

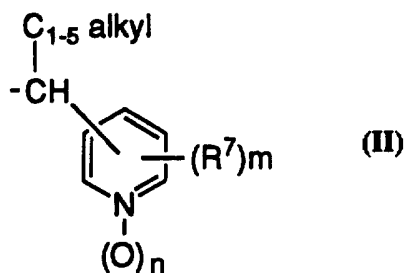
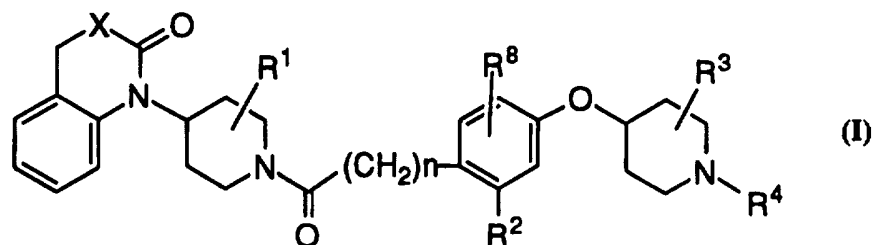
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(54) Title: TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS



(57) Abstract

Compounds of formula (I) wherein X is selected from CH₂ or O; provided that when R¹ and R³ are both simultaneously hydrogen then (a) R⁸ is C₁₋₅ alkyl or halogen, and R² is C₁₋₅ alkoxy, or (b) R⁴ is (II); and the pharmaceutically acceptable salts thereof. Such compounds are useful in mammals as oxytocin receptor antagonists for the treatment of preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery.

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TITLE OF THE INVENTION

TOCOLYTIC OXYTOCIN RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

5 This application is a continuation-in-part of U.S. Serial No. 08/378,113, filed January 24, 1995, the contents of which are hereby incorporated by reference.

 The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture;
10 such compounds are generally pharmacologically useful as agents in obstetric and gynecologic therapy in mammals. More specifically, the compounds of the present invention can be used in the treatment of preterm labor, dysmenorrhea and for stopping labor preparatory to Caesarean delivery.

15

BACKGROUND OF THE INVENTION

 In the field of obstetrics, one of the most important problems is the management of preterm labor. A significant number of the pregnancies progressing past 20 weeks of gestation experience
20 premature labor and delivery, which is a leading cause of neonatal morbidity and mortality. Despite major advances in neonatal care, retention of the fetus *in utero* is preferred in most instances.

 Tocolytic (uterine-relaxing) agents that are currently in use include β_2 -adrenergic agonists, magnesium sulfate and ethanol.
25 Ritodrine, the leading β_2 -adrenergic agonist, causes a number of cardiovascular and metabolic side effects in the mother, including tachycardia, increased renin secretion, hyperglycemia (and reactive hypoglycemia in the infant). Other β_2 -adrenergic agonists, including terbutaline and albuterol have side effects similar to those of ritodrine.
30 Magnesium sulfate at plasma concentrations above the therapeutic range of 4 to 8 mg/dL can cause inhibition of cardiac conduction and neuromuscular transmission, respiratory depression and cardiac arrest, thus making this agent unsuitable when renal function is impaired. Ethanol is as effective as ritodrine in preventing premature labor, but it

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does not produce a corresponding reduction in the incidence of fetal respiratory distress that administration of ritodrine does.

It has been proposed that a selective oxytocin antagonist would be the ideal tocolytic agent. In the last few years, evidence has accumulated to strongly suggest that the hormone oxytocin may be a physiological initiator of labor in several mammalian species including humans. Oxytocin is believed to exert this effect in part by directly contracting the uterine myometrium and in part by enhancing the synthesis and release of contractile prostaglandins from the uterine endometrium/decidua. These prostaglandins may, in addition, be important in the cervical ripening process. By these mechanisms, the process of labor (term and preterm) is initiated by a heightened sensitivity of the uterus to oxytocin, resulting in part as a result of a well-documented increase in the number of oxytocin receptors in this tissue. This "up-regulation" of oxytocin receptors and enhanced uterine sensitivity appears to be due to trophic effects of rising plasma levels of estrogen towards term. By blocking oxytocin, one would block both the direct (contractile) and indirect (enhanced prostaglandin synthesis) effects of oxytocin on the uterus. A selective oxytocin blocker, or antagonist, would likely be more efficacious for treating preterm labor than current regimens. In addition, since oxytocin at term has major effects only on the uterus, such an oxytocin antagonizing compound would be expected to have few, if any, side effects.

The compounds of the present invention can also be useful in the treatment of dysmenorrhea. This condition is characterized by cyclic pain associated with menses during ovulatory cycles. The pain is thought to result from uterine contractions and ischemia, probably mediated by the effect of prostaglandins produced in the secretory endometrium. By blocking both the direct and indirect effects of oxytocin on the uterus, a selective oxytocin antagonist can be more efficacious for treating dysmenorrhea than current regimens. An additional use for the present invention is for the stoppage of labor preparatory (i.e., prior) to Caesarean delivery.

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It is, therefore, a purpose of this invention to provide substances which more effectively antagonize the function of oxytocin in disease states in animals, preferably mammals, especially in humans. It is another purpose of this invention to prepare novel compounds which more selectively inhibit oxytocin. It is still another purpose of this invention to provide a method of antagonizing the functions of oxytocin in disease states in mammals. It is also a purpose of this invention to develop a method of preventing or treating oxytocin-related disorders of preterm labor and dysmenorrhea by antagonizing oxytocin.

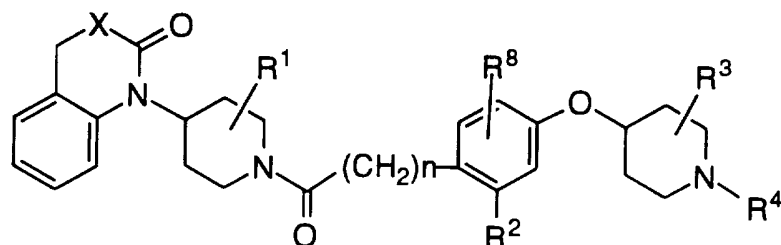
It has now been found that compounds of the present invention are antagonists of oxytocin and bind to the oxytocin receptor. When the oxytocin receptor is bound by the compounds of the present invention, oxytocin is antagonized by being blocked from its receptor and thus being unable to exert its biologic or pharmacologic effects. These compounds are useful in the treatment and prevention of oxytocin-related disorders of animals, preferably mammals and especially humans. These disorders are primarily preterm labor and dysmenorrhea. The compounds would also find usefulness for stoppage of labor preparatory to Caesarean delivery. Additionally, such compounds are useful in inducing contraception in mammals inasmuch as oxytocin antagonists have now been shown to inhibit the release of oxytocin-stimulated luteinizing hormone (LH) by anterior pituitary cells.

Compounds of the present invention are also inhibitors of vasopressin and can bind to the vasopressin receptor. These compounds are useful in inducing vasodilation, treating hypertension, inducing diuresis and inhibiting platelet agglutination.

SUMMARY OF THE INVENTION

The compounds and their pharmaceutically acceptable salts of the present invention are of the general formula

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wherein

X is selected from CH₂ or O;

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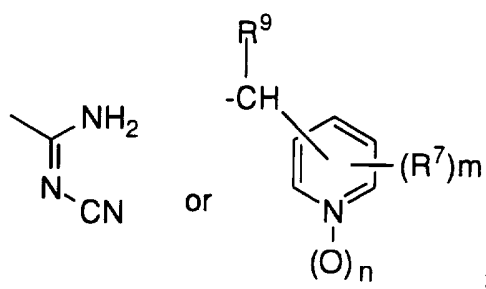
R¹ is selected from hydrogen, mono- or di-C₁₋₅ alkyl, C₁₋₅ alkoxy-substituted C₁₋₅ alkyl, CO₂H or CONH₂;

R² is selected from hydrogen or C₁₋₅ alkoxy;

10

R³ is selected from hydrogen, C₁₋₅ alkyl, di-, tri- or tetra-methyl, C₁₋₅ alkoxy-substituted C₁₋₅ alkyl, hydroxy-substituted C₁₋₅ alkyl, C₁₋₅ alkoxycarbonyl, CO₂H or CONH₂;

15 R⁴ is selected from hydrogen, C₁₋₅ alkoxycarbonyl, C₁₋₁₀ alkyl, C₃₋₈ cycloalkyl-substituted C₁₋₅ alkyl, COR⁵, SO₂R⁶,



R⁵ is selected from C₁₋₁₀ alkyl, C₁₋₅ alkoxy or NHCOR⁶;

20 R⁶ is C₁₋₁₀ alkyl;

R⁷ is selected from hydrogen, halogen, amino, mono- or di-C₁₋₅ alkylamino, C₁₋₁₀ alkyl or C₃₋₈ cycloalkyl;

- 5 -

R^8 is selected from hydrogen, C₁₋₅ alkyl or halogen;

R^9 is selected from hydrogen and C₁₋₅ alkyl;

5

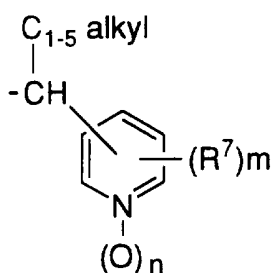
n is an integer of from 0 to 1; and

m is an integer of from 1 to 3;

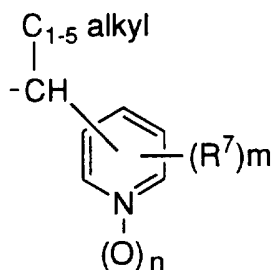
provided that when R^1 and R^3 are both simultaneously hydrogen: then

10 (a) R^8 is C₁₋₅ alkyl or halogen, and R^2 is C₁₋₅ alkoxy, or

(b) R^4 is



15 Thus, the only time that R^1 and R^3 can both simultaneously be hydrogen, is when one of two things occurs: (a) either R^8 is C₁₋₅ alkyl or halogen, and R^2 is C₁₋₅ alkoxy; or (b) R^4 is



In other words, if neither (a) nor (b) applies, then R^1 and R^3 can not both simultaneously be hydrogen.

20 In one embodiment of the instant invention are the compounds wherein

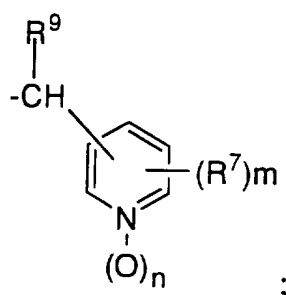
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R¹ is selected from hydrogen, C₁₋₅ alkyl or CONH₂;

R³ is selected from hydrogen, C₁-5 alkyl, C₁-5 alkoxy-substituted C₁-5 alkyl, C₁-5 alkoxycarbonyl, CO₂H or CONH₂;

5

R⁴ is selected from hydrogen, C₁₋₅ alkyl, C₃₋₈ cycloalkyl-substituted C₁₋₅ alkyl, COR⁵, SO₂R⁶ or



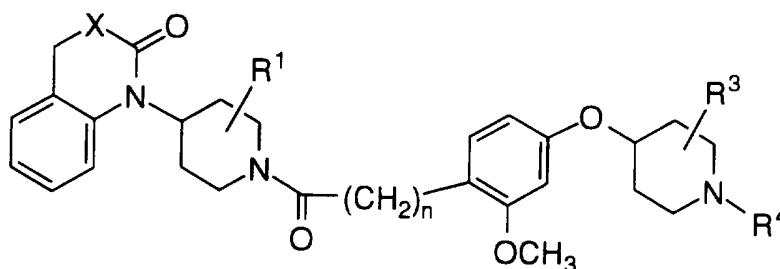
10 R⁵ is C₁₋₅ alkyl;

R⁶ is C₁₋₅ alkyl;

15 R⁷ is selected from hydrogen, chlorine, amino, mono- or di-C₁₋₅ alkylamino, C₁₋₅ alkyl or C₃₋₈ cycloalkyl; and

m is an integer of from 1 to 3, preferably, 1 to 2; where R^2 , R^8 , R^9 and n are as defined above.

In a class are the compounds of the formula



20

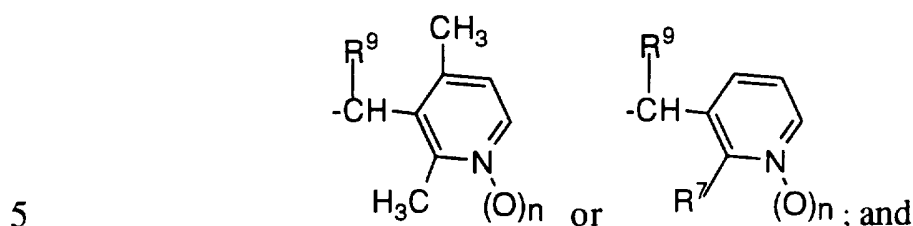
wherein

R³ is selected from hydrogen, C₁-5 alkyl, CH₂OCH₃,

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C₁₋₅ alkoxy carbonyl, CO₂H or CONH₂;

R⁴ is selected from hydrogen, methyl, ethyl, isopropyl, CH₂-cyclopropyl, COCH₃, SO₂CH₃.

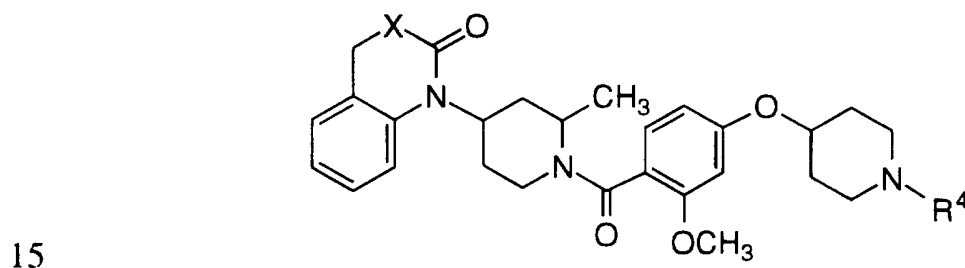


R⁷ is selected from hydrogen, methyl, ethyl, isopropyl or cyclopropyl; where R¹, R⁹ and n are as defined above.

In a subclass are the compounds wherein X is O; where R¹,
10 R³, R⁴, R⁷, R⁹ and n are as defined above.

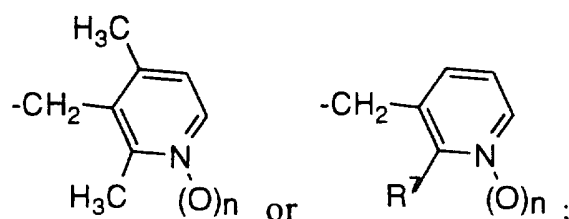
In a second subclass are the compounds wherein X is CH₂; where R¹, R³, R⁴, R⁷, R⁹ and n are as defined above.

Illustrative of the invention are the compounds of the structure



wherein

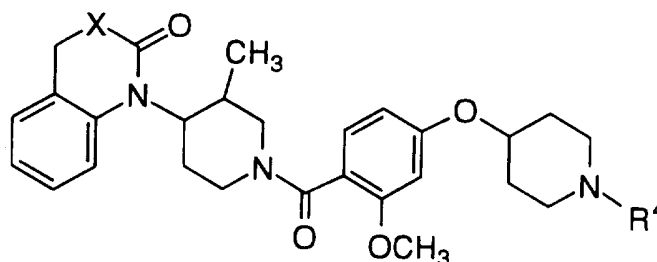
R⁴ is selected from hydrogen, isopropyl, COCH₃, SO₂CH₃.



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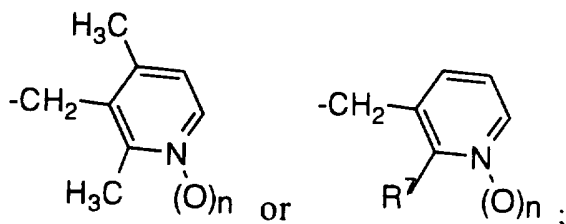
where X, R⁷ and n are as defined above.

Further illustrating the invention are compounds of the formula



5 wherein

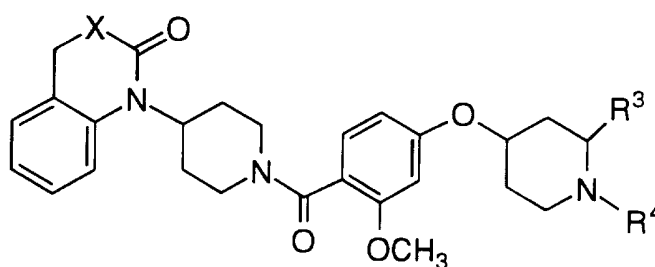
R⁴ is selected from hydrogen, isopropyl, COCH₃, SO₂CH₃,



where X, R⁷ and n are as defined above.

10

Exemplifying the invention are compounds of the formula

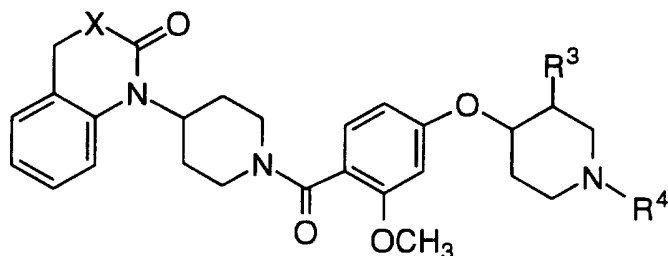


wherein R³ is selected from C₁₋₅ alkyl, CH₂OCH₃, CO₂CH₂CH₃, CO₂H or CONH₂; where X and R⁴ are as defined above. Preferably, R³ is C₁₋₅ alkyl.

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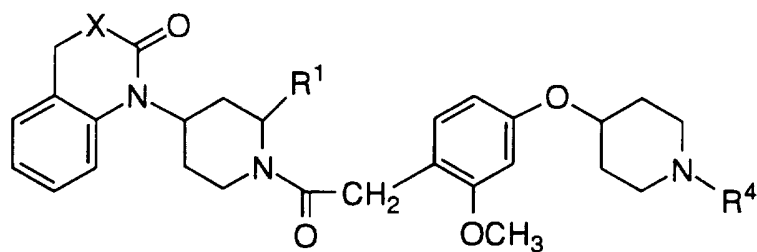
An example of the invention are compounds of the formula

- 9 -



wherein R^3 is C_{1-5} alkyl; where X and R^4 are as defined above.

An illustration of the invention are compounds of the formula



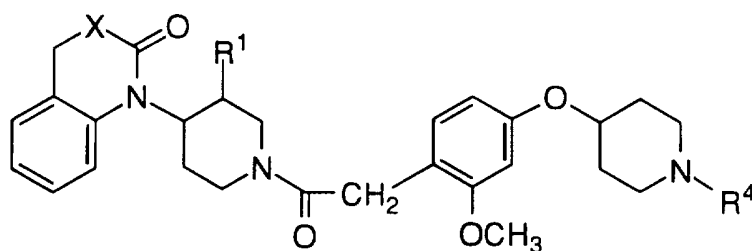
5

wherein

R^1 is selected from methyl or $CONH_2$; and

- 10 R^4 is selected from hydrogen, methyl, ethyl, isopropyl, CH_2 -cyclopropyl, $COCH_3$ or SO_2CH_3 ; where X is as defined above.

More specifically exemplifying the invention are compounds of the formula



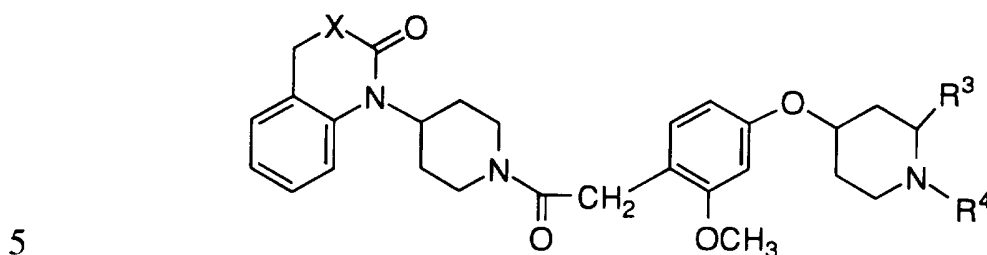
15 wherein

R^1 is C_{1-5} alkyl; and

- 10 -

R⁴ is selected from hydrogen, methyl, ethyl, isopropyl, CH₂-cyclopropyl, COCH₃ or SO₂CH₃; where X is as defined above.

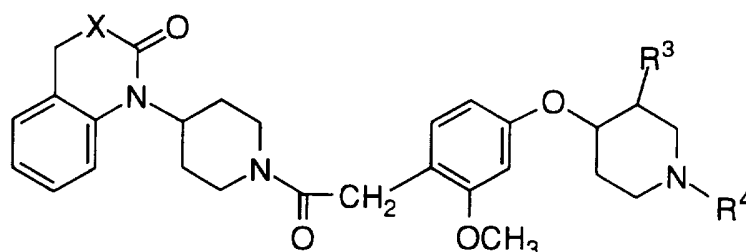
Another example of the invention are compounds of the formula



wherein

R³ is selected from C₁-5 alkyl, CH₂OCH₃, C₁-5 alkoxy carbonyl, CO₂H or CONH₂; where X and R⁴ are as defined above.

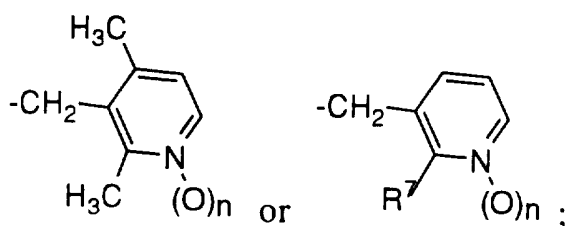
10 Further exemplifying the invention are compounds of the formula



wherein

15 R³ is C₁-5 alkyl; and

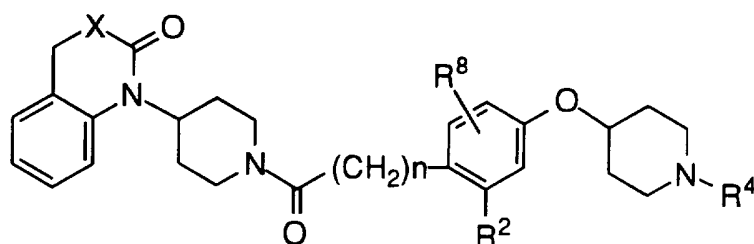
R⁴ is selected from hydrogen, isopropyl, COCH₃, SO₂CH₃,



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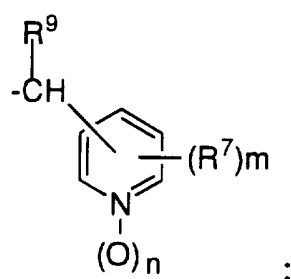
where X, R⁷ and n are as defined above.

More particularly illustrating the invention are compounds of the formula



5 wherein

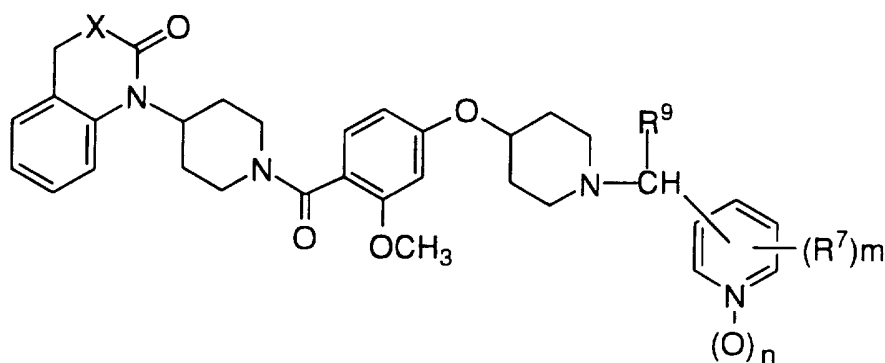
R⁴ is



10 R⁷ is selected from hydrogen, chlorine, amino, mono- or di-C₁-5 alkylamino, C₁-5 alkyl or C₃-8 cycloalkyl; and

R⁹ is C₁-5 alkyl; where X, R², R⁸, m and n are as defined above.

Another illustration of the invention are compounds of the
15 formula



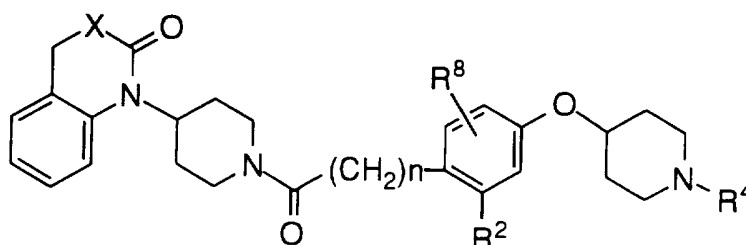
- 12 -

wherein

R^7 is selected from hydrogen, C1-5 alkyl and C3-8 cycloalkyl; and

5 R^9 is methyl; where X, m and n are as defined above.

Still another example of the invention are compounds of the formula

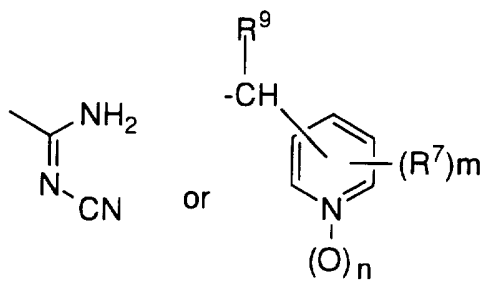


wherein

10

R^2 is C1-5 alkoxy;

R^4 is selected from C1-3 alkoxycarbonyl, C1-10 alkyl, C3-8 cycloalkyl-substituted C1-5 alkyl, COR^5 , SO_2R^6 ,



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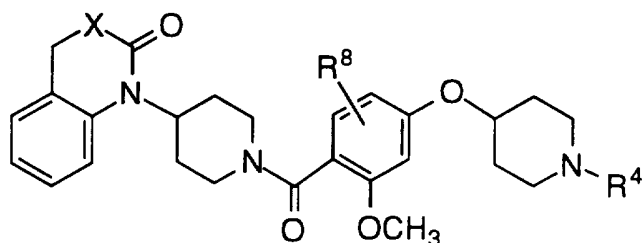
R^5 is selected from C2-10 alkyl or $NHCOR^6$; and

R^8 is selected from C1-5 alkyl or halogen; where X, R^6 , R^7 , R^9 , m and n are as defined above.

20

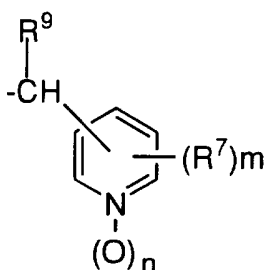
More specifically exemplifying the invention are compounds of the formula

- 13 -



wherein

R⁴ is



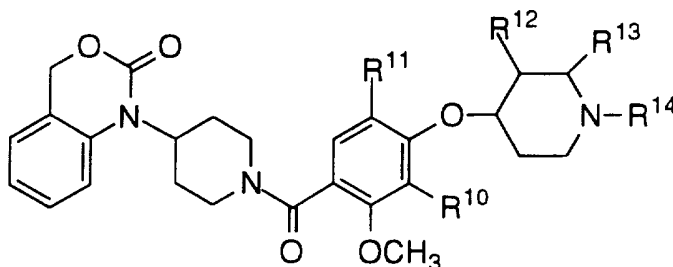
5

R⁷ is selected from hydrogen, C₁-5 alkyl or C₃-8 cycloalkyl;

R⁸ is selected from methyl, fluorine, chlorine or bromine; and

10 R⁹ is hydrogen or methyl; where X, m and n are as defined above.

In a preferred embodiment of the instant invention is a compound of the formula

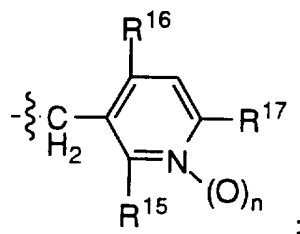


15 wherein R¹⁰ and R¹¹ are each independently selected from hydrogen, halogen or C₁-6 alkyl;

R¹² and R¹³ are each independently selected from hydrogen, C₁-6 alkyl or CO₂-C₁-6 alkyl;

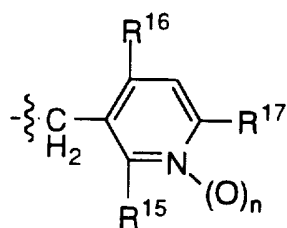
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R¹⁴ is selected from hydrogen, CO-C₁₋₆ alkyl, CO₂-C₁₋₆ alkyl or



R¹⁵, R¹⁶ and R¹⁷ are each independently selected from hydrogen or C₁₋₆ alkyl; and

- 5 n is integer from zero to one;
provided that when R¹⁰, R¹¹, R¹² and R¹³ are all simultaneously hydrogen, then R¹⁴ is

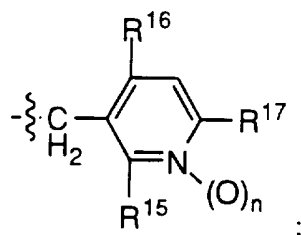


- wherein R¹⁵, R¹⁶ and R¹⁷ are each independently C₁₋₆ alkyl;
10 and the pharmaceutically acceptable salts thereof.

In a class of this preferred embodiment is the compound

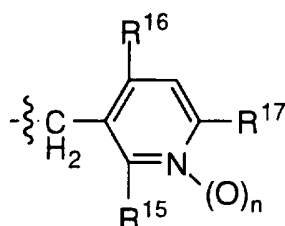
wherein

- R¹⁰ is selected from hydrogen or methyl;
R¹¹ is selected from hydrogen, bromine or fluorine;
15 R¹² is selected from hydrogen or methyl;
R¹³ is selected from hydrogen or CO₂CH₃;
R¹⁴ is selected from hydrogen, COCH₃, CO₂C(CH₃)₃ or

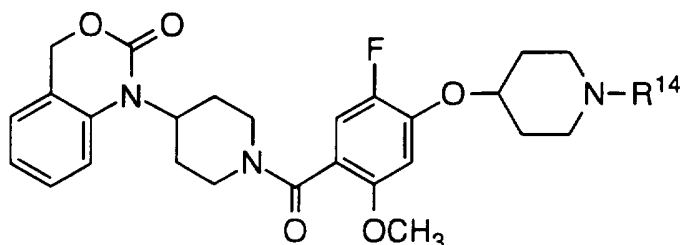


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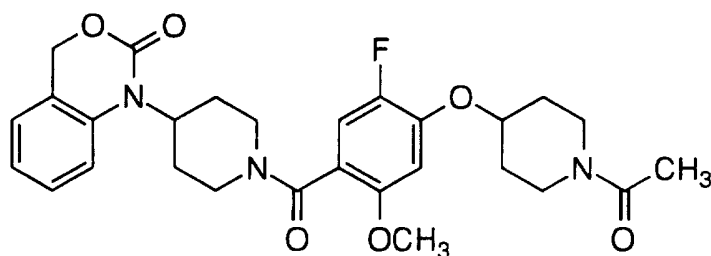
- R¹⁵, R¹⁶ and R¹⁷ are each independently selected from hydrogen, methyl, ethyl or 2-propyl; and
 n is integer from zero to one;
 provided that when R¹⁰, R¹¹, R¹² and R¹³ are all simultaneously
 5 hydrogen, then R¹⁴ is



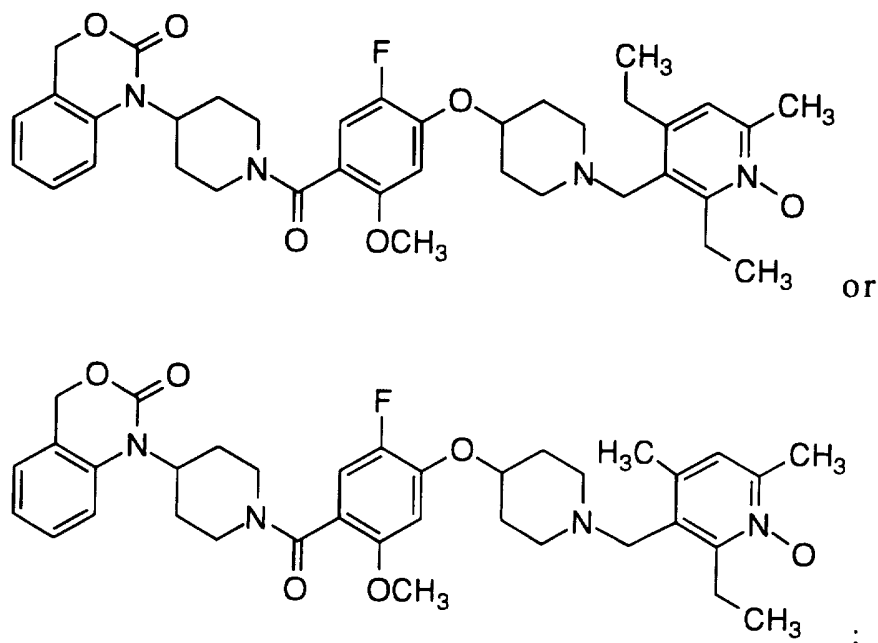
- wherein R¹⁵, R¹⁶ and R¹⁷ are each independently selected from methyl, ethyl or 2-propyl;
 and the pharmaceutically acceptable salts thereof.
 10 In a subclass of this preferred embodiment is the compound of the formula



- wherein all other variables are as defined above;
 and the pharmaceutically acceptable salts thereof.
 15 Exemplifying this preferred embodiment is the compound selected from



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and the pharmaceutically acceptable salts thereof.

- 5 More specifically illustrating the instant invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of any of the compounds of the instant invention described above to prevent preterm labor in a mammal in need thereof.

- 10 Further illustrating the invention is a method of eliciting an oxytocin antagonizing effect in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of any of the compounds of the instant invention described above.

- 15 A further illustration of the instant invention are methods of treating preterm labor, stopping labor preparatory to cesarian delivery, and treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of any of the compounds of the instant invention described above.

- 20 Further exemplifying the invention are methods of increasing fertility and embryonic survival in a farm animal, and controlling the timing of estrus in a farm animal, comprising administering to the farm animal a pharmacologically effective amount

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of any of the oxytocin antagonist compounds of the present invention described above.

Another example of the invention is a method for improving survival of a farm animal neonate comprising controlling
5 timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal which is expected to deliver the neonate within 24 hours a pharmacologically effective amount of any of the compounds of the present invention described above.

Additional examples of the invention are the use of any of
10 the compounds described above in the preparation of a medicament for the treatment of preterm labor, dysmenorrhea or stoppage of labor prior to cesarian delivery in a mammal in need thereof.

More particularly illustrating the invention is a drug which is useful for treating preterm labor, dysmenorrhea or stopping labor
15 prior to cesarian delivery in a mammal in need thereof, the effective ingredient of the said drug being any of the compounds described above.

Additional illustrations of the instant invention are methods of antagonizing vasopressin from binding to its receptor site, inducing vasodilation, treating hypertension, inducing diuresis and inhibiting
20 platelet agglutination in a mammal in need thereof comprising the step of administering to said mammal a pharmacologically effective amount of any of the compounds of the instant invention described above.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this
25 invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following:

Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium, Camsylate, Carbonate,
30 Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isothionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate,

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Methylbromide, Methylnitrate, Methylsulfate, Mucate, Napsylate, Nitrate, N-methylglucamine ammonium salt, Oleate, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Salicylate, Stearate, Sulfate, Subacetate, Succinate, 5 Tannate, Tartrate, Teoclate, Tosylate, Triethiodide and Valerate.

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. Therefore, where a compound is chiral, the 10 separate enantiomers, substantially free of the other, are included within the scope of the invention; further included are all mixtures of the two enantiomers. Also included within the scope of the invention are polymorphs and hydrates of the compounds of the instant invention.

The term "pharmacologically effective amount" shall mean 15 that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this 20 range (i.e., methyl, ethyl, 1-propyl, 2-propyl, n-butyl, t-butyl, etc.).

The term "aryl" shall mean phenyl, naphthyl or fluorenyl.

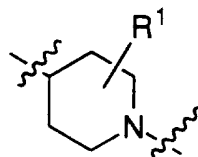
The term "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl). 25

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkoxyaryloxy) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C1-10) shall refer independently to the number of carbon atoms in an alkyl or 30 cyclic alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "halogen" shall include iodine, bromine, chlorine and fluorine.

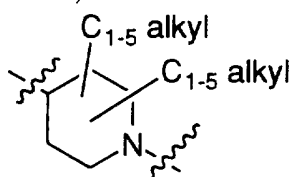
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As used herein, in the definition of R^1 , the term "mono- or di- C_{1-5} alkyl" shall mean that the piperidine ring containing the R^1 substituent can be mono- or di-substituted with a C_{1-5} alkyl group.



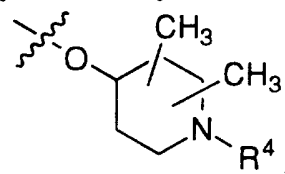
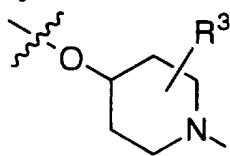
Thus, when R^1 is di- C_{1-5} alkyl, then

shall mean



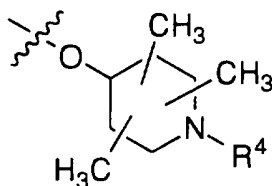
5

. Moreover, when R^1 is di- C_{1-5} alkyl, the C_{1-5} alkyl groups can be the same or different. Similarly, in the definition of R^3 , the term "di-, tri- or tetra-methyl" shall mean that the piperidine ring containing the R^3 substituent can be di-, tri- or tetra-substituted with a methyl group. Thus, when R^3 is dimethyl, trimethyl and

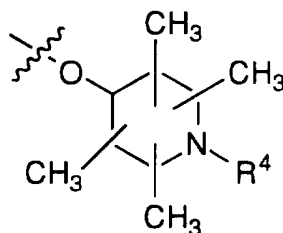


10 tetramethyl, then

shall mean



and



, respectively.

The term "preterm labor" shall mean expulsion from the uterus of a viable infant before the normal end of gestation, or more particularly, onset of labor with effacement and dilation of the cervix before the 37th week of gestation. It may or may not be associated with vaginal bleeding or rupture of the membranes.

The term "dysmenorrhea" shall mean painful menstruation. The term "Caesarean delivery" shall mean incision through the abdominal and uterine walls for delivery of a fetus.

20 The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent.

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Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally.

5 The ability of the compounds of the present invention to antagonize oxytocin makes these compounds useful as pharmacologic agents for mammals, especially for humans, for the treatment and prevention of disorders wherein oxytocin may be involved. Examples of such disorders include preterm labor and especially dysmenorrhea.
10 These compounds may also find usefulness for stoppage of labor preparatory to Cesarean delivery.

 The present invention is also directed to combinations of the compounds of formula I with one or more agents useful in the treatment of oxytocin related disorders such as preterm labor,
15 dysmenorrhea and stopping labor prior to cesarean delivery. For example, the compounds of the instant invention may be effectively administered in combination with effective amounts of other agents used in the treatment of preterm labor, such as antenatal steroids (e.g., dexamethasone). Preferred combinations are simultaneous or
20 alternating treatments of an oxytocin receptor antagonist of the present invention and an antenatal steroid. These combinations have beneficial effects on the neonate by both decreasing uterine activity to prolong gestation and increasing fetal maturation. In accordance with the method of the present invention, the individual components of the
25 combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood
30 that the scope of combinations of the compounds of this invention with other agents useful for treating oxytocin related conditions includes in principle any combination with any pharmaceutical composition useful for treating preterm labor, dysmenorrhea or stopping labor prior to cesarean delivery.

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The oxytocin antagonist compounds of the present invention are also useful for improving reproductive efficiency in farm animals. In certain farm animals (e.g., sheep, cattle, swine, horses and goats), the beginning of the estrous cycle is typically marked by behavioral estrus when the female animal accepts the male for mating. Ovulation of the ovarian follicle occurs shortly after onset of estrus and cells in the follicle give rise to the corpus luteum. The cells that form the corpus luteum produce progesterone and they also produce oxytocin. The secretion of oxytocin from the corpus luteum and/or pituitary acts on the uterine endometrium to stimulate the secretion of prostaglandins (in particular PGF) which, in turn, causes the regression of the corpus luteum of the ovary. PGF is, therefore, the luteolytic hormone. In the cycling animal (i.e., where mating and fertilization have not occurred), destruction of the corpus luteum removes the source of progesterone which is key to the preparation of the uterus for pregnancy. The presence of a viable conceptus (i.e., the embryo and its associated membranes) is necessary to prevent the luteolytic process. In fact, the first key signal that the conceptus must produce is the one to prevent regression of the corpus luteum (i.e., the maternal recognition of pregnancy signal). Thus, in the animal where mating and fertilization have occurred, the conceptus secretes a factor that antagonizes the action of oxytocin to induce luteolysis. This results in maintenance of a functioning corpus luteum and the continued secretion of progesterone which is obligatory to the initiation of pregnancy.

