (ret time); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J*=6.8 Hz, 6 H), 1.33 - 1.37 (m, 12 H), 1.85 - 1.98 (m, 2 H), 2.05 - 2.12 (m, 2 H), 2.63 (q, *J*=7.2, 14.4 Hz, 2 H), 3.38 - 3.67 (m, 14 H), 5.16 - 5.19 (m, 2 H), 6.58 - 6.61 (m, 2 H), 7.27 (s, 4 H), 7.81 - 7.83 (m, 2 H), 8.23 - 8.25 (m, 2 H).

Example 530

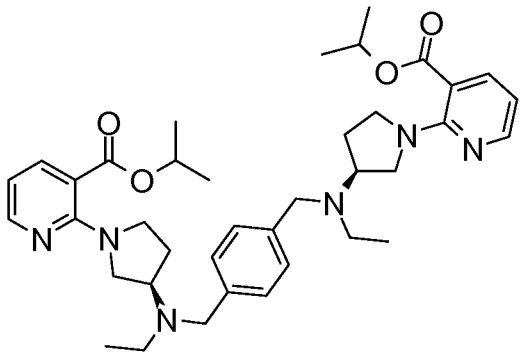
Bis(1-methylethyl) 2,2'-{benzene-1,3-diylbis[methanediyl(ethylimino) (3*R*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate)



LC-MS *m/z* 657.5 $(M+H)^+$, 2.31 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, *J*=6.8 Hz, 6 H) 1.33 - 1.36 (m, 12 H) 1.88 - 1.95 (m, 2 H) 2.05 - 2.10 (m, 2 H) 2.63 (q, *J* = 7.2, 14.4 Hz, 2 H) 3.37 - 3.69 (m, 14 H) 5.16 - 5.19 (m, 2 H) 6.58 - 6.61 (m, 2 H), 7.23 - 7.30 (m, 4 H) 7.81 - 7.83 (m, 2 H) 8.23 - 8.25 (m, 2 H).

Example 531

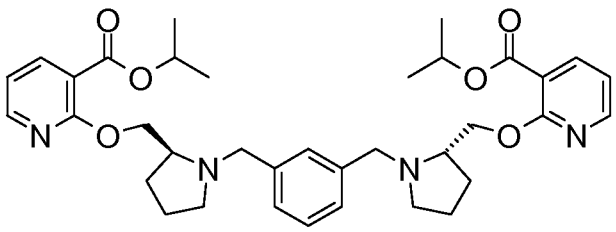
1-Methylethyl 2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*S*)-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate



LC-MS *m/z* 657.4 $(M+H)^+$, 2.34 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, *J*=6.8 Hz, 6 H) 1.33 - 1.37 (m, 12 H) 1.85 - 1.98 (m, 2 H) 2.05 - 2.12 (m, 2 H) 2.63 (q, *J*=7.2, 14.4 Hz, 2 H) 3.38 - 3.67 (m, 14 H) 5.16 - 5.19 (m, 2 H), 6.58 - 6.61 (m, 2 H) 7.27 (s, 4 H) 7.81 - 7.83 (m, 2 H) 8.23 - 8.25 (m, 2 H).

Example 532

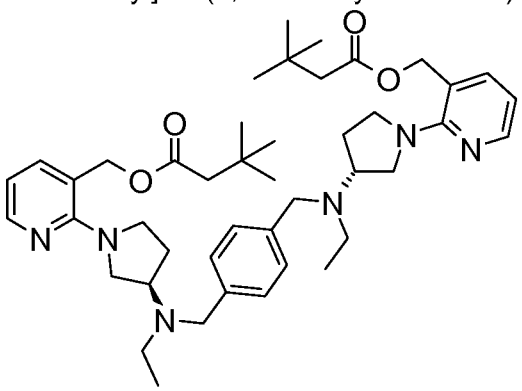
Bis(1-methylethyl) 2,2'-{benzene-1,3-diylbis[methanediyl(2*S*)-1,2-pyrrolidinediyl methanediyloxy]}di(3-pyridinecarboxylate)



LC-MS *m/z* 631 $(M+H)^+$, 1.09 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 2 H), 8.10-8.07 (m, 2 H), 7.24-7.18 (m, 4 H), 6.91-6.88 (m, 2 H), 5.26-5.16 (m, 2 H), 4.53-4.49 (m, 2 H), 4.30-4.26 (m, 2 H), 4.23-4.19 (d, *J* = 12.8 Hz, 2 H), 3.43-3.40 (d, *J* = 12.8 Hz, 2 H), 3.05-2.98 (m, 2 H), 2.93-2.89 (m, 2 H), 2.27-2.21 (m, 2 H), 2.08-1.98 (m, 2 H), 1.84-1.66 (m, 6 H), 1.33-1.31 (dd, *J* = 1.2 Hz, 1.6, 12 H).

Example 533

Benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) hydrochloride

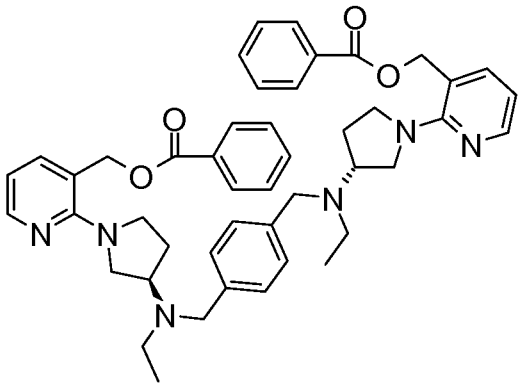


A mixture of (R)-(2-(3-(ethylamino)pyrrolidin-1-yl)pyridin-3-yl)methyl 3,3-dimethylbutanoate (426 mg, 1.3 mmol) and 1,4-bis(bromomethyl)benzene (176 mg, 0.7 mmol) in acetone (10 mL) was heated to 60 °C. K_2CO_3 (184 mg, 1.3 mmol) was added. It was heated at reflux for 2 h. The reaction mixture was filtered. The filtrate was concentrated to obtain the crude product.

Another batch of material was prepared with same reactants and reagents under similar reaction conditions as above, the product of which, was combined with crude product as identified above. The combined crude material was purified by silica gel column eluting with a mixture of 10 % ethyl acetate, 4 % of Et_3N in petroleum ether to give the free base of the title compound (300 mg, 36 %) as yellow oil. It was dissolved in 5 mL of ether; the solution of HCl in ether (2 mL, 1 mol/L) was added. It was stirred at room temperature for 10 min. Solvent was removed to give the title compound (310 mg, 99 % combined yield of two (2) batches of product) as white solid. LC-MS *m/z* 741.4 $(M+H)^+$, 1.28 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 6 H) 3.01-3.64 (m, 14 H) 5.07-5.15 (m, 4 H) 6.76-6.79 (m, 2 H) 7.57-7.73 (m, 6 H) 8.15-8.16 (m, 2 H) 12.84 (s, 1 H)

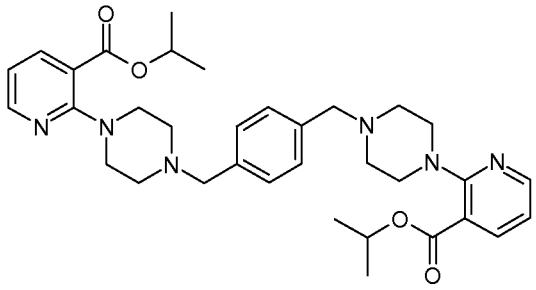
Example 534

Benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl -2,3-pyridinediylmethanediyl] dibenzoate hydrochloride



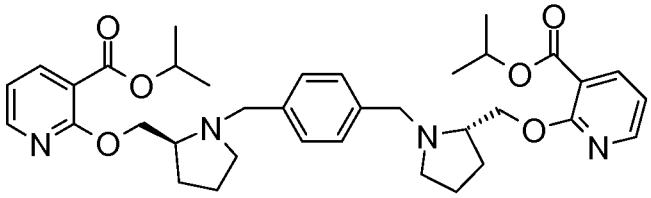
LC-MS *m/z* 753.3 $(M+H)^+$, 1.34 min (ret time); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19-1.25 (m, 6 H) 2.59-3.18 (m, 8 H) 4.15-4.49 (m, 14 H) 5.47 (s, 4 H) 6.83 (s, 2 H) 7.44-8.23 (m, 18 H) 12.73 (s, 1 H)

Example 535
Bis(1-methylethyl) 2,2'-[benzene-1,4-diylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridinecarboxylate)



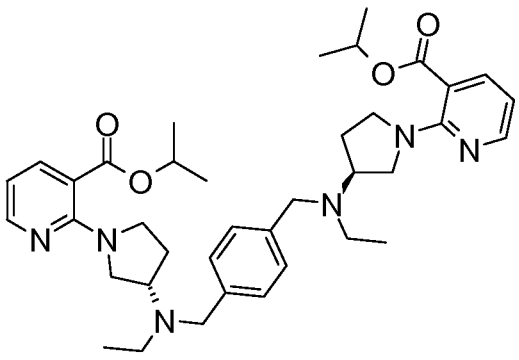
LC-MS *m/z* 601.4 $(M+H)^+$, 0.83 min (ret time).