Administration of an oxytocin antagonist of the present invention at this critical period after fertilization (i.e., just prior to or during the period of maternal recognition of pregnancy) supplements the natural signal from the conceptus (i.e., maternal recognition of pregnancy) to prolong corpus luteal function. The result is to increase pregnancy rates by enhancing the chances of impregnation through a reduction in embryonic loss. Thus, to improve fertility and embryonic survival in a farm animal, a mated animal, for example, a mated ewe, is treated with an oxytocin antagonist compound beginning on between day 10 to day 15 after onset of estrus. The oxytocin antagonist compound is

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administered to the mated animal for a period of one day to three weeks, preferably one week to three weeks, most preferably one week to two weeks.

5 The compounds of the present invention are also useful for
controlling the timing of parturition in farm animals so that delivery of
the neonates occurs during the daytime. Approximately 80% of
livestock are delivered at night and up to 5 to 10% of newborns die
because the deliveries are not monitored properly. An oxytocin
antagonist compound of the present invention administered to the
10 mother on the evening before expected delivery delays parturition so
that the delivery occurs during the daylight hours. By delaying the
timing of parturition, proper monitoring of the delivery and the
neonates is ensured, resulting in increased survival rates of the
newborns.

15 In addition, the oxytocin antagonists of the instant invention
can also be used to control the timing of estrus in a cycling farm animal
by preventing luteal regression. An oxytocin antagonist compound of
the instant invention is administered to a cycling farm animal prior to
expected estrus to prevent regression of the corpus luteum. Daily
20 administration of the compound retards estrus until administration of
the compound ceases. Preferably, the oxytocin antagonist compound is
administered at least 1 day prior to expected estrus. By delaying estrus
in a group of farm animals, a farmer can synchronize estrus among the
group to provide time and cost savings in farm management.

25 The compounds of the present invention also bind to the
vasopressin receptor and are therefore useful as vasopressin antagonists.
Vasopressin antagonists are useful in the treatment or prevention of
disease states involving vasopressin disorders, including their use as
diuretics and their use in congestive heart failure.

30 The compounds of the present invention can be
administered in such oral dosage forms as tablets, capsules (each
including timed release and sustained release formulations), pills,
powders, granules, elixers, tinctures, suspensions, syrups and emulsions.
Likewise, they may also be administered in intravenous (both bolus and

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infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a tocolytic agent.

5 The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound
10 or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

 Oral dosages of the present invention, when used for the
15 indicated effects, will range between about 0.03-6.0 gm/day orally. More particularly, when administered orally for the treatment of preterm labor, an effective daily dose will be in the range of 0.05 mg/kg to about 100 mg/kg of body weight, preferably, from 0.5 mg/kg to 50 mg/kg, administered in single or divided dose. For oral
20 administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of
25 the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from 0.01 to about 1.0 mg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be
30 administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be

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administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

5 In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the
10 like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary,
15 suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes
20 and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

25 The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

30 Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran

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copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

Boc = t-butyloxycarbonyl
BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
DCC = 1,3-dicyclohexylcarbodiimide
DCM = dichloromethane
DEAD = diethyl azodicarboxylate
DIEA = diisopropylethylamine
DMAP = 4-dimethylaminopyridine
DMF = dimethylformamide
Et = ethyl
EtOAc = ethyl acetate
EtOH = ethanol
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FAB MS = fast atom bombardment mass spectroscopy
HOBT or HBT = 1-hydroxybenzotriazole
HPLC = high performance liquid chromatography
LDA = lithium diisopropylamide
m-CPBA or MCPBA = meta-chloroperoxybenzoic acid
Me = methyl
MeOH = methanol
MOM = methoxymethyl
NCS = N-chlorosuccinimide
NMR = nuclear magnetic resonance

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Ph = phenyl

PPTS = pyridinium p-toluenesulfonate

TFA = trifluoroacetic acid

THF = tetrahydrofuran

5 TLC = thin layer chromatography

TMEDA = N, N, N', N'-tetramethylethylenediamine

TMS = trimethylsilyl

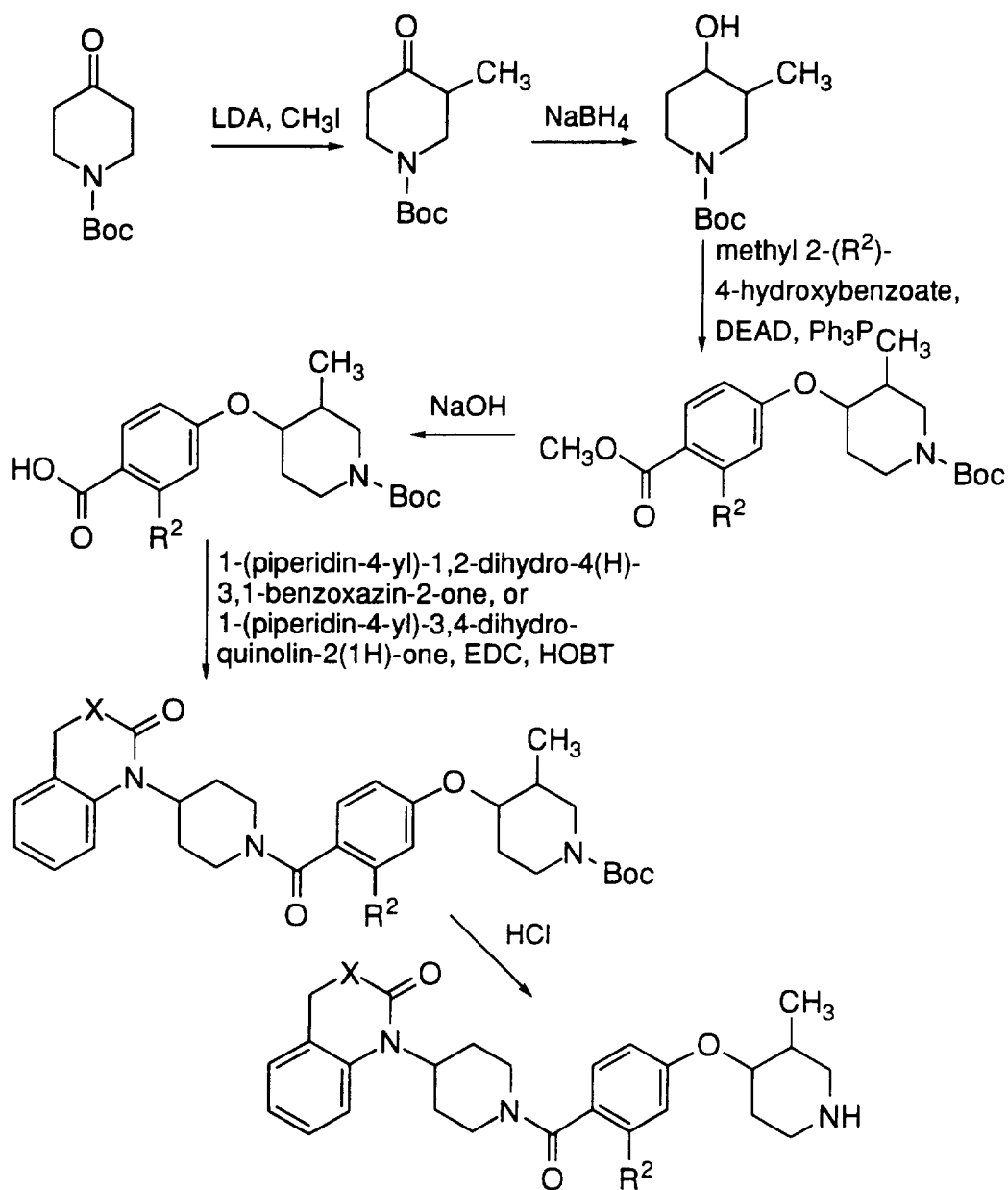
TMS-allyl = allyltrimethylsilane

10 The compounds of the present invention can be prepared readily according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is
15 those of ordinary skill in this art, but are not mentioned in greater detail.

 The compounds and pharmaceutically acceptable salts of the present invention can be synthesized according to the general methods outlined in Schemes 1-17 and the description of the schemes which
20 follow. In Schemes 1-17 which follow, the variables "X," "R¹," "R²," "R³" and "R⁷" are as defined above.

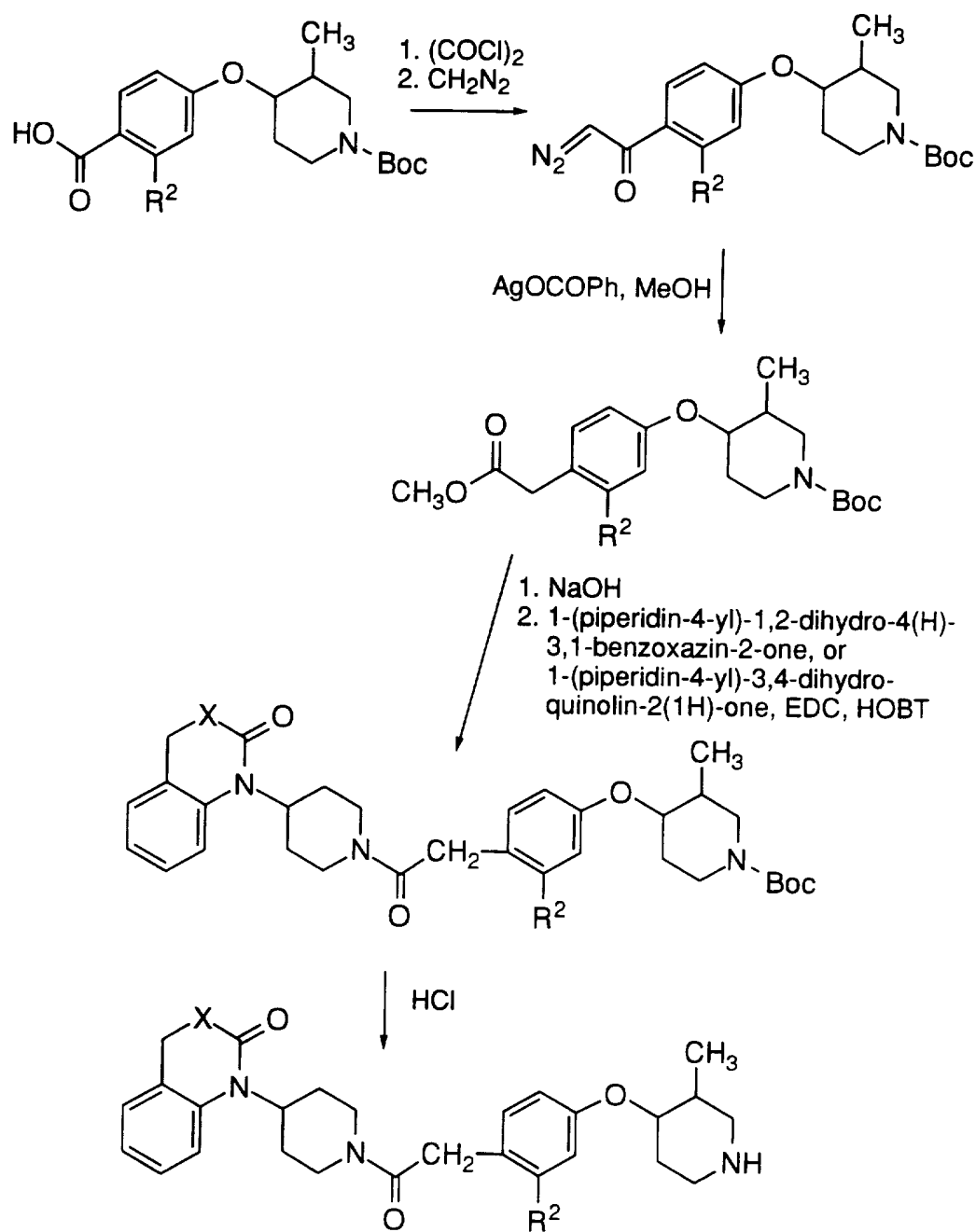
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SCHEME 1



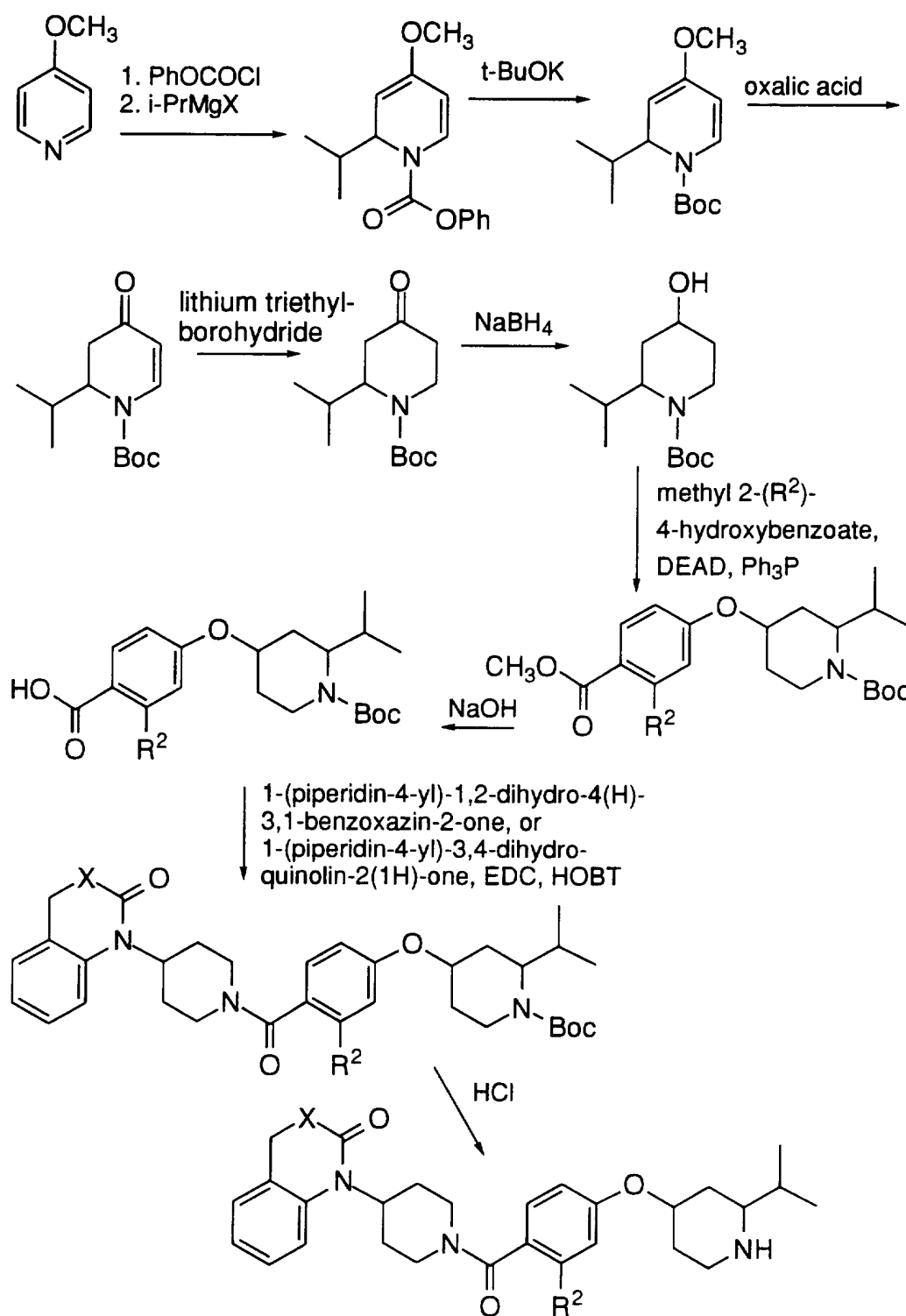
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SCHEME 1 (CONT'ED)



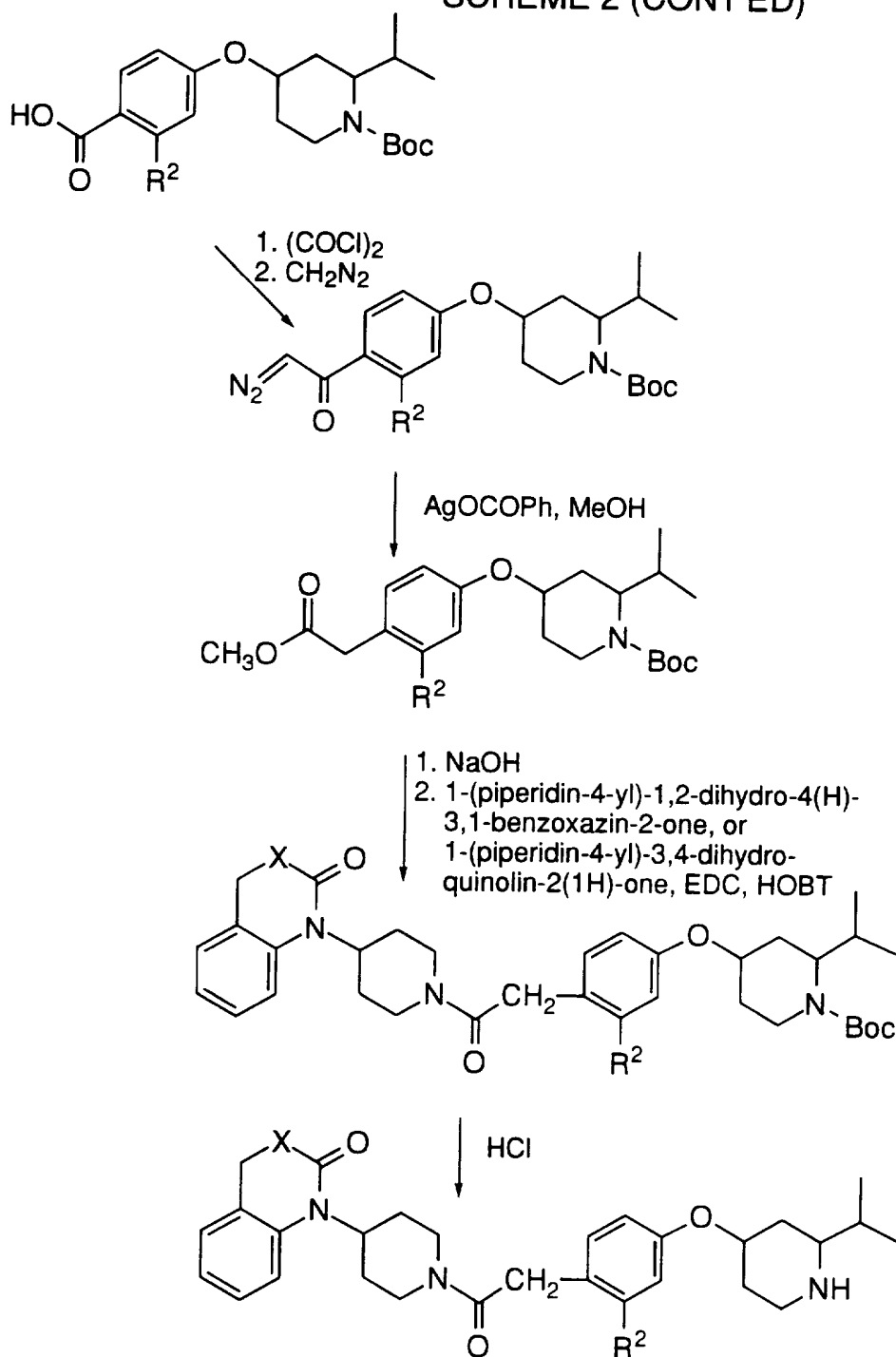
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SCHEME 2



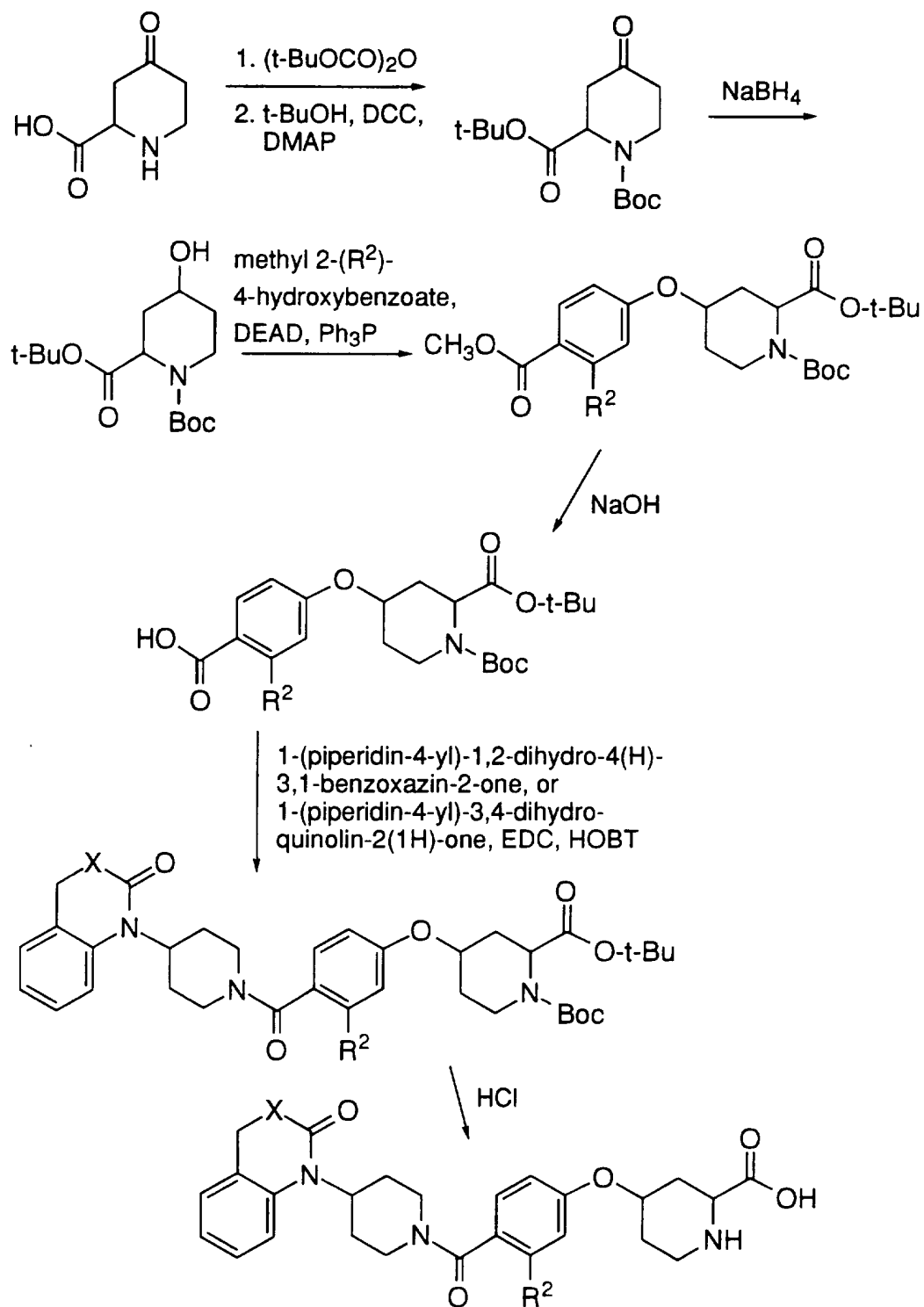
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SCHEME 2 (CONT'ED)



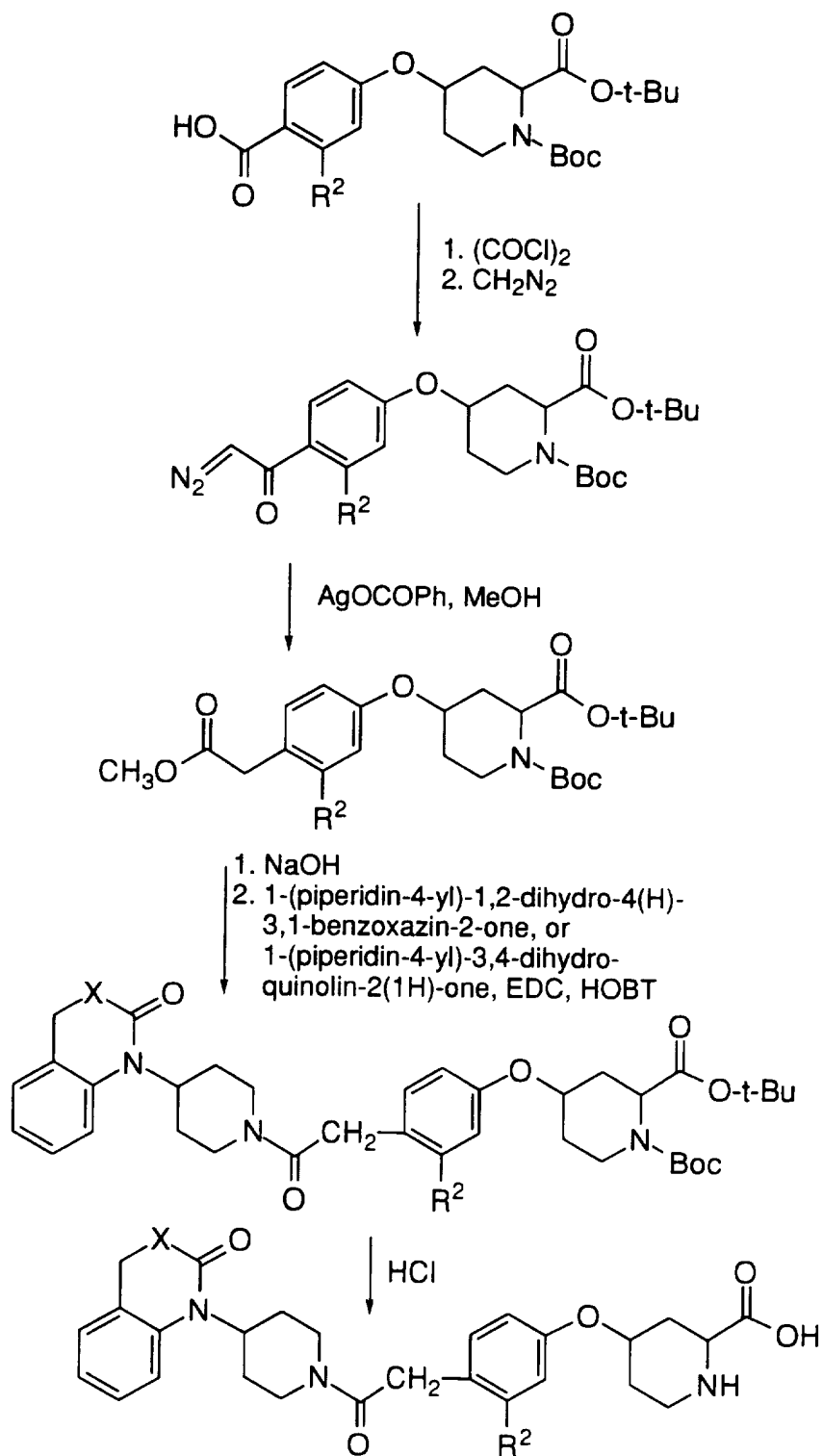
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SCHEME 3



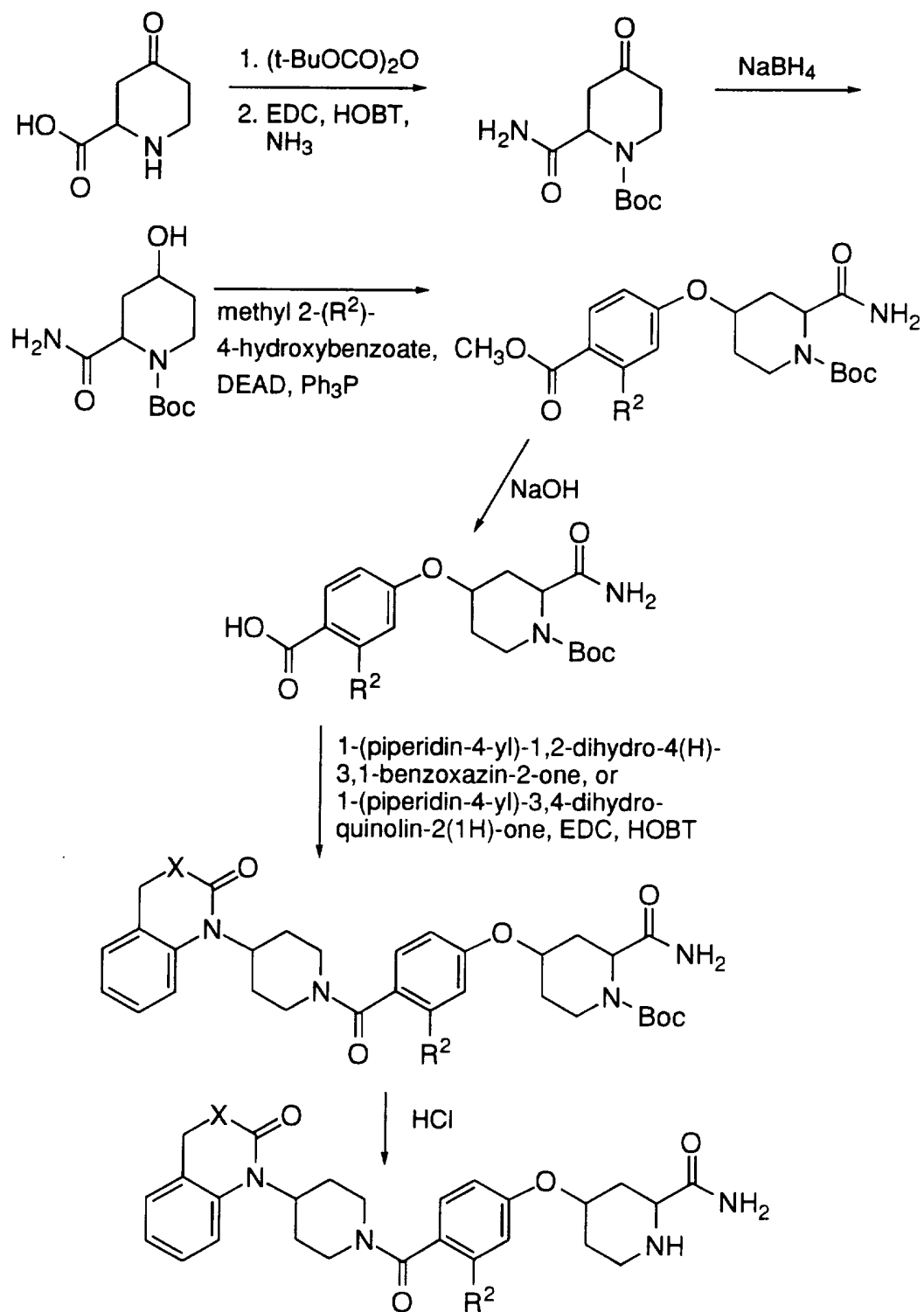
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SCHEME 3 (CONT'D)



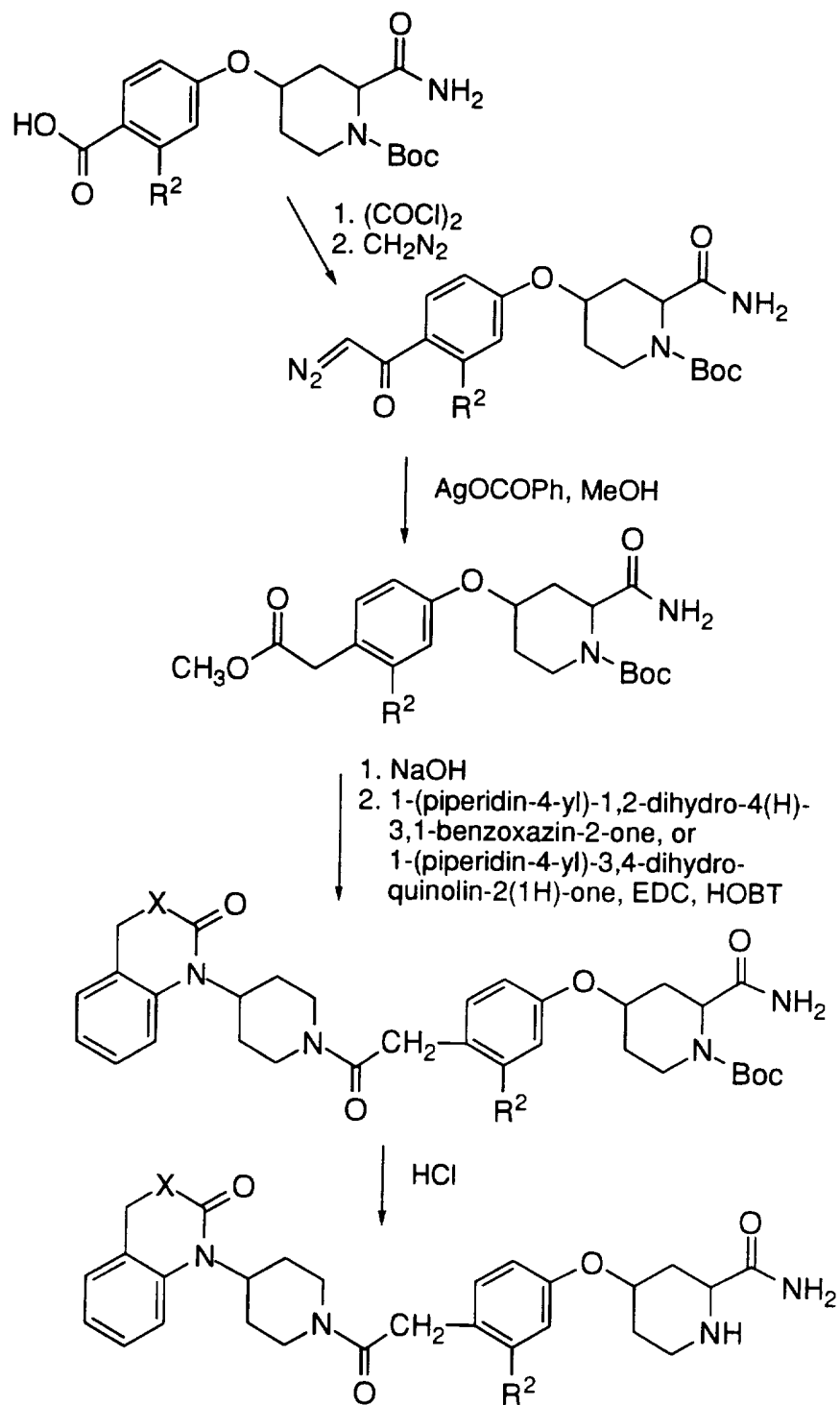
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SCHEME 4



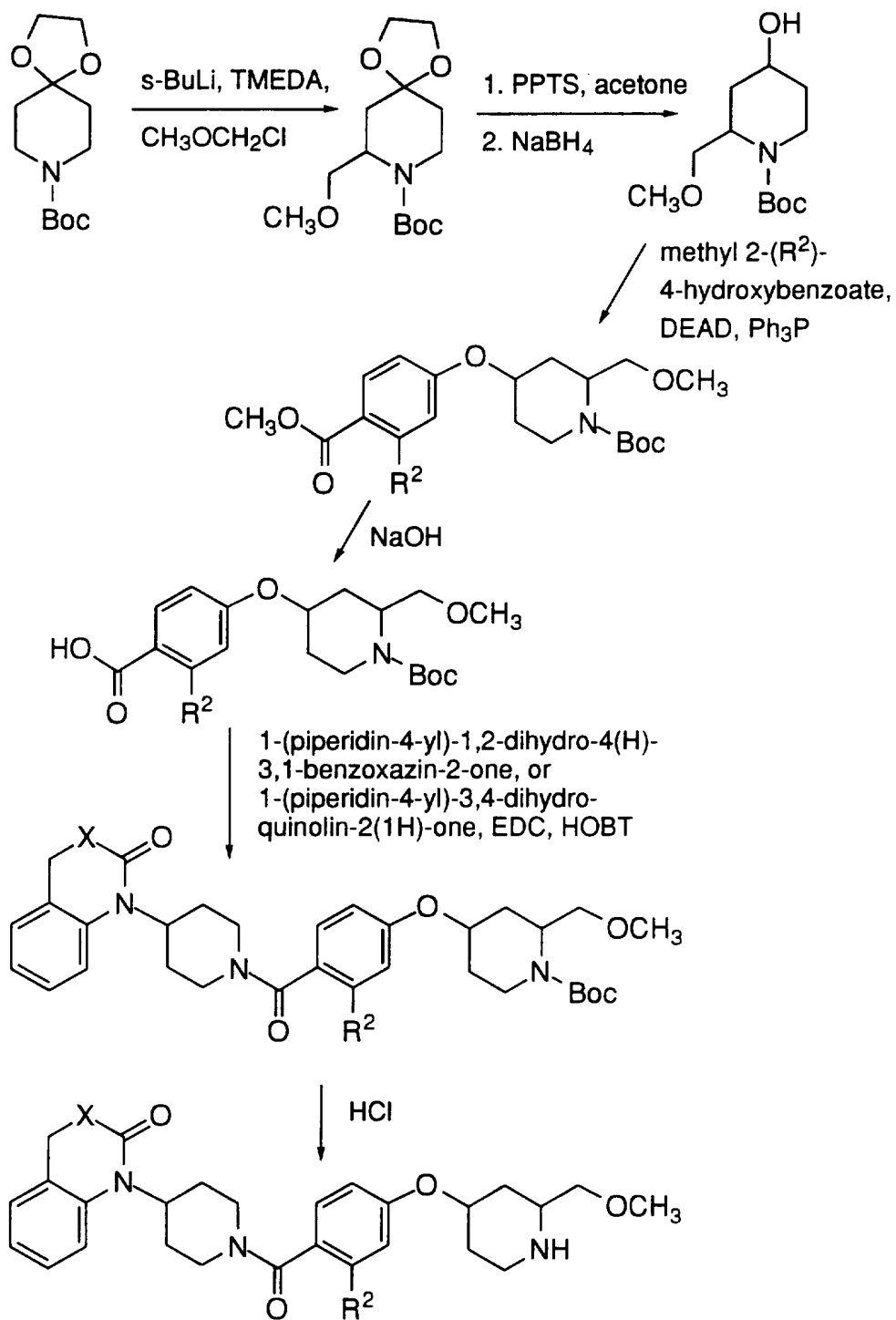
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SCHEME 4 (CONT'ED)



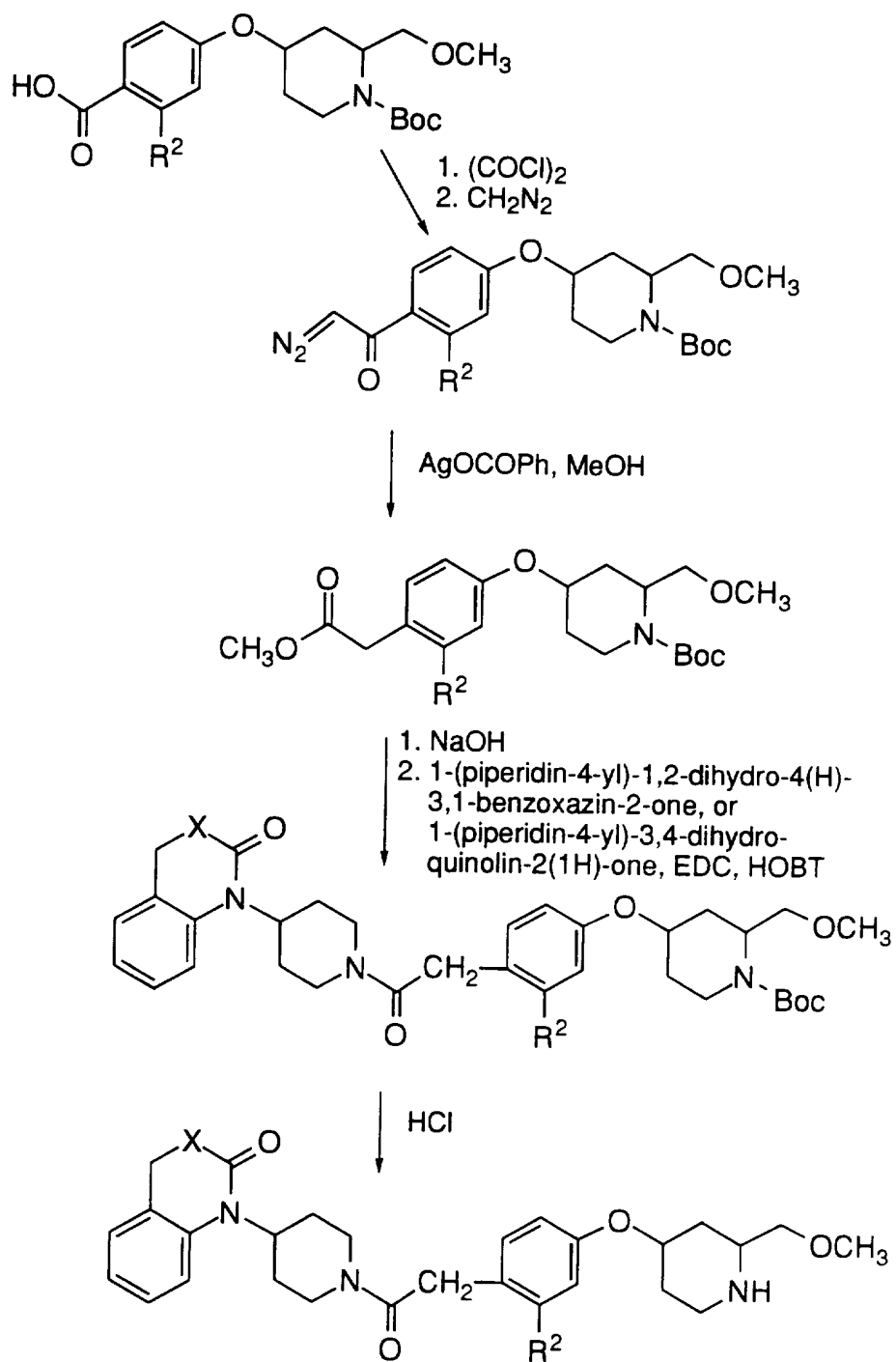
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SCHEME 5



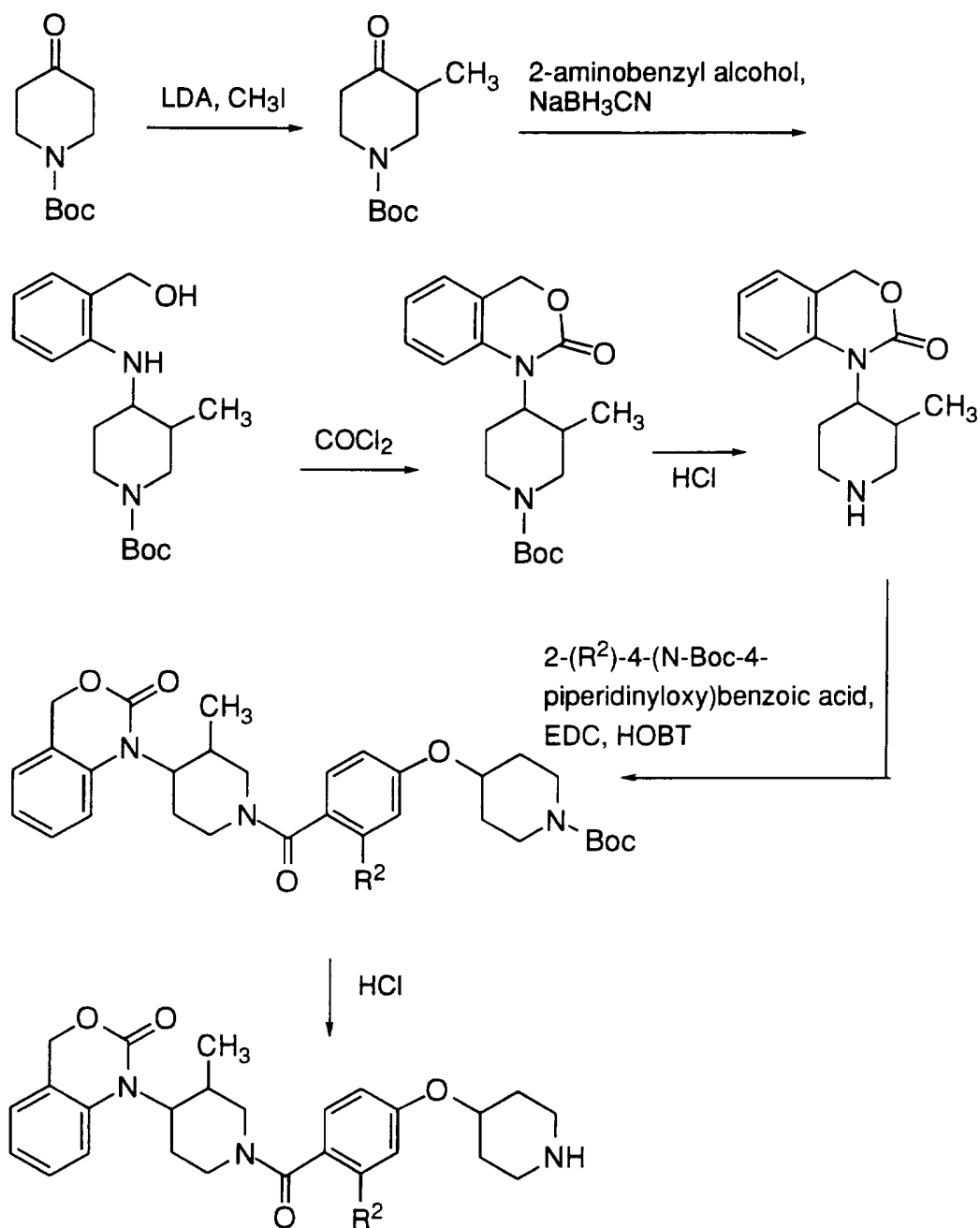
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SCHEME 5 (CONT'D)



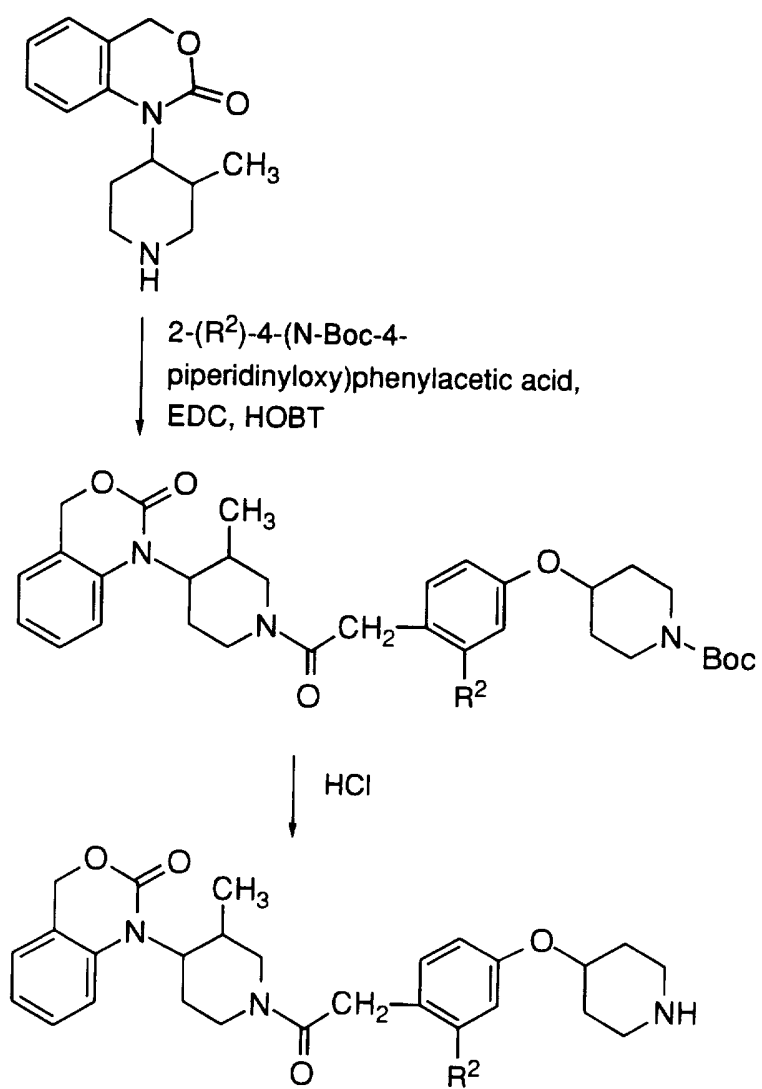
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SCHEME 6



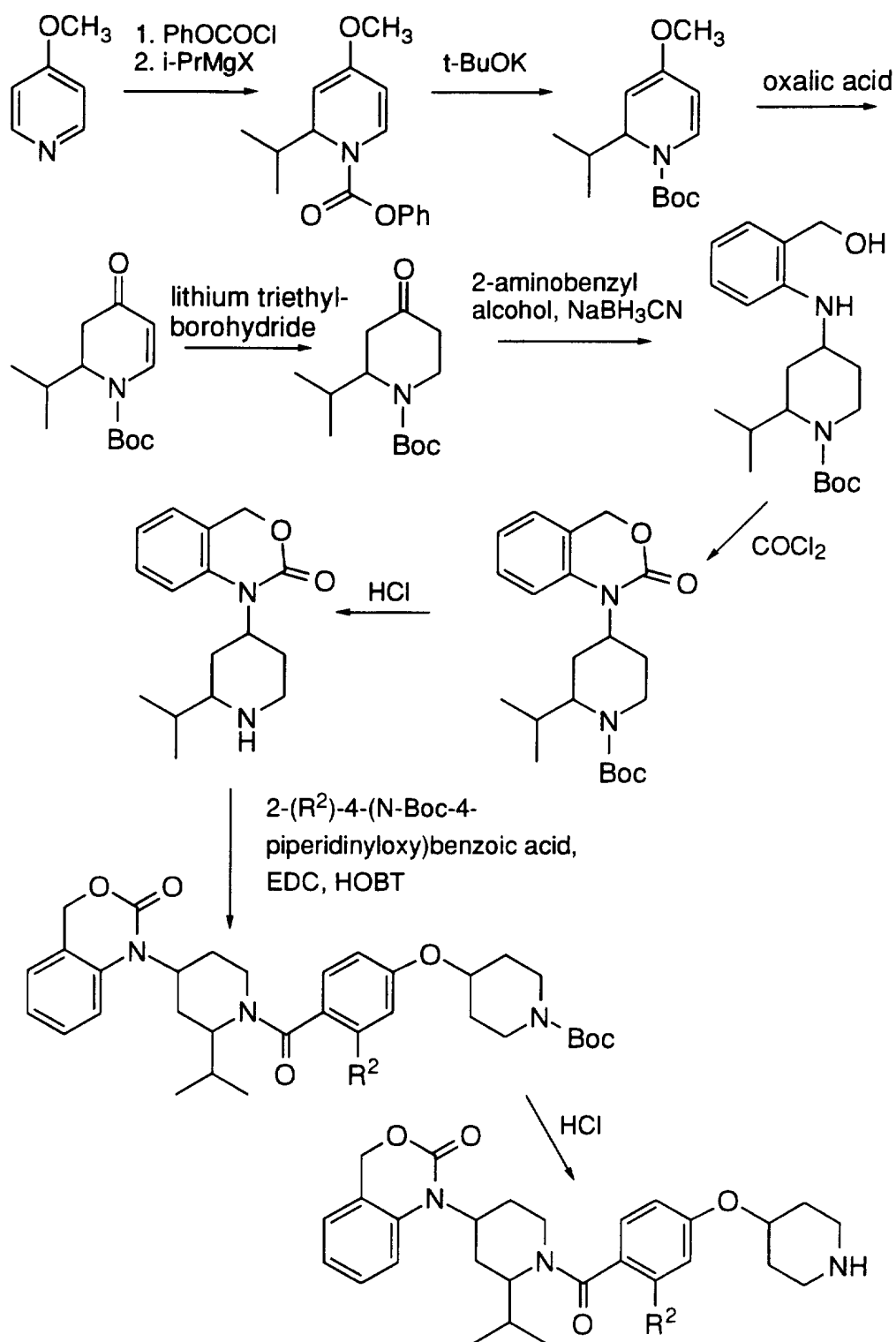
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SCHEME 6 (CONT'D)



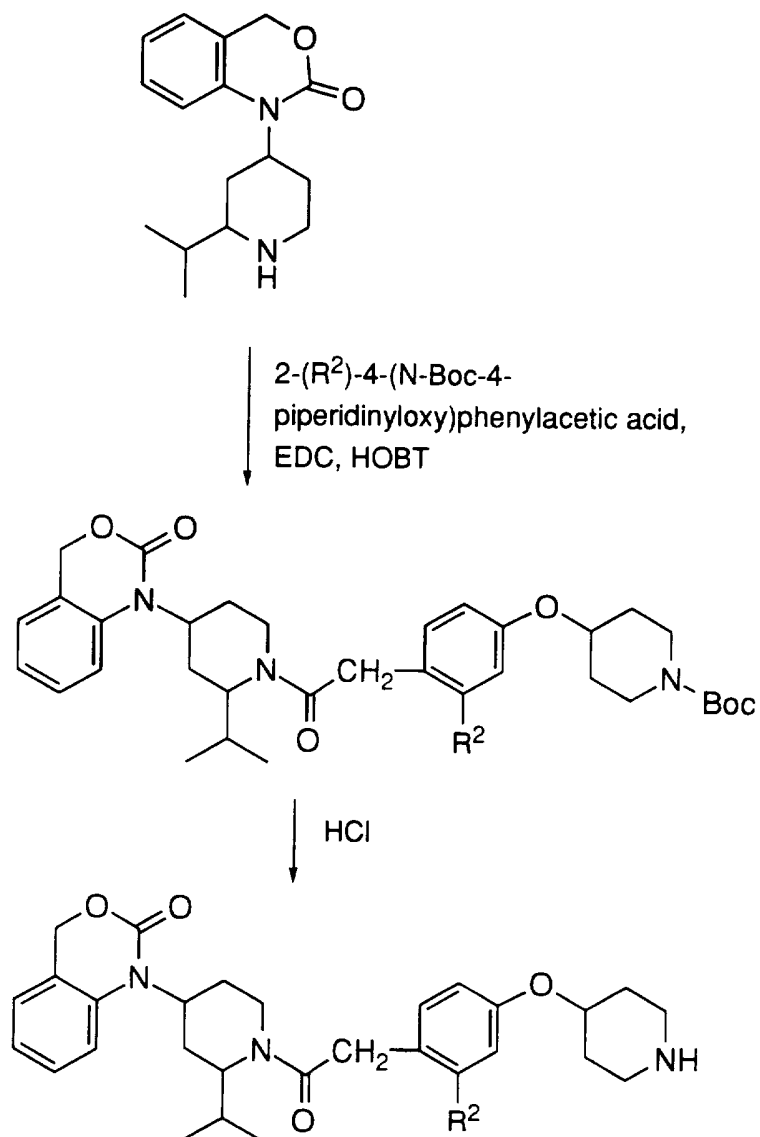
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SCHEME 7



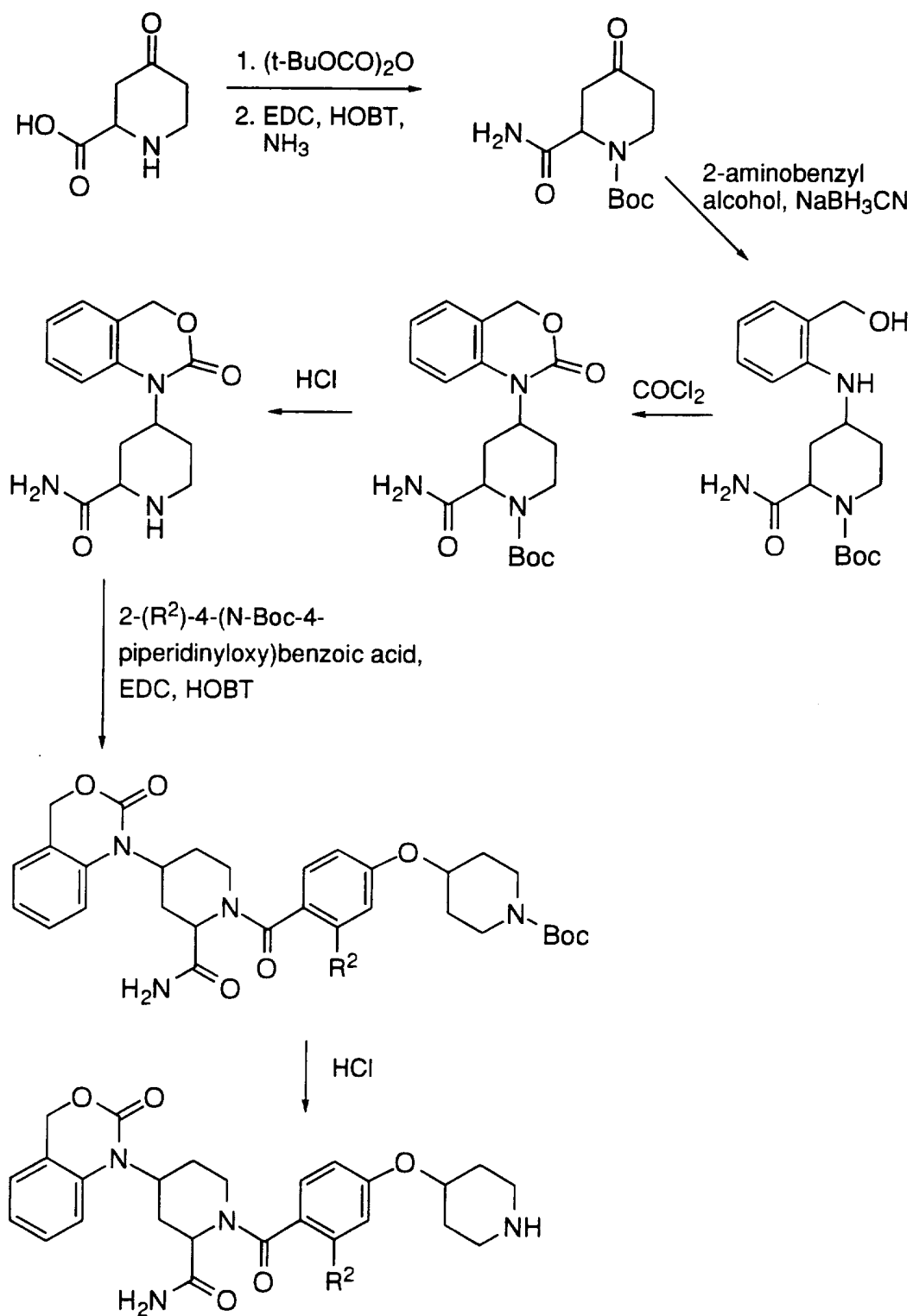
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SCHEME 7 (CONT'ED)



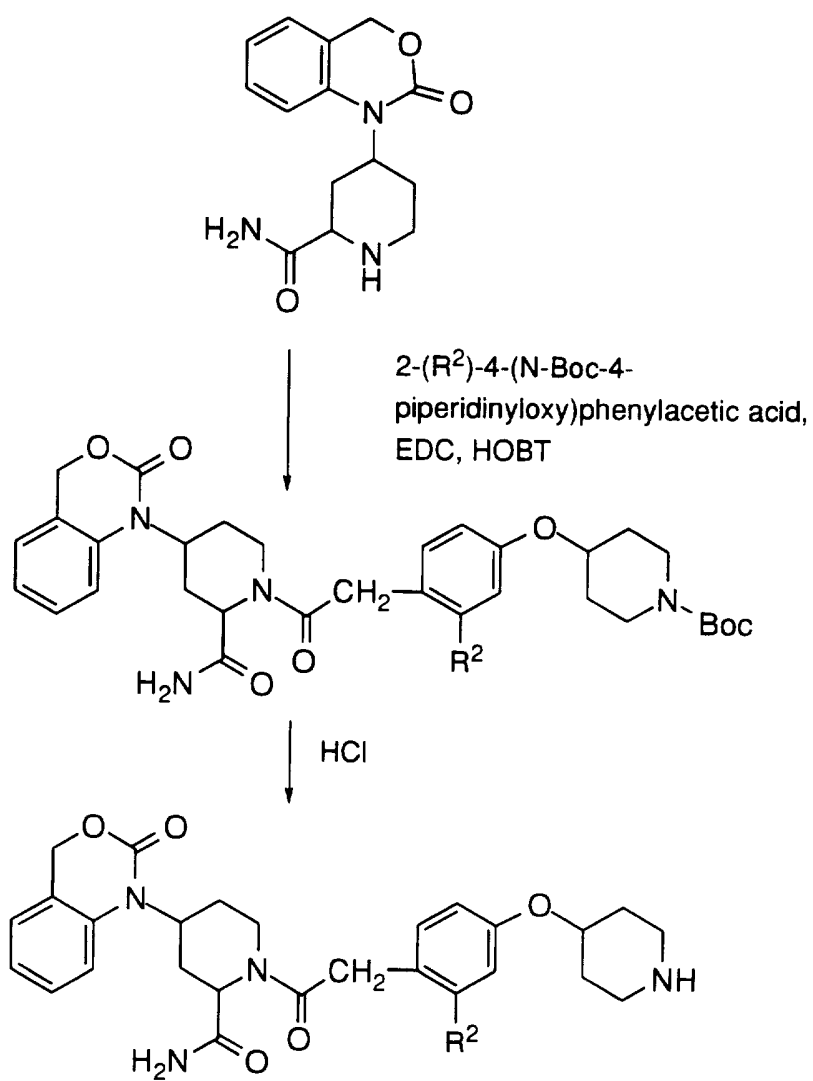
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SCHEME 8



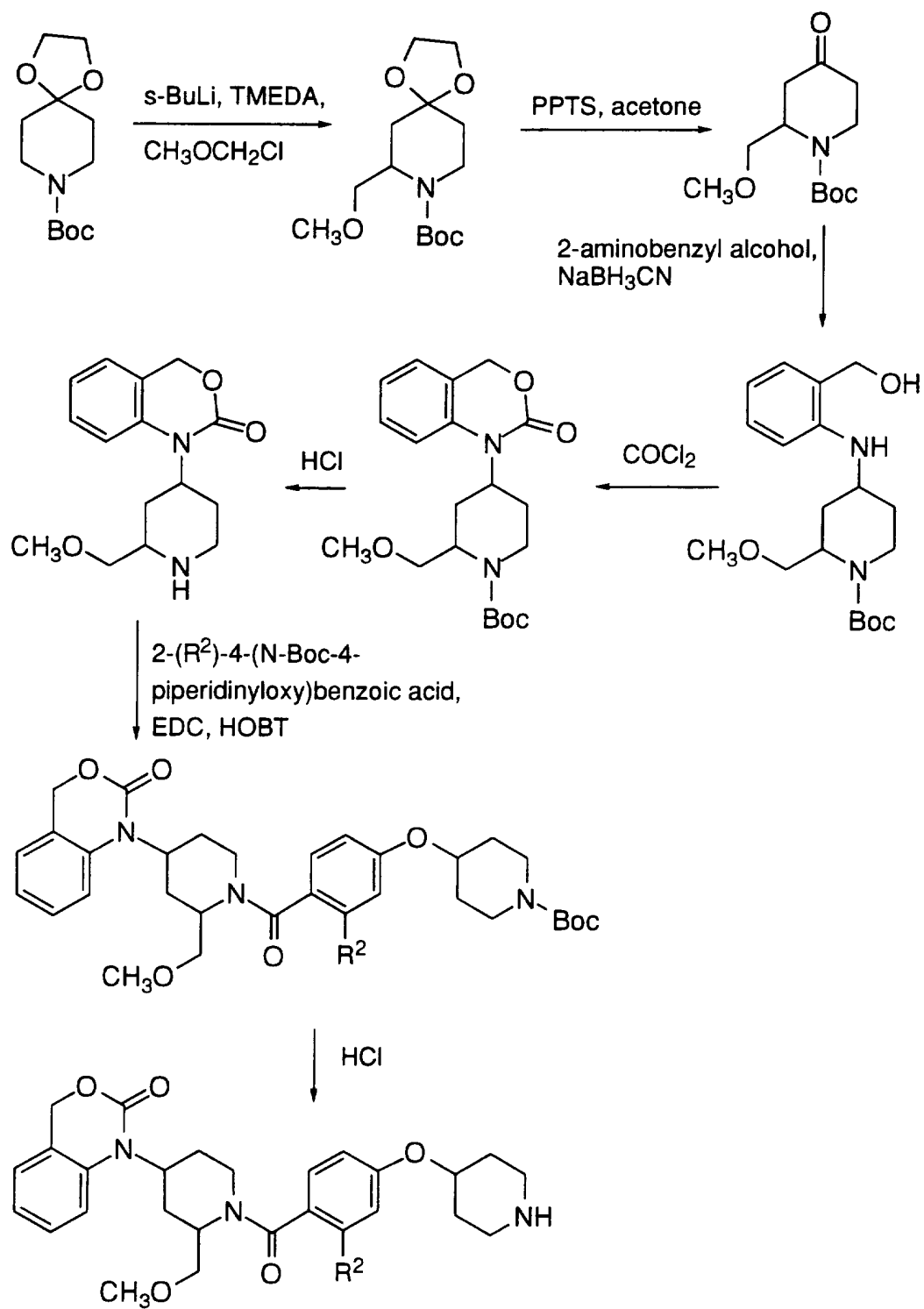
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SCHEME 8 (CONT'ED)



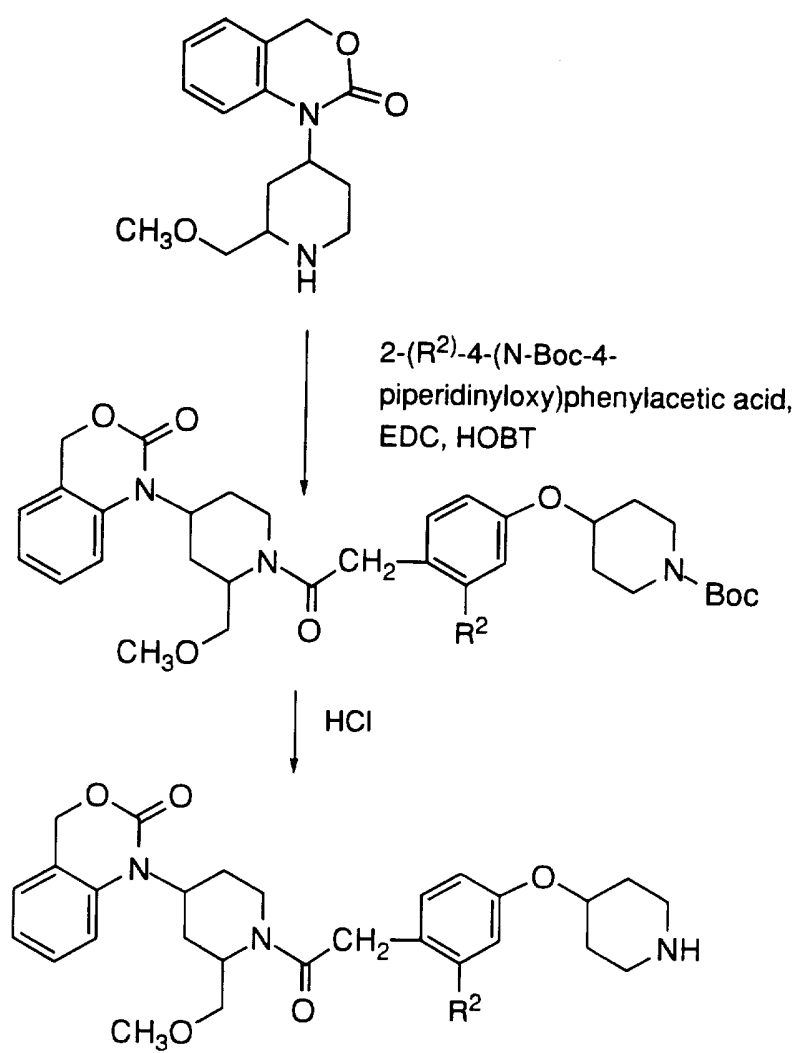
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SCHEME 9



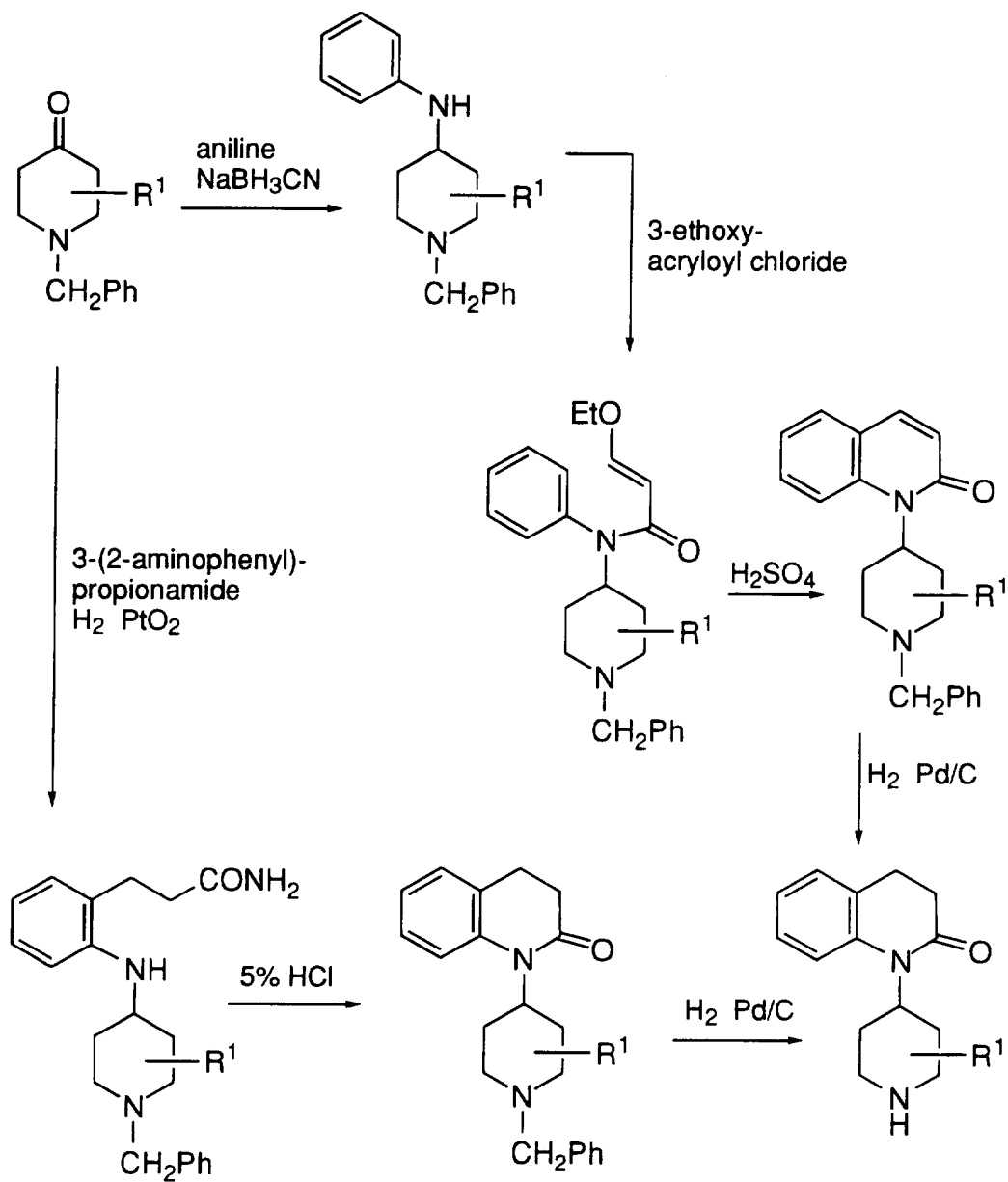
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SCHEME 9 (CONT'ED)



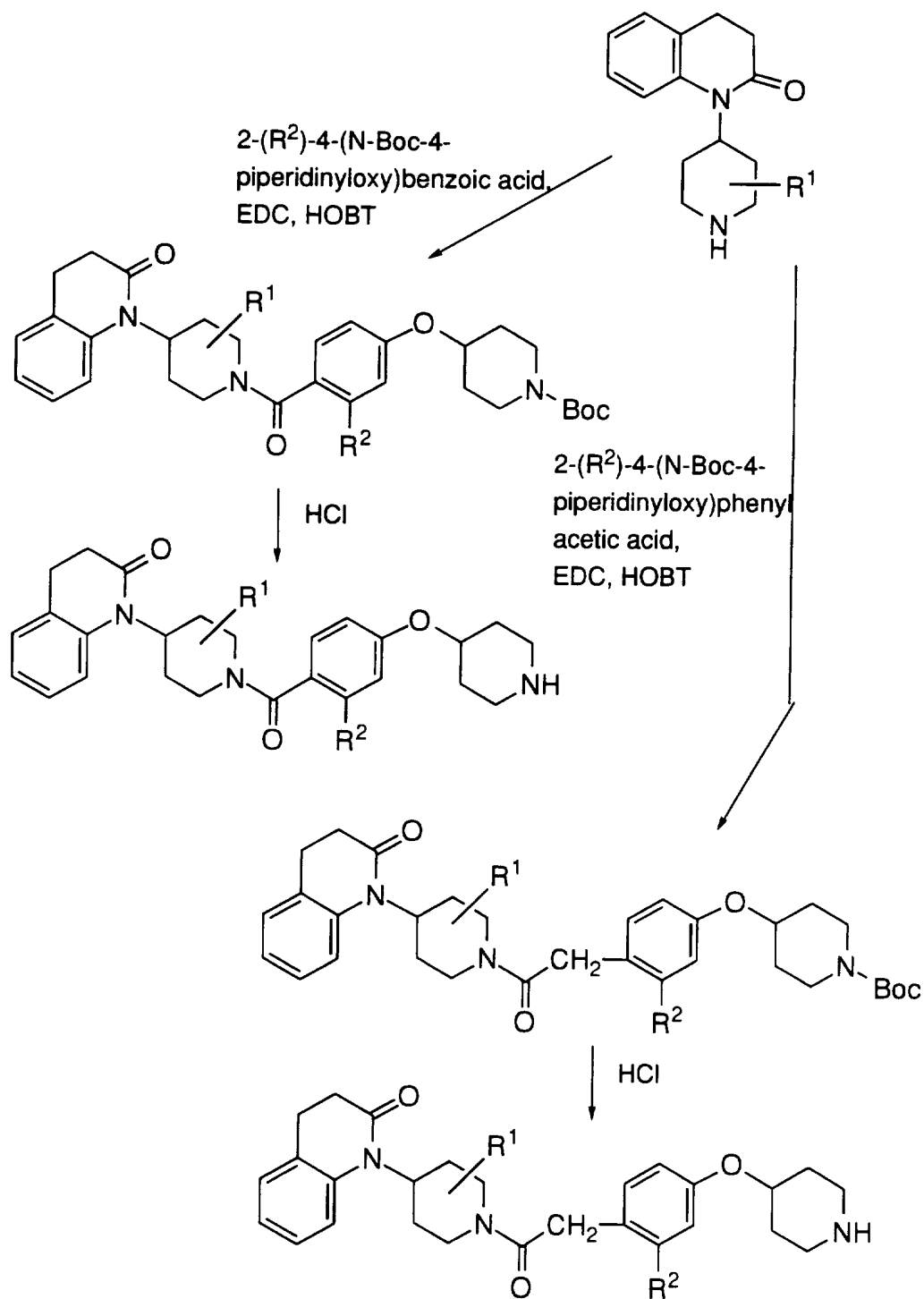
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SCHEME 10



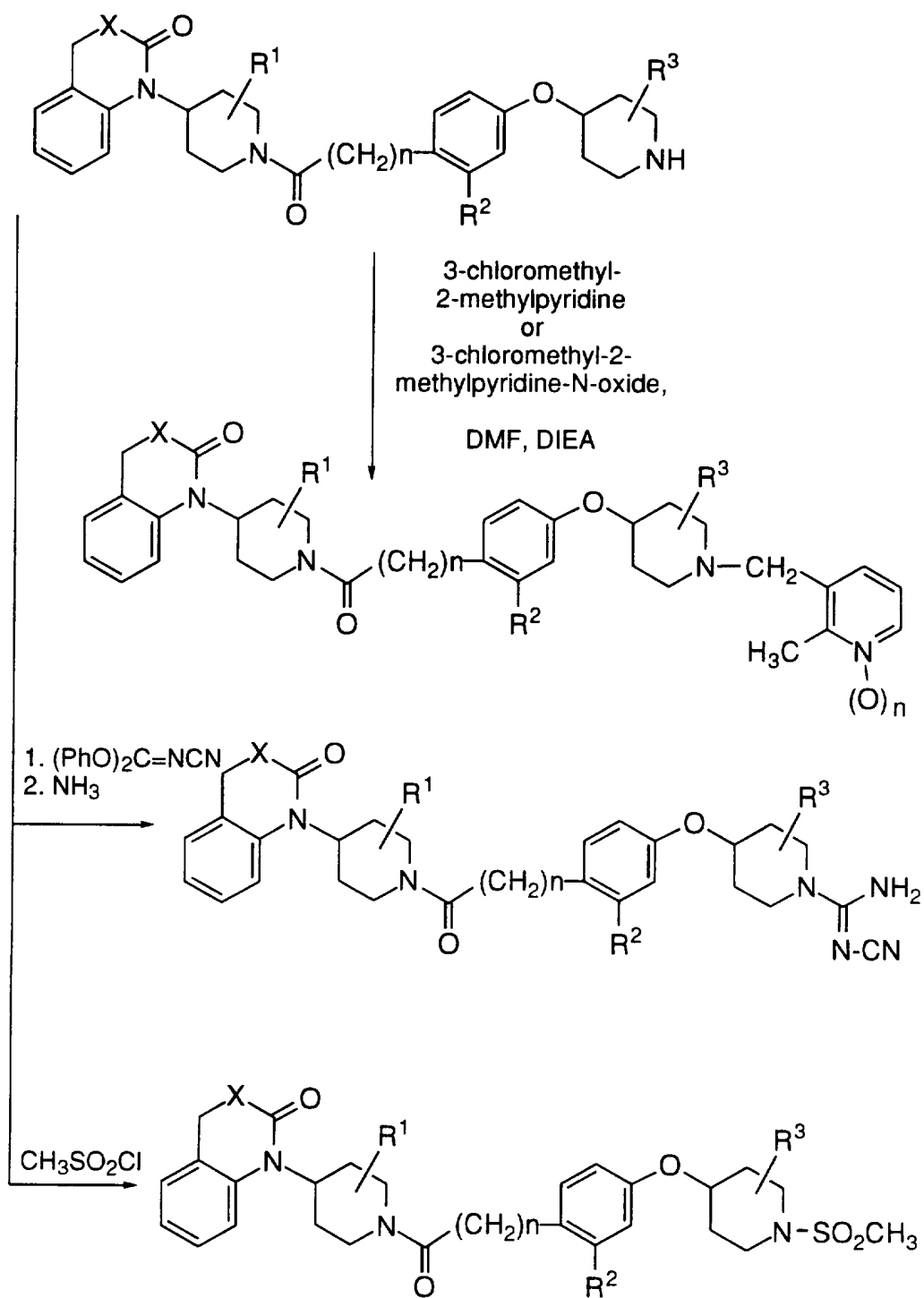
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SCHEME 10 (CONT'ED)



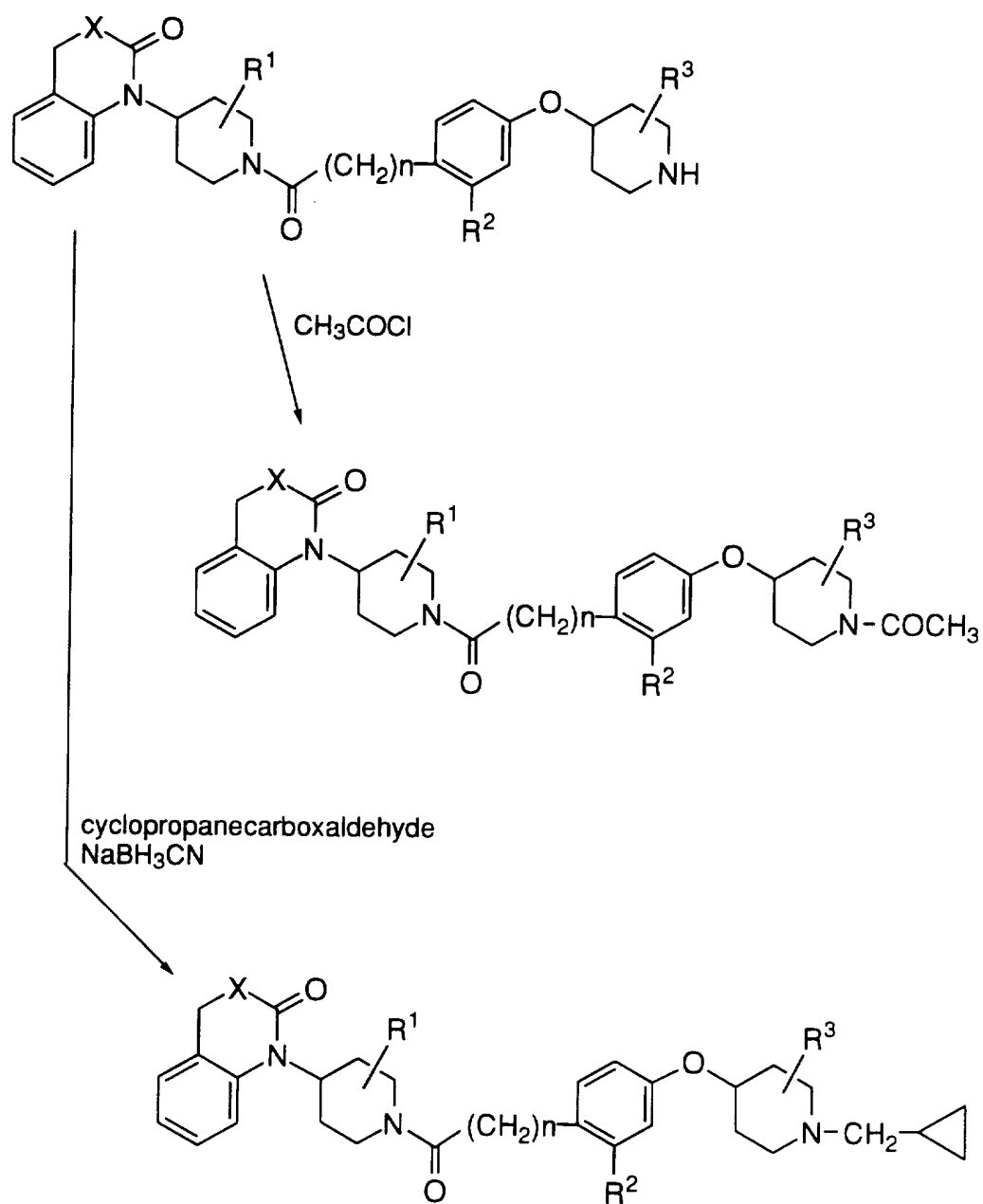
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SCHEME 11