Example 536
Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(2*S*)-1,2-pyrrolidinediyl methanediyloxy]}di(3-pyridinecarboxylate)



^1H NMR (400 MHz, $CDCl_3$) δ 8.26-8.25 (m, 2 H), 8.10-8.09 (m, 2 H), 7.28-7.23 (m, 4 H), 6.94-6.89 (m, 2 H), 5.26-5.18 (m, 2 H), 4.53-4.49 (m, 2 H), 4.31-4.27 (m, 2 H), 4.24-4.21 (m, *J* = 12.8 Hz, 2 H), 3.42-3.39 (d, *J* = 12.8 Hz, 2 H), 3.03-3.02 (m, 2 H), 2.91 (m, 2 H), 2.24-2.21 (m, 2 H), 2.04-2.03 (m, 2 H), 1.79-1.71 (m, 6 H), 1.33-1.32 (d, *J* = 4.8 Hz, 12 H).

Example 537
Bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*S*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate)



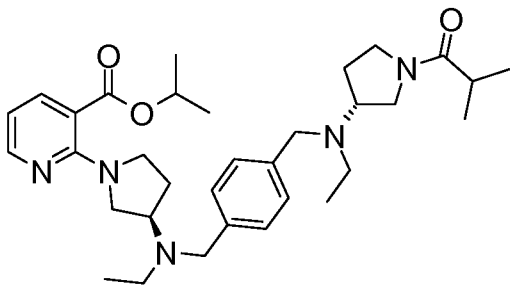
1,4-bis(bromomethyl)benzene (2.53 g, 9.58 mmol) was added to a suspension of 1-methylethyl 2-[(3S)-3-(ethylamino)-1-pyrrolidinyl]-3-pyridinecarboxylate (7.8 g, 19.93 mmol) and potassium carbonate (8.29 g, 60.0 mmol) in acetonitrile (75 mL) at ambient temperature. The resulting suspension was allowed to stir. After 17 hrs an additional 0.3 g of amine starting material was added. After ~22 hrs the reaction suspension was filtered, washed with ethyl acetate and the filtrate concentrated to give 8.63 g of tan gum. This was taken into ethyl acetate and extracted with water (2x). The organic phase was then extracted with HCl solution (pH 1-2) (4x). The organic phase was extracted with brine (1x), dried over magnesium sulfate, filtered, and concentrated to give 5.95 g of a clear, light brown liquid. This was passed through a plug of silica gel using a 2L fritted funnel filled ~1/2 with silica gel. A solvent gradient consisting of 5%, 10% , 20%, 30%, 40%, 50%, and 100% ethyl acetate/hexanes was used to elute the product and gave 4.0 g of clear, colorless oil (isolate A).

The combined acidic aqueous phase was basified with 6N NaOH and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated to give 0.73 g of a clear, light tan oil. This was passed through a plug of silica gel using a 1L fritted funnel filled ~1/2 with silica gel. 100% DCM was used as eluent followed by 100% ethyl acetate to give 0.71 g of a clear, colorless oil (isolate B).

The combined isolates A and B were subjected to purification via Gilson HPLC purification method under the following conditions: Column: XBridge 30x150 mm 5u, Mobile phase: Acetonitrile: Water + 0.1% NH_4OH, Flow rate: 40 ml/min, Gradient: 80%-100%B for 10 min. to give 3.672 g of clear, oil. This was taken into 10 mL of methanol afterwhich time 0.711 g of L-tartaric acid was added and the suspension stirred to complete dissolution. The resulting solution was concentrated to a gel. The gel was re-dissolved in methanol and ether added. The solution was concentrated and pumped to a white solid. This was taken into ~80 mL of water and lyophilized to

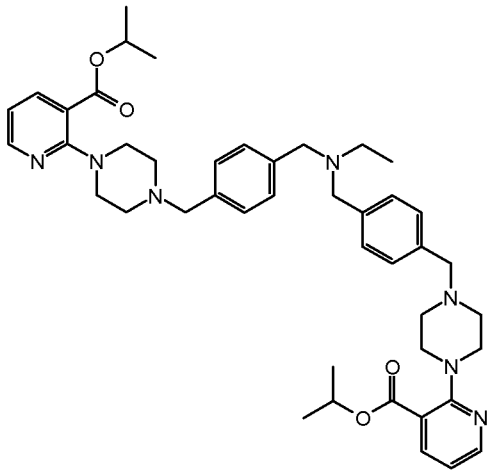
give 3.14 g of a white solid. LC/MS m/z - 657.8 (M+H); ^{1}H NMR (400 MHz, $MeOD_4$) δ 1.18 (t, *J*=8 Hz, 6 H), 1.38 (t, J=8 Hz,12 H), 2.01-2.12 (m, 2 H), 2.3-2.4 (m, 2 H), 2.87 (q, *J*=8 Hz, 4 H), 3.50 - 3.68 (m, 10 H), 3.90-4.05 (m, 2 H), 4.45 (s, 2H), 5.15-5.21 (m, 2H), 6.72 - 6.65 (m, 2 H), 7.45 (s, 4 H), 7.90 - 7.92 (m, 2 H), 8.21 - 8.22 (m, 2 H).

Example 42
1-Methylethyl 2-[(3*R*)-3-(ethyl{[4-({ethyl[(3*R*)-1-(2-methylpropanoyl)-3-pyrrolidinyl] amino} methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate (recited supra, reiterated here)



To a solution of 1-methylethyl 2-[(3*R*)-3-(ethylamino)-1-pyrrolidinyl]-3-pyridinecarboxylate (85 mg, 0.385 mmol) and potassium carbonate (160 mg, 1.155mmol) in acetone (10 mL) at room temperature was added (3*R*)-*N*-{[4-(bromomethyl)phenyl]methyl}-*N*-ethyl-1- (2-methylpropanoyl)-3-pyrrolidinamine (230 mg, 0.385 mmol) in one portion. The resulting mixture was heated to reflux for 24 h. It was cooled to room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give crude product. It was purified by Pre-TLC eluting with EtOAc to give the title compound (26 mg, 11 %) as pale yellow solid. LC-MS m/z 564.4 $(M+H)^+$, 2.21min (ret time); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.26-8.24 (m, 1H), 7.84-7.82 (m,1H), 7.83-7.28(m, 4H), 6.65-6.7- (m, 1H), 5.20-5.17 (m, 1H), 3.70-3.28(m,14H), 2.66-2.59 (m,5H), 2.10-1.90(m, 4H), 1.38-1.34 (m,6H), 1.14-0.99 (m, 12H).

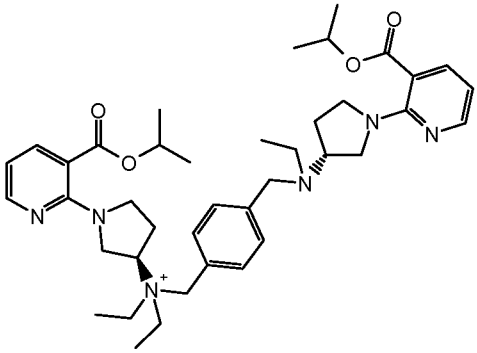
Example 538
Bis(1-methylethyl)2,2'-[(ethylimino)bis(methanediylbenzene-4,1-diylmethanediyl-4,1-piperazinediyl)]di(3-pyridinecarboxylate)



LC-MS *m/z* 748.1 $(M+H)^+$ 0.80 (ret time).

Example 539

(3*R*)-*N*,*N*-diethyl-*N*-{[4-({ethyl[(3*R*)-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}-1-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-

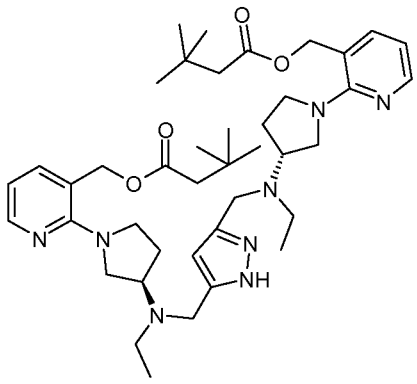


3-pyrrolidinaminium

LC-MS *m/z* 685.8 $(M)^+$ 0.80 (ret time).

Example 540

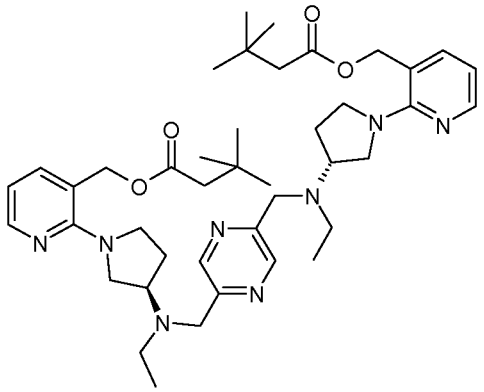
1H-pyrazole-3,5-diylbis[methanediyl(ethylimino)(3R)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) quaternary hydrochloride



LC-MS m/z = 731 (M+H), 0.87 minutes (retention time).