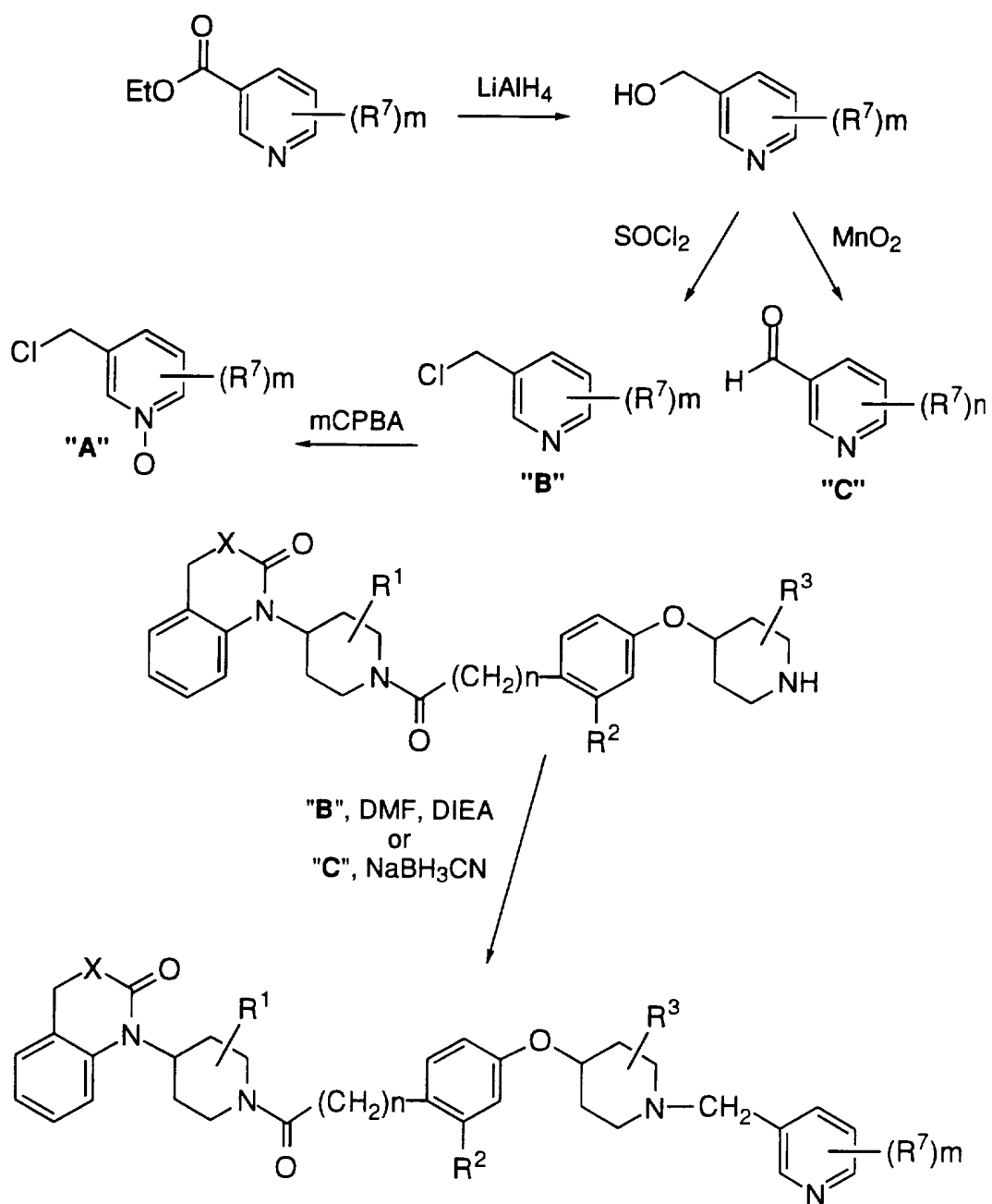
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SCHEME 11 (CONT'D)



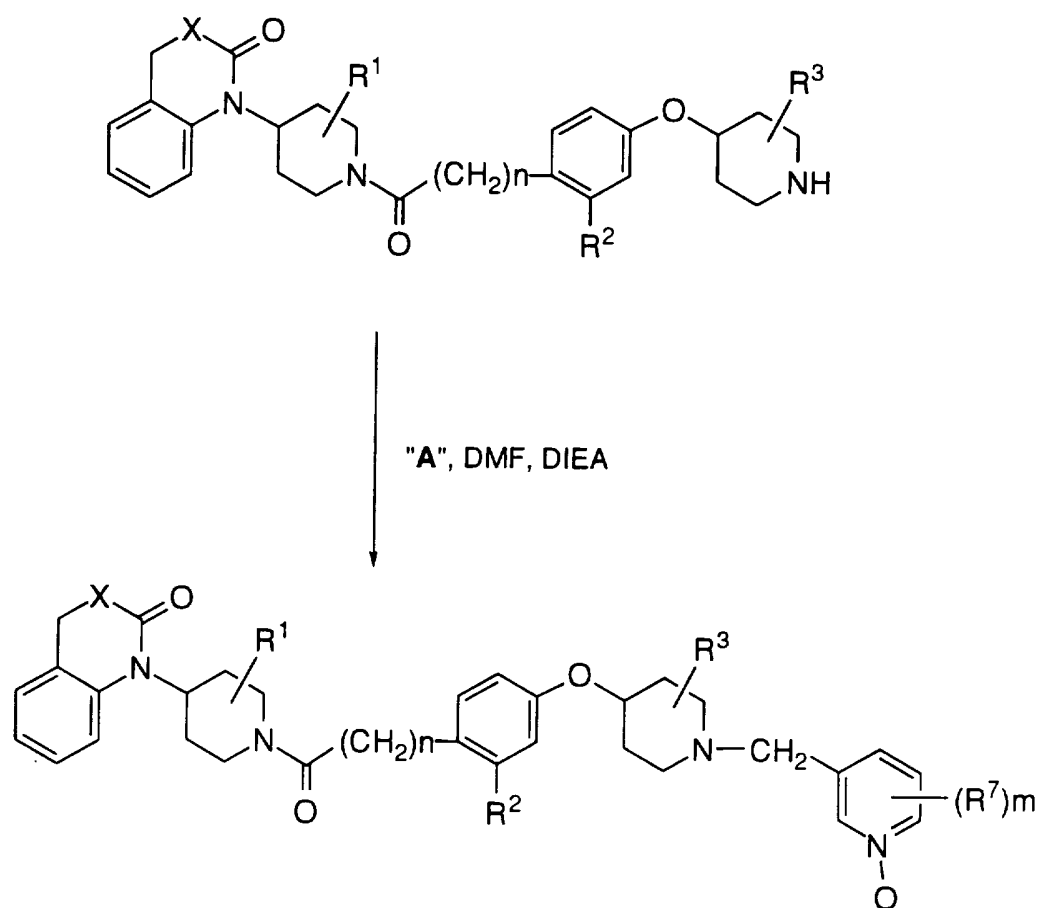
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SCHEME 12



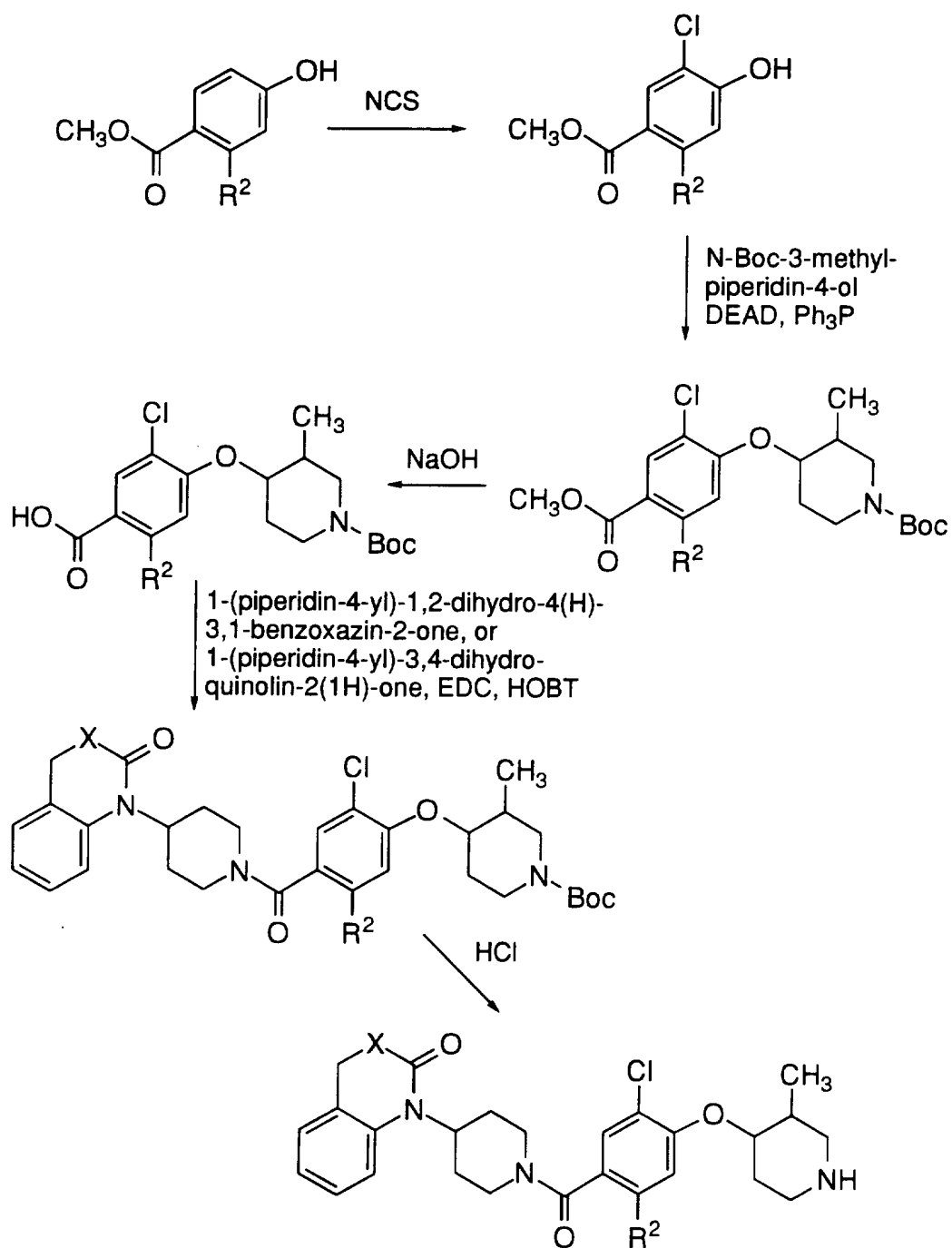
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SCHEME 12 (CONT'ED)



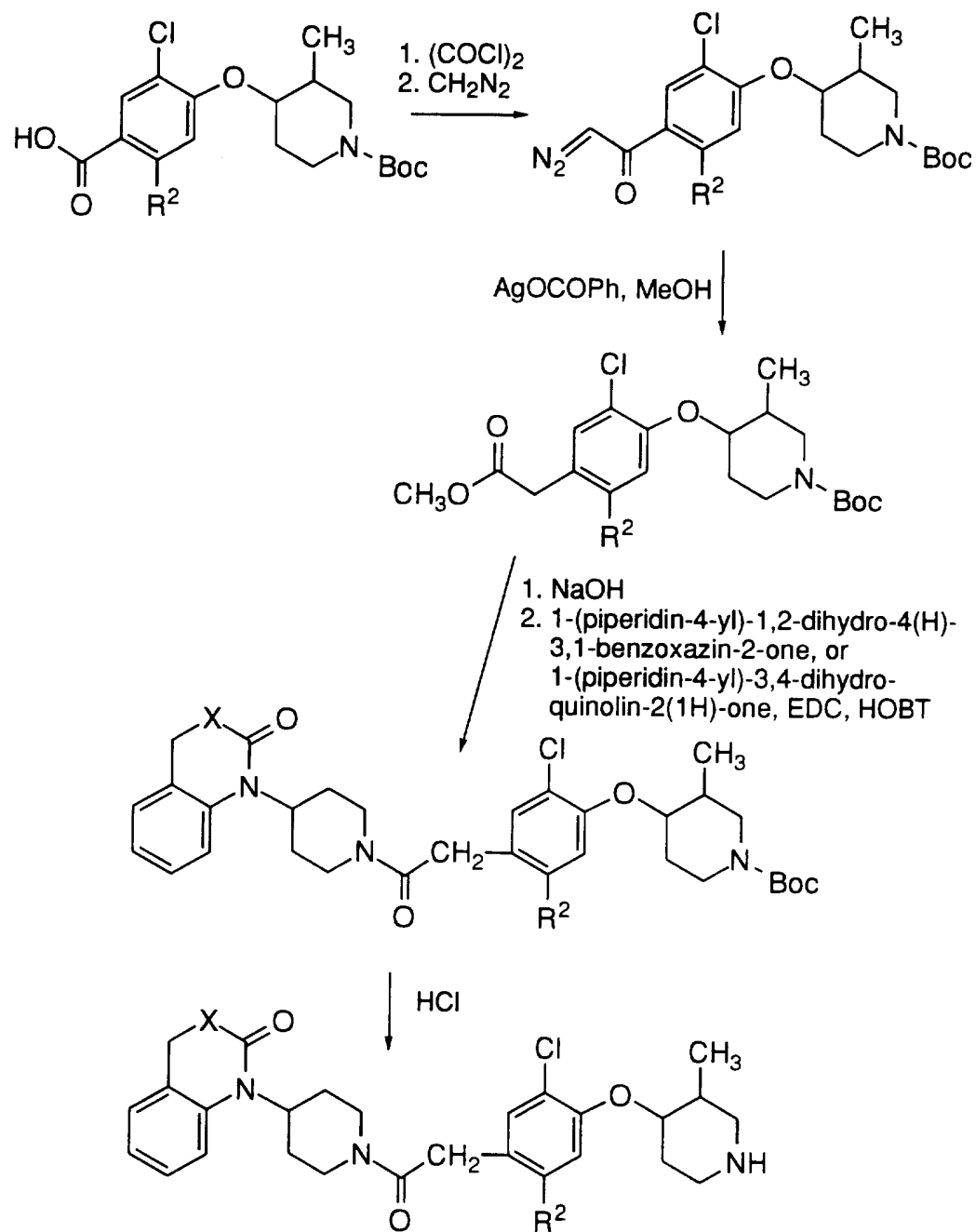
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SCHEME 13



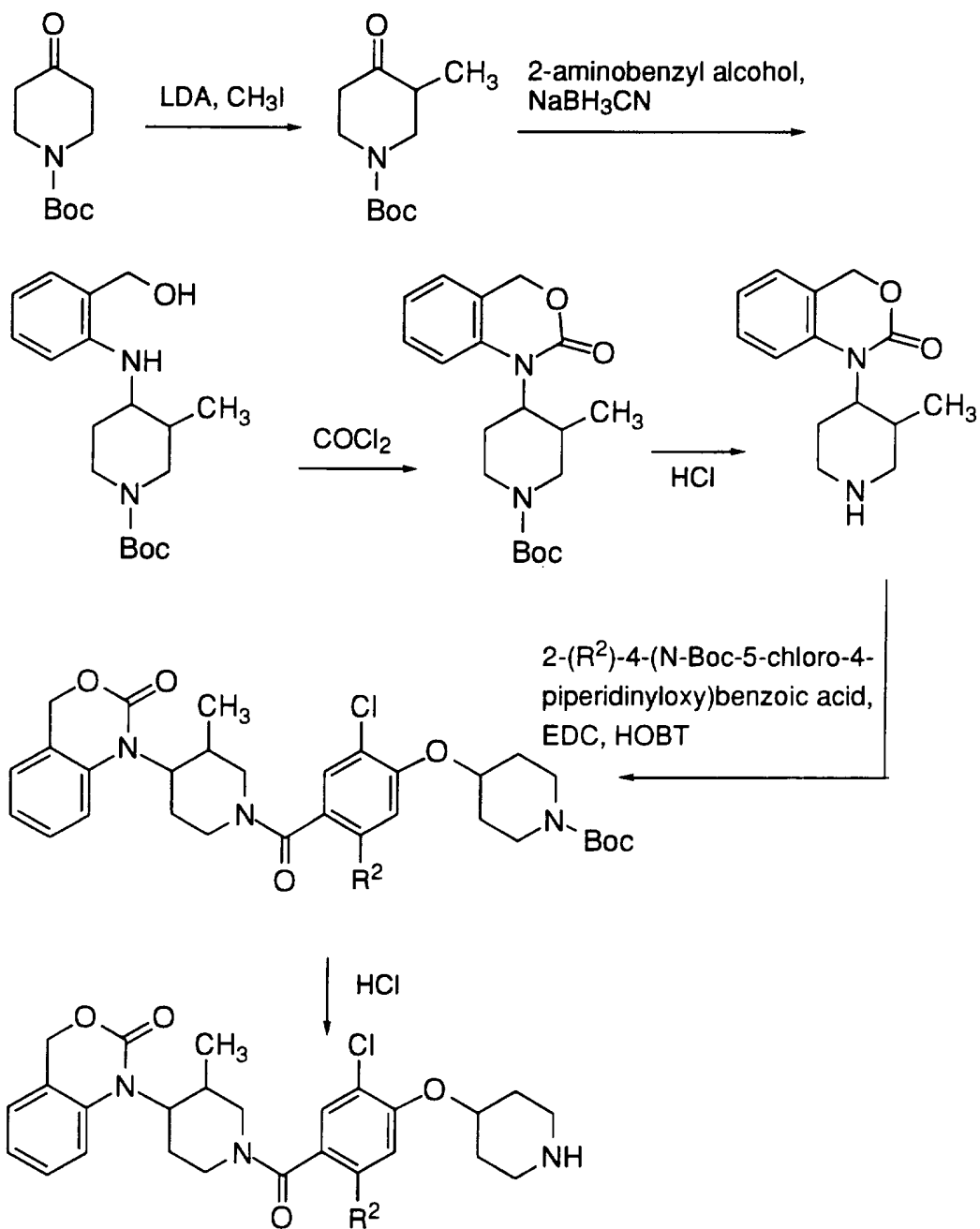
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SCHEME 13 (CONT'ED)



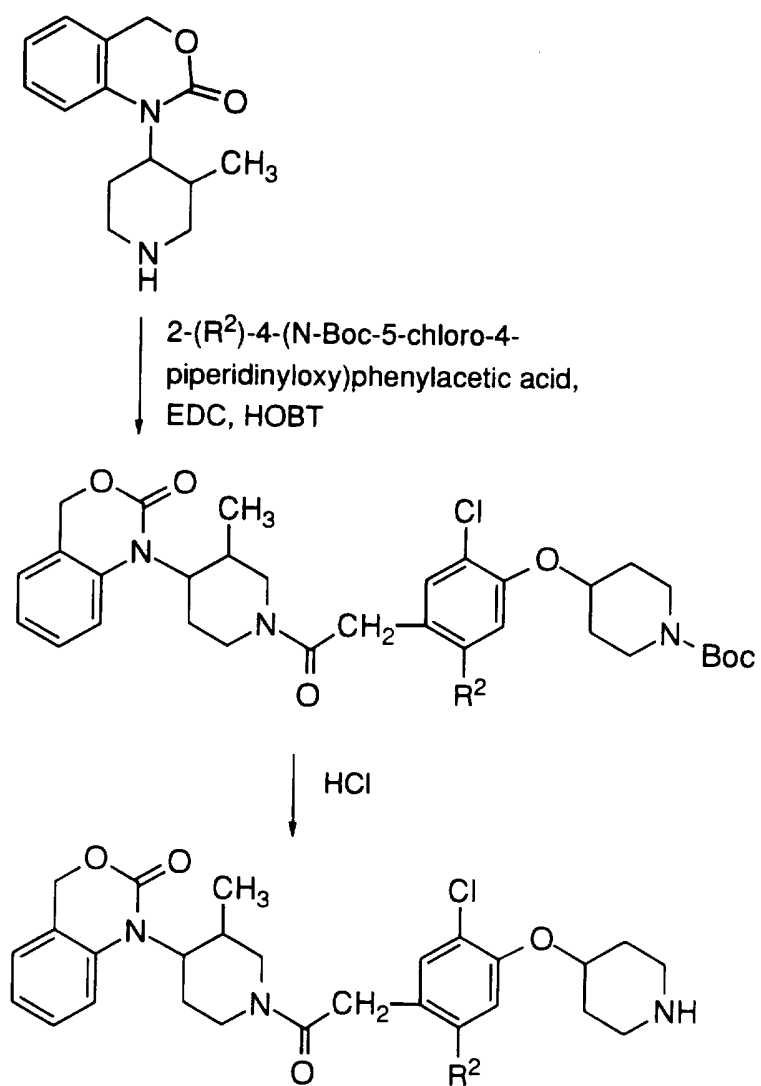
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SCHEME 14



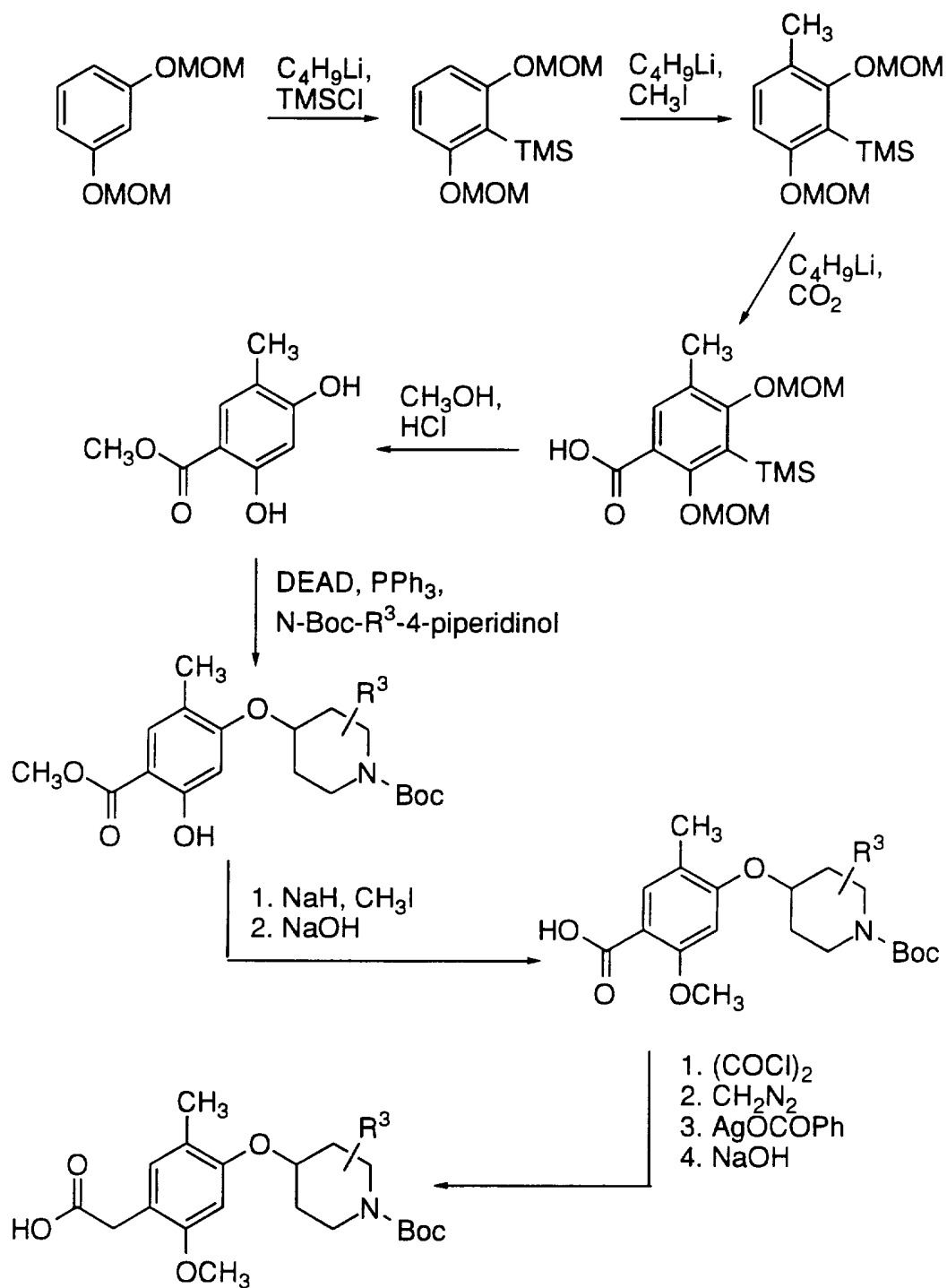
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SCHEME 14 (CONT'ED)



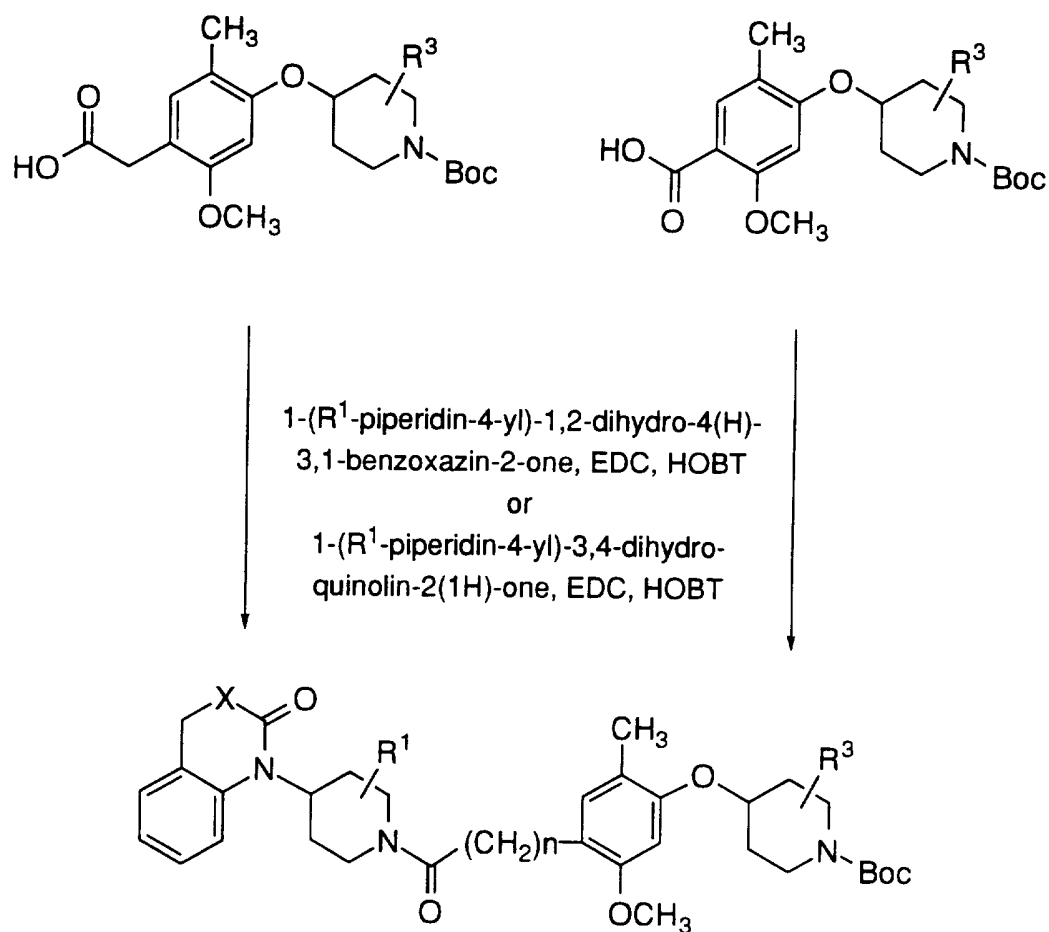
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SCHEME 15



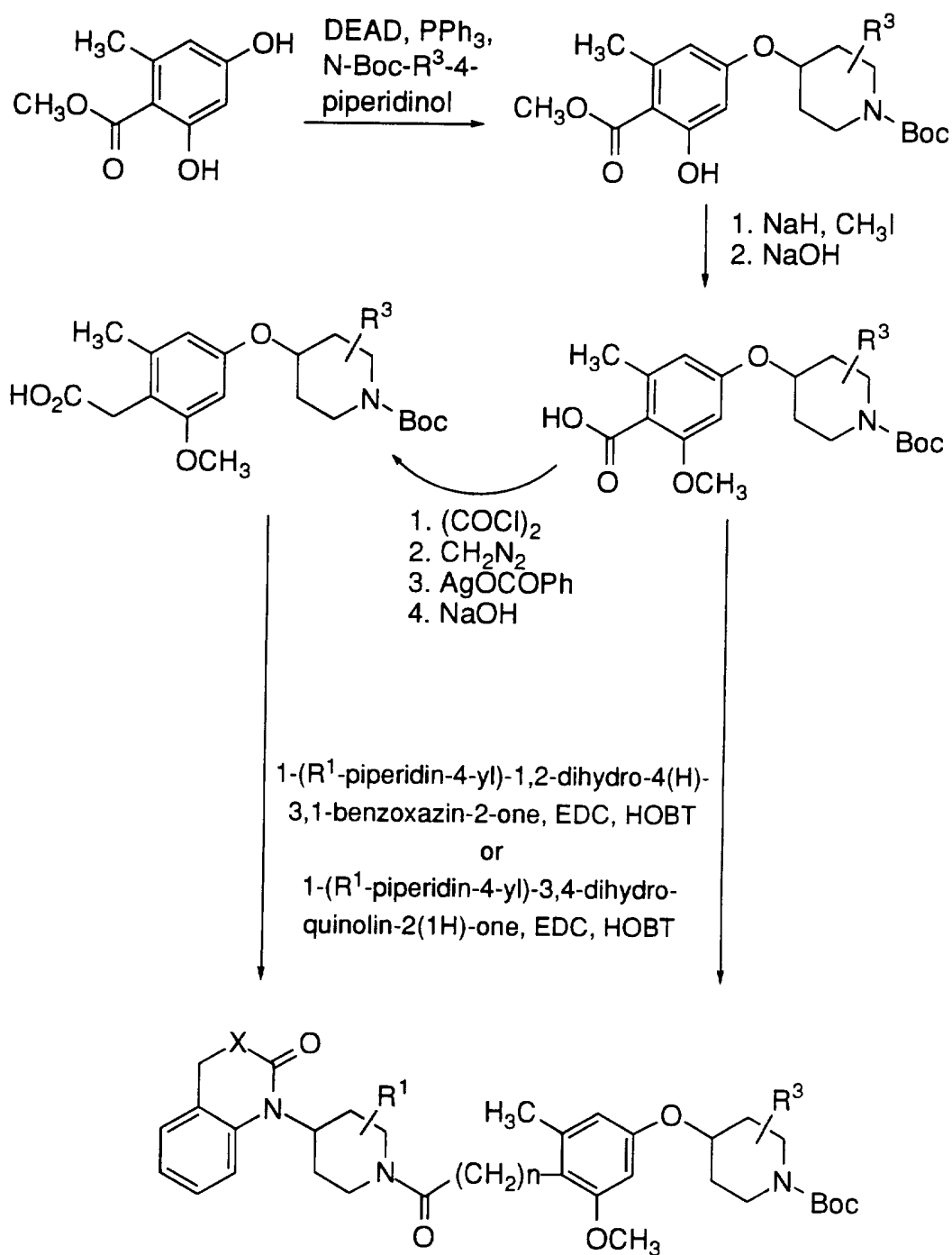
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SCHEME 15 (CONTINUED)



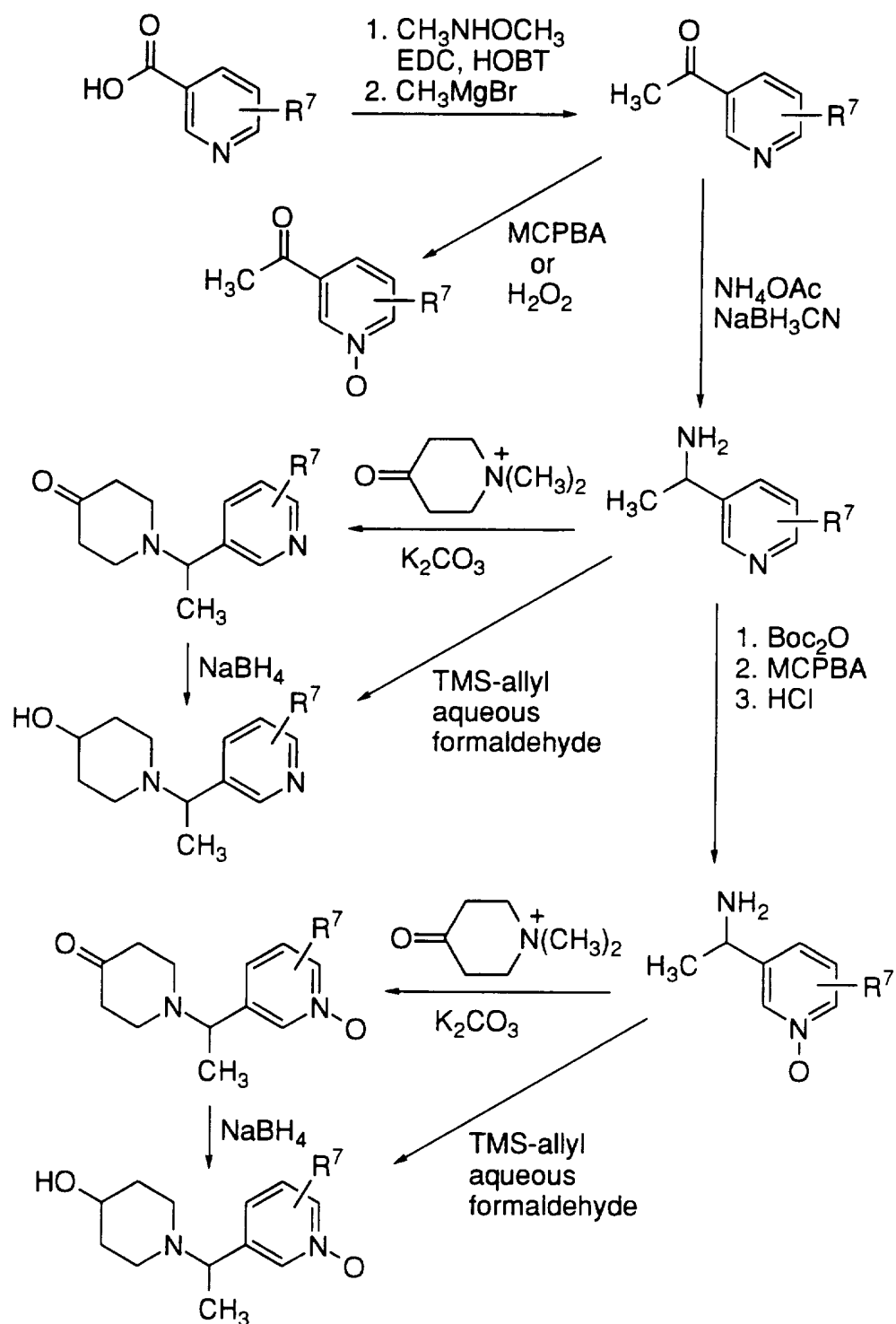
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SCHEME 16



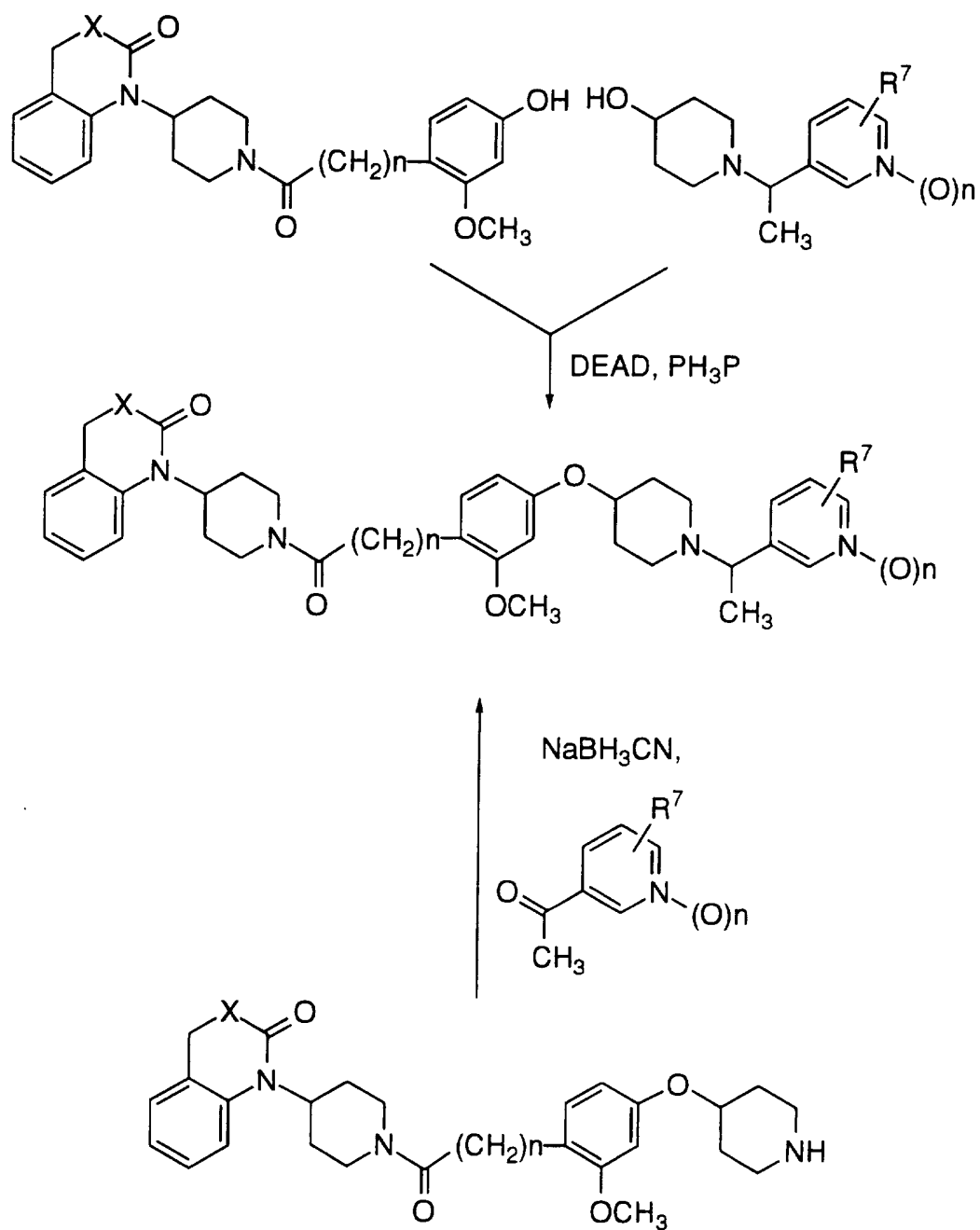
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SCHEME 17



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SCHEME 17 (CONTINUED)



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Compounds of the present invention where R^1 or R^3 are non-hydrogen substituents requires the preparation of piperidin-4-ones or piperidin-4-ols that are substituted at the 2- or 3-position. Examples for the preparation of such 2- or 3-substituted piperidin-4-ones and 2- or 3-substituted piperidin-4-ols and their subsequent conversion to compounds of the present invention are given in Schemes 1-9. A broad range of substituents can be introduced at the R^1 and R^3 positions using methods as exemplified in Schemes 1-9 and by other methods familiar to those with ordinary skill in the art. Schemes 1 and 6 utilize a ketone alkylation process and Schemes 5 and 9 utilize processes similar to those described by P. Beak and co-workers (Tetrahedron Letters, 1989, vol. 30, pp. 1197-1200, Journal of Organic Chemistry, 1990, vol. 55, pp. 2578-2580) to obtain 3-substituted piperidin-4-ones and 2-substituted piperidin-4-ols that can be used as intermediates to prepare compounds of the present invention containing non-hydrogen R^1 and R^3 substituents. Schemes 2 and 7 utilize processes similar to those described by D. L. Comins and co-workers (Tetrahedron Letters, 1989, vol. 30, pp. 5053-5056, Tetrahedron Letters, 1986, vol. 27, pp. 4549-4552) and Schemes 3, 4, and 8 utilize 4-ketopipericolic acid (C. Muhlemann, et al., Organic Syntheses, D. L. Coffen, editor, 1993, vol. 72, pp. 200-206) for the preparation of 2-substituted piperidin-4-ones and 2-substituted piperidin-4-ols that can be used as intermediates to obtain compounds of the present invention containing non-hydrogen R^1 and R^3 substituents. Processes that involve cyclization of ene-iminium species (for example: S. Hayes, et al., Journal of Organic Chemistry, 1991, vol. 56, pp. 4084-4086, and C. Agami, et al., Tetrahedron, 1992, vol. 48, pp. 431-442) are also useful for the preparation of 2- or 3-substituted piperidin-4-ones and 2- or 3-substituted piperidin-4-ols that can be used as intermediates to obtain compounds of the present invention containing non-hydrogen R^1 and R^3 substituents. Piperidin-4-ones and piperidin-4-ols substituted at the 2- or 3-position can be used to prepare compounds of the present invention with R^1 being a non-hydrogen substituent and which contain either the 1,2-dihydro-4(H)-3,1-benzoxazinone ring system ($X = O$; Schemes 6-9) or the 3,4-dihydro-

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2(1H)-quinolinone ring system ($X = CH_2$; Scheme 10). The 3,4-dihydro-2(1H)-quinolinone ring system can be prepared using methods analogous to those described by H. Ogawa and co-workers (Journal of Medicinal Chemistry, 1993, vol. 36, pp. 2011-2017) as indicated in

5 Scheme 10. A variety of R^4 substituents can be incorporated into the compounds of the present invention as exemplified in Scheme 11. For example, the piperidine nitrogen can be derivatized by alkylation with an alkyl halide, by reductive alkylation with an aldehyde and a reducing agent such as sodium cyanoborohydride, by acylation with an activated

10 carbonyl compound (e.g., carboxylic acid chloride, hydroxybenzotriazole ester, carboxylic acid anhydride, chloroformate, etc.), by guanylation with a cyanoimine derivative, or by sulfonylation with a sulfonyl chloride or sulfonic acid anhydride. Compounds of the present invention in which the R^4 substituent is a substituted or

15 unsubstituted picolyl or picolyl N-oxide group can be prepared as exemplified in Scheme 12. A substituted or unsubstituted pyridinyl ester is converted to an alcohol using a reducing agent such as lithium aluminum hydride. The alcohol is converted to an aldehyde using an oxidizing agent such as manganese dioxide, or converted to a

20 chloromethyl derivative by treatment with a chlorinating agent such as thionyl chloride. The aldehyde can be used to reductively alkylate the free piperidine, or the chloromethyl derivative can be used to alkylate the piperidine, giving compounds of the present invention in which R^4 is a substituted or an unsubstituted picolyl group. Treatment of the

25 chloromethyl derivative with an oxidizing agent such as m-chloroperoxybenzoic acid gives the chloromethylpyridine-N-oxide derivative, which is then used to alkylate the piperidine to provide compounds of the present invention in which R^4 is a substituted or an unsubstituted picolyl N-oxide group. Syntheses of intermediates for

30 preparation of compounds of the present invention in which R^8 is halogen or alkyl are given in Schemes 13-16. Reagents such as N-chlorosuccinimide or N-bromosuccinimide, N-iodosuccinimide, iodine, bromine, fluorine, etc., can be used to halogenate a para-hydroxy benzoic acid derivative as shown in Scheme 13, which can then be

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further derivatized to obtain compounds of the present invention in which R^8 is halogen as shown in Schemes 13 and 14. Directed ortho metalation reactions can be used to prepare alkylated aromatics as shown in Scheme 15, which can then be further elaborated to benzoic acid and phenylacetic acid derivatives which are useful for preparing compounds of the present invention in which R^8 is an alkyl group as shown in Schemes 15 and 16. Syntheses of intermediates which are useful for preparing compounds of the present invention in which an alkyl group is substituted at the R^9 position are given in Scheme 17.

Pyridine carboxylic acid derivatives can be converted to pyridyl alkyl ketones, which can then be used to reductively alkylate the terminal piperidine ring to give compounds of the present invention in which an alkyl group is substituted at the R^9 position. Alternatively, the pyridyl alkyl ketone derivatives can be reductively aminated with ammonia and the resulting aminoalkyl pyridines can be converted to pyridinylalkyl piperidinols by reaction with 1,1-dimethyl-4-piperidinone using a procedure similar to that reported by M. E. Kuehne and co-worker (Journal of Organic Chemistry, 1991, vol. 56, pp. 2701-2712) followed by ketone reduction, or by reaction with allyltrimethylsilane and aqueous formaldehyde using a procedure similar to that reported by P. A. Grieco and co-workers (Journal of the American Chemical Society, 1986, vol. 108, pp. 3512-3513). The pyridinylalkyl piperidinols are then used in ether forming reactions to give compounds of the present invention in which R^9 is alkyl as shown in Scheme 17.

It is understood that the R^1 , R^3 , R^8 , and R^9 substituents in compounds of the present invention include but are not limited to the specific substituents given in Schemes 1-17. Also, Schemes 1-17 serve to exemplify methods for preparation of compounds of the present invention, but other methods and variations of those given, which are familiar to those of ordinary skill in the art, are also useful for preparing compounds of the present invention.

The most preferred compounds of the invention are any or all of those specifically set forth in these Examples and the following Tables 1-12. These compounds are not, however, to be construed as

forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

All solvents were reagent grade and stored over 4Å molecular sieves. THF was distilled from calcium hydride under inert atmosphere. Dioxane was dried and freed of peroxides by passage through a column of activity I neutral alumina. Determination of reaction pH was estimated by spotting an aliquot from the reaction mixture on wetted E. Merck "colorpHast" pH 1-14 indicator strips. Silica coated TLC plates were used to monitor all reactions (E. Merck, 5 x 10 cm Silica Gel 60 F254). MeOH(NH₃) used for TLC refers to a methanol solution saturated with NH₃ gas at 0°C. Pressurized silica gel column chromatography using 230-400 mesh silica gel was performed according to the method of Still, Kahn, and Mitra (*J. Org. Chem.* (1978) vol. 43, p.2923). All temperatures are degrees Celsius unless noted otherwise.

Analytical HPLC were run on a Spectra Physics SP4270/8800 instrument using the following conditions:

Column: Vydac C₁₈, 0.21 x 15 cm

25 UV detection at 214 nm

Mobile Phases A = 0.1% by volume TFA in H₂O; B = MeOH;
C = 0.1% by volume TFA in acetonitrile

Method A:

30	Gradient	T = 0 min, 95% A, 5% C T = 15 min, 5% A, 95% C
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Flow = 2.0 mL/min

Method B:

Gradient	T = 0 min, 95% A, 5% C
	T = 30 min, 5% A, 95% C

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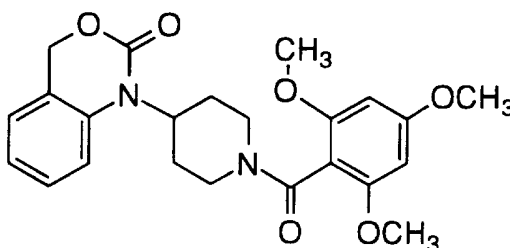
Flow = 1.5 mL/min

¹H NMR spectra were measured at 300 MHz on a Varian XL-300, at 400 MHz on a Varian XL-400, and at 360 MHz on a Nicolet NT-360 using (CH₃)₄Si as an internal standard. All NMRs for the compounds of the Examples which follow were consistent with structures. Fast atom bombardment mass spectra (FAB MS) were obtained on a VG-ZAB-HF spectrometer.

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EXAMPLE 1

1-((1-(2,4,6-Trimethoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



15 Step 1. 1-t-Butyloxycarbonyl-4-piperidinone (20 g, 0.10 mol), 2-aminobenzyl alcohol (13 g, 0.11 mol), and acetic acid (14 mL, 0.22 mol) were dissolved in dry toluene (500 mL). The solution was refluxed under inert atmosphere for 3 h with azeotropic removal of water. The solution was cooled to ambient temperature and concentrated under reduced pressure to one half of the original volume. To the solution was added NaBH₃CN (20 g, 0.32 mol) and dry THF (300 mL). Acetic acid (10 mL, 0.15 mmol) was added dropwise over a period of about 1 h. The reaction was stirred at ambient temperature for 24 h. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc layer was washed with saturated aqueous NaHCO₃ (3x 500 mL) and brine (250 mL). The EtOAc layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography, using a gradient elution of 15-30% EtOAc-

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hexanes. 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)phenylamino)piperidine was obtained as a gum (TLC: R_f = 0.30 (30:70 EtOAc:hexanes); HPLC(method A) retention time = 8.89 min).

5 Step 2. 1-t-Butyloxycarbonyl-4-((2-hydroxymethyl)phenylamino)-piperidine (24 g, 78 mmol) from step 1 above was dissolved in dry THF (250 mL) and cooled to 0°C under an atmosphere of nitrogen. To the solution was added DIEA (41 mL, 0.24 mol) and triphosgene (8.54 g, 28.8 mmol). The reaction was stirred at
10 0°C for 1h, and then at ambient temperature for 24 h. Ether (250 mL) was added, the mixture was cooled to 0°C and then filtered to remove the hydrochloride salt of DIEA. The filtrate solvents were removed under reduced pressure and the residue was dissolved in EtOAc (750 mL). The EtOAc solution was washed with 5% aqueous citric acid (2x 500 mL),
15 water (250 mL), and saturated aqueous NaHCO₃ (2x 500 mL). The EtOAc layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was boiled in ether (ca. 200 mL) until the solid had dissolved. Cooling overnight gave 1-(N-t-butyloxycarbonyl-4-piperidiny)-4H-3,1-benzoxazin-2(1H)-one as off-
20 white crystals, mp 143-145°C (TLC: R_f = 0.28 (30:70 EtOAc:hexanes); HPLC(method A) retention time = 8.77 min; FAB MS: m/z 333 (M^+ + H)).

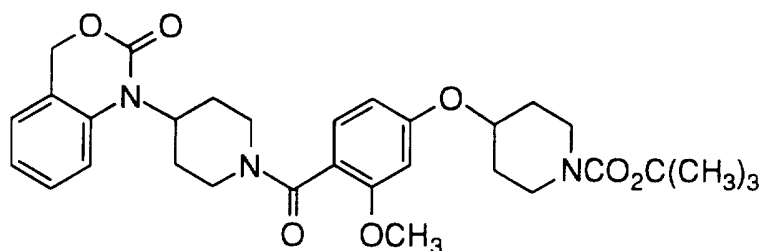
Step 3. A stirred solution of 1-(N-t-butyloxycarbonyl-4-piperidiny)-4H-3,1-benzoxazin-2(1H)-one (19 g, 57 mmol) from step 2
25 above in EtOAc (500 mL) was cooled to 0°C. HCl gas was bubbled through the solution for 30 min. Stirring was continued at 0°C for 1 h, during which time a precipitate had formed, and the reaction was warmed to ambient temperature for 1 h. The stirred suspension was cooled to 0°C and cold ether (250 mL) was added. The precipitate was
30 collected by filtration and washed with ether. The solid was dried under reduced pressure for 18 h, giving 1-(4-piperidiny)-4H-3,1-benzoxazin-2(1H)-one hydrochloride as a white amorphous solid (TLC: R_f = 0.29 (90:10:1 CH₂Cl₂:MeOH:NH₄OH); HPLC(method A) retention time = 3.88 min; FAB MS: m/z 233 (M^+ + H)).

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- Step 4: To a solution of the hydrochloride salt of 1-(4-piperidinyloxy)-4(H)-3,1-benzoxazin-2(1H)-one (150 mg, 0.56 mmol) from Step 3 above in DMF (5 mL) was added 2,4,6-trimethoxybenzoic acid (120 mg, 0.56 mmol), HOBT (92 mg, 0.60 mmol), and EDC (140 mg, 0.73 mmol). To the stirred solution was added DIEA (0.19 mL, 1.1 mmol) until the reaction was pH 7 as judged by spotting an aliquot on wetted E. Merck "colorpHast" pH 1-14 indicator strips. The reaction was stirred at ambient temperature for 18 h and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with 5% aqueous citric acid (25 mL), water (25 mL), and saturated aqueous NaHCO₃ (25 mL). The EtOAc layer was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 1-3% MeOH-CHCl₃. The title compound was obtained as an amorphous solid.
- Analysis calculated for (C₂₃H₂₆N₂O₆, 0.6 H₂O)
 C, 63.17; H, 6.27; N, 6.41
Found C, 63.13; H, 5.98; N, 6.14
TLC: R_f = 0.37 (98:2 CHCl₃:MeOH)
HPLC (method A): retention time 7.77 min
FAB MS: m/z 427 (M⁺ + H)

EXAMPLE 2

- 1-(1-(4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)-piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



- Step 1: To a stirred solution of triphenylphosphine (57.2 g, 0.218 mol) and methyl 2,4-dihydroxybenzoate (29.2 g, 0.174 mol) in

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dry THF (250 mL) at 0°C was added a solution of N-t-butyloxy-4-piperidinol (43.8 g, 0.218 mol) and diethyl azodicarboxylate (37.9 mL, 0.218 mol) in dry THF (150 mL) dropwise over a period of 2 h. The resulting solution was warmed to ambient temperature over 2 h and stirred for an additional 16 h. The solvent was concentrated to half of the original volume under reduced pressure, ether (200 mL) was added, and the mixture was cooled to 0°C for 3 h. The precipitated triphenylphosphine oxide was removed by filtration and washed with cold ether, and the filtrate solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 10-25% EtOAc-hexane. Methyl 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-hydroxybenzoate was obtained as a waxy solid.

Step 2: To a solution of methyl 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-hydroxybenzoate (50 g, 0.14 mol) from Step 1 above and iodomethane (17.4 mL, 0.28 mol) in DMF (300 mL) at 0°C was added NaH (6.55 g of a 60% suspension in mineral oil, 0.164 mol) in several portions over a period of 2 h. The resulting suspension was warmed to ambient temperature and stirred for 18 h. The mixture was quenched with methanol (5 mL) and concentrated under reduced pressure. The residue was suspended in EtOAc (500 mL) and washed with water (2x 250 mL) and brine (250 mL). The EtOAc layer was dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by pressurized silica gel column chromatography using a gradient elution of 20-40% EtOAc-hexane. Methyl 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoate was obtained as a gum that solidified on standing (TLC: R_f = 0.25 (3:1 hexane:EtOAc); HPLC (method A) retention time = 9.72 min).

Step 3: Methyl 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoate (35 g, 96 mmol) from Step 2 above was dissolved in MeOH (250 mL) and to the solution was added 2 N NaOH (100 mL, 200 mmol). The stirred mixture was warmed to 70°C for 3 h. The solution was cooled to ambient temperature, concentrated under reduced pressure, cooled to 0°C and 0.5 M aqueous citric acid solution (300

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mL) was added. To the suspension was added EtOAc (500 mL) and water (300 mL). The EtOAc layer was separated and the aqueous phase was washed with EtOAc (200 mL). The combined EtOAc layers were washed with brine (250 mL), dried (MgSO₄), filtered, and the solvent
5 was removed under reduced pressure to give 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoic acid as a foam that solidified on standing in vacuo (HPLC (method A) retention time = 8.46 min).

Step 4: 4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoic acid from step 3 above was coupled to the
10 hydrochloride salt of 1-(4-piperidinyloxy)-4(H)-3,1-benzoxazin-2(1H)-one from step 3 of Example 1 using the procedure given in step 4 of Example 1. The crude product was purified by pressurized silica gel column chromatography using a gradient elution of 1-4% MeOH-DCM. The title compound was obtained as a white foam by evaporation of a
15 DCM solution under reduced pressure.

Analysis calculated for (C₃₁H₃₉N₃O₇, 0.35 DCM, 0.1 H₂O)

C, 63.04; H, 6.73; N, 7.04

Found C, 63.05; H, 6.77; N, 7.20

20 TLC: R_f = 0.15 (98:2 DCM:MeOH)

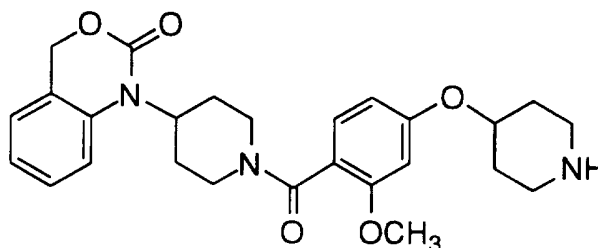
HPLC (method A): retention time 10.06 min

FAB MS: m/z 566 (M⁺ + H)

EXAMPLE 3

25

1-(1-(4-(4-Piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



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1-(1-(4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 2 (5.0 g, 8.8 mmol) was treated with 4N HCl in dioxane (40 mL) at ambient temperature for 1 h. The dioxane was evaporated under reduced pressure and the residue was triturated in EtOAc-ether and filtered. The solid was dried in vacuo for 24 h to give the hydrochloride salt of the title compound. A small portion of this material was purified to greater than 99% homogeneity by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The TFA salt of the title compound was obtained as an amorphous solid by lyophilization.

Analysis calculated for (C₂₆H₃₁N₃O₅, 1.35 TFA, 0.25 H₂O)

C, 55.24; H, 5.31; N, 6.73

Found C, 55.27; H, 5.29; N, 6.70

TLC: R_f = 0.33 (90:10:0.5 DCM:MeOH:NH₄OH)

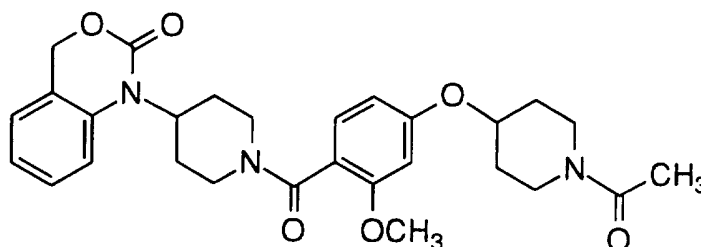
HPLC (method A): retention time 6.14 min

FAB MS: m/z 466 (M⁺ + H)

20

EXAMPLE 4

1-(1-(4-(4-(N-Acetyl)piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



25

To a solution of the hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one (0.25 g; 0.50 mmol) from Example 3 in DCM (5 mL) at ambient temperature was added acetic anhydride (0.75 mmol) and DIEA (1.0 mmol). The solution was stirred at ambient temperature

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for 24 h, diluted with DCM (20 mL), washed with saturated aqueous NaHCO₃ (50 mL), dried (MgSO₄), and filtered. The solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using a gradient elution of 2-5% MeOH-DCM. The title compound was obtained as an amorphous solid by lyophilization from acetonitrile-H₂O.

Analysis calculated for (C₂₈H₃₃N₃O₆, 0.05 CH₃CN, 1.4 H₂O)

C, 63.06; H, 6.77; N, 7.99

10 Found C, 63.11; H, 6.44; N, 7.95

TLC: R_f = 0.28 (95:5 DCM:MeOH)

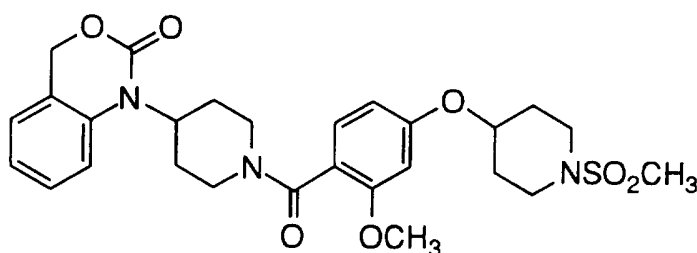
HPLC (method A): retention time 7.35 min

FAB MS: m/z 507 (M⁺ + H)

15

EXAMPLE 5

1-(1-(4-(N-Methylsulfonyl-4-piperidinyloxy)-2-methoxybenzoyl)-piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



20 The hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 3 (0.25 g; 0.50 mmol) was mesylated with methanesulfonyl chloride (0.60 mmol) and DIEA (1.1 mmol) in DCM (10 mL) at ambient temperature for 18 h. The mixture was diluted with DCM (20 mL) and washed with saturated aqueous NaHCO₃ (50 mL), dried (MgSO₄), and filtered. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. The title compound was obtained as a white solid by lyophilization.

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Analysis calculated for (C₂₇H₃₃N₃O₆S, 1.3 TFA, 0.25 H₂O)

C, 51.05; H, 5.04; N, 6.03

Found C, 51.04; H, 5.03; N, 6.40

5 TLC: R_f = 0.28 (95:5:0.5 DCM:MeOH:NH₄OH)

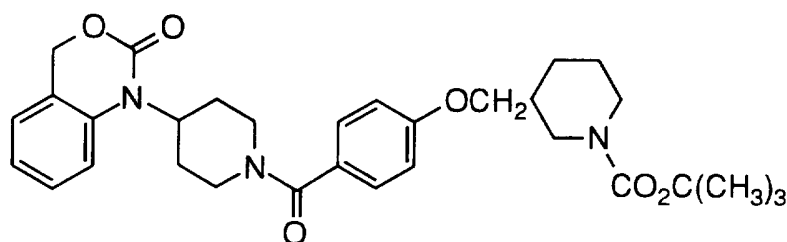
HPLC (method A): retention time 8.30 min

FAB MS: m/z 544 (M⁺ + H)

EXAMPLE 6

10

1-(1-(4-(1-t-Butyloxycarbonyl-3-piperidinylmethoxy)benzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



15 Step 1: N-t-Butyloxycarbonyl-3-piperidinylmethanol was etherified with ethyl 4-hydroxybenzoate using the procedure given in Step 1 of Example 2. The crude product was purified by pressurized silica gel column chromatography using a gradient elution of 10-25% EtOAc-hexanes. 4-(N-t-Butyloxycarbonyl-3-

20 Step 2: 4-(N-t-Butyloxycarbonyl-3-piperidinylmethoxy)benzoic acid ethyl ester was saponified with aqueous NaOH in MeOH using the procedure given in Step 3 of Example 2. 4-(N-t-Butyloxycarbonyl-3-piperidinylmethoxy)benzoic acid was obtained as a foam by evaporation of a DCM solution.

25 Step 3: 4-(N-t-Butyloxycarbonyl-3-piperidinylmethoxy)benzoic acid was coupled to the hydrochloride salt of 1-(4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one from step 3 of Example 1 using the procedure described in step 4 of Example 1. The crude product was purified by pressurized silica gel column

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chromatography using a gradient elution of 1-4% MeOH-DCM. The title compound was obtained as a white foam by evaporation of a DCM solution under reduced pressure.

Analysis calculated for (C₃₁H₃₉N₃O₆, 1.1 CH₂Cl₂)

5 C, 59.95; H, 6.46; N, 6.53

Found C, 59.54; H, 6.65; N, 7.05

TLC: R_f = 0.24 (97:3 DCM:MeOH)

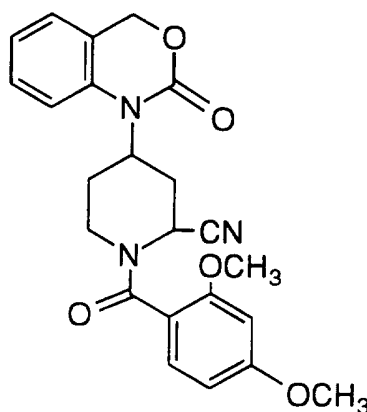
HPLC (method A): retention time 10.55 min

FAB MS: m/z 550 (M⁺ + H)

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EXAMPLE 7

1-(1-(2,4-dimethoxybenzoyl)-2-cyano-4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one



15

Step 1: 1-(4-Piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride (150 mg, 0.559 mmol) from Step 3 of Example 1 (988 mg, 3.68 mmol) was treated with aqueous sodium carbonate and the resulting free base was extracted into ether. The dried (sodium sulfate) ether layer was evaporated *in vacuo* and the residue evaporated three times from methylene chloride/methanol. The residue was treated with methylene chloride and filtered to remove insoluble material. The methylene chloride solution was evaporated to dryness *in vacuo* and the residue treated with acetic acid (0.197 mL) and water (2 mL). To the resulting solution was added an aqueous

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suspension of pulverized calcium hypochlorite (637 mg). The mixture was stirred at ambient temperature for 30 min, then combined with water and extracted with ether. The ether layer was washed with water and with brine, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo* to give 1-(N-chloro-4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one.

Step 2: 1-(N-Chloro-4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one from Step 1 above (230 mg, 0.86 mmol) was dissolved in warm ether (30 mL) and the solution was added dropwise to a suspension of potassium superoxide (135 mg, 1.9 mmol) and 18-crown-6 (10 mg, 0.04 mmol) in ether (10 mL). The mixture was stirred at ambient temperature for five days, with two additional lots of 135 mg each of potassium superoxide being added on the second and third days. The reaction was filtered and the filtrate was added dropwise to an ether solution of trimethylsilylcyanide (0.172 mL, 128 mg, 1.3 mmol). The mixture was stirred at ambient temperature for 18 hours, then evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with 4:96 MeOH:CH₂Cl₂. The combined product fractions were evaporated to dryness *in vacuo*, and the residue was evaporated twice from ether to give 1-(2-cyano-4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one (FAB MS: M+H @ m/z=258).

Step 3: 1-(2-Cyano-4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one from Step 2 above (198 mg, 0.77 mmol) was dissolved in methylene chloride (2 mL) and treated with 2,4-dimethoxybenzoyl chloride (170 mg, 0.84 mmol) followed by triethylamine (0.12 mL, 85 mg, 0.85 mmol). The mixture was stirred at ambient temperature for one hour, then chromatographed on silica gel eluted with 1:9 ether:CH₂Cl₂. The product fractions were combined and evaporated to dryness *in vacuo*. The residue was crystallized from ether to give the title compound: mp 176-177°C.
TLC: R_f= 0.33 (1:9 ether:CH₂Cl₂)
FAB MS: M+H @ m/e= 422

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Anal. cal'd for C₂₃H₂₃N₃O₅:

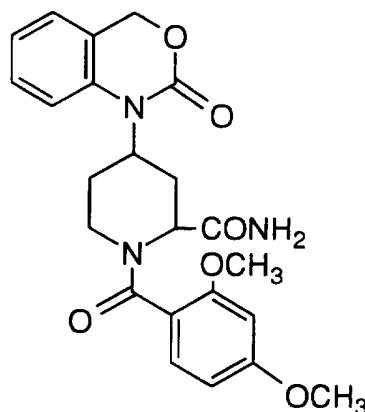
C, 65.54; H, 5.50; N, 9.97.

Found: C, 65.51; H, 5.52; N, 9.89.

5

EXAMPLE 8

1-(1-(2,4-dimethoxybenzoyl)-2-carboxamido-4-piperidiny)-4(H)-3,1-benzoxazin-2(1H)-one



- 10 1-(1-(2,4-dimethoxybenzoyl)-2-cyano-4-piperidiny)-4(H)-
3,1-benzoxazin-2(1H)-one from Example 7 (18.4 mg, 0.044 mmol) was
dissolved in warm 95% ethanol (2 mL). The solution was cooled, and
aqueous sodium hydroxide (0.005 mL of a 10% solution; 0.0125
mmol)) was added followed by 30% hydrogen peroxide (0.005 ml, 0.05
15 mmol). The mixture was stirred at 45-50°C for 6 h, then at ambient
temperature for 66 hr. The mixture was concentrated in a stream of
nitrogen, and the residue was treated with water, made basic with
saturated sodium bicarbonate solution, and extracted with ethyl acetate.
The organic layers were combined and washed with brine, dried over
20 sodium sulfate, and filtered, and the filtrate was evaporated to dryness
in vacuo. The residue was chromatographed on silica gel eluted with
3:97 MeOH:CH₂Cl₂. The product fractions were combined and
evaporated to dryness *in vacuo*, and the residue was crystallized from
ether to yield the title compound: mp 210-212°C.
25 Anal. cal'd for C₂₃H₂₅N₃O₆•0.05 C₄H₁₀O•0.45H₂O:

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C, 61.74; H, 5.90; N, 9.31.

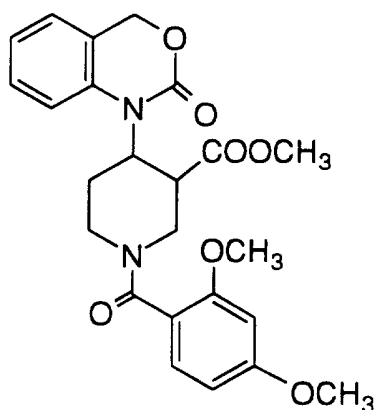
Found: C, 61.66; H, 5.61; N, 9.01.

TLC: R_f =0.33 (3:97 MeOH:CH₂Cl₂)FAB MS: M+H @ m/z = 440

5

EXAMPLE 9

1-(1-(2,4-Dimethoxybenzoyl)-3-methoxycarbonyl-4-piperidiny1)-4(H)-
3,1-benzoxazin-2(1H)-one



10

Step 1: Methyl 4-oxo-3-piperidinecarboxylate hydrochloride (3.5 g, 18.1 mmol) was stirred in methylene chloride (30 mL) and treated with di-*t*-butyl dicarbonate (3.6 g, 16.5 mmol) followed by triethylamine added dropwise to maintain the pH of the mixture (moistened E. Merck colorpHast sticks) in the range 7-8. The mixture was stirred at ambient temperature for 18 h, then washed with 1 N HCl followed by saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo* to give methyl 1-Boc-4-oxo-3-piperidinecarboxylate.

Step 2: Methyl 1-Boc-4-oxo-3-piperidinecarboxylate from Step 1 above (3.86 g, 15 mmol) was combined with 2-aminobenzyl alcohol (1.5 g, 12.2 mmol) and acetic acid (1.29 mL, 1.35 g, 22.5 mmol) in methanol (10 mL). Sodium cyanoborohydride (0.94 g, 15 mmol) was added and the mixture was stirred at ambient temperature for 3.5 h. The solvent was removed *in vacuo* and the residue treated with ethyl acetate (100 mL). The solution was washed with saturated

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aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with 1:4, 1:2, and 3:5 EtOAc:hexane. The combined product fractions were evaporated to dryness *in vacuo* to give methyl 1-Boc-4-(2-hydroxymethylphenylamino)-3-piperidine carboxylate.

Step 3: Methyl 1-Boc-4-(2-hydroxymethylphenylamino)-3-piperidine carboxylate from Step 2 above (4.1 g, 11.3 mmol) was stirred in THF (40 mL) in an ice bath and treated with triphosgene (1.11 g, 3.74 mmol) followed by triethylamine (4.7 mL, 3.41 g, 33.7 mmol). The mixture was stirred at ambient temperature for 18 h, then treated with an additional 0.47 g of triphosgene and 1.9 mL of triethylamine, and stirred an additional 4.5 h. Water was added and the mixture was extracted with ethyl acetate. The combined ethyl acetate layers were washed with 2 N HCl then with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel eluted with CHCl₃ followed by 1:99 MeOH:CHCl₃. The combined product fractions were evaporated to dryness *in vacuo* to give methyl 1-Boc-4-(3,1-benzoxazin-2-one-1-yl)-3-piperidine carboxylate.

Step 4: Methyl 1-Boc-4-(3,1-benzoxazin-2-one-1-yl)-3-piperidine carboxylate from Step 3 above (0.6 g, 1.5 mmol) was stirred in ethyl acetate in an ice bath, then saturated with HCl gas and stirred another 15 min in the cold. The mixture was evaporated *in vacuo*. Three portions of ethyl acetate were successively added and evaporated *in vacuo* to give methyl 4-(3,1-benzoxazin-2-one-1-yl)-3-piperidine carboxylate hydrochloride.

Step 5: Methyl 4-(3,1-benzoxazin-2-one-1-yl)-3-piperidine carboxylate hydrochloride from Step 4 above (0.26 g, 0.97 mmol) was stirred in methylene chloride (10 mL), and 2,4-dimethoxybenzoyl chloride (0.19 g, 0.95 mmol) was added followed by triethylamine (0.26 mL, 0.19 g, 1.9 mmol). The mixture was stirred at ambient temperature for 2.5 h, then chromatographed on silica gel eluted with 500:10:1 CHCl₃:MeOH:NH₄OH. The combined product fractions were evaporated to dryness *in vacuo*. The residue was rechromatographed on

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silica gel eluted with 4:1 EtOAc:hexane and the combined product fractions were evaporated to dryness *in vacuo* to give the title compound as a mixture of diastereomers (amorphous solid): mp 75-100°C (indistinct).

5 Anal. cal'd for C₂₄H₂₆N₂O₇•0.05 EtOAc•0.6 H₂O:

 C, 61.88; H, 5.92; N, 5.96.

Found: C, 61.75; H, 5.87; N, 6.29.

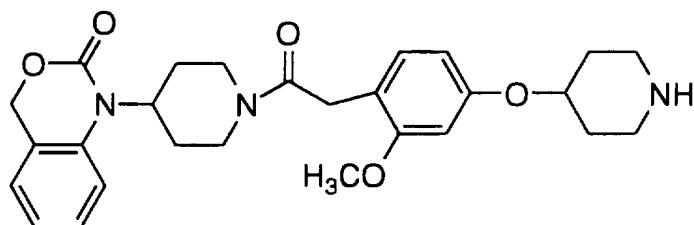
TLC: R_f= 0.26, 0.39 (EtOAc)

FAB MS: M+H @ m/z= 455

10 HPLC: 38% + 58%

EXAMPLE 10

15 1-(1-(4-(4-piperidinyloxy)-2-methoxyphenylacetyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



20 Step 1: To a solution of 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)benzoic acid (3.2 g; 9.1 mmol) from Step 3 of Example 2 in THF was added thionyl chloride (1 mL; 13.7 mmol) and pyridine (2 drops) while under a nitrogen atmosphere. The solution was stirred for 4 hours and then concentrated under reduced pressure to dryness. The residue was suspended in ether and filtered, and the filtrate was concentrated to dryness to yield 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)benzoyl chloride.

25 Step 2: A two phase mixture of ether (66 mL) and 40% aqueous potassium hydroxide (20 mL) was cooled to 0°C and N-nitroso-methylurea (6.6 g) was added portionwise over 30 minutes. The resulting yellow diazomethane/ether solution was decanted and dried over potassium hydroxide. The diazomethane/ether solution was

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decanted and cooled to 0°C. At this point, a solution of 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)benzoyl chloride from Step 1 above in THF was added dropwise to the diazomethane/ether solution. The resulting bronze solution was warmed to ambient temperature and stirred for 3 hours. Nitrogen was bubbled through the reaction mixture for 1 hour to remove excess diazomethane and the solution was concentrated under reduced pressure to dryness. The residue was purified by pressurized silica gel column chromatography (elute with 6:94 ether:methylene chloride) to yield 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)phenyldiazomethyl ketone.

Step 3: A solution of 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)phenyldiazomethyl ketone (930 mg; 2.48 mmol) from Step 2 above in dry methanol (7 mL) was refluxed and a solution of freshly prepared silver benzoate (100 mg) in triethylamine (1 mL) was added portionwise over 45 minutes. The solution was refluxed for an additional 30 minutes, then cooled and filtered. The filtrate was concentrated to dryness and the crude oil was purified by pressurized silica gel column chromatography (elute with 5:95 methanol:methylene chloride) to yield methyl 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)phenylacetate.

Step 4: To a solution of methyl 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)phenylacetate (1.37 g; 3.6 mmol) from Step 3 above in 27 mL of THF was added aqueous lithium hydroxide solution (4.5 mL; 1.01M) dropwise. The reaction mixture was stirred for 16 hours and concentrated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and 0.5 M aqueous hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2x). The combined organic extracts were dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure to yield 2-methoxy-4-(N-t-butyloxycarbonyl-4-piperidinyloxy)phenylacetic acid.

Step 5: To a solution of the hydrochloride salt of 1-(4-piperidinyl)-4(H)-3,1-benzoxazin-2(1H)-one from Step 3 of Example 1 (250 mg; 0.93 mmol) in 8 mL of DMF was added 2-methoxy-4-(N-t-

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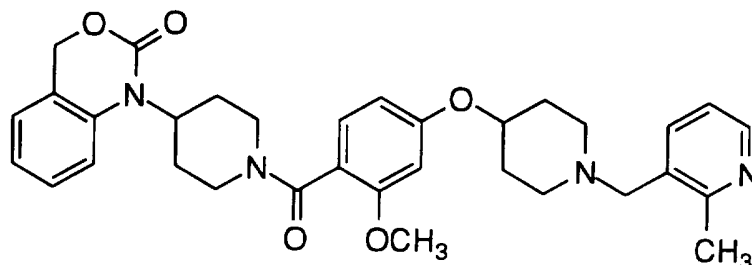
butyloxycarbonyl-4-piperidinyloxy)phenylacetic acid (340 mg; 0.93 mmol) from step 4 above, EDC (213 mg; 1.11 mmol), and HOBT (147 mg; 1.09). Triethylamine (0.55 mL) was added to make the solution basic (pH 8-9). After stirring for 18 hours, the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and sodium bicarbonate (sat., aqueous). The ethyl acetate layer was washed with saturated aqueous sodium bicarbonate and brine, dried, filtered, and concentrated under reduced pressure to an oil. The crude solid was purified by pressurized silica gel column chromatography (elute with 3:97 methanol:methylene chloride). 1-(1-(4-(1-tert-Butyloxycarbonyl-4-piperidinyloxy)-2-methoxyphenylacetyl)-piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one was obtained as a white solid from ether.

Step 6: 1-(1-(4-(1-tert-Butyloxycarbonyl-4-piperidinyloxy)-2-methoxyphenylacetyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Step 5 above (0.20 g, 0.35 mmol) was dissolved in ethyl acetate and cooled in an ice bath. Once cool, the solution was saturated with gaseous HCl for 30 minutes. The mixture was evaporated to dryness. Ether was added and removed *in vacuo* three times, and the residue was triturated with ether and filtered to yield the hydrochloride salt of the title compound as a white solid. Analysis: Calc'd for C₂₇H₃₃N₃O₅, 1.45 HCl 0.95 H₂O
Calc'd: C, 58.96; H, 6.66; N, 7.64.
Found: C, 58.94; H, 6.66; N, 7.70.
FAB MS: M/Z = 480 (M⁺ + H)

EXAMPLE 11

1-(1-(4-(1-(2-methyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one

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To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one hydrochloride from Example 3 (125 mg, 0.249 mmol) in DMF (5 mL) was added 3-chloromethyl-2-methylpyridine (36.9 mg, 0.260 mmol) and DIEA (96.5 mg, 0.13 mL, 0.747 mmol). The solution was stirred at 40°C for 18 hours. The solvent was removed under reduced pressure. The residue was partitioned between aqueous saturated NaHCO₃ (10 mL) and methylene chloride. The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 95:5:0.5 methylene chloride:methanol:NH₄OH as eluant. The title compound was dissolved in methanol and 1.0 equivalent of 1 N aqueous HCl was added. The solution was evaporated to dryness under reduced pressure. The residue was crystallized from a mixture of ethyl acetate and methanol to give the monohydrochloride salt of the title compound as a white crystalline solid.

Analysis calculated for C₃₃H₃₈N₄O₅, 1.0 HCl, 1.6 H₂O

C, 62.32; H, 6.69; N, 8.81

Found C, 62.44; H, 6.29; N, 8.80

TLC: R_f = 0.28 (95:5:0.5 DCM:MeOH:NH₄OH)

HPLC (Method A) retention time 5.79 min

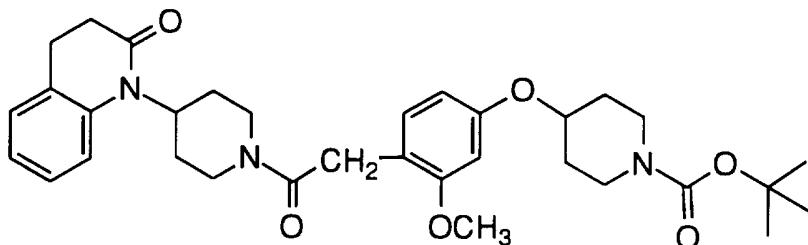
FAB MS: m/z = 571 (M⁺ + H)

25

EXAMPLE 12

1-(1-(4-(N-tert-Butyloxycarbonyl-4-piperidinyloxy)-2-methoxyphenyl-acetyl)piperidin-4-yl)-3,4-dihydro-2(1H)-quinolinone

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To 30 mL of DMF was added 1-(piperidin-4-yl)-3,4-dihydro-2(1H)-quinolinone (1.0 gm, 4.34 mmol; prepared by the method of Ogawa et al. *J. Med. Chem.* 1993, vol. 36, pages 2011-2017).