Example 541

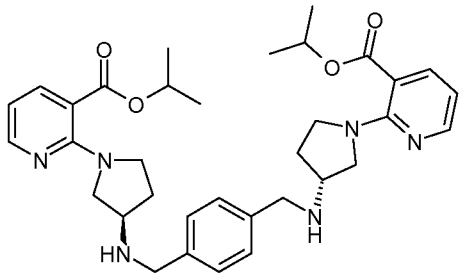
2,5-pyrazinediylbis[methanediyl(ethylimino)(3R)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) hydrochloride



LC-MS m/z = 743 (M+H), 0.68 minutes (retention time).

Example 542

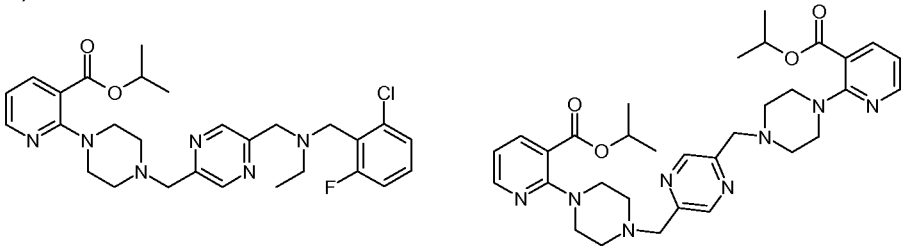
bis(1-methylethyl)2,2'-{benzene-1,4-diylbis[methanediylimino(3R)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate)



LC-MS m/z = 601 (M+H), 0.69 minutes (retention time).

Example 510 (Reiterated Here – Mixture of Products, Inc. DImer

bis(1-methylethyl) 2,2'-[2,5-pyrazinediylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridine carboxylate)



The resulting mixture was purified by Gilson HPLC (Xbridge 19 X 150 mm 5u preparatory column), eluting at 18 mL/min with a linear gradient running from 50% to 100 % with acetonitrile and 0.1 % aqueous NH_4OH over 20 minutes to give the freebase of:

- 1-methylethyl2-{4-[(5-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}-2-

pyrazinyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate (29 mg, 26%). LC-MS m/z = 541 (M+H), 0.69 minutes (retention time).

- bis(1-methylethyl)2,2'-[2,5-pyrazinediylbis(methanediyl-4,1-piperazinediyl)]di(3-pyridinecarboxylate) (24 mg, 19%). LC-MS m/z = 602 (M+H), 0.74 minutes (retention time).

Example 511

A Two Part Study To Investigate The Safety And Tolerability, Pharmacokinetics And Pharmacodynamics Of 1-Methylethyl 2-{4-[(4-{[[(2-Chloro-6-Fluorophenyl)Methyl] (Ethyl)Amino]Methyl}Phenyl)Methyl]-1-Piperazinyl}-3-Pyridinecarboxylate In Healthy Subjects. Part A: An Open Label, Dose Escalating, Rinse, Gargle And Spit Study. Part B: A Randomised, Double-Blind, Placebo Controlled, Inhaled Dose Escalating Study Using Nebulised Lidocaine For Blinding Purposes.

Description:

The purpose of this study was to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) effects of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate in healthy subjects.

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate is a blocker of neuronal voltage gated sodium channels in development for the treatment of chronic cough, excessive cough and post-viral and viral (acute) cough. Inhaled pan Na_V inhibitors are associated with oropharyngeal sensation perturbation and so this study will establish the potential local sensate effects of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate at multiples of the predicted inhaled therapeutic dose. This study also aims to define the maximum tolerated dose of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate.

The study was run as two consecutive parts:

Part A

Part A of this study was conducted in 12 healthy volunteers to investigate the safety and tolerability of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate, in particular examining oropharyngeal sensation perturbation. Part A was an open label, oral, single-dose escalating rinse, gargle and spit study. Assessments of sensate changes included 4 point scale, assessment of sensation on base of tongue, sensation of temperature, assessment of taste, a water swallow test and assessment of potential paraesthesias.

Part A also included PK assessments to investigate the PK profile of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate.

Two alternating cohorts of six subjects were enrolled into this part of the study. Each subject was administered three ascending doses of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate as a solution for gargling, with at least 48 hours washout between doses. The doses investigated in Part A were 3, 6, 15, 30, 60 and 120 µg. Administration of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate followed a staggered schedule to assure minimal exposure to the compound until preliminary clinical safety data were collected. For the first dose of both cohorts in Part A, the administration of the first dose was staggered: only two subjects were dosed first and monitored for a minimum of 24 hours before progressing with subsequent subjects, following review of safety data by the Investigator. The remaining subjects in the cohort were dosed the following day. There were dose escalation meetings following completion of each dose level in Part A. Follow-up of each subject was 7-14 days after the last dose.

Part B

Part B of this study was a randomised, double blind, placebo controlled, inhaled dose escalation study over two study days per dose to examine the possible adverse events such as transient mouth, throat and upper airway numbness in healthy volunteers. Similar assessments of sensations to those used in Part A were performed. The potential for systemic cardiovascular (CV) or central nervous system (CNS) effects was also assessed. Pharmacodynamic effects of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylatewere investigated in Part B using a capsaicin cough challenge. The study investigated whether 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate can alter the capsaicin cough threshold (as determined by the capsaicin concentration required to induce 2 or more (C2) and 5 or more (C5) coughs) in healthy volunteers. Part B also included PK assessments to investigate the PK profile of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate. Placebo was used as a control and nebulised lidocaine was used for control and blinding purposes only.

Two cohorts of 8 subjects were randomised into this part of the study. The first

cohort only started once all data from Part A had been reviewed by the Data Review Board. The second cohort only started the study once all data from Cohort 1 had been reviewed by the Data Review Board. There were dose escalation meetings between each dose in Part B. Each subject took part in four treatment periods, and in each treatment period, doses were administered via nebuliser on two consecutive days, with a minimum of 24 hours between doses. Dosing on Day 2 occurred only after all available safety and tolerability data are reviewed by the Investigator and do not indicate any safety concerns. The treatment periods included three ascending doses of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate, and a treatment period with placebo administered on Day 1 and lidocaine administered on Day 2. The doses investigated in Part B were 25, 100, 250, 500, 1000 and 2000 µg. Subjects were randomised to receive three ascending doses of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate (with each dose given on two consecutive days) and placebo and lidocaine.

Administration of 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate followed a staggered schedule to assure minimal exposure to the compound until preliminary clinical safety data were collected. In both cohorts in Part B, the administration of the first dose only was staggered: only two subjects were dosed first and monitored for 12 hours before progressing with the remaining subjects, following review of safety data by the Investigator. There was a washout of at least 6 days between treatment periods. A higher dose in the next treatment period was only administered following a review of the interim safety and pharmacokinetic profile of the previous dose by the Data Review Board. Withdrawn subjects were replaced where possible. Follow-up of each subject occurred 7-14 days after the last dose.

Subject: Safety and tolerability, capsaicin challenge, oral 1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate, pharmacokinetics, pharmacodynamics, chronic cough, C2, C5, anaesthesia, lidocaine.

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

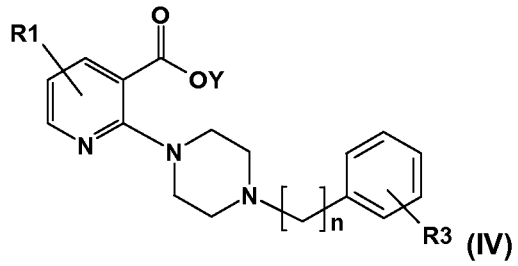
The various references to journals, patents, and other publications which are

cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

CLAIMS

What is claimed is:

1. A method for treating post viral cough, viral cough or viral acute cough, which comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (IV):



(IV)

wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -straight or branched C_{1-6} alkoxy, $-O(CH_2)_xOR_{1d}$, $-C(O)R_{1e}$, $-C(O)OR_{1f}$, -phenyl,$-(CH_2)_x$-phenyl, $-(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted phenyloxy, $-(CH_2)_x$-phenyloxy, $-(CH_2)_x$-piperazinyl, $-(CH_2)_x$-substituted piperazinyl, $-(CH_2)_x$-N-substituted piperazinyl, $-(CH_2)_x$ NRC(O)-phenyl, $-(CH_2)_x$ NRC(O)-substituted phenyl, $-O-(CH_2)_x$-phenyl, $-O-(CH_2)_x$ -substituted phenyl, $-O(CH_2)_x$ -1,4-benzodioxinyl, $-O(CH_2)_x$ -naphthalenyl, $-O(CH_2)_x$-tetrazolyl, -S-phenyl, $-S(CH_2)_x$ phenyl, $-SO_2R_{1g}$, $-SO_2N(R_{1g})_2$, $-(CH_2)_x$ $-N(R_{1h})$ $-(CH_2)_x$ R_{1i};

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, $-O(CH_2)_y$ CN, -OC(O)OH, $-OC(O)R_{1j}$, $-C(O)OR_{1k}$, $-O(CH_2)_yOR_{1l}$,- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1m}R_{1n}$, $-SO_2R_{1o}$, $-S(CH_2)_yR_{1p}$, $-NR_{1q}C(O)R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, -OC(O)OH, $-OC(O)R_{1s}$, $-C(O)OR_{1t}$,–$SO_2N(R_{1u})_2$–,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

wherein:

R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof.