- 5 To the stirred solution was added 4-(N-tert-butyloxycarbonyl-4-piperidin-1-yl)-2-methoxyphenylacetic acid (1.59 gm, 4.34 mmol) from Step 4 of Example 10, followed by HOBt (730 mg, 4.8 mmol), EDC (911 mg, 4.8 mmol) and DIEA (1.0 mL, 5.7). After stirring at ambient temperature for 18 h the solvent was removed under reduced
- 10 pressure and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with water (2x) and brine, and was dried over anhydrous MgSO_4 . The solution was filtered and the solvent was removed under reduced
- 15 pressure to give an oil which was purified by pressurized silica gel column chromatography using 98:2 CH_2Cl_2 :MeOH as eluant. The product-containing fractions were evaporated under reduced pressure to give the title compound as an amorphous solid.

Analysis: $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_6 \cdot 0.2 \text{ H}_2\text{O}$

C, 68.17; H, 7.53; N, 7.23

20 Found C, 68.60; H, 7.50; N, 7.27

TLC: $R_f = 0.45$ (95:5 CHCl_3 :MeOH)

HPLC (method A): retention time = 10.34 min, purity = 99%

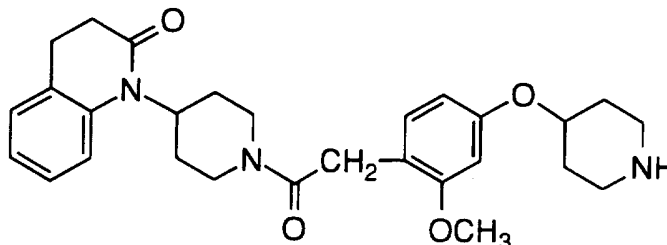
FAB MS: $m/z = 578$ ($M + H^+$)

25

EXAMPLE 13

1-(1-(4-(4-piperidin-1-yl)-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)-2-methoxyphenyl)-4-oxo-4-(tert-butoxycarbonyl)piperidin-1-yl)-3,4-dihydro-2(1H)-quinolinone

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To 75 mL of dry ethyl acetate under N₂ was added 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-methoxyphenylacetyl)-piperidin-4-yl)-3,4-dihydro-2(1H)-quinolinone (1.2 g, 2 mmol) from Example 12, and the solution was cooled to 0°C in an ice-water bath. HCl gas was bubbled into the solution at 0°C for 30 min. The solution was stirred for an additional 30 min at 0°C then the ice bath was removed and N₂ was bubbled through the solution to remove the excess HCl. Addition of hexane caused precipitation of the HCl salt. The solid was dried *in vacuo* to remove solvent and then was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with water and brine and was dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The residue was dissolved in methylene chloride and the solvent was removed under reduced pressure to give the title compound as an amorphous solid.

Analysis: C₂₈H₃₅N₃O₄, 1.3 CH₂Cl₂, 0.15 H₂O

C, 59.57; H, 6.47; N, 7.11

Found C, 59.59; H, 6.28; N, 7.23

TLC: R_f = 0.15 (90:10 CHCl₃:MeOH)

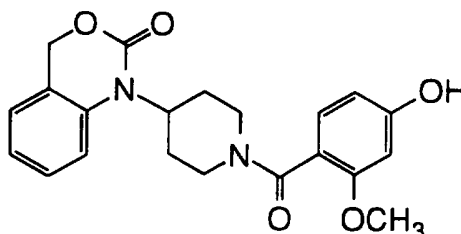
HPLC (method A): retention time = 7.1 min

FAB MS: m/z = 478 (M + H⁺)

EXAMPLE 14

1-(1-(4-Hydroxy-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one

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Step 1. To a well-stirred, 0°C solution of methyl 2,4-dihydroxybenzoate (50 g, 300 mmol) in acetone (1000 mL) was added K₂CO₃ (150 g, 1000 mmol) and benzyl bromide (39 mL, 330 mmol).

- 5 The solution was allowed to warm to ambient temperature over 48 h. The mixture was filtered through celite and the filtrate solvent was removed under reduced pressure. The residue was dissolved in EtOAc (1000 mL) and washed with water (250 mL) and saturated aqueous NaHCO₃ (500 mL). The EtOAc layer was dried (MgSO₄), filtered, and
- 10 the EtOAc was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 5:1 hexanes:EtOAc as eluant. Methyl 4-benzyloxy-2-hydroxybenzoate was obtained as a white powder.

- Step 2. To a stirred, 0°C solution of methyl 4-benzyloxy-2-hydroxybenzoate (12 g, 46 mmol) from step 1 above in DMF (150 mL) was added NaH (2.76 g of a 60% suspension in mineral oil, 69 mmol) and methyl iodide (7.2 mL, 116 mmol). The solution was warmed to ambient temperature and stirred for 18 h. The reaction mixture was poured onto ice and the resulting solution was extracted
- 20 with ether (3 x 200 mL). The organic phase was dried (MgSO₄), filtered and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 4:1 hexanes:EtOAc as eluant. Methyl 4-benzyloxy-2-methoxybenzoate was obtained as a white powder.

- 25 Step 3. A round-bottomed flask containing methyl 4-benzyloxy-2-methoxybenzoate (16.48 g, 60 mmol) from step 2 above was purged with argon and 10% palladium on carbon catalyst was added (2 g). Methanol (200 mL) was slowly added followed by HOAc (2 mL). The solution was kept under 1 atm of H₂ and stirred for 24 h.
- 30 The catalyst was removed by filtration through celite and the filtrate

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solvents were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:1 hexanes:EtOAc as eluant. Methyl 4-hydroxy-2-methoxybenzoate was obtained as an amorphous solid.

- 5 Step 4. To a stirred solution of methyl 4-hydroxy-2-methoxybenzoate (11 g, 60 mmol) from step 3 above in THF:H₂O (100 mL:10 mL) was added LiOH·H₂O (3 g, 71 mmol). The solution was stirred for 24 h and then made acidic (pH 5) by the addition of 10% aqueous HCl. The solution was extracted with CH₂Cl₂ (3 x 50 mL).
 10 The combined organic layers were dried (MgSO₄) and filtered. The filtrate solvent was evaporated under reduced pressure to afford 4-hydroxy-2-methoxybenzoic acid as an amorphous solid.

- Step 5: 1-(4-Piperidiny1)-4(H)-3,1-benzoxazin-2(1H)-one hydrochloride from Step 3 of Example 1 and 2-methoxy-4-hydroxybenzoic acid from Step 4 above were coupled using the
 15 procedure given in step 4 of Example 1. The crude product was purified by pressurized silica gel column chromatography using 98:2 DCM:MeOH as eluant. The title compound was obtained as an amorphous solid.

- 20 Analysis: C₂₁H₂₂N₂O₅ 0.2 MeOH

calc.	C	65.48	H	5.91	N	7.21
found		65.44		5.77		7.39

TLC: R_f = 0.4 (95:5 CHCl₃:MeOH)

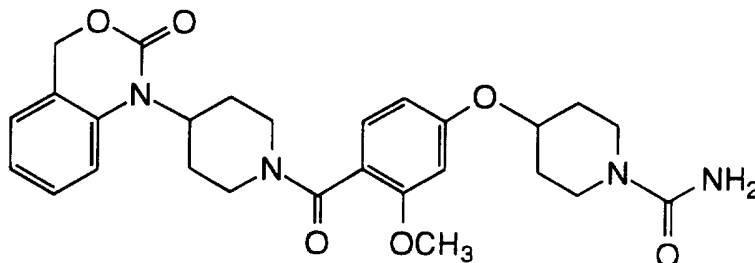
HPLC (method A): retention time = 7.21 min

- 25 FAB MS: m/z = 383 (M + H⁺)

EXAMPLE 15

- 1-(1-(4-(4-(N-Aminocarbonyl)piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one
-
- 30

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5 The hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-methoxy benzoyl)piperidin-4-yl)--4(H)-3,1-benzoxazin-2(1H)-one (1 g, 2.15 mmol) from Example 3 was dissolved in 20 ml of water to give a solution with pH 1.7. The pH of the solution was adjusted to 3 with the addition of 50% potassium hydroxide and 208 mg (2.58 mmol) of potassium isocyanate was added. The reaction was stirred at ambient temperature overnight, then heated to 75° C for 12 hr while maintaining the pH at approximately 3. (HCl was employed to lower the pH when required.) After 36 hr, the reaction mixture was concentrated to dryness and the residue was partitioned between chloroform and water/methanol. The organic phase was washed with water and brine, then dried and concentrated yielding a semi-solid. This material was chromatographed on silica gel (chloroform-methanol, 96:4, v/v) to yield the title compound.

15 Elem. Anal. calc'd for $C_{27}H_{32}N_4O_6 \cdot 0.3 \text{ MeOH} \cdot 0.3 \text{ CHCl}_3$:

Calc'd: C, 59.33; H, 6.24; N, 9.88.

Found: C, 59.35; H, 6.22; N, 9.58.

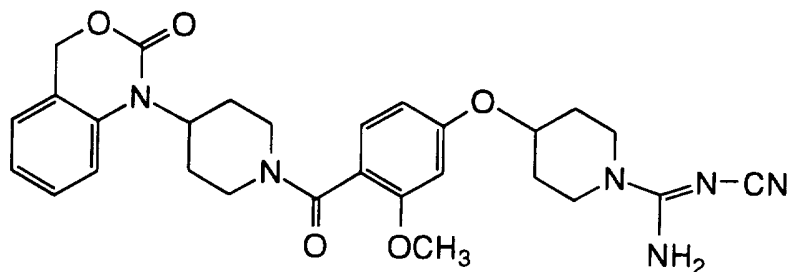
FAB MS: m/z 509 ($M^+ + H$).

20

EXAMPLE 16

1-(1-(4-(4-(N-(N'-Cyanoamidine))piperidinyloxy)-2-methoxybenzoyl)-piperidin-4-yl)--4(H)-3,1-benzoxazin-2(1H)-one

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Step 1: To 10 ml of water containing 258 mg of potassium carbonate was added 10 ml of ethyl acetate containing the hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-2-methoxy benzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one (1.0 g, 1.7 mmol) from Example 3. To this mixture was added 405 mg (1.7 mmol) of N-cyanodiphenyl-imidocarbonate. The reaction mixture was stirred for 2 hr at ambient temperature, diluted with ethyl acetate and the layers were separated. The organic phase was washed with water, then was dried, and concentrated to give of *N*-[1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl) piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one]-*N'*-cyano-*O*-phenylisourea as a white amorphous solid.

Step 2: A solution of 30 ml of methanol containing 500 mg of *N*-[1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl) piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one]-*N'*-cyano-*O*-phenylisourea from step 1 above was saturated with ammonia at 0° C. The reaction flask was capped with a septum and the reaction was allowed to stand at ambient temperature overnight. The reaction mixture was cooled and more ammonia was added. After a total reaction time of 24 hr, all volatiles were removed in vacuo and the residue was chromatographed on silica gel (chloroform-isopropanol, 98:2, v/v) to give the title compound. Elem. Anal. calc'd for C₂₈H₃₂N₆O₅•0.25 IPA•0.25CHCl₃:

Calc'd: C, 60.32; H, 5.98; N, 14.55.

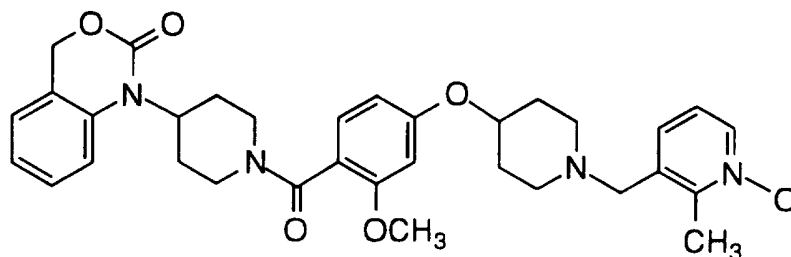
Found: C, 60.57; H, 5.91; N, 14.51.

FAB MS: *m/z* 533 (M⁺ + H).

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EXAMPLE 17

1-(1-(4-(1-(N-oxo-2-methyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



5

Step 1. To a stirred solution of ethyl 2-methylnicotinate (1.50 g, 9.09 mmol) from step 1 above in THF (65 mL) at 0°C was added LAH (9.1 mL of a 1.0 M solution in THF; 9.1 mmol). The mixture was stirred at ambient temperature for 18 h and then quenched by the sequential addition of ethyl acetate (0.1 mL), water (0.1 mL), 15% aqueous NaOH (0.1 mL) and water (0.28 mL). The solids were removed by filtration through celite and the filtrate solvents were removed under reduced pressure. 3-Hydroxymethyl-2-methylpyridine was obtained as an oil (TLC: R_f = 0.40 (5:95 MeOH:CH₂Cl₂)).

Step 2. To a stirred solution of 3-hydroxymethyl-2-methylpyridine (1.00 g, 8.13 mmol) from step 1 above in CH₂Cl₂ (40 mL) at ambient temperature was added SOCl₂ (9.5 g, 80 mmol). The mixture was stirred for 4 h, and the solvent and excess SOCl₂ were evaporated under reduced pressure. The residue was partitioned between CH₂Cl₂ (50 mL) and saturated aqueous NaHCO₃ (100 mL). The organic layer was separated, and the aqueous layer was washed with additional CH₂Cl₂ (2 x 40 mL). The combined organic layers were evaporated under reduced pressure to give 3-chloromethyl-2-methylpyridine as a solid which was used in the next step without purification (TLC: R_f = 0.85 (95:5 CH₂Cl₂:MeOH); FAB MS m/z 142 (M⁺ + H)).

Step 3. To a stirred solution of 3-chloromethyl-2-methylpyridine (0.50 g; 3.5 mmol) from step 2 above in CHCl₃ (40 mL) was added MCPBA (1.1 g of 50% MCPBA by weight; 3.5 mmol).

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After 1.5 h, the solution was extracted with saturated aqueous NaHCO₃ (40 mL), water (40 mL), dried (MgSO₄), filtered, and evaporated under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3 CH₂Cl₂:MeOH as eluant. 3-Chloromethyl-2-methylpyridine-N-oxide was obtained as a solid (TLC: R_f = 0.30 (97:3 CH₂Cl₂:MeOH); FAB MS m/z 158 (M⁺ + H)).

Step 4: To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 3 (6.24 g, 13.4 mmol) in DMF (150 mL) under argon atmosphere was added 3-chloromethyl-2-methylpyridine-N-oxide from Step 3 above (2.33 g, 14.8 mmol) and DIEA (3.5 mL, 20 mmol). The reaction mixture was stirred at ambient temperature for 48 hours. The solvent was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (100 mL) and CH₂Cl₂ (100 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant to give the title compound. To a solution of the title compound (500 mg) in MeOH (10 mL) was added 1.1 equivalents of aqueous HCl and the solvent was removed under reduced pressure. The residue was dissolved in 5:1 H₂O:CH₃CN and lyophilized to give a white solid. The amorphous HCl salt (500 mg) was dissolved in hot isopropanol (8 mL). Cooling to ambient temperature gave a crystalline mono-hydrochloride, mono-hydrate salt of the title compound.

Analysis calculated for C₃₃H₃₈N₄O₆, 1.0 HCl, 1.0 H₂O

 C, 61.81; H, 6.45; N, 8.74

Found C, 61.54; H, 6.32; N, 8.60

TLC: R_f = 0.30 (95:5:0.5 CH₂Cl₂:MeOH:NH₄OH)

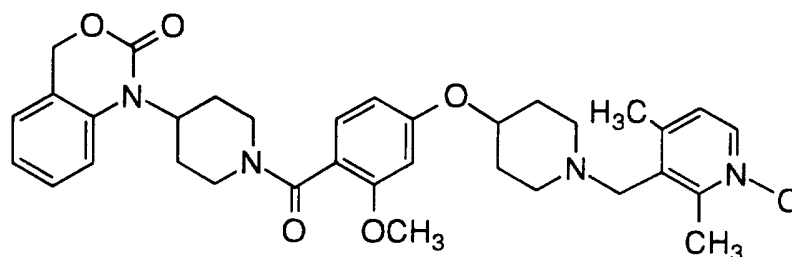
HPLC (method A) retention time = 5.84 min

FAB MS m/z 587 (M⁺ + H)

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EXAMPLE 18

1-(1-(4-(1-(N-oxo-2,4-dimethyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



5

Ethyl 2,4-dimethylnicotinate, prepared by the method of Ohno, et al., Journal of the American Chemical Society (1979), vol. 101, pp. 7036-7040, was converted in three steps to 3-chloromethyl-2,4-dimethylpyridine N-oxide using procedures analogous to those given in steps 1-3 of Example 17. 3-Chloromethyl-2,4-dimethylpyridine N-oxide (0.94 g; 5.4 mmol) and 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 3 (2.0 g; 4.3 mmol) were coupled using the procedure given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using a gradient elution of 99:1:0.05 to 97:3:0.015 CH₂Cl₂:MeOH:NH₄OH. A methanolic solution of the free base of the title compound containing 2 equivalents of 2 N aqueous HCl was evaporated under reduced pressure. The residue was lyophilized from H₂O:CH₃CN to give the hydrochloride salt of the title compound as an amorphous solid.

15

Analysis calculated for C₃₄H₄₀N₄O₆, 1.55 HCl, 0.55 H₂O

C, 61.21; H, 6.44; N, 8.40

Found C, 61.20; H, 6.44; N, 8.23

TLC: R_f = 0.22 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)

25 HPLC (method A) retention time = 6.10 min

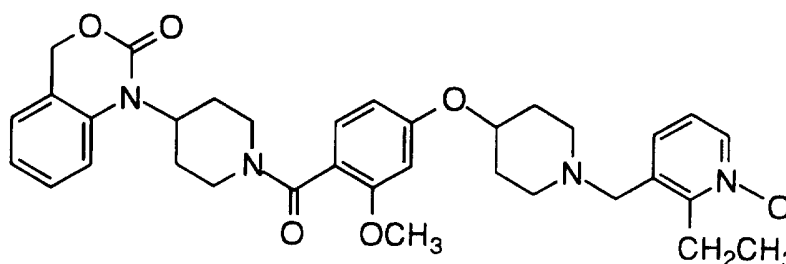
FAB MS m/z 601 (M⁺ + H)

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EXAMPLE 19

1-(1-(4-(1-(N-oxo-2-ethyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one

5



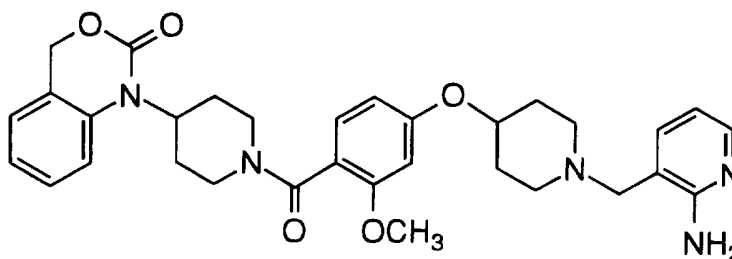
2-Ethylnicotinic acid, obtained by the method of J. Epszajn, et al., Synthetic Communications (1992), vol. 22, pp. 1239-1247, was converted to methyl 2-ethylnicotinate by treatment with HCl in MeOH. 3-Chloromethyl-2-ethylpyridine N-oxide was obtained from methyl 2-ethylnicotinate in three steps using procedures analogous to those given in steps 1-3 of Example 17. 3-Chloromethyl-2-ethylpyridine N-oxide (0.23 g; 1.3 mmol) and 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 3 (0.50 g; 1.1 mmol) were coupled using the procedure given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using a gradient elution of 99:1:0.05 to 97:3:0.015 CH₂Cl₂:MeOH:NH₄OH. The hydrochloride salt of the title compound was obtained by evaporation of a MeOH solution of the free base containing 2 equivalents of 2 N aqueous HCl. The residue was lyophilized from H₂O:CH₃CN to give the hydrochloride salt of the title compound as an amorphous solid.

Analysis calculated for C₃₄H₄₀N₄O₆, 1.25 HCl, 0.15 H₂O
 C, 62.92; H, 6.45; N, 8.63
 25 Found C, 62.91; H, 6.45; N, 8.66
 TLC: R_f = 0.22 (98:2:0.1 CH₂Cl₂:MeOH:NH₄OH)
 HPLC (method A) retention time = 6.10 min
 FAB MS m/z 601 (M⁺ + H)

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EXAMPLE 20

1-(1-(4-(1-(2-amino-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



5

Step 1: To a stirred solution of 3-methyl-2-phthalimidopyridine (A. E. Moormann et al., Synthetic Communications (1987), vol. 17, pp. 1695-1699; 0.50 g; 2.1 mmol) in CH₂Cl₂ (20 mL) was added N-bromosuccinimide (0.37 g; 2.1 mmol). The solution was stirred at ambient temperature for 24 h. The solvent was removed under reduced pressure and the crude 3-bromomethyl-2-phthalimidopyridine was dissolved in DMF (10 mL). To the DMF solution was added 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 3 (0.95 g; 2.0 mmol) followed by DIEA (0.54 mL; 3.1 mmol). The reaction mixture was stirred at ambient temperature for 24 h. The DMF was removed under reduced pressure and the residue was partitioned between CH₂Cl₂ and saturated aqueous NaHCO₃ solution. The organic phase was washed with brine, dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 95:5:0.25 CH₂Cl₂:MeOH:NH₄OH as eluant to give 1-(1-(4-(1-(2-phthalimido-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one as an amorphous solid (TLC_{Rf} = 0.49 (92:8:0.4 CH₂Cl₂:MeOH:NH₄OH); HPLC RT = 12.9 min (Method B), FAB MS m/z = 702 (M⁺ + 1)).

20

25

Step 2: To a solution of 1-(1-(4-(1-(2-phthalimido-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Step 1 above (0.90 g; 1.3 mmol)

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in EtOH (10 mL) was added hydrazine (0.083 mL; 2.6 mmol). The reaction mixture was stirred at ambient temperature for 72 h. The solvent was removed under reduced pressure and the residue was purified by preparative reverse phase HPLC using a water-acetonitrile gradient containing 0.1% TFA. The fractions containing product were lyophilized to give the TFA salt of the title compound as an amorphous solid.

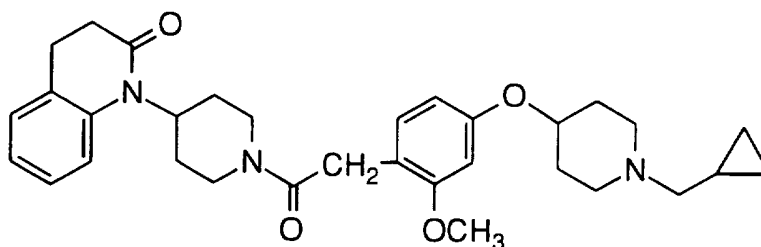
Analysis calculated for $C_{32}H_{37}N_5O_5$, 2.7 TFA, 0.55 H_2O
C, 50.57; H, 4.62; N, 7.87

10 Found C, 50.51; H, 4.64; N, 7.84
TLC: R_f = 0.35 (92:8:0.4 CH_2Cl_2 :MeOH: NH_4OH)
HPLC (Method B) retention time = 9.8 min
FAB MS m/z 572 ($M^+ + H$)

15

EXAMPLE 21

1-(1-(4-(1-cyclopropylmethyl-4-piperidinyloxy)-2-methoxyphenylacetyl)piperidin-4-yl)-3,4-dihydroquinolin-2-one



20 To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxyphenylacetyl)piperidin-4-yl)-3,4-dihydroquinolin-2-one from Example 13 (1.0 g; 2.1 mmol) and cyclopropane carboxaldehyde (0.22 g; 3.1 mmol) in 99:1 MeOH:HOAc (25 mL) was added $NaBH_3CN$ (0.26 g; 4.2 mmol). The mixture was stirred at ambient temperature for 18 h. The solvents were removed under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative reverse phase HPLC using a water-

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acetonitrile gradient containing 0.1% TFA. The fractions containing product were lyophilized to give the TFA salt of the title compound as an amorphous solid.

Analysis calculated for $C_{32}H_{41}N_3O_4$, 1.9 TFA, 0.1 H_2O

5 C, 57.31; H, 5.79; N, 5.60

Found C, 57.31; H, 5.80; N, 5.85

TLC: R_f = 0.5 (90:10 CH_2Cl_2 :MeOH)

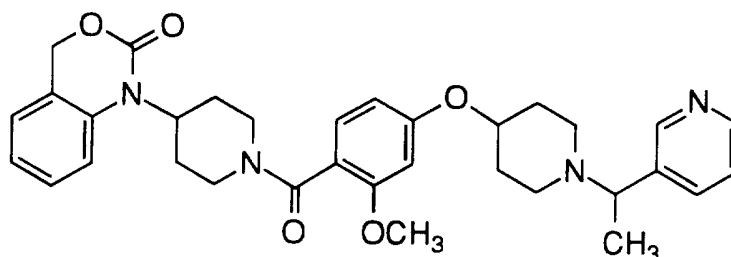
HPLC (method A) retention time = 7.8 min

FAB MS m/z 532 ($M^+ + H$)

10

EXAMPLE 22

1-(1-(4-(1-(1-(3-pyridyl)ethyl)-piperidin-4-yloxy)-2-methoxybenzoyl)-piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



15

To stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one from Example 3 (0.20 g; 0.43 mmol) in dichloroethane (2.15 mL) was added 3-acetylpyridine (0.095 mL, 0.86 mmol) and sodium triacetoxyborohydride (182 mg, 0.86 mmol). Approximately 0.1 mL of acetic acid was added. The solution was stirred at ambient temperature for a total of 5 days. Every 24 h an additional 2 equivalents each of the 3-acetylpyridine and sodium triacetoxyborohydride was added to the reaction mixture. The reaction solvent was removed under reduced pressure and the residue was purified by pressurized silica gel column chromatography using 95:5 CH_2Cl_2 :MeOH(NH_3) and then further purified by preparative reverse-phase HPLC using an acetonitrile-water gradient containing 0.1% TFA. Removal of solvent by lyophilization gave the TFA salt of title compound as an amorphous powder.

20

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TLC: R_f = 0.70 [4:1 CH₂Cl₂:MeOH(NH₃)]

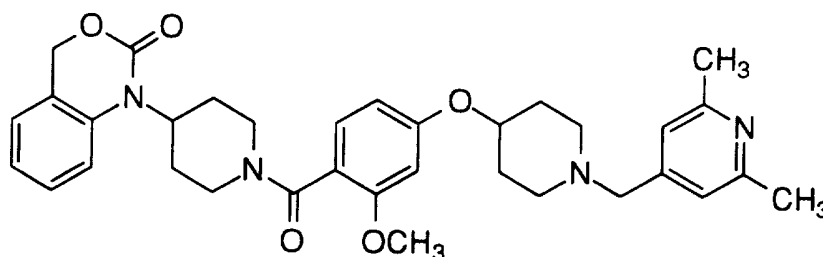
HPLC (method A): retention time 5.83 min.

FAB MS: m/z 571 ($M^+ + H$)

5

EXAMPLE 23

1-(1-(4-(1-(2,6-dimethyl-4-pyridylmethyl)-piperidin-4-yloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



10 To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one hydrochloride from Example 3 (125 mg, 0.249 mmol) in DMF (5 mL) was added 4-chloromethyl-2,6-dimethylpyridine (47.1 mg, 0.299 mmol) and DIEA (96.5 mg, 0.13 mL, 0.747 mmol). The solution was
15 stirred at 50°C for 18 hours. The solvent was removed under reduced pressure. The residue was partitioned between aqueous saturated NaHCO₃ (10 mL) and methylene chloride. The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column
20 chromatography using 5% methanol in methylene chloride as eluant. The product was further purified by preparative reverse phase HPLC using an acetonitrile:water gradient containing TFA. The TFA salt of the title compound was obtained as a white amorphous solid by lyophilization.

25 Analysis calculated for C₃₄H₄₁N₄O₅, 2.5 TFA, 0.4 CH₂Cl₂

C, 52.30; H, 4.94; N, 6.19

Found C, 52.28; H, 4.84; N, 6.33

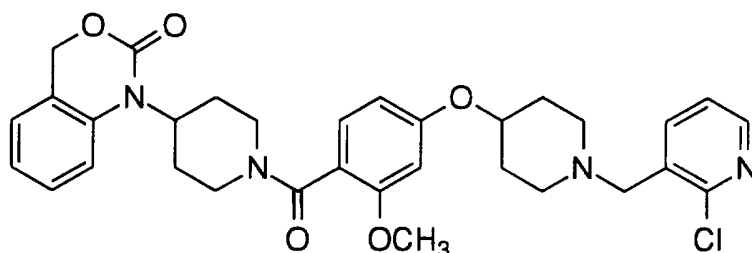
TLC: R_f = 0.28 in 5% methanol in methylene chloride

HPLC (Method A) retention time 5.79 min

FAB MS m/z 585 ($M^+ + H$)

EXAMPLE 24

5 1-(1-(4-(1-(2-chloro-3-pyridylmethyl)-piperidin-4-yloxy)-2-methoxy-
benzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one



To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4(H)-3,1-benzoxazin-2(1H)-one hydrochloride from Example 3 (125 mg, 0.249 mmol) in DMF (5 mL) was added 3-chloromethyl-2-chloropyridine (48.4 mg, 0.299 mmol) and DIEA (96.5 mg, 0.13 mL, 0.747 mmol). The solution was stirred at 50°C for 18 hours. The solvent was removed under reduced pressure. The residue was partitioned between aqueous saturated NaHCO₃ (10 mL) and methylene chloride. The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 3% methanol in methylene chloride as eluant. The product was further purified by preparative reverse phase HPLC using an acetonitrile:water gradient containing TFA. The TFA salt of the title compound was obtained as a white amorphous solid by lyophilization. Analysis calculated for C₃₂H₃₅ClN₄O₅, 1.65 TFA

C, 54.40; H, 4.74; N, 7.19

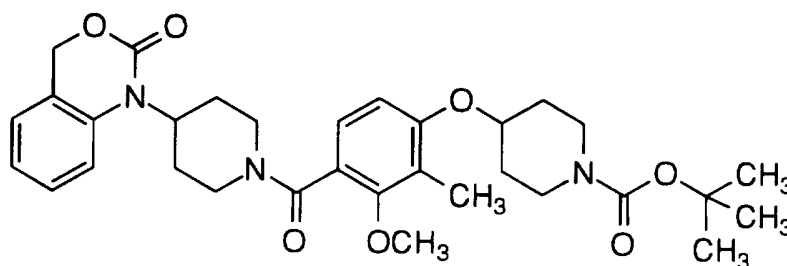
Found C, 54.34; H, 4.81; N, 7.26

25 TLC: $R_f = 0.24$ in 3% methanol in methylene chloride
HPLC (Method A) retention time 6.69 min
FAB MS m/z 591 ($M^{++} + H$)

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EXAMPLE 25

1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



5
4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxy-3-methylbenzoic acid (1.0 g, 2.7 mmol) was prepared from methyl 2,4-dihydroxy-3-methylbenzoate using a three step procedure analogous to steps 1-3 of Example 2. 1-(4-Piperidinyloxy)-4H-3,1-benzoxazin-2(1H)-one
10 hydrochloride and 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-methoxy-3-methylbenzoic acid were coupled using the procedure given in step 4 of Example 1. The crude product was purified by pressurized silica gel column chromatography using a gradient elution of 1-3% MeOH:CH₂Cl₂.
15 1-(1-(4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis: calculated for (C₃₂H₄₁N₃O₇, 0.85 H₂O)

C, 64.60; H, 7.23; N, 7.06

Found C, 64.57; H, 6.96; N, 7.10

20 TLC: R_f = 0.45 (95:5 CH₂Cl₂:MeOH)

HPLC (method B) retention time = 19 min

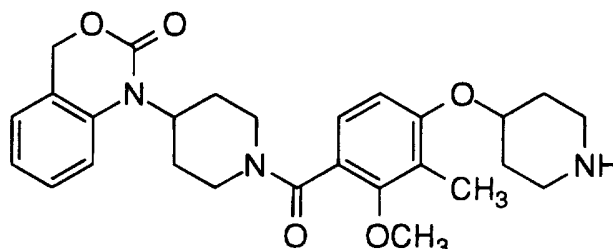
FAB MS: m/z 580 (M⁺ + H)

EXAMPLE 26

25

1-(1-(4-(4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

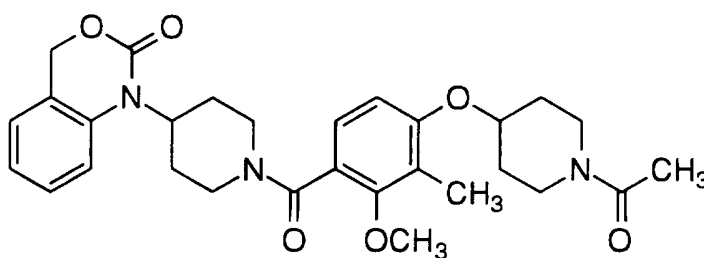
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- A stirred solution of 1-(1-(4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (1.5 g, 2.6 mmol) from Example 25 above in EtOAc (50 mL) was
- 5 cooled to 0°C. HCl gas was bubbled through the solution for 30 min, during which time a precipitate had formed. The mixture was warmed to ambient temperature and stirred for 1 h. The suspension was cooled to 0°C and the solid was collected by filtration and washed with cold EtOAc. The solid was dried under reduced pressure for 18 h, giving
- 10 the hydrochloride salt of the title compound as a white amorphous solid. Analysis: calculated for (C₂₇H₃₃N₃O₅, 2.3 HCl, 0.15 EtOAc)
- C, 57.49; H, 6.38; N, 7.29
- Found C, 57.43; H, 6.32; N, 7.28
- TLC: R_f = 0.1 (90:10:1 CH₂Cl₂:MeOH:NH₄OH)
- 15 HPLC (method B) retention time = 10.5 min
- FAB MS: m/z 480 (M⁺ + H)

EXAMPLE 27

- 20 1-(1-(4-(N-acetyl-4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



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To a stirred solution of 1-(1-(4-(4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.50 g, 1.0 mmol) from Example 26 above in CH₂Cl₂ (20 mL) was added acetic anhydride (0.32 mL, 3.1 mmol) and DIEA (0.52 mL, 3.0 mmol). The reaction mixture was stirred at ambient temperature for 18 h. The solution was diluted with CH₂Cl₂ (50 mL) and was washed with saturated aqueous NaHCO₃ (3x 75 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 98:2 CH₂Cl₂:MeOH as eluant to give the title compound as an amorphous solid.

Analysis: calculated for (C₂₉H₃₅N₃O₆, 0.75 H₂O)

C, 65.09; H, 6.88; N, 7.85

Found C, 65.09; H, 6.70; N, 7.84

TLC: R_f = 0.45 (95:5:0.5 CH₂Cl₂:MeOH:NH₄OH)

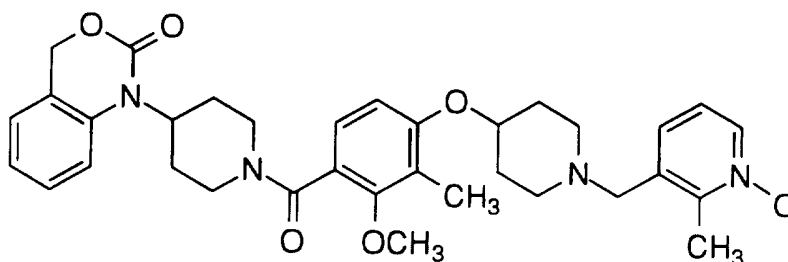
HPLC (method B) retention time = 13.3 min

FAB MS: m/z 522 (M⁺ + H)

20

EXAMPLE 28

1-(1-(4-(1-(N-oxo-2-methyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



25 1-(1-(4-(4-Piperidinyloxy)-2-methoxy-3-methylbenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.50 g, 1.0 mmol) from Example 26 in DMF and 3-chloromethyl-2-methylpyridine-N-oxide from step 3 of Example 17 were coupled using a procedure analogous to that given in step 4 of Example 17. The title compound was purified

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by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The title compound was obtained as an amorphous solid.

Analysis calculated for C₃₄H₄₀N₄O₆, 0.65 CH₂Cl₂, 0.05 H₂O

5 C, 63.36; H, 6.35; N, 8.53

Found C, 63.37; H, 6.23; N, 8.69

TLC: R_f = 0.32 (95:5:0.5 CH₂Cl₂:MeOH:NH₄OH)

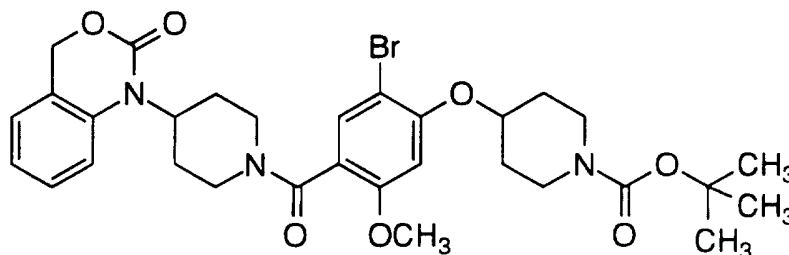
HPLC(method B) retention time = 10.2 min

FAB MS m/z 601 (M⁺ + H)

10

EXAMPLE 29

1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



15

4-(N-t-Butoxycarbonyl-4-piperidinyloxy)-2-methoxy-5-bromobenzoic acid (1.0 g, 2.7 mmol) was prepared from methyl 2,4-dihydroxy-5-bromobenzoate using a three step procedure analogous to steps 1-3 of Example 2. 1-(4-Piperidinyl)-4H-3,1-benzoxazin-2(1H)-one

20 hydrochloride and 4-(N-t-butoxycarbonyl-4-piperidinyloxy)-2-methoxy-5-bromobenzoic acid were coupled using the procedure given in step 4 of Example 1. The title compound was purified by pressurized silica gel column chromatography using 40% EtOAc:hexanes as eluant and was obtained as an amorphous solid.

25 Analysis: calculated for (C₃₁H₃₈BrN₃O₇, 0.20 EtOAc, 1.5 H₂O)

C, 55.48; H, 6.22; N, 6.11

Found C, 55.49; H, 5.94; N, 6.08

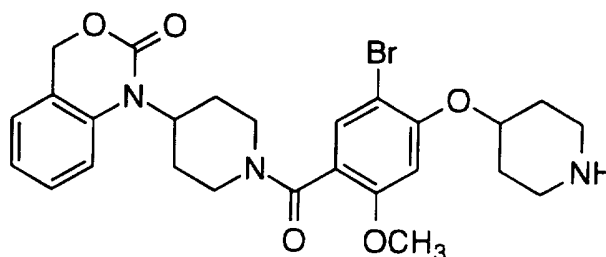
TLC: R_f = 0.30 (4:1 hexanes:EtOAc)

HPLC (method A) retention time = 10.5 min

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EXAMPLE 30

1-(1-(4-(4-piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-
5 4H-3,1-benzoxazin-2(1H)-one



The title compound was prepared from 1-(1-(4-(N-tert-butylloxycarbonyl-4-piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of
10 Example 29 using a procedure analogous to that given in step 3 of Example 1. The hydrochloride salt of the title compound was obtained as an amorphous solid.

Analysis: calculated for (C₂₆H₃₀BrN₃O₅, 1.85 HCl, 0.15 EtOAc)

C, 51.10; H, 5.33; N, 6.72

15 Found C, 51.14; H, 5.30; N, 6.73

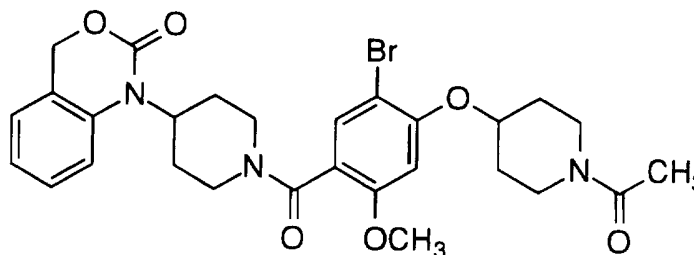
TLC: R_f = 0.11 (95:5:0.5 CH₂Cl₂:MeOH:NH₄OH)

HPLC (method A) retention time = 6.6 min

EXAMPLE 31

20

1-(1-(4-(N-acetyl-4-piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



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The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 30 using a procedure analogous to that given in Example 4. The title compound was purified by pressurized silica gel column chromatography using 98:2 CH₂Cl₂:MeOH as eluant and was obtained as an amorphous solid by evaporation from EtOAc-CH₂Cl₂ under reduced pressure.

Analysis: calculated for (C₂₈H₃₂BrN₃O₆, 0.05 EtOAc, 0.45 CH₂Cl₂)
C, 56.12; H, 5.47; N, 6.85

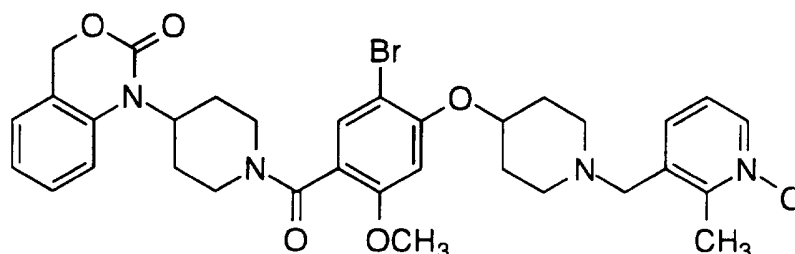
Found C, 56.11; H, 5.45; N, 6.87

TLC: R_f = 0.34 (98:2 CH₂Cl₂:MeOH)

HPLC (method A) retention time = 8.0 min

EXAMPLE 32

1-(1-(4-(1-(N-oxo-2-methyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



1-(1-(4-(4-Piperidinyloxy)-2-methoxy-5-bromobenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride (0.50 g, 1.0 mmol) from Example 30 in DMF and 3-chloromethyl-2-methylpyridine-N-oxide from step 3 of Example 17 were coupled using a procedure analogous to that given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of the title compound was obtained as an amorphous solid by lyophilization from CH₃CN-H₂O containing aqueous HCl.

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Analysis: calculated for (C₃₃H₃₇BrN₄O₆, 2.5 HCl, 1.2 H₂O)

C, 51.99; H, 5.54; N, 7.35

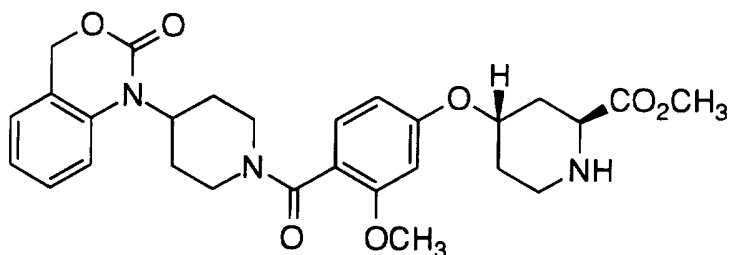
Found C, 51.98; H, 5.44; N, 7.33

TLC: R_f = 0.34 (96:4:0.4 CH₂Cl₂:MeOH:NH₄OH)

5 HPLC (method A) retention time = 6.4 min

EXAMPLE 33

10 1-(1-(4-(trans-2-methoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. To a stirred, 0°C solution of 1-{1-[4-hydroxy-2-methoxybenzoyl]-piperidin-4-yl}-4H-3,1-benzoxazin-2(1H)-one (0.40 g, 1.0 mmol) from Example 14 and triphenylphosphine (0.58 g, 2.2 mmol) in dry THF (15 mL) was added a solution of DEAD (0.35 mL, 2.2 mmol) and N-Boc-cis-2-methoxycarbonyl-4-hydroxypiperidine (0.54 g, 2.1 mmol; prepared by the method given in, J. Org. Chem. (1991) vol. 56, p. 4085) in dry THF (5 mL) over a period of 2 h. The mixture was warmed to ambient temperature and stirred for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (50 mL) and extracted with saturated aqueous NaHCO₃ (25 mL), water (25 mL), and brine (25 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:1 EtOAc:CH₂Cl₂ as eluant to give 1-(1-(4-(N-Boc-2-methoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid.

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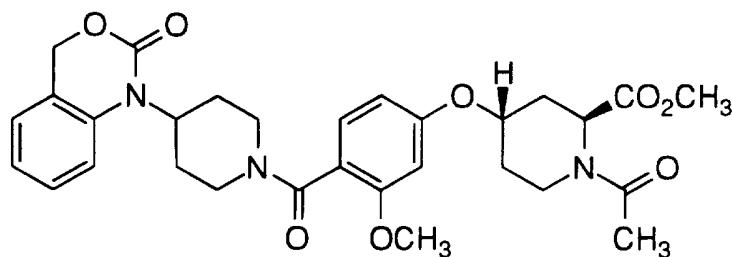
Step 2. To a solution of 1-(1-(4-(N-Boc-2-methoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one (0.37 g, 0.59 mmol) from step 1 above in CH₂Cl₂ (10 mL) was added TFA (3 mL). The solution was stirred at ambient temperature for 2 h. The solvents were removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (50 mL) and extracted with saturated aqueous NaHCO₃ (2x 25 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 1:1 EtOAc:CH₂Cl₂ as eluant. 1-(1-(4-(trans-2-methoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one as an amorphous solid by lyophilization from CH₃CN:H₂O.

Analysis calculated for C₂₈H₃₃N₃O₇, 0.6 H₂O
 15 C, 62.93; H, 6.45; N, 7.86
 Found C, 62.90; H, 6.23; N, 7.80
 TLC: R_f = 0.4 (95:5:0.5 CH₂Cl₂:MeOH:NH₄OH)
 HPLC (method A) retention time = 7.1 min
 FAB MS m/z 524 (M⁺ + H)

20

EXAMPLE 34

1-(1-(4-(N-acetyl-trans-2-methoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



25

The title compound was prepared from 1-(1-(4-(trans-2-methoxycarbonyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 33 using a procedure analogous to that given in Example 4. The title compound was purified

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by pressurized silica gel column chromatography using 98:2 CH₂Cl₂:MeOH as eluant and was obtained as an amorphous solid by lyophilization from CH₃CN:H₂O.

Analysis calculated for C₃₀H₃₅N₃O₈, 1.2 H₂O

5 C, 61.35; H, 6.42; N, 7.16

Found C, 61.34; H, 6.17; N, 7.08

TLC: R_f = 0.45 (95:5 CH₂Cl₂:MeOH)

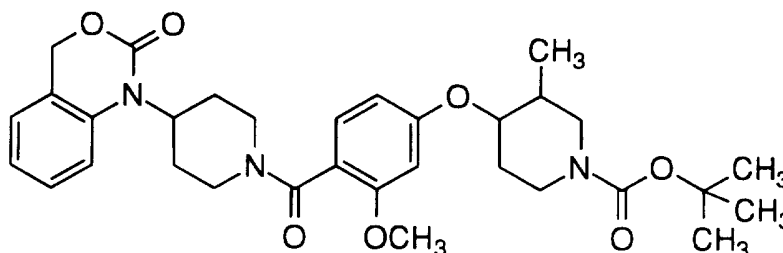
HPLC (method A) retention time = 7.5 min

FAB MS m/z 566 (M⁺ + H)

10

EXAMPLE 35

1-(1-(4-(N-tert-butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



15

Step 1. To a solution of LDA (44 mmol) in THF (150 mL) at -78°C was added N-Boc-4-piperidinone (8.0 g, 40 mmol) in THF (50 mL) over a period of 30 min. The solution was stirred at -78°C for 3 h, and iodomethane (5.8 g, 40 mmol) was added. The resulting solution was stirred at -78°C for 2 h and then warmed to ambient temperature for 18 h. The mixture was diluted with saturated aqueous NH₄Cl (150 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were dried (MgSO₄), filtered, and the solvents were removed under reduced pressure. The residue was purified using pressurized silica gel column chromatography using a gradient elution of 100:0 to 95:5 hexanes:EtOAc. N-Boc-3-methyl-4-piperidinone was obtained as an oil.

20

Step 2. To a stirred solution of N-Boc-3-methyl-4-piperidinone (3.4 g, 12.7 mmol) from step 1 above in MeOH (30 mL) at

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0°C was added sodium borohydride (0.48 g, 12.7 mmol) over a period of 30 min. The mixture was warmed to ambient temperature and stirred for 18 h. The mixture was diluted with water (100 mL) and extracted with CH₂Cl₂ (3x 30 mL). The combined organic layers were
5 dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using a gradient elution of 100:0 to 90:10 hexanes:EtOAc. N-Boc-3-methyl-4-hydroxypiperidine was obtained as an oil.

10 Step 3. N-Boc-3-methyl-4-hydroxypiperidine from step 2 above was coupled to methyl 2-methoxy-4-hydroxybenzoate from step 3 of Example 14 using Mitsunobu conditions as given in step 1 of Example 2. Methyl 4-(N-tert-butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoate was purified by pressurized silica
15 gel column chromatography using a gradient elution of 100:0 to 90:10 hexanes:EtOAc and was obtained as an amorphous solid.

Step 4. Methyl 4-(N-tert-butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoate from step 3 above was saponified using the procedure given in step 3 of Example 2. 4-(N-tert-
20 butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoic acid was obtained as an amorphous solid.

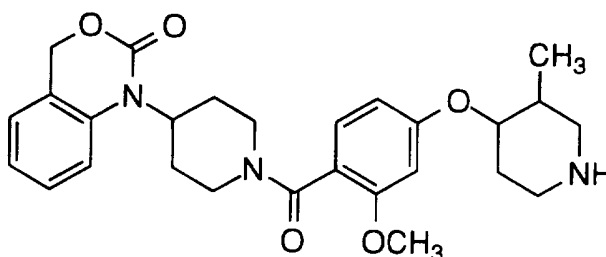
Step 5. 4-(N-tert-butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoic acid from step 4 above was coupled to 1-(4-piperidinyl)-4H-3,1-benzoxazin-2(1H)-one hydrochloride from
25 step 3 of Example 1 using the procedure given in step 4 of Example 1. 1-(1-(4-(N-tert-butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis calculated for C₃₂H₄₁N₃O₇, 0.6 DMF, 0.25 CH₂Cl₂
30 C, 63.42; H, 7.14; N, 7.82
Found C, 63.41; H, 7.10; N, 7.91
TLC: R_f = 0.35 (95:5 CH₂Cl₂:MeOH)
HPLC (method A) retention time = 10.3 min
FAB MS m/z 580 (M⁺ + H)

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EXAMPLE 36

1-(1-(4-(3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-
 5 4H-3,1-benzoxazin-2(1H)-one



1-(1-(4-(N-tert-butyloxycarbonyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 35 was converted to 1-(1-(4-(3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one using the
 10 procedure given in step 3 of Example 1. The hydrochloride salt of the title compound was obtained as an amorphous solid.

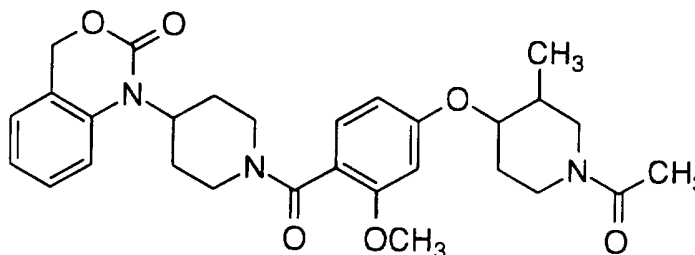
Analysis calculated for C₂₇H₃₃N₃O₅, 2.3 HCl, 0.25 CH₃CN
 C, 57.56; H, 6.33; N, 7.93

15 Found C, 57.56; H, 6.52; N, 7.96
 TLC: R_f = 0.2 (80:20 CH₂Cl₂:MeOH(NH₃))
 HPLC (method A) retention time = 6.5 min
 FAB MS m/z 479 (M⁺ + H)

20

EXAMPLE 37

1-(1-(4-(N-acetyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



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1-(1-(4-(3-Methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 36 was converted to 1-(1-(4-(N-acetyl-3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one using the procedure given in

- 5 Example 4. The title compound was obtained as an amorphous solid.

Analysis calculated for $C_{29}H_{35}N_3O_6$, 0.5 H_2O

C, 65.64; H, 6.70; N, 7.83

Found C, 66.78; H, 6.76; N, 8.06

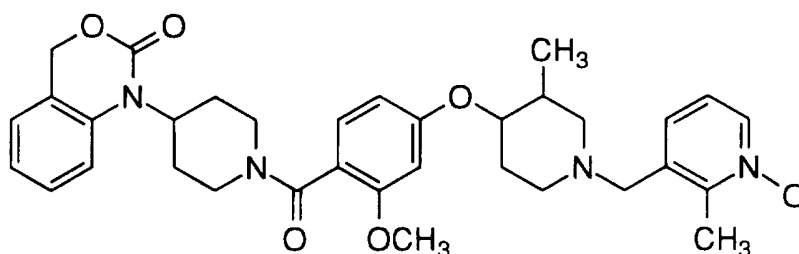
TLC: $R_f = 0.75$ (90:10 CH_2Cl_2 :MeOH(NH_3))

- 10 HPLC(method A) retention time = 7.5 min

FAB MS m/z 522 ($M^+ + H$)

EXAMPLE 38

- 15 1-(1-(4-(1-(N-oxo-2-methyl-3-pyridylmethyl)-3-methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



1-(1-(4-(3-Methyl-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 36 and 3-chloromethyl-2-methylpyridine-N-oxide from step 3 of Example 17 were coupled using a procedure analogous to that given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using 97:3:0.3 CH_2Cl_2 :MeOH: NH_4OH as eluant and was obtained as an amorphous solid.

- 25 Analysis calculated for $C_{34}H_{40}N_4O_6$, 1.1 CH_2Cl_2

C, 60.73; H, 6.13; N, 8.07

Found C, 60.75; H, 6.07; N, 7.94

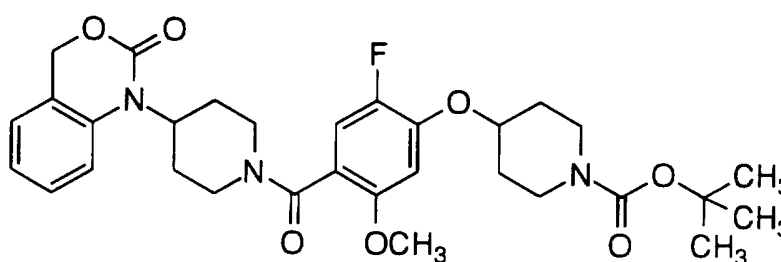
TLC: $R_f = 0.6$ (90:10 CH_2Cl_2 :MeOH(NH_3))

HPLC (method A) retention time = 6.5 min

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FAB MS m/z 601 ($M^+ + H$)EXAMPLE 39

5 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



10 Step 1. Methyl 4-hydroxy-2-methoxybenzoate (10 g, 55 mmol) from step 3 of Example 14 and 1-fluoro-3,5-dichloropyridinium trifluoromethanesulfonate (21 g, 66 mmol) were refluxed in dichloromethane (250 mL) for 48 h. The solution was washed with 5% aqueous citric acid (250 mL) and the organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 99:1 CH_2Cl_2 :MeOH as eluant. Crystallization from ether gave methyl 5-fluoro-4-hydroxy-2-methoxybenzoate.

15 Step 2. Methyl 5-fluoro-4-hydroxy-2-methoxybenzoate from step 1 above was coupled to N-Boc-4-piperidinol using Mitsunobu conditions as given in step 1 of Example 2. Methyl 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoate was obtained as a gum (TLC R_f = 0.19 (3:7 EtOAc:hexanes); HPLC (method A) retention time = 9.9 min).

20 Step 3. Methyl 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoate from step 2 above was saponified using the procedure given in step 3 of Example 2. 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoic acid was obtained as an amorphous solid (HPLC (method A) retention time = 8.6 min).

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Step 4. 4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoic acid from step 3 above and 1-(4-piperidinyloxy)-4H-3,1-benzoxazin-2(1H)-one hydrochloride from step 3 of Example 1 were coupled using the procedure given in step 4 of Example 1. 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis calculated for $C_{31}H_{38}FN_3O_7$, 0.2 EtOAc, 0.25 H_2O

C, 63.04; H, 6.67; N, 6.94

10 Found C, 63.06; H, 6.56; N, 6.93

TLC: $R_f = 0.17$ (4:1 EtOAc:hexanes)

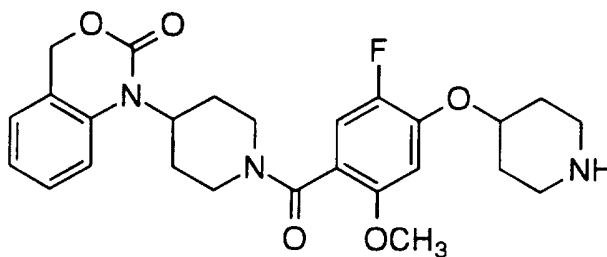
HPLC (method A) retention time = 9.8 min

FAB MS m/z 584 ($M^+ + H$)

15

EXAMPLE 40

1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



20 The title compound was prepared from 1-(1-(4-(N-tert-butyloxycarbonyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 39 using the procedure given in step 3 of Example 1. The hydrochloride salt of 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.

Analysis calculated for $C_{26}H_{30}FN_3O_5$, 2.0 HCl, 0.15 EtOAc

C, 56.08; H, 5.87; N, 7.38

Found C, 56.02; H, 5.94; N, 7.37

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TLC: $R_f = 0.12$ (96:4:0.4 CH_2Cl_2 :MeOH: NH_4OH)

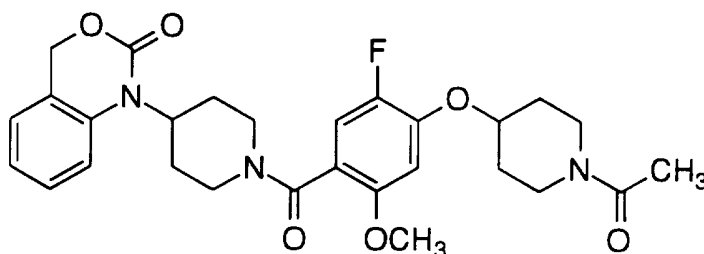
HPLC(method A) retention time = 6.2 min

FAB MS m/z 484 ($\text{M}^+ + \text{H}$)

5

EXAMPLE 41

1-(1-(4-(N-acetyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)-
 piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

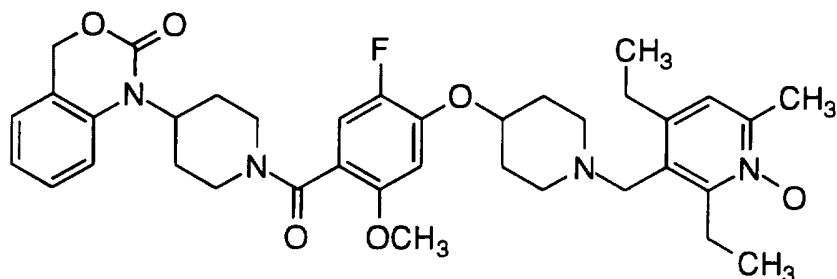


- 10 The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 40 using the procedure given in Example 4. 1-(1-(4-(N-acetyl-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained as an amorphous solid.
- 15 Analysis calculated for $\text{C}_{28}\text{H}_{32}\text{FN}_3\text{O}_6$, 0.45 EtOAc, 0.65 H_2O
 C, 62.03; H, 6.45; N, 7.28
 Found C, 62.02; H, 6.22; N, 7.26
 TLC: $R_f = 0.33$ (97:3 CH_2Cl_2 :MeOH)
 HPLC (method A) retention time = 7.4 min
- 20 FAB MS m/z 526 ($\text{M}^+ + \text{H}$)

EXAMPLE 42

- 1-(1-(4-(1-(N-oxo-2,4-diethyl-6-methyl-3-pyridylmethyl)-4-
 25 piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-
 benzoxazin-2(1H)-one
-

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Step 1. Ethyl propionylacetate (25 g, 0.17 mol), hexan-2,4-dione (12.5 g, 0.11 mol), and ammonium acetate (51 g, 0.66 mol) were combined and heated with stirring at 110°C for 96 h. The
5 reaction mixture was diluted with EtOAc (300 mL) and washed with water (2x 150 mL) and brine (100 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 92:8 hexanes:EtOAc as eluant. Ethyl 2,6-
10 diethyl-4-methylnicotinate ($R_f = 0.38$ (9:1 hexanes:EtOAc)) was isolated as the major product and ethyl 2,4-diethyl-6-methylnicotinate ($R_f = 0.25$ (9:1 hexanes:EtOAc)) was isolated as the minor product.

Step 2. To a solution of ethyl 2,4-diethyl-6-methylnicotinate (0.55 g, 2.5 mmol) from step 1 above in THF (65 mL) at 0°C was added LAH (2.5 mL of a 1.0 M solution in THF; 2.5 mmol).
15 The mixture was stirred at ambient temperature for 18 h and then quenched by the sequential addition of ethyl acetate (0.1 mL), water (0.1 mL), 15% aqueous NaOH (0.1 mL) and water (0.28 mL). The solids were removed by filtration through celite and the filtrate solvents
20 were removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 99:1 CH₂Cl₂:MeOH as eluant. 2,4-Diethyl-3-hydroxymethyl-6-methylpyridine was obtained as an oil (TLC $R_f = 0.32$ (98:2 CH₂Cl₂:MeOH; FAB MS $m/z = 180$ ($M^+ + H$)).

25 Step 3. To a solution of 2,4-diethyl-3-hydroxymethyl-6-methylpyridine (0.35 g, 2.0 mmol) from step 2 above in CH₂Cl₂ (15 mL) was added thionyl chloride (0.9 g, 8 mmol) dropwise. The mixture was stirred at ambient temperature for 18 h and the solvent was removed under reduced pressure. The residue was partitioned between

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CH₂Cl₂ (50 mL) and saturated aqueous NaHCO₃ (50 mL). The organic phase was dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. The residue was purified by pressurized silica gel column chromatography using 85:15 hexanes:EtOAc as eluant. 3-Chloromethyl-2,4-diethyl-6-methylpyridine was obtained as an amorphous solid (TLC R_f = 0.10 (9:1 hexanes:EtOAc); FAB MS m/z = 198 (M⁺ + H)).

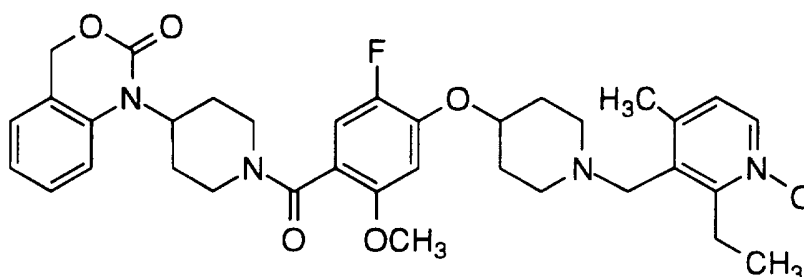
Step 4. To a solution of 3-chloromethyl-2,4-diethyl-6-methylpyridine (0.32 g, 1.6 mmol) from step 3 above in CHCl₃ (25 mL) was added MCPBA (0.70 g of a 50% by weight mixture; 2.0 mmol) and the mixture was stirred at ambient temperature for 18 h. The solution was extracted with saturated aqueous NaHCO₃ (2x 20 mL), dried (MgSO₄), filtered, and the solvent was removed under reduced pressure. 3-Chloromethyl-2,4-diethyl-6-methylpyridine-N-oxide was obtained as an amorphous solid (TLC R_f = 0.39 (96:4 CHCl₃:MeOH); FAB MS m/z = 214 (M⁺ + H)).

Step 5. 3-Chloromethyl-2,4-diethyl-6-methylpyridine-N-oxide from step 4 above and 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 40 were reacted using the procedure given in step 4 of Example 17. The crude product was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of 1-(1-(4-(1-(N-oxo-2,4-diethyl-6-methyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained by lyophilization from CH₃CN-H₂O containing aqueous HCl. Analysis calculated for C₃₇H₄₅FN₄O₆, 0.7 HCl, 2.3 H₂O
C, 61.06; H, 6.97; N, 7.70
Found C, 61.04; H, 6.97; N, 7.72
TLC: R_f = 0.30 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)
HPLC (method A) retention time = 6.7 min
FAB MS m/z 661 (M⁺ + H)

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EXAMPLE 43

1-(1-(4-(1-(N-oxo-2-ethyl-4-methyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



Step 1. Ethyl 2-ethyl-4-methylnicotinate was prepared in a manner analogous to that reported for ethyl 2,4-dimethylnicotinate by Ohno et al., *J. Am. Chem. Soc.* (1979) vol. 101, p. 7036. Ethyl propionylacetate (25 g, 0.17 mol), acetaldehyde (10.6 g, 0.24 mol), and acetaldehyde-ammonia complex (11.7 g, 0.09 mol) were combined and heated at 90°C for 96 h. The mixture was evaporated under reduced pressure to remove water and excess reagents. The residue was distilled under reduced pressure (ca. 1 Torr) and the fraction boiling from 140-155°C was collected and further purified by pressurized silica gel column chromatography using a gradient elution of 95:5 to 85:15 CH₂Cl₂:EtOAc. Ethyl 2-ethyl-6-methylnicotinate (R_f = 0.28 (92:8 CH₂Cl₂:EtOAc)) was isolated as the major product and ethyl 2-ethyl-4-methylnicotinate (R_f = 0.17 (92:8 CH₂Cl₂:EtOAc)) was isolated as the minor product.

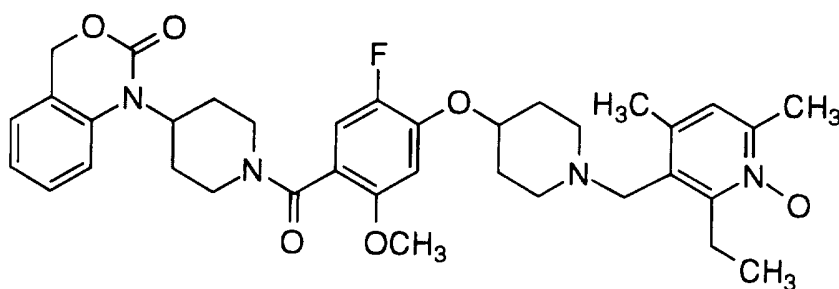
Steps 2-5. Ethyl 2-ethyl-4-methylnicotinate from step 1 above was converted to 3-chloromethyl-2-ethyl-4-methylpyridine-N-oxide in three steps using procedures analogous to those given in steps 1-3 in Example 17, and 3-chloromethyl-2-ethyl-4-methylpyridine-N-oxide was used to alkylate 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 40 using a procedure analogous to that given in step 4 of Example 17. The crude product was purified by pressurized silica gel

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- column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of 1-(1-(4-(1-(N-oxo-2-ethyl-4-methyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained by lyophilization from CH₃CN-H₂O containing aqueous HCl.
- 5 Analysis calculated for C₃₅H₄₁FN₄O₆, 2.5 HCl, 0.95 H₂O
 C, 56.73; H, 6.18; N, 7.56
 Found C, 56.72; H, 6.07; N, 7.60
 TLC: R_f = 0.24 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)
- 10 HPLC (method A) retention time = 6.4 min
 FAB MS m/z 633 (M⁺ + H)

EXAMPLE 44

- 15 1-(1-(4-(1-(N-oxo-2-ethyl-4,6-dimethyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



- 20 Step 1. Ethyl propionylacetate, pentan-2,4-dione, and ammonium acetate were reacted to give ethyl 2-ethyl-4,6-dimethylnicotinate using a procedure analogous to that given in step 1 of Example 42.

- 25 Steps 2-5. Ethyl 2-ethyl-4,6-dimethylnicotinate from step 1 above was converted to 3-chloromethyl-4,6-dimethyl-2-ethylpyridine-N-oxide in three steps using procedures analogous to those given in steps 2-4 of Example 42, and 3-chloromethyl-4,6-dimethyl-2-ethylpyridine-N-oxide was used to alkylate 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one

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one from Example 40 using a procedure analogous to that given in step 4 in Example 17. The crude product was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of 1-(1-(4-(1-(N-oxo-2-ethyl-4,6-

5 dimethyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained by lyophilization from CH₃CN-H₂O containing aqueous HCl. Analysis calculated for C₃₆H₄₃FN₄O₆, 2.5 HCl, 1.4 H₂O

C, 56.66; H, 6.38; N, 7.34

10 Found C, 56.68; H, 6.27; N, 7.42

TLC: R_f = 0.22 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)

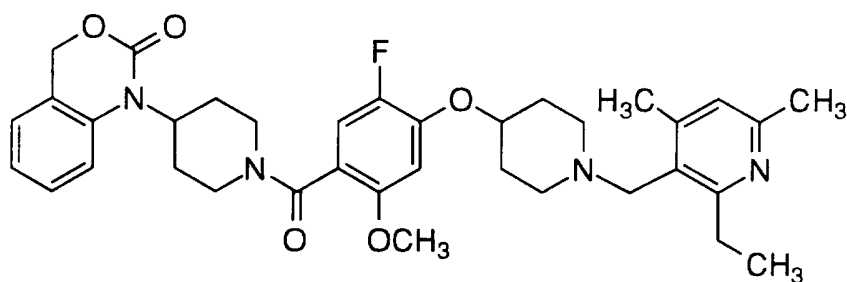
HPLC (method A) retention time = 6.4 min

FAB MS m/z 647 (M⁺ + H)

15

EXAMPLE 45

1-(1-(4-(1-(2-ethyl-4,6-dimethyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



20

Step 1. Ethyl propionylacetate, pentan-2,4-dione, and ammonium acetate were reacted to give ethyl 2-ethyl-4,6-dimethylnicotinate using a procedure analogous to that given in step 1 of Example 42.

25

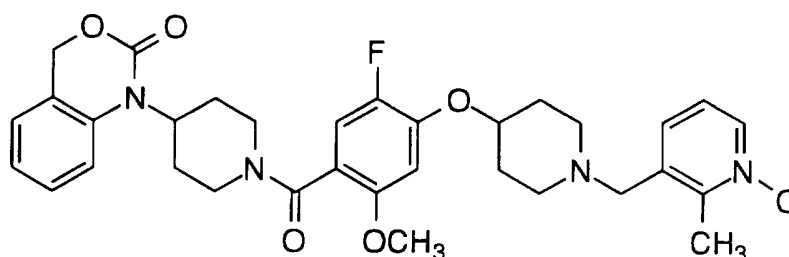
Steps 2-4. Ethyl 2-ethyl-4,6-dimethylnicotinate from step 1 above was converted to 3-chloromethyl-4,6-dimethyl-2-ethylpyridine in two steps using procedures analogous to those given in steps 2 and 3 of Example 42, and 3-chloromethyl-4,6-dimethyl-2-ethylpyridine was used

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- to alkylate 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 40 using a procedure analogous to that given in step 4 in Example 17. The crude product was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of 1-(1-(4-(1-(2-ethyl-4,6-dimethyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one was obtained by lyophilization from CH₃CN-H₂O containing aqueous HCl.
- Analysis calculated for C₃₆H₄₃FN₄O₅, 1.65 HCl, 0.05 H₂O
 C, 62.49; H, 6.52; N, 8.10
 Found C, 62.47; H, 6.43; N, 8.01
 TLC: R_f = 0.28 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)
 HPLC (method A) retention time = 6.0 min
 FAB MS m/z 631 (M⁺ + H)

EXAMPLE 46

- 1-(1-(4-(1-(N-oxo-2-methyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one
-



- The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 40 and 3-chloromethyl-2-methylpyridine-N-oxide from step 3 of Example 17 using the procedure given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The

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hydrochloride salt of the title compound was obtained as an amorphous solid by lyophilization from CH₃CN-H₂O containing aqueous HCl.

Analysis calculated for C₃₃H₃₇FN₄O₆, 2.4 HCl, 0.25 H₂O

C, 56.89; H, 5.77; N, 8.04

5 Found C, 56.89; H, 5.77; N, 7.90

TLC: R_f = 0.26 (96:4:0.4 CH₂Cl₂:MeOH:NH₄OH)

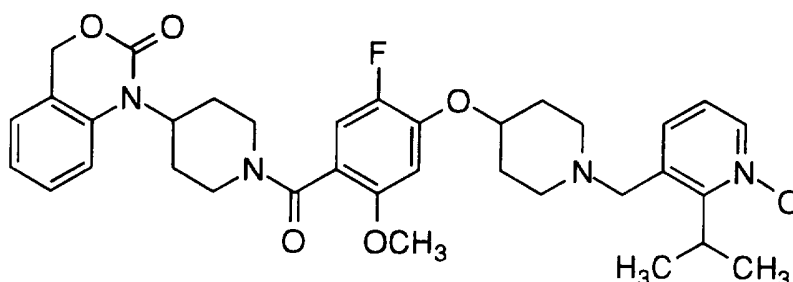
HPLC (method A) retention time = 6.1 min

FAB MS m/z 604 (M⁺ + H)

10

EXAMPLE 47

1-(1-(4-(1-(N-oxo-2-isopropyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



15

Ethyl 2-isopropylpicotinate was converted in three steps to 3-chloromethyl-2-isopropylpyridine-N-oxide using procedures analogous to those given in steps 1-3 in Example 17. The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 40 and 3-chloromethyl-2-isopropylpyridine-N-oxide using the procedure given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of the title compound was obtained as an amorphous solid by lyophilization from CH₃CN-H₂O containing aqueous HCl.

25

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Analysis calculated for C₃₅H₄₁FN₄O₆, 2.5 HCl, 0.7 H₂O

C, 57.07; H, 6.14; N, 7.61

Found C, 57.09; H, 6.07; N, 7.52

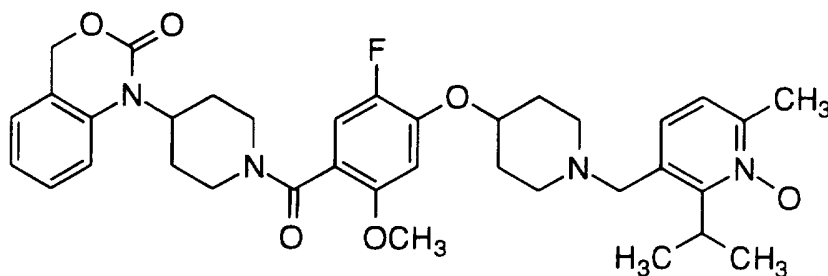
TLC: R_f = 0.32 (96:4:0.4 CH₂Cl₂:MeOH:NH₄OH)

5 HPLC (method A) retention time = 6.7 min

FAB MS m/z 633 (M⁺ + H)

EXAMPLE 48

10 1-(1-(4-(1-(N-oxo-2-isopropyl-6-methyl-3-pyridylmethyl)-4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



15 Ethyl 2-isopropyl-6-methylnicotinate was prepared using a procedure analogous to that given in step 1 of Example 43 using ethyl 3-oxo-4-methylpentanoate in place of ethyl propionylacetate. Ethyl 2-isopropyl-6-methylnicotinate was converted in three steps to 3-chloromethyl-2-isopropyl-6-methylpyridine-N-oxide using procedures analogous to those given in steps 1-3 in Example 17. The title compound was

20 prepared from 1-(1-(4-(4-piperidinyloxy)-5-fluoro-2-methoxybenzoyl)-piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one of Example 40 and 3-chloromethyl-2-isopropyl-6-methylpyridine-N-oxide using the procedure given in step 4 of Example 17. The title compound was

25 purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of the title compound was obtained as an amorphous solid by lyophilization from CH₃CN-H₂O containing aqueous HCl.

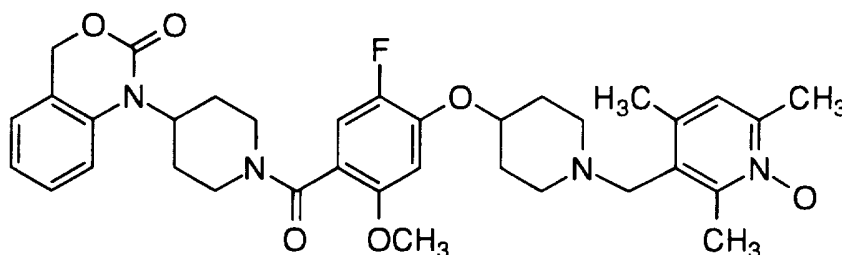
Analysis calculated for C₃₆H₄₃FN₄O₆, 2.5 HCl, 0.35 H₂O

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C, 58.09; H, 6.26; N, 7.53
 Found C, 58.09; H, 6.21; N, 7.48
 TLC: R_f = 0.35 (96:4:0.4 CH₂Cl₂:MeOH:NH₄OH)
 HPLC (method A) retention time = 6.8 min
 5 FAB MS m/z 647 ($M^+ + H$)

EXAMPLE 49

10 1-(1-(4-(1-(N-oxo-2,4,6-trimethyl-3-pyridylmethyl)-4-piperidinyloxy)-
 5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-
 2(1H)-one



Ethyl 2,4,6-trimethylnicotinate was prepared using a procedure
 analogous to that given in step 1 of Example 42 using ethyl acetoacetate
 15 in place of ethyl propionylacetate. Ethyl 2,4,6-trimethylnicotinate was
 converted in three steps to 3-chloromethyl-2,4,6-trimethylpyridine-N-
 oxide using procedures analogous to those given in steps 1-3 in Example
 17. The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-
 5-fluoro-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-
 20 one of Example 40 and 3-chloromethyl-2,4,6-trimethylpyridine-N-
 oxide using the procedure given in step 4 of Example 17. The title
 compound was purified by pressurized silica gel column
 chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The
 hydrochloride salt of the title compound was obtained as an amorphous
 25 solid by lyophilization from CH₃CN-H₂O containing aqueous HCl.
 Analysis calculated for C₃₅H₄₁FN₄O₆, 1.6 HCl, 0.95 H₂O
 C, 58.35; H, 6.33; N, 7.91
 Found C, 59.32; H, 6.33; N, 7.90
 TLC: R_f = 0.25 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)

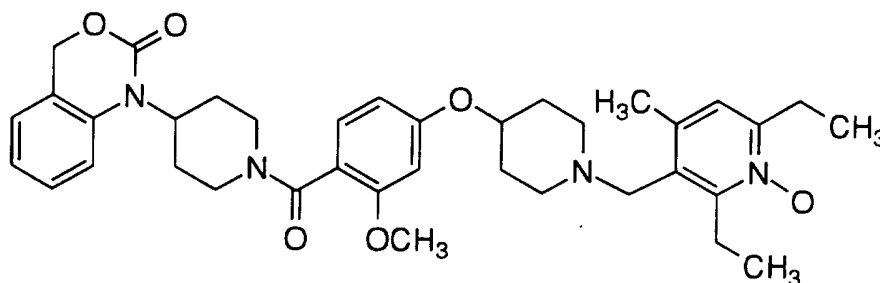
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HPLC (method A) retention time = 6.2 min

FAB MS m/z 633 ($M^+ + H$)EXAMPLE 50

5

1-(1-(4-(1-(N-oxo-2,6-diethyl-4-methyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



- 10 Ethyl 2,6-diethyl-4-methylnicotinate from step 1 of Example 42 was converted in three steps to 3-chloromethyl-2,6-diethyl-4-methylpyridine-N-oxide using procedures analogous to those given in steps 1-3 in Example 17. The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 3 and 3-chloromethyl-2,6-diethyl-4-methylpyridine-N-oxide using the procedure given in step 4 of Example 17. The title compound was purified by pressurized silica gel column chromatography using 97:3:0.3 CH_2Cl_2 :MeOH: NH_4OH as eluant. The hydrochloride salt of the title compound was obtained as an amorphous solid by lyophilization from CH_3CN-H_2O containing aqueous HCl.

Analysis calculated for $C_{37}H_{46}N_4O_6$, 2.0 HCl, 0.05 H_2O

C, 62.01; H, 6.77; N, 7.82

Found C, 61.99; H, 6.74; N, 7.70

- 25 TLC: $R_f = 0.24$ (97:3:0.3 CH_2Cl_2 :MeOH: NH_4OH)

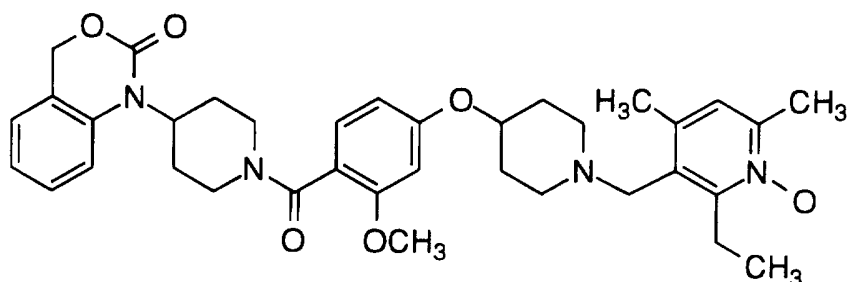
HPLC (method A) retention time = 6.7 min

FAB MS m/z 643 ($M^+ + H$)

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EXAMPLE 51

1-(1-(4-(1-(N-oxo-2-ethyl-4,6-dimethyl-3-pyridylmethyl)-4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one



The title compound was prepared from 1-(1-(4-(4-piperidinyloxy)-2-methoxybenzoyl)piperidin-4-yl)-4H-3,1-benzoxazin-2(1H)-one from Example 3 and 3-chloromethyl-4,6-dimethyl-2-ethylpyridine-N-oxide from Example 44 using the procedure given in step 4 of Example 17.

The title compound was purified by pressurized silica gel column chromatography using 97:3:0.3 CH₂Cl₂:MeOH:NH₄OH as eluant. The hydrochloride salt of the title compound was obtained as an amorphous solid by lyophilization from CH₃CN-H₂O containing aqueous HCl.