2. The method for treating post viral cough, viral cough or viral acute cough according to claim 1, wherein the compound of Formula (IV) is selected from

1-methylethyl 2-[4-({3-[(2-thienylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate; 1-methylethyl 2-{4-[(3-{[(2-chloro-4-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-nitrophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(acetyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-[4-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylpropyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

[(3-{[4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl}phenyl)oxy]acetic acid;

1-methylethyl 2-[4-({3-[(2-hydroxyethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-

pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({2-[(2-chloroethyl)oxy]ethyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenyloxy)-3-pyridinecarboxylate;

1-methylethyl 4-[(2-fluorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(3-chlorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(4-cyanophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(ethyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-({3-[(ethyloxy)carbonyl]phenyl}amino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(2-ethylphenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(methyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-(phenylamino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenylthio)-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(methyloxy)phenyl]thio}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate; 1-methylethyl 2-[4-({2-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate; 1-methylethyl 2-{4-[(3-{[2-(trifluoromethyl)phenyl]amino}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[2-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylphenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({2-[(trifluoromethyl)oxy]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({3-(ethyloxy)carbonyl]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[2-fluoro-6-(trifluoromethyl)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(ethyloxy)phenyl]methyl}-1-piperazinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-(2-thienylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({4-[(trifluoromethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[4-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({2-[(phenylmethyl)oxy] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluoro-2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-

3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chloro-4-fluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({3-[(trifluoromethyl)oxy]phenyl} oxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chloro-4-fluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(ethyloxy)phenyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(3-furanylmethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(ethyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(5-methyl-2-thienyl)methyl]amino}

methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[2-(ethyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(methyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-furanylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-thienylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({4-[(methyloxy)carbonyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-cyano-4-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3,5-dimethyl-4-isoxazolyl)methyl]-1-piperazinyl}-4-methyl-3-

pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetylamino)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[1-(3-pyridinyl)-1*H*-pyrrol-2-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(1*H*-tetrazol-5-yl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methylsulfonyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-[(cyanomethyl)oxy]-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({1,2,5-trimethyl-4-[(methyloxy)carbonyl]-1*H*-pyrrol-3-yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(1-piperidinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-methyl-1-piperazinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({1-[3-cyano-4-(methyloxy)-2-pyridinyl]-1*H*-pyrrol-2-yl}methyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2,4-dichlorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-methyl-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(ethyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4,5-bis(methyloxy)-2-[(phenylmethyl)oxy] phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-dimethyl-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-hydroxy-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-

(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(methyloxy)-4-({[4-(methyloxy)phenyl]methyl} oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,4-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-bromophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(3-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-fluoro-3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(9*H*-fluoren-2-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(4-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-

pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-4-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(9-ethyl-9*H*-carbazol-3-yl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(dibenzo[*b*,*d*]furan-4-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-chloro-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-3-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-4-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(1,1-dimethylethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-4-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3'-(methyloxy)-2-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[3-(trifluoromethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-

piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(butyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(butyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-

piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(5-chloro-2-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({4-[(2-chloro-6-fluorophenyl)methyl]-1-piperazinyl} methyl)phenyl]methyl}1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(phenylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[4-(2-pyridinylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[3-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[4-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-Methylethyl-2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-Methylethyl-2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;1-Methylethyl-2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride;

1-Methylethyl-2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate dihydrochloride;

1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate;

1-methylethyl 2-(4-{[4-({ethyl[(2-{[(1-methylethyl)oxy]carbonyl}phenyl) methyl] amino} methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(3-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-[4-({2-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate hydrochloride;

1-Methylethyl2-[4-({3-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl2-[4-({4-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl2-{4-[(4-{[({2-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[({3-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[({4[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-Methylethyl 2-{4-[(4-{[[2-(2-chloro-6-fluorophenyl)ethyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride hydrochloride ;

1-methylethyl 2-(4-{[4-({ethyl[(3-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(4-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2,6-difluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[[(2,6-dichlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[[(3-chlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-{4-[(4-{[[(4-chlorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-

1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chlorophenyl)methyl](ethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl][3-(2-oxo-1-pyrrolidinyl)propyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(2-methyl-3-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-fluorophenyl)methyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(2-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] ;methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[3-(2-chloro-6-fluorophenyl)propyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}_-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)carbonyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate quaternary hydrochloride1-methylethyl2-(4-{[4-({[(2-fluorophenyl)carbonyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylcarbonyl)amino]methyl}phenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate trihydrochloride;1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride; or

a pharmaceutically acceptable salt thereof.

3. The method for treating post viral cough, viral cough or viral acute cough according to claim 2, wherein the compound of Formula (IV) is selected from

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino)(3S)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate);

benzene-1,4-diylbis[methanediyl(ethylimino)(3R)-3,1-pyrrolidinediyl-2,3-pyridinediylmethanediyl] bis(3,3-dimethylbutanoate;

1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl) -3-pyridinecarboxylate;

1-methylethyl 2-[(3R)-3-(ethyl{[4-({ethyl[(3R)-1-(1-{2-[(1-methylethyl)oxy]-2-oxoethyl}ethenyl)-3-pyrrolidinyl]amino}methyl)phenyl]methyl}amino)-1-pyrrolidinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

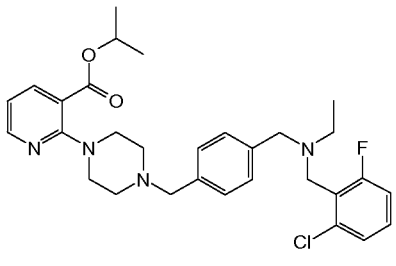
1-methylethyl 2-{(3R)-3-[ethyl({2-[(phenylmethyl)oxy]phenyl}methyl)amino]-1-

pyrrolidinyl}-3-pyridinecarboxylate;

bis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(2S)-1,2-pyrrolidinediylmethanediyloxy]}di(3-pyridinecarboxylate); or

a pharmaceutically acceptable salt thereof.

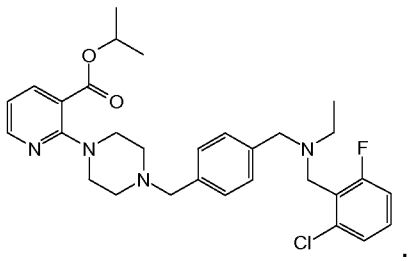
4. A method for treating post viral cough, viral cough or viral acute cough, which comprises administering to a subject in need thereof a therapeutically effective amount of compound which is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



;or

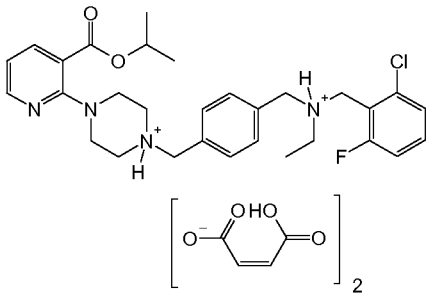
a pharmaceutically acceptable salt thereof.

5. The method for treating post viral cough, viral cough or viral acute cough according to claim 4, wherein the compound is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



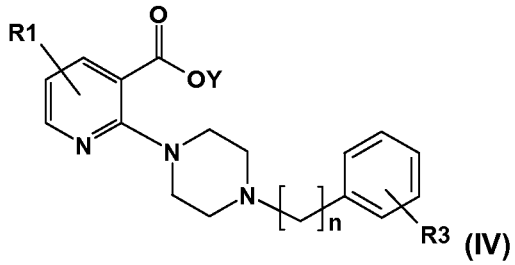
.

6. The method for treating post viral cough, viral cough or viral acute cough according to claim 4, wherein the compound which is 1-[(4-{[[(2-Chloro-6-fluorophenyl) methyl](ethyl) ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methyl ethyl) oxy]carbonyl}-2-pyridinyl) piperazin-1-ium di-maleate



7. A method for treating post viral cough, viral cough or viral acute cough, which comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprised of:

[a] a compound of Formula (IV):



(IV)

wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -straight or branched C_{1-6} alkoxy, $-O(CH_2)_xOR_{1d}$, $-C(O)R_{1e}$, $-C(O)OR_{1f}$, -phenyl,$-(CH_2)_x$-phenyl, $-(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted phenyloxy, $-(CH_2)_x$-phenyloxy, $-(CH_2)_x$-piperazinyl, $-(CH_2)_x$-substituted piperazinyl, $-(CH_2)_x$-N-substituted piperazinyl, $-(CH_2)_x$ NRC(O)-phenyl, $-(CH_2)_x$ NRC(O)-substituted phenyl, $-O-(CH_2)_x$-phenyl, $-O-(CH_2)_x$ -substituted phenyl, $-O(CH_2)_x$ -1,4-benzodioxinyl, $-O(CH_2)_x$ -naphthalenyl, $-O(CH_2)_x$-tetrazolyl, -S-phenyl, $-S(CH_2)_x$ phenyl, $-SO_2R_{1g}$, $-SO_2N(R_{1g})_2$, $-(CH_2)_x$ $-N(R_{1h})$ $-(CH_2)_x$ $R_{1i;}$

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, $-O(CH_2)_y$ CN, -OC(O)OH, $-OC(O)R_{1j}$, $-C(O)OR_{1k}$, $-O(CH_2)_yOR_{1l}$,- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1m}R_{1n}$, $-SO_2R_{1o}$, $-S(CH_2)_yR_{1p}$, $-NR_{1q}C(O)R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, -OC(O)OH, $-OC(O)R_{1s}$, $-C(O)OR_{1t}$,–$SO_2N(R_{1u})_2$–,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

wherein:

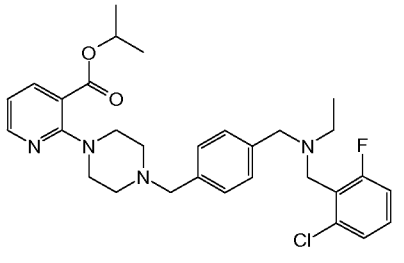
R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof; and

[b] at least one pharmaceutically acceptable adjuvant, excipient or carrier.

8. A method for treating post viral cough, viral cough or viral acute cough, which comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising:

[a] a compound which is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



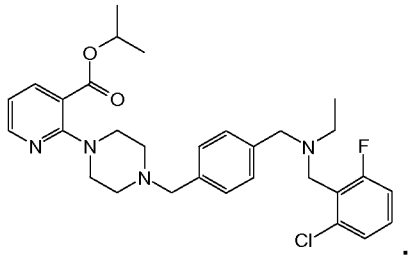
;or

a pharmaceutically acceptable salt thereof; and

[b] at least one pharmaceutically acceptable adjuvant, excipient or carrier.

9. The method for treating post viral cough, viral cough or viral acute cough according to claim 8, wherein the pharmaceutical composition comprises:

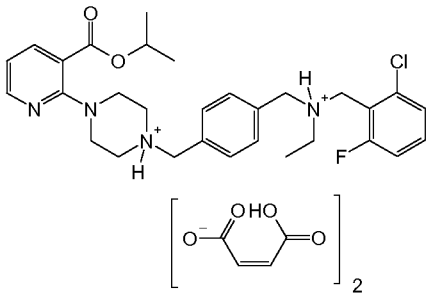
[a] the compound 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl] (ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



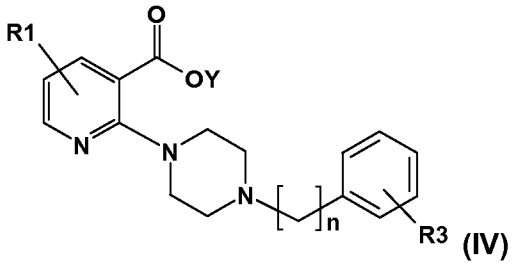
.

10. The method for treating post viral cough, viral cough or viral acute cough according to claim 8, wherein the pharmaceutical composition comprises:

[a] the compound 1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl) ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate



11. Use of a compound for Formula (IV) for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough:



(IV)

wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -straight or branched C_{1-6} alkoxy, $-O(CH_2)_xOR_{1d}$, $-C(O)R_{1e}$, $-C(O)OR_{1f}$, -phenyl,$-(CH_2)_x$-phenyl, $-(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted phenyloxy, $-(CH_2)_x$-phenyloxy, $-(CH_2)_x$-piperazinyl, $-(CH_2)_x$-substituted piperazinyl, $-(CH_2)_x$-N-substituted piperazinyl, $-(CH_2)_x$ NRC(O)-phenyl, $-(CH_2)_x$ NRC(O)-substituted phenyl, $-O-(CH_2)_x$-phenyl, $-O-(CH_2)_x$ -substituted phenyl, $-O(CH_2)_x$ -1,4-benzodioxinyl, $-O(CH_2)_x$ -naphthalenyl, $-O(CH_2)_x$-tetrazolyl, -S-phenyl, $-S(CH_2)_x$ phenyl, $-SO_2R_{1g}$, $-SO_2N(R_{1g})_2$, $-(CH_2)_x$ $-N(R_{1h})$ $-(CH_2)_x$ R_{1i};

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched

C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, $-O(CH_2)_y$ CN, -OC(O)OH, $-OC(O)R_{1j}$, $-C(O)OR_{1k}$, $-O(CH_2)_yOR_{1l}$,- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1m}R_{1n}$, $-SO_2R_{1o}$, $-S(CH_2)_yR_{1p}$, $-NR_{1q}C(O)R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, -OC(O)OH, $-OC(O)R_{1s}$, $-C(O)OR_{1t}$,--$SO_2N(R_{1u})_2$-,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

wherein:

R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof.

12. Use of a compound for Formula (IV) for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough according to claim 11, wherein

the compound of Formula (IV) is selected from

1-methylethyl 2-[4-({3-[(2-thienylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate; 1-methylethyl 2-{4-[(3-{[(2-chloro-4-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-nitrophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(acetyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-[4-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylpropyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

[(3-{[4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl}phenyl)oxy]acetic acid;

1-methylethyl 2-[4-({3-[(2-hydroxyethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({2-[(2-chloroethyl)oxy]ethyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenyloxy)-3-pyridinecarboxylate;

1-methylethyl 4-[(2-fluorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(3-chlorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(4-cyanophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(ethyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-({3-[(ethyloxy)carbonyl]phenyl}amino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(2-ethylphenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(methyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-(phenylamino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenylthio)-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(methyloxy)phenyl]thio}-2-[4-(phenylmethyl)-1-piperazinyl]-3-

pyridinecarboxylate; 1-methylethyl 2-[4-({2-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate; 1-methylethyl 2-{4-[(3-{[2-(trifluoromethyl)phenyl]amino}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[2-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylphenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({2-[(trifluoromethyl)oxy]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({3-(ethyloxy)carbonyl]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[2-fluoro-6-(trifluoromethyl)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(ethyloxy)phenyl]methyl}-1-piperazinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-(2-thienylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-

pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({4-[(trifluoromethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[4-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({2-[(phenylmethyl)oxy] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluoro-2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chloro-4-fluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({3-[(trifluoromethyl)oxy]phenyl} oxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-

pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chloro-4-fluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(ethyloxy)phenyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(3-furanylmethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(ethyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(5-methyl-2-thienyl)methyl]amino} methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[2-(ethyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(methyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-furanylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-thienylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({4-[(methyloxy)carbonyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-cyano-4-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3,5-dimethyl-4-isoxazolyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetylamino)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[1-(3-pyridinyl)-1*H*-pyrrol-2-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(1*H*-tetrazol-5-yl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methylsulfonyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-[(cyanomethyl)oxy]-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({1,2,5-trimethyl-4-[(methyloxy)carbonyl]-1*H*-pyrrol-3-yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(1-piperidinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-methyl-1-piperazinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({1-[3-cyano-4-(methyloxy)-2-pyridinyl]-1*H*-pyrrol-2-yl}methyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2,4-dichlorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-

piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-methyl-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(ethyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4,5-bis(methyloxy)-2-[(phenylmethyl)oxy] phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-dimethyl-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-hydroxy-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(methyloxy)-4-({[4-(methyloxy)phenyl]methyl} oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,4-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-bromophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(3-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-fluoro-3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(9*H*-fluoren-2-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(4-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-4-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(9-ethyl-9*H*-carbazol-3-yl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(dibenzo[*b*,*d*]furan-4-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-chloro-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-3-biphenylyl}methyl)-1-piperazinyl]-3-

pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-4-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(1,1-dimethylethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-4-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3'-(methyloxy)-2-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[3-(trifluoromethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(butyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-

piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(butyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(5-chloro-2-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl} methyl)-

1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({4-[(2-chloro-6-fluorophenyl)methyl]-1-piperazinyl} methyl)phenyl]methyl}1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(phenylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[4-(2-pyridinylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[3-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[4-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-Methylethyl-2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-Methylethyl-2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;1-Methylethyl-2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride;

1-Methylethyl-2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine

carboxylate dihydrochloride;

1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate;

1-methylethyl 2-(4-{[4-({ethyl[(2-{[(1-methylethyl)oxy]carbonyl}phenyl) methyl] amino} methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(3-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-[4-({2-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate hydrochloride;

1-Methylethyl2-[4-({3-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl2-[4-({4-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl2-{4-[(4-{[({2-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[({3-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[({4[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-Methylethyl 2-{4-[(4-{[[2-(2-chloro-6-fluorophenyl)ethyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride hydrochloride ;

1-methylethyl 2-(4-{[4-({ethyl[(3-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(4-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2,6-difluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[[(2,6-dichlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-

piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[[(3-chlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-{4-[(4-{[[(4-chlorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chlorophenyl)methyl](ethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl][3-(2-oxo-1-pyrrolidinyl)propyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(2-methyl-3-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-fluorophenyl)methyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(2-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] ;methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[3-(2-chloro-6-fluorophenyl)propyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}_-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)carbonyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl)phenyl]

methyl}-1-piperazinyl)-3-pyridine carboxylate quaternary hydrochloride1-methylethyl2-(4-{[4-({[(2-fluorophenyl)carbonyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylcarbonyl)amino]methyl}phenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

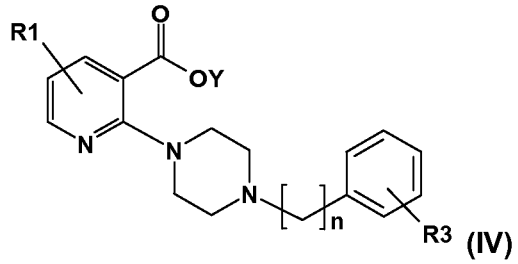
1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate trihydrochloride;1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride; or

a pharmaceutically acceptable salt thereof.

13. Use of a pharmaceutical composition for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough, wherein the pharmaceutical composition comprises:

[a] a compound of Formula (IV):



(IV)

wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -straight or branched C_{1-6} alkoxy, $-O(CH_2)_xOR_{1d}$, $-C(O)R_{1e}$, $-C(O)OR_{1f}$, -phenyl,$-(CH_2)_x$-phenyl, $-(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted

phenyloxy, -$(CH_2)_x$-phenyloxy, -$(CH_2)_x$-piperazinyl, -$(CH_2)_x$-substituted piperazinyl, -$(CH_2)_x$-N-substituted piperazinyl, -$(CH_2)_x$ NRC(O)-phenyl, -$(CH_2)_x$ NRC(O)-substituted phenyl, -O-$(CH_2)_x$-phenyl, -O-$(CH_2)_x$ -substituted phenyl, -O$(CH_2)_x$ -1,4-benzodioxinyl, -O$(CH_2)_x$ -naphthalenyl, -O$(CH_2)_x$-tetrazolyl, -S-phenyl, -S$(CH_2)_x$ phenyl, -SO_2R_{1g}, -$SO_2N(R_{1g})_2$, -$(CH_2)_x$ -N(R_{1h}) -$(CH_2)_x$ $R_{1i;}$

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, -NO_2,-halogen, -$(CH_2)_y$ -OH, -O$(CH_2)_y$ CN, -OC(O)OH, -OC(O)R_{1j}, -C(O)OR_{1k}, -O$(CH_2)_y$OR_{1l},- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, -$NR_{1m}R_{1n}$, -SO_2R_{1o}, -S$(CH_2)_y$$R_{1p}$, -$NR_{1q}$C(O)$R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, -NO_2,-halogen, -$(CH_2)_y$ -OH, -OC(O)OH, -OC(O)R_{1s}, -C(O)OR_{1t},--$SO_2N(R_{1u})_2$-,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

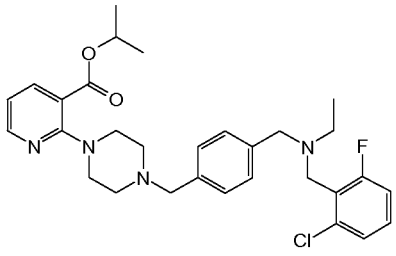
wherein:

R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof; and

[b] at least one pharmaceutically acceptable adjuvant, excipient or carrier.

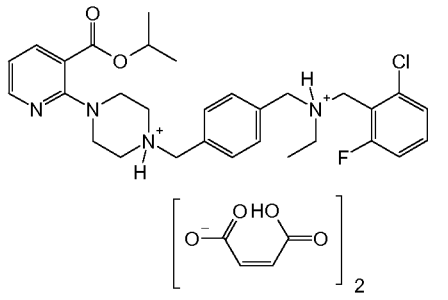
14. Use of a compound which is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



;or

a pharmaceutically acceptable salt thereof for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough.

15. Use of a compound for for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough according to claim 14, wherein the pharmaceutically acceptable salt of the compound is 1-[(4-{[[(2-Chloro-6-fluorophenyl) methyl](ethyl) ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methyl ethyl) oxy]carbonyl}-2-pyridinyl) piperazin-1-ium di-maleate:

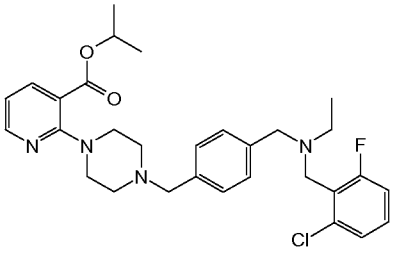


.

16. Use of a pharmaceutical composition for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough, wherein the pharmaceutical composition comprises:

[a] compound which is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-

pyridinecarboxylate

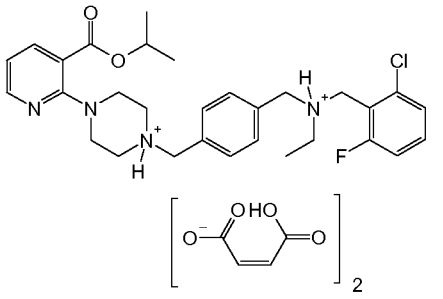


;or

a pharmaceutically acceptable salt thereof; and

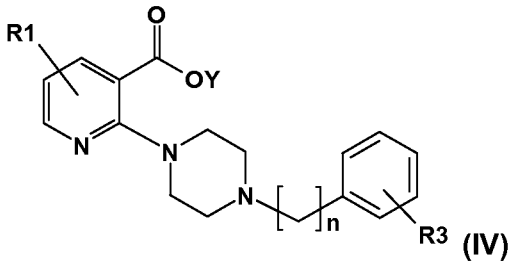
[b] at least one pharmaceutically acceptable adjuvant, excipient or carrier.

17. Use of a pharmaceutical composition for manufacture of a medicament for treatment of post viral cough, viral cough or viral acute cough according to claim 16, wherein the pharmaceutically acceptable salt of the compound is 1-[(4-{[[(2-Chloro-6-fluorophenyl) methyl](ethyl) ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methyl ethyl) oxy]carbonyl}-2-pyridinyl) piperazin-1-ium di-maleate:



.

18. Use of a compound for Formula (IV) for treating post viral cough, viral cough or viral acute cough:



wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -straight or branched C_{1-6} alkoxy, $-O(CH_2)_xOR_{1d}$, $-C(O)R_{1e}$, $-C(O)OR_{1f}$, -phenyl,$-(CH_2)_x$-phenyl, $-(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted phenyloxy, $-(CH_2)_x$-phenyloxy, $-(CH_2)_x$-piperazinyl, $-(CH_2)_x$-substituted piperazinyl, $-(CH_2)_x$-N-substituted piperazinyl, $-(CH_2)_x$ NRC(O)-phenyl, $-(CH_2)_x$ NRC(O)-substituted phenyl, $-O-(CH_2)_x$-phenyl, $-O-(CH_2)_x$ -substituted phenyl, $-O(CH_2)_x$ -1,4-benzodioxinyl, $-O(CH_2)_x$ -naphthalenyl, $-O(CH_2)_x$-tetrazolyl, -S-phenyl, $-S(CH_2)_x$ phenyl, $-SO_2R_{1g}$, $-SO_2N(R_{1g})_2$, $-(CH_2)_x$ $-N(R_{1h})$ $-(CH_2)_x$ R_{1i};

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$ -OH, $-O(CH_2)_y$ CN, -OC(O)OH, $-OC(O)R_{1j}$, $-C(O)OR_{1k}$, $-O(CH_2)_yOR_{1l}$,- straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1m}R_{1n}$, $-SO_2R_{1o}$, $-S(CH_2)_yR_{1p}$, $-NR_{1q}C(O)R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$ -OH, -OC(O)OH, $-OC(O)R_{1s}$, $-C(O)OR_{1t}$,--$SO_2N(R_{1u})_2$-,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

wherein:

R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof.

19. Use of a compound for Formula (IV) for treating post viral cough, viral cough or viral acute cough according to claim 18, wherein the compound of Formula (IV) is selected from

1-methylethyl 2-[4-({3-[(2-thienylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate; 1-methylethyl 2-{4-[(3-{[(2-chloro-4-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-methylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-nitrophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-

3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-{4-[(3-{[(2-chloro-6-fluorophenyl)methyl]oxy} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(acetyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

1-methylethyl 2-[4-({3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylpropyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;

[(3-{[4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)-1-piperazinyl] methyl}phenyl)oxy]acetic acid;

1-methylethyl 2-[4-({3-[(2-hydroxyethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({2-[(2-chloroethyl)oxy]ethyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenyloxy)-3-pyridinecarboxylate;

1-methylethyl 4-[(2-fluorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(3-chlorophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(4-cyanophenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(ethyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(1-methylethyl)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-({3-[(ethyloxy)carbonyl]phenyl}amino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-[(2-ethylphenyl)amino]-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-{[4-(methyloxy)phenyl]amino}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-(phenylamino)-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-(phenylmethyl)-1-piperazinyl]-4-(phenylthio)-3-pyridinecarboxylate;

1-methylethyl 4-{[2-(methyloxy)phenyl]thio}-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate; 1-methylethyl 2-[4-({2-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate; 1-methylethyl 2-{4-[(3-{[2-(trifluoromethyl)phenyl]amino}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[2-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-methylphenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({2-[(trifluoromethyl)oxy]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({3-(ethyloxy)carbonyl]phenyl}amino) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[2-fluoro-6-(trifluoromethyl)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,6-difluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-fluorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-chlorophenyl)amino]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]amino} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(ethyloxy)phenyl]methyl}-1-piperazinyl)-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-(2-thienylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({4-[(trifluoromethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-(4-{[4-(propyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 4-phenyl-2-[4-({2-[(phenylmethyl)oxy] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluoro-2-methylphenyl)methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(1-methylethyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-4-phenyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chloro-4-fluorophenyl)oxy]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({3-[(trifluoromethyl)oxy]phenyl} oxy)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-

piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,4-difluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-chloro-4-fluorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,3-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2-chlorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(trifluoromethyl)phenyl]oxy}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dichlorophenyl)oxy]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-methylphenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-fluorophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(ethyloxy)phenyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)oxy]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(3-furanylmethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(ethyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(5-methyl-2-thienyl)methyl]amino} methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[2-(ethyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(ethyl{[3-(methyloxy)phenyl]methyl}amino) methyl]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-furanylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[ethyl(2-thienylmethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({4-[(methyloxy)carbonyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-(phenylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-(3-furanylmethyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-{4-[(5-methyl-2-thienyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-cyanophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-cyano-4-fluorophenyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3,5-dimethyl-4-isoxazolyl)methyl]-1-piperazinyl}-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetylamino)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(acetyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[1-(3-pyridinyl)-1*H*-pyrrol-2-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(1*H*-tetrazol-5-yl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[4-(methylsulfonyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-[(cyanomethyl)oxy]-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-4-methyl-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-[4-({1,2,5-trimethyl-4-[(methyloxy)carbonyl]-1*H*-pyrrol-3-yl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(1-piperidinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-

3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-morpholinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 4-methyl-2-(4-{[2-(4-methyl-1-piperazinyl)-1,3-thiazol-5-yl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({1-[3-cyano-4-(methyloxy)-2-pyridinyl]-1*H*-pyrrol-2-yl}methyl)-1-piperazinyl]-4-methyl-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2,4-dichlorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis(methyloxy)-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-(methyloxy)-3-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chlorophenyl)methyl]oxy}-3-(ethyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-methyl-4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-fluorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(ethyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-2-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4,5-bis(methyloxy)-2-[(phenylmethyl)oxy] phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,5-dimethyl-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-hydroxy-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(2-chloro-6-fluorophenyl)methyl]oxy}-3-(methyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-{[(4-chlorophenyl)methyl]oxy}-3-(methyloxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(methyloxy)-4-({[4-(methyloxy)phenyl]methyl} oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-bromophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3,4-bis[(phenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-(methyloxy)-4-[(phenylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-chloro-6-fluorophenyl)methyl]oxy}phenyl) methyl]-1-

piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-bromophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,5-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(2-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(3-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-fluoro-3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(9*H*-fluoren-2-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-(4-biphenylylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-methylphenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(3,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-methyl-4-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(9-ethyl-9*H*-carbazol-3-yl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-(dibenzo[*b*,*d*]furan-4-ylmethyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-

pyridinecarboxylate;

1-methylethyl 2-{4-[(4'-chloro-3-biphenylyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(2-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,4-dichlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-fluorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-3-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4'-[(methyloxy)carbonyl]-4-biphenylyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-cyanophenyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[4-(1,1-dimethylethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({2-[(4-chlorophenyl)thio]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2'-(trifluoromethyl)-4-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3'-(methyloxy)-2-biphenylyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[3-(trifluoromethyl)phenyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[2-(phenyloxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(butyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-

piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(3-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({3-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(methyloxy)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[3-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1,1-dimethylethyl)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-chlorophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4,5-trifluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(dimethylamino)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,4-difluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(butyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-ethylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-fluoro-6-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(5-chloro-2-fluorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-cyanophenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(4-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,6-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(ethyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,4-dimethylphenyl)methyl]oxy}phenyl) methyl]-1-

piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-fluoro-3-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(1-naphthalenylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methylsulfonyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(2-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(3,5-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2,3-dichlorophenyl)methyl]oxy}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[({4-[(methyloxy)carbonyl]phenyl}methyl) oxy]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-chloro-2-(methyloxy)phenyl]methyl}oxy) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(2-methylphenyl)methyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[4-(1-methylethyl)phenyl]methyl}oxy)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-[4-({4-[(4-biphenylylmethyl)oxy]phenyl}methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,5-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[3-(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2,4-bis(methyloxy)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({[2-(trifluoromethyl)phenyl]methyl}oxy) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({4-[(2-chloro-6-fluorophenyl)methyl]-1-piperazinyl} methyl)phenyl]methyl}1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[4-(phenylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[4-(2-pyridinylmethyl)-1-piperazinyl]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[3-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl]phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;1-methylethyl 2-[4-({4-[(4-{[4-(methyloxy) phenyl]methyl}-1-piperazinyl)methyl] phenyl} methyl)-1-piperazinyl]-3-pyridinecarboxylate;

1-Methylethyl-2-{4-[(3-{[4-(methyloxy)phenyl]oxy}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-Methylethyl-2-(4-{[2'-(trifluoromethyl)-3-biphenylyl]methyl}-1-piperazinyl)-3-pyridine carboxylate;1-Methylethyl-2-(4-{[3-({[2-(methyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate hydrochloride;

1-Methylethyl-2-(4-{[3-({[4-(ethyloxy)phenyl]methyl}oxy)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-Methylethyl 2-[4-({4-[(ethylamino)methyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate dihydrochloride;

1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate;

1-methylethyl 2-(4-{[4-({ethyl[(2-{[(1-methylethyl)oxy]carbonyl}phenyl) methyl] amino} methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(3-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl) phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-(4-{[4-({ethyl[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)methyl] amino} methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-[4-({2-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate hydrochloride;

1-Methylethyl2-[4-({3-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl2-[4-({4-[(dimethylamino)sulfonyl]phenyl}methyl)-1-piperazinyl]-3-pyridine carboxylate;

1-methylethyl2-{4-[(4-{[({2-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[({3-[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-

{[({4[(dimethylamino)sulfonyl]phenyl}methyl)(ethyl)amino] methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-Methylethyl 2-{4-[(4-{[[2-(2-chloro-6-fluorophenyl)ethyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride hydrochloride ;

1-methylethyl 2-(4-{[4-({ethyl[(3-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(4-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2,6-difluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[[(2,6-dichlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl 2-{4-[(4-{[[(3-chlorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;1-methylethyl2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate;

1-methylethyl 2-{4-[(4-{[[(4-chlorophenyl)methyl](ethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chlorophenyl)methyl](ethyl)amino]methyl} phenyl)methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl][3-(2-oxo-1-pyrrolidinyl)propyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(3-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(2-methyl-3-pyridinyl)methyl]amino}methyl) phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-fluorophenyl)methyl]amino}methyl)phenyl]methyl}-1-

piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-{4-[(2-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino] ;methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl2-{4-[(4-{[[3-(2-chloro-6-fluorophenyl)propyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}_-3-pyridinecarboxylate;

1-methylethyl 2-(4-{[4-({ethyl[(2-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate dihydrochloride;

1-methylethyl2-{4-[(4-{[ethyl(phenylmethyl)amino]methyl}phenyl)methyl]-1-piperazinyl}-3-pyridine carboxylate dihydrochloride;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)carbonyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({ethyl[(6-methyl-2-pyridinyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate quaternary hydrochloride1-methylethyl2-(4-{[4-({[(2-fluorophenyl)carbonyl]amino}methyl)phenyl]methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl 2-{4-[(4-{[(phenylcarbonyl)amino]methyl}phenyl)methyl]-1-piperazinyl} -3-pyridinecarboxylate;

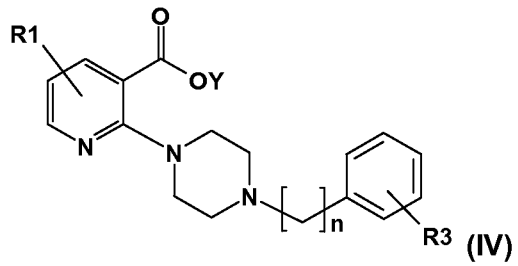
1-methylethyl 2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]oxy}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridinecarboxylate;

1-methylethyl2-(4-{[4-({[(2-chloro-6-fluorophenyl)methyl]amino}methyl)phenyl] methyl}-1-piperazinyl)-3-pyridine carboxylate trihydrochloride;1-methylethyl2-{4-[(4-{[[(2-chloro-6-fluorophenyl)carbonyl](ethyl)amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride; or

a pharmaceutically acceptable salt thereof.

20. Use of a pharmaceutical composition for treating post viral cough, viral cough or viral acute cough, wherein the pharmaceutical composition comprises:

[a] a compound of Formula (IV):



(IV)

wherein:

n is 0 or an integer from 1 to 5;

Y is straight or branched C_{1-6} alkyl or cycloalkyl;

R_1 is H, halogen, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, $-NHR_{1a}$, $-SR_{1b}$ or $-OR_{1c}$;

R_3 is one or more substituents independently selected from -H, -OH, -CN, halogen, straight or branched C_{1-6} alkyl, -straight or branched C_{1-6} haloalkyl, -straight or branched C_{1-6} alkoxy, -straight or branched C_{1-6} alkoxy, $-O(CH_2)_xOR_{1d}$, $-C(O)R_{1e}$, $-C(O)OR_{1f}$, -phenyl,$-(CH_2)_x$-phenyl, $-(CH_2)_x$-substituted phenyl, -phenyloxy, -substituted phenyloxy, $-(CH_2)_x$-phenyloxy, $-(CH_2)_x$-piperazinyl, $-(CH_2)_x$-substituted piperazinyl, $-(CH_2)_x$-N-substituted piperazinyl, $-(CH_2)_x$ NRC(O)-phenyl, $-(CH_2)_x$ NRC(O)-substituted phenyl, $-O-(CH_2)_x$-phenyl, $-O-(CH_2)_x$ -substituted phenyl, $-O(CH_2)_x$ -1,4-benzodioxinyl, $-O(CH_2)_x$ -naphthalenyl, $-O(CH_2)_x$-tetrazolyl, -S-phenyl, $-S(CH_2)_x$ phenyl, $-SO_2R_{1g}$, $-SO_2N(R_{1g})_2$, $-(CH_2)_x$ $-N(R_{1h})$ $-(CH_2)_x$ R_{1i};

wherein:

R_{1a} ,R_{1b} or R_{1c} as defined in R_1 above is phenyl or substituted phenyl;

R, R_{1d}, R_{1e}, R_{1f}, R_{1g} or R_{1h} as defined in R_3 is H, straight or branched C_{1-6} alkyl;

R_{1i} is phenyl, substituted phenyl, furanyl, substituted furanyl, thienyl, or substituted thienyl;

x as defined for substituents defined above is 0 or an integer from 1 to 5;

wherein:

each substitutent as defined in R_3 above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$-OH, $-O(CH_2)_y$ CN, -OC(O)OH, $-OC(O)R_{1j}$, $-C(O)OR_{1k}$, $-O(CH_2)_yOR_{1l}$,- straight or branched C_{1-6} alkyl,-

straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} straight or branched alkoxy, $-NR_{1m}R_{1n}$, $-SO_2R_{1o}$, $-S(CH_2)_yR_{1p}$, $-NR_{1q}C(O)R_{1r}$, aryl or heteroaryl;

wherein:

y as defined for variables above is 0 or an integer from 1 to 5,

R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} is H, straight or branched C_{1-6} alkyl, phenyl, substituted phenyl, pyridinyl, or substituted pyridinyl, -C(O)-phenyl, –C(O)substituted phenyl or $(CH_2)_x$-2-oxo-1-pyrrolidinyl or $(CH_2)_x$-2-oxo-N-pyrrolidinyl; or

wherein:

x is 0 or an integer from 1 to 5;

each phenyl or substituted phenyl substitutent as defined in R_{1j}, R_{1k}, R_{1l}, R_{1m}, R_{1n}, R_{1o}, R_{1p} ,R_{1q} or R_{1r} above further is optionally substituted by one or more of following substituents selected from: -H, -OH, -CN, $-NO_2$,-halogen, $-(CH_2)_y$ -OH, -OC(O)OH, $-OC(O)R_{1s}$, $-C(O)OR_{1t}$,--$SO_2N(R_{1u})_2$-,straight or branched C_{1-6} alkyl,- straight or branched C_{1-6} haloalkyl, - straight or branched C_{1-6} alkoxy;

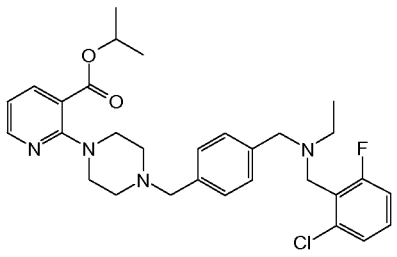
wherein:

R_{1s}, R_{1t}, or R_{1u} as defined above is H, straight or branched C_{1-6} alkyl, phenyl or substituted phenyl; or

a pharmaceutically acceptable salt thereof; and

[b] at least one pharmaceutically acceptable adjuvant, excipient or carrier.

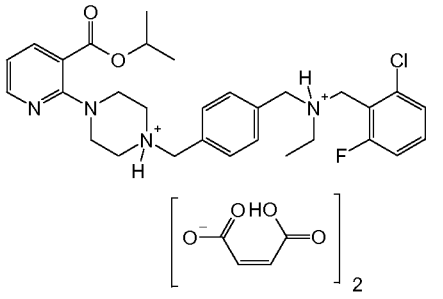
21. Use of a compound which is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate



;or

a pharmaceutically acceptable salt thereof for treating post viral cough, viral cough or viral acute cough.

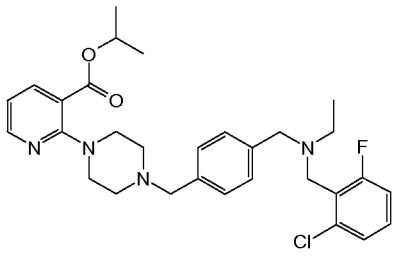
22. Use of a compound for treating post viral cough, viral cough or viral acute cough according to claim 21, wherein the pharmaceutically acceptable salt of the compound is 1-[(4-{[[(2-Chloro-6-fluorophenyl) methyl](ethyl) ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methyl ethyl) oxy]carbonyl}-2-pyridinyl) piperazin-1-ium di-maleate



.

23. Use of a pharmaceutical composition for treating post viral cough, viral cough or viral acute cough, wherein the pharmaceutical composition comprises:

[a] compound which is 1-Methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl) amino]methyl} phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate

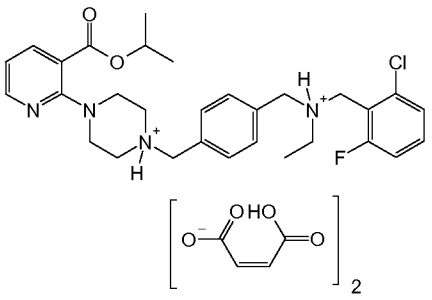


;or

a pharmaceutically acceptable salt thereof; and

[b] at least one pharmaceutically acceptable adjuvant, excipient or carrier.

24. Use of a pharmaceutical composition for treating post viral cough, viral cough or viral acute cough according to claim 23, wherein the pharmaceutically acceptable salt of the compound is 1-[(4-{[[(2-Chloro-6-fluorophenyl) methyl](ethyl) ammonio]methyl}phenyl) methyl]-4-(3-{[(1-methyl ethyl) oxy]carbonyl}-2-pyridinyl) piperazin-1-ium di-maleate



25. A compound which is :

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate;

1-[(4-{[[(2-Chloro-6-fluorophenyl)methyl](ethyl)ammonio]methyl}phenyl)methyl]-4-(3-{[(1-methylethyl)oxy]carbonyl}-2-pyridinyl)piperazin-1-ium di-maleate;

1-methylethyl 2-{4-[(4-{[[(2-chloro-6-fluorophenyl)methyl](ethyl)amino]methyl}phenyl) methyl]-1-piperazinyl}-3-pyridinecarboxylate dihydrochloride;

Benzene-1,4-diylbis[methanediyl(ethylimino)(3*R*)-3,1-pyrrolidinediyl-2,3-pyridinediyl methanediyl] bis(3,3-dimethylbutanoate) hydrochloride; orBis(1-methylethyl) 2,2'-{benzene-1,4-diylbis[methanediyl(ethylimino) (3*S*)-3,1-pyrrolidinediyl]}di(3-pyridinecarboxylate).