Analysis calculated for C₃₆H₄₄N₄O₆, 2.5 HCl, 0.05 H₂O
 C, 59.98; H, 6.52; N, 7.77
 Found C, 60.00; H, 6.34; N, 7.86
 TLC: R_f = 0.21 (97:3:0.3 CH₂Cl₂:MeOH:NH₄OH)
 HPLC (method A) retention time = 6.2 min
 FAB MS m/z 629 (M⁺ + H)

EXAMPLE 52

As a specific embodiment of an oral composition, 100 mg of the compound of Example 22 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

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EXAMPLE 53
RAT & HUMAN OT/AVP BINDING ASSAYS

The high affinity binding of [³H]oxytocin (OT) to uterine
5 tissue and [³H]arginine vasopressin (AVP) to liver (AVP-V₁ site) and
kidney (AVP-V₂ site) tissue was determined using crude membrane
preparations as described previously [Pettibone, D.J., et al., *J.*
Pharmacol. and Exper. Ther., 256(1): 304-308 (1991)]. Uterine tissue
was taken from nonpregnant adult Sprague-Dawley rats (Taconic
10 Farms, Germantown, NY) pretreated (18-24 h) with diethylstilbestrol
propionate (DES; 300 µg/kg, i.p.). Uterine tissue (full thickness) was
also taken with informed consent from nonlabor pregnant women
undergoing cesarean section at 38 to 39 weeks gestation (Oregon Health
Sciences Center, Portland, OR). Liver and kidney medulla samples
15 were taken from male rats and from human surgical and early
postmortem donors (National Disease Research Interchange,
Philadelphia PA; Analytical Biological Services, Wilmington, DE).

Competition studies were conducted at equilibrium using 1
nM [³H]OT or 0.5 nM [³H]AVP in the following buffer: 50 mM Tris, 5
20 mM MgCl₂, 0.1% bovine serum albumin. Nonspecific binding was
determined using 1 µM unlabeled OT or AVP in their respective assays.
The binding reactions were initiated by the addition of tissue
preparation and terminated by filtration using a Skatron cell harvester
(model 7019, Skatron, Inc., Sterling, VA). K_i values were calculated
25 for each compound using three to six separate IC₅₀ determinations
(K_i=IC₅₀/[1 - c/K_d]); [Cheng, Y-C; Prusoff, W.H.; *Biochem Pharmacol*
22:3099 (1973)] with mean K_d values obtained from replicate (n = 3)
equilibrium saturation binding assays (10 point, 100 fold concentration
range): [³H]OT rat uterus, 0.69 nM; human myometrium, 1.1 nM;
30 [³H]AVP: rat liver, 0.21 nM; rat kidney, 0.27 nM; human liver, 0.27
nM; human kidney, 1.4 nM. Computer analysis of the saturation assays
by EBDA/LIGAND [McPherson, G.A.: *Kinetic, Ebda, Ligand, Lowry:*
A Collection of Radioligand Binding Analysis Programs, Elsevier
Science Publishers, Amsterdam (1985)] indicated that both radioligands
35 apparently bound to single sites in all tissues examined. The final

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protein concentration for the various tissues in each assay ranged from 150 to 300 µg/ml [Lowry, P.H.; Rosebrough, N.J.; Farr, A.L.; Randall, R.J.; *J. Biol. Chem.*, 193:265-275 (1951)].

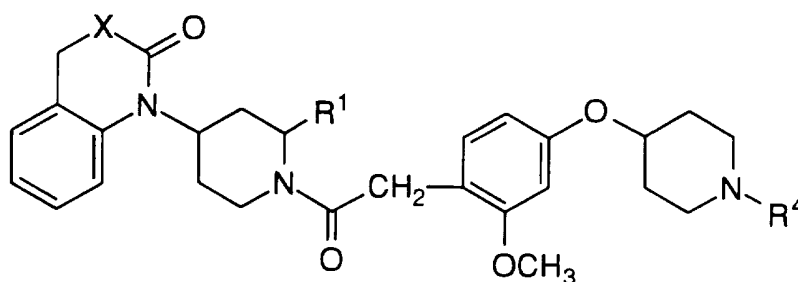
IC₅₀ values were determined for the [³H]OT and [³H]AVP binding assays by linear regression of the relation log concentration of compound vs. percent inhibition of specific binding. Data is either reported as a given percentage of inhibition at a specified concentration, or if an IC₅₀ was calculated, as a nanomolar concentration.

Representative compounds of the present invention were found to have IC₅₀ values for the human oxytocin receptor in the range of 2 nM to 1,000 nM.

The oxytocin antagonistic effect of the compounds of the present invention can be further evaluated according to the *in vitro* and/or *in vivo* functional assays described in detail in D.J. Pettibone et al., *Drug Devel.Res.* 1993, 30, 129-142.

Additional preferred oxytocin antagonist compounds of the instant invention, useful for treating oxytocin-related conditions such as preterm labor, dysmenorrhea and stopping labor prior to cesarean delivery, are shown below in Tables 1 through 12.

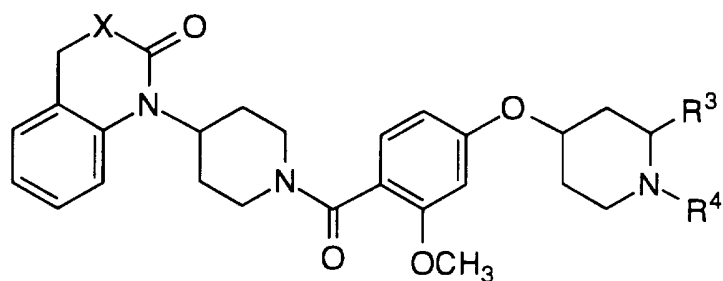
TABLE 1



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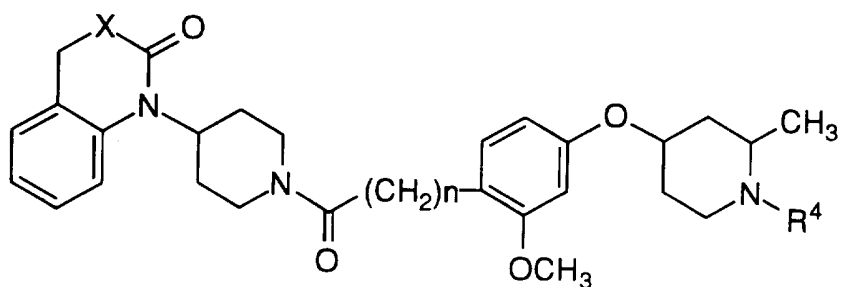
<u>X</u>	<u>R¹</u>	<u>R⁴</u>
O	CH ₃	H
O	CH ₃	CH ₃
O	CH ₃	CH ₂ CH ₃
O	CH ₃	isopropyl
O	CH ₃	CH ₂ -cyclopropyl
O	CH ₃	COCH ₃
O	CH ₃	SO ₂ CH ₃
O	CONH ₂	H
O	CONH ₂	CH ₃
O	CONH ₂	CH ₂ CH ₃
O	CONH ₂	isopropyl
O	CONH ₂	CH ₂ -cyclopropyl
O	CONH ₂	COCH ₃
O	CONH ₂	SO ₂ CH ₃
CH ₂	CH ₃	H
CH ₂	CH ₃	CH ₃
CH ₂	CH ₃	CH ₂ CH ₃
CH ₂	CH ₃	isopropyl
CH ₂	CH ₃	CH ₂ -cyclopropyl
CH ₂	CH ₃	COCH ₃
CH ₂	CH ₃	SO ₂ CH ₃
CH ₂	CONH ₂	H
CH ₂	CONH ₂	CH ₃
CH ₂	CONH ₂	CH ₂ CH ₃
CH ₂	CONH ₂	isopropyl
CH ₂	CONH ₂	CH ₂ -cyclopropyl
CH ₂	CONH ₂	COCH ₃
CH ₂	CONH ₂	SO ₂ CH ₃

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TABLE 2

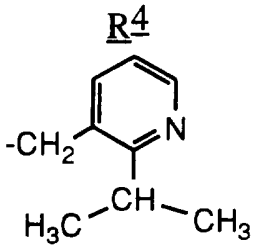
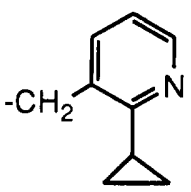
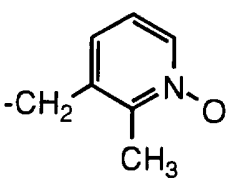
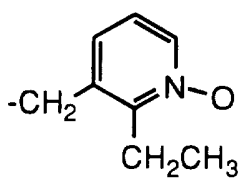
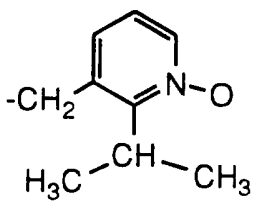
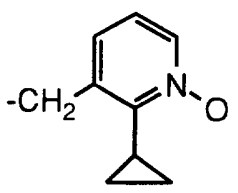
<u>X</u>	<u>R³</u>	<u>R⁴</u>
O	CO ₂ H	H
O	CO ₂ H	CH ₃
O	CO ₂ H	CH ₂ CH ₃
O	CO ₂ H	isopropyl
O	CO ₂ Et	H
O	CO ₂ Et	CH ₃
O	CO ₂ Et	CH ₂ CH ₃
O	CO ₂ Et	isopropyl
O	CONH ₂	H
O	CONH ₂	CH ₃
O	CONH ₂	CH ₂ CH ₃
O	CONH ₂	isopropyl
CH ₂	CO ₂ H	H
CH ₂	CO ₂ H	CH ₃
CH ₂	CO ₂ H	CH ₂ CH ₃
CH ₂	CO ₂ H	isopropyl
CH ₂	CO ₂ Et	H
CH ₂	CO ₂ Et	CH ₃
CH ₂	CO ₂ Et	CH ₂ CH ₃
CH ₂	CO ₂ Et	isopropyl
CH ₂	CONH ₂	H
CH ₂	CONH ₂	CH ₃
CH ₂	CONH ₂	CH ₂ CH ₃
CH ₂	CONH ₂	isopropyl

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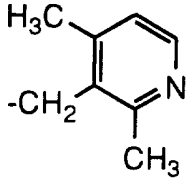
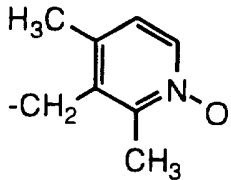
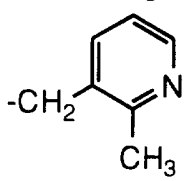
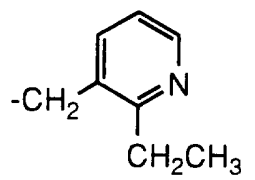
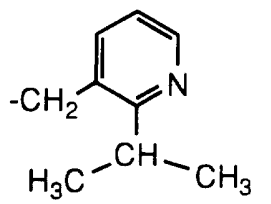
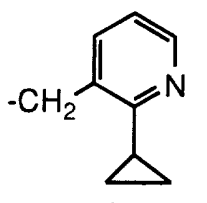
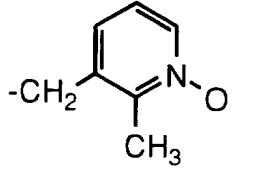
TABLE 3

<u>X</u>	<u>R⁴</u>	<u>n</u>
O	H	0
O	CH ₃	0
O	CH ₂ CH ₃	0
O	isopropyl	0
O	CH ₂ -cyclopropyl	0
O	COCH ₃	0
O	SO ₂ CH ₃	0
O		0
O		0
O		0
O		0

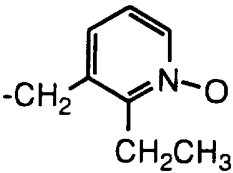
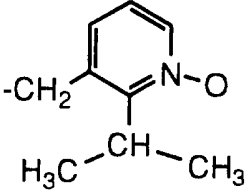
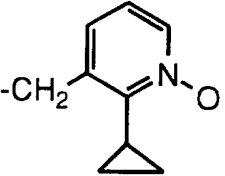
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<u>X</u>	<u>R⁴</u>	<u>n</u>
O		0
O		0
O		0
O		0
O		0
O		0
O	H	1
O	CH ₃	1
O	CH ₂ CH ₃	1
O	isopropyl	1
O	CH ₂ -cyclopropyl	1
O	COCH ₃	1
O	SO ₂ CH ₃	1
CH ₂	H	0

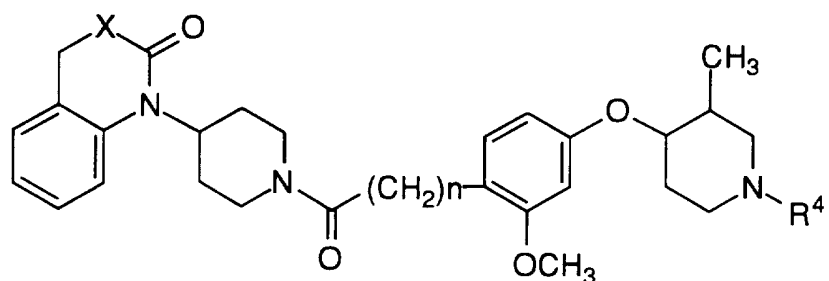
- 128 -

<u>X</u>	<u>R⁴</u>	<u>n</u>
CH ₂	CH ₃	0
CH ₂	CH ₂ CH ₃	0
CH ₂	isopropyl	0
CH ₂	CH ₂ -cyclopropyl	0
CH ₂	COCH ₃	0
CH ₂	SO ₂ CH ₃	0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0

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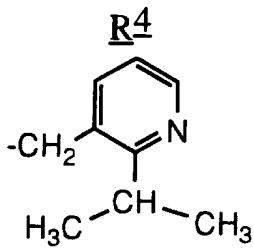
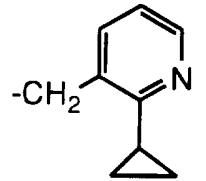
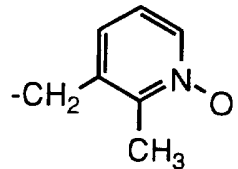
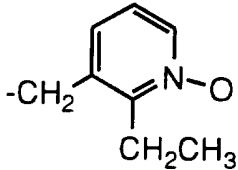
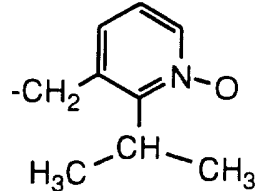
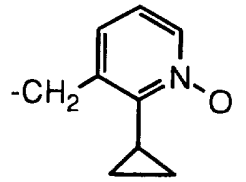
<u>X</u>	<u>R⁴</u>	<u>n</u>
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂	H	1
CH ₂	CH ₃	1
CH ₂	CH ₂ CH ₃	1
CH ₂	isopropyl	1
CH ₂	CH ₂ -cyclopropyl	1
CH ₂	COCH ₃	1
CH ₂	SO ₂ CH ₃	1

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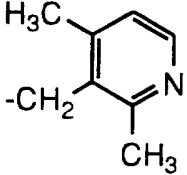
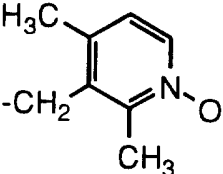
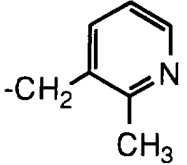
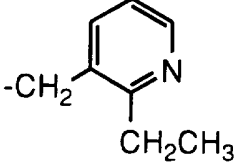
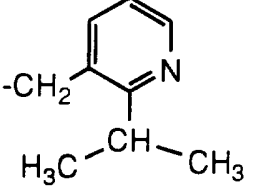
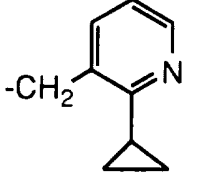
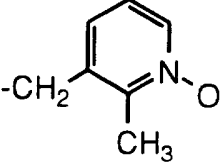
TABLE 4

<u>X</u>	<u>R⁴</u>	<u>n</u>
O	H	0
O	CH ₃	0
O	CH ₂ CH ₃	0
O	isopropyl	0
O	CH ₂ -cyclopropyl	0
O	COCH ₃	0
O	SO ₂ CH ₃	0
O		0
O		0
O		0
O		0

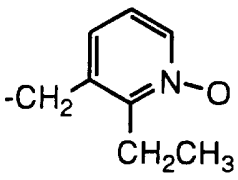
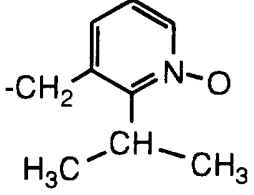
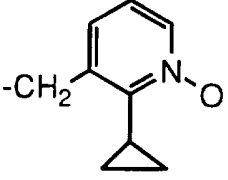
- 131 -

<u>X</u>	<u>R⁴</u>	<u>n</u>
O		0
O		0
O		0
O		0
O		0
O		0
O	H	1
O	CH ₃	1
O	CH ₂ CH ₃	1
O	isopropyl	1
O	CH ₂ -cyclopropyl	1
O	COCH ₃	1
O	SO ₂ CH ₃	1
CH ₂	H	0

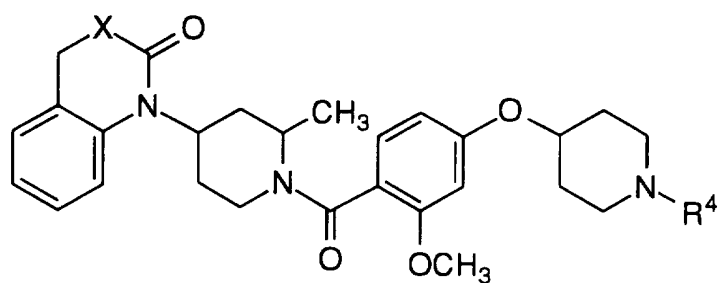
- 132 -

<u>X</u>	<u>R⁴</u>	<u>n</u>
CH ₂	CH ₃	0
CH ₂	CH ₂ CH ₃	0
CH ₂	isopropyl	0
CH ₂	CH ₂ -cyclopropyl	0
CH ₂	COCH ₃	0
CH ₂	SO ₂ CH ₃	0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂		0

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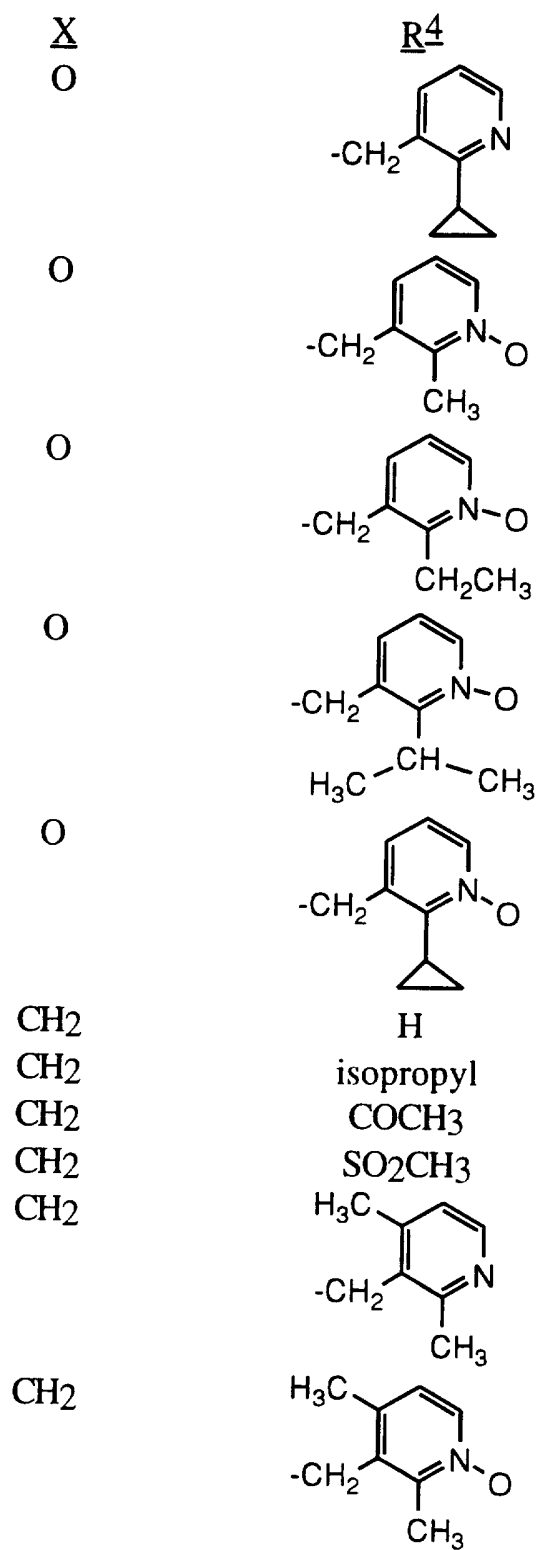
<u>X</u>	<u>R⁴</u>	<u>n</u>
CH ₂		0
CH ₂		0
CH ₂		0
CH ₂	H	1
CH ₂	CH ₃	1
CH ₂	CH ₂ CH ₃	1
CH ₂	isopropyl	1
CH ₂	CH ₂ -cyclopropyl	1
CH ₂	COCH ₃	1
CH ₂	SO ₂ CH ₃	1

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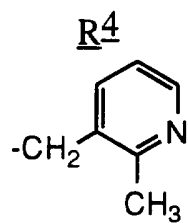
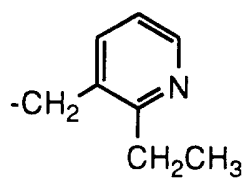
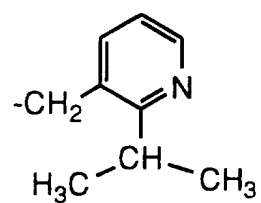
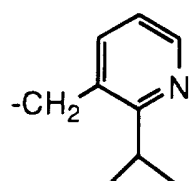
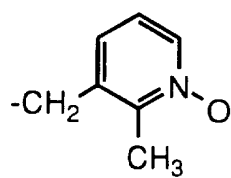
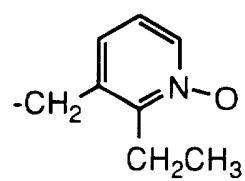
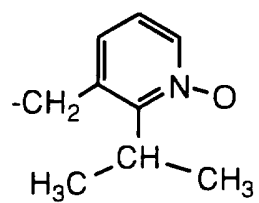
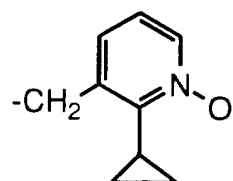
TABLE 5

<u>X</u>	<u>R⁴</u>
O	H
O	isopropyl
O	COCH ₃
O	SO ₂ CH ₃
O	
O	
O	
O	
O	

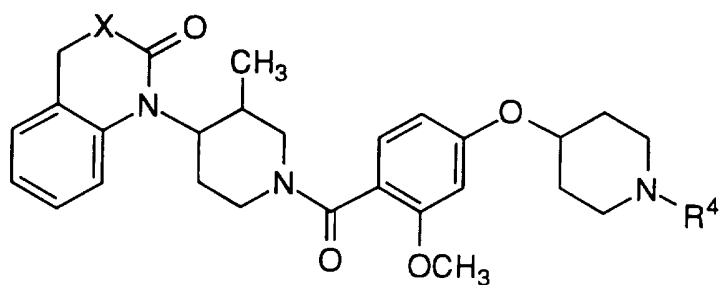
- 135 -



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 $\frac{X}{CH_2}$ CH₂CH₂CH₂CH₂CH₂CH₂CH₂

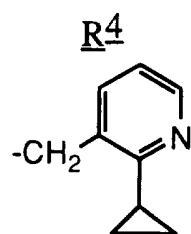
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TABLE 6

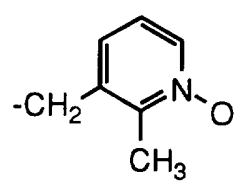
<u>X</u>	<u>R⁴</u>
O	H
O	isopropyl
O	COCH ₃
O	SO ₂ CH ₃
O	
O	
O	
O	
O	
O	

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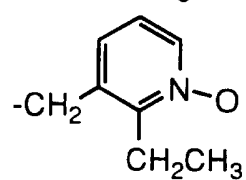
X
O



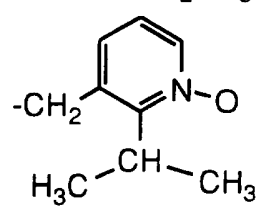
O



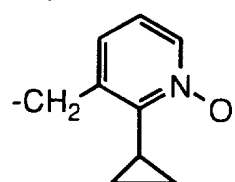
O



O



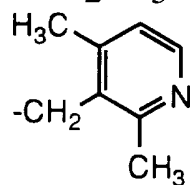
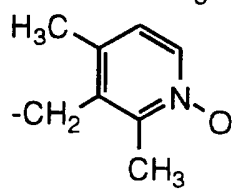
O

CH₂

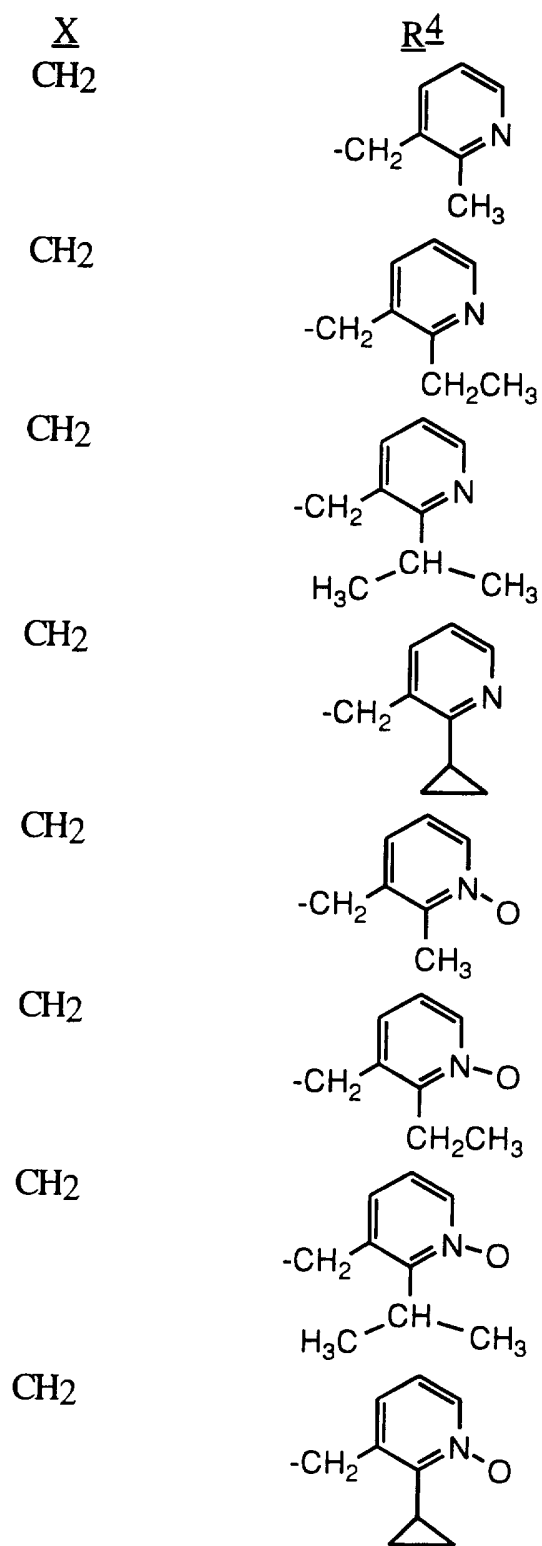
H

CH₂

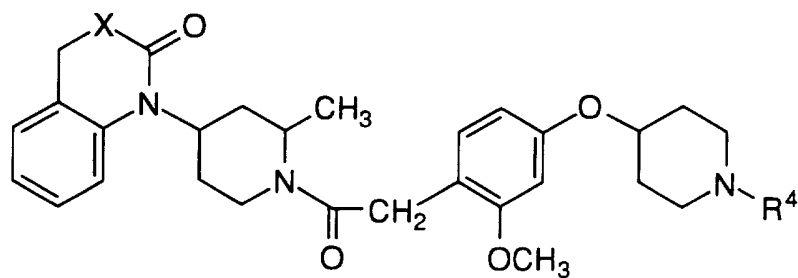
isopropyl

CH₂COCH₃CH₂SO₂CH₃CH₂CH₂

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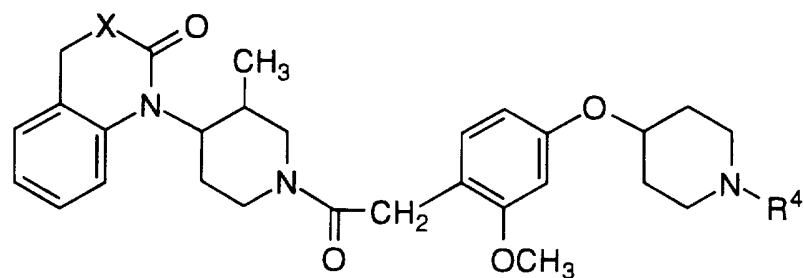


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TABLE 7

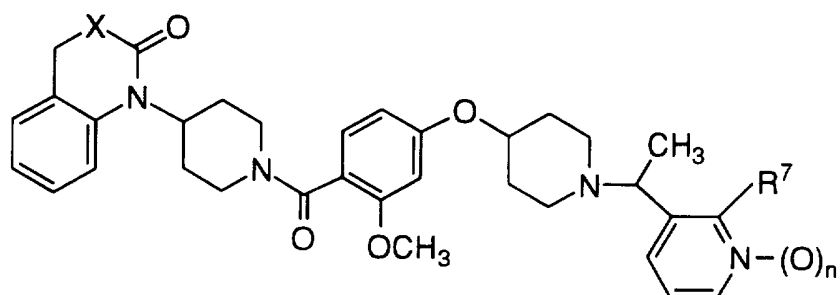
<u>X</u>	<u>R⁴</u>
O	H
O	isopropyl
O	COCH ₃
O	SO ₂ CH ₃
O	CH ₃
O	CH ₂ CH ₃
O	CH ₂ -cyclopropyl
CH ₂	H
CH ₂	isopropyl
CH ₂	COCH ₃
CH ₂	SO ₂ CH ₃
CH ₂	CH ₃
CH ₂	CH ₂ CH ₃
CH ₂	CH ₂ -cyclopropyl

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TABLE 8

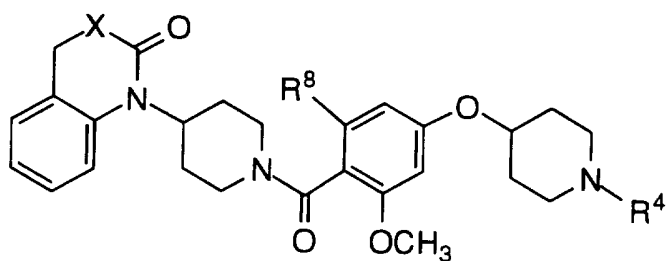
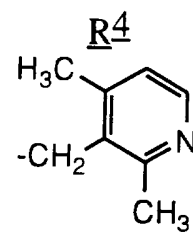
<u>X</u>	<u>R⁴</u>
O	H
O	isopropyl
O	COCH ₃
O	SO ₂ CH ₃
O	CH ₃
O	CH ₂ CH ₃
O	CH ₂ -cyclopropyl
CH ₂	H
CH ₂	isopropyl
CH ₂	COCH ₃
CH ₂	SO ₂ CH ₃
CH ₂	CH ₃
CH ₂	CH ₂ CH ₃
CH ₂	CH ₂ -cyclopropyl

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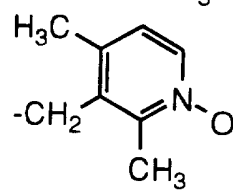
TABLE 9

<u>X</u>	<u>R⁷</u>	<u>n</u>
O	H	0
O	CH ₃	0
O	CH ₂ CH ₃	0
O	isopropyl	0
O	cyclopropyl	0
O	H	1
O	CH ₃	1
O	CH ₂ CH ₃	1
O	isopropyl	1
O	cyclopropyl	1
CH ₂	H	0
CH ₂	CH ₃	0
CH ₂	CH ₂ CH ₃	0
CH ₂	isopropyl	0
CH ₂	cyclopropyl	0
CH ₂	H	1
CH ₂	CH ₃	1
CH ₂	CH ₂ CH ₃	1
CH ₂	isopropyl	1
CH ₂	cyclopropyl	1

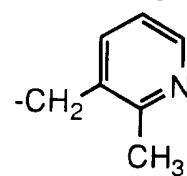
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TABLE 10X
OR⁸
CH₃

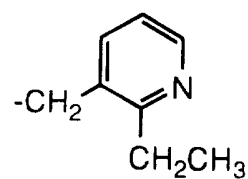
O

CH₃

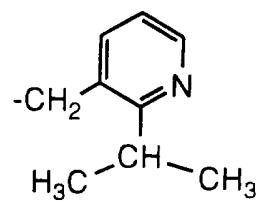
O

CH₃

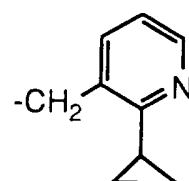
O

CH₃

O

CH₃

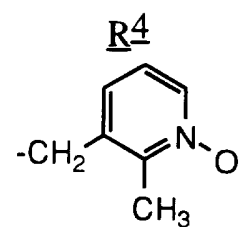
O

CH₃

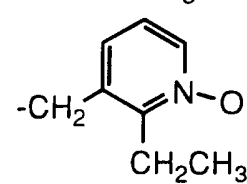
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X
O

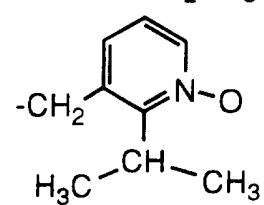
R⁸
CH₃



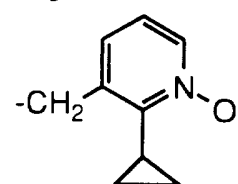
O

CH₃

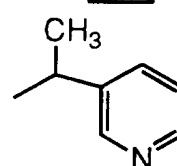
O

CH₃

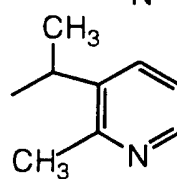
O

CH₃

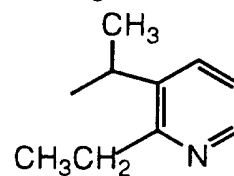
O

CH₃

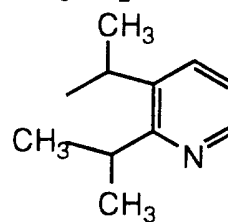
O

CH₃

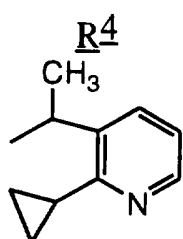
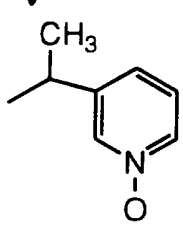
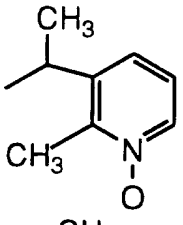
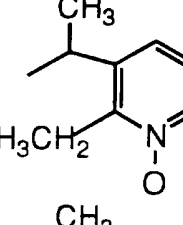
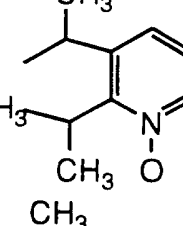
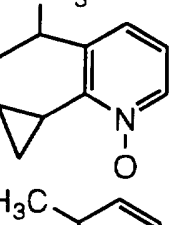
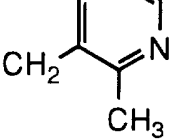
O

CH₃

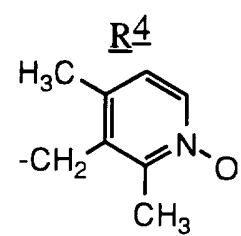
O

CH₃

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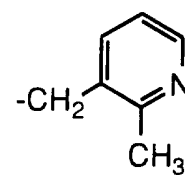
$\frac{\underline{X}}{O}$	$\frac{\underline{R^8}}{CH_3}$	
O	CH ₃	
O	CH ₃	
O	CH ₃	
O	CH ₃	
O	CH ₃	
O	F	

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X
OR⁸
F

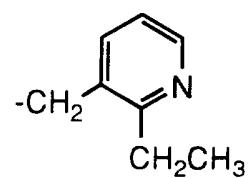
O

F



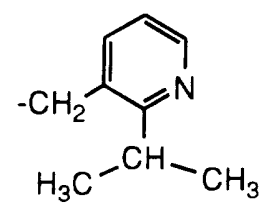
O

F



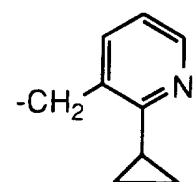
O

F



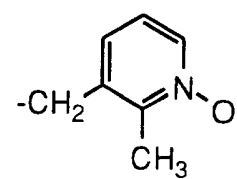
O

F



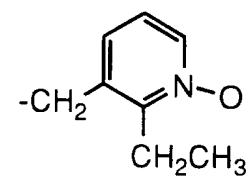
O

F



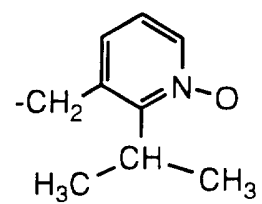
O

F

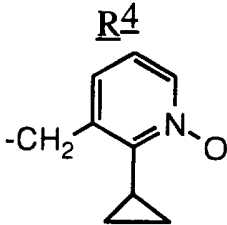
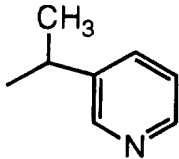
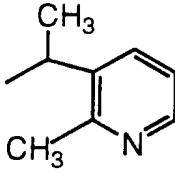
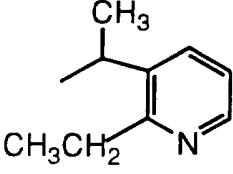
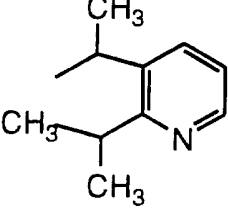
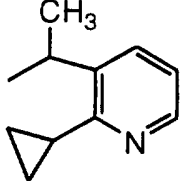
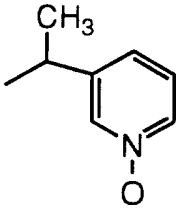
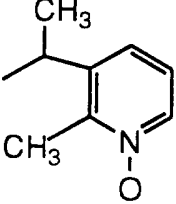


O

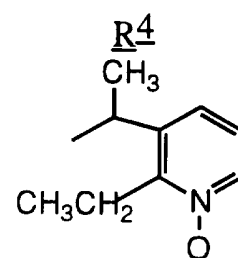
F



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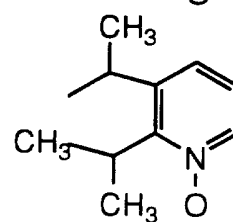
$\frac{X}{O}$	$\frac{R^8}{F}$	
O	F	
O	F	
O	F	
O	F	
O	F	
O	F	
O	F	

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X
OR⁸
F

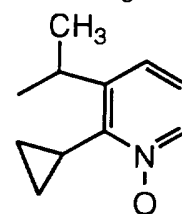
O

F



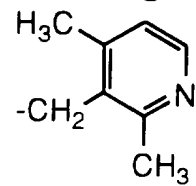
O

F



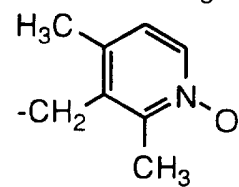
O

Cl



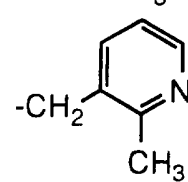
O

Cl

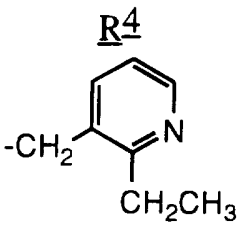
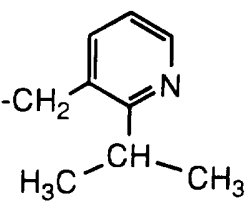
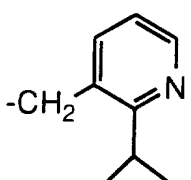
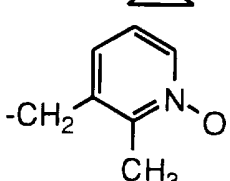
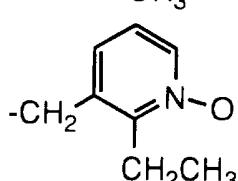
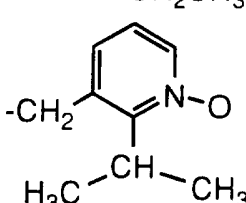
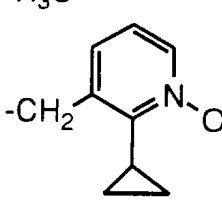


O

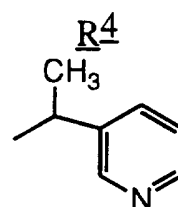
Cl



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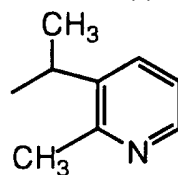
$\frac{X}{O}$	$\frac{R^8}{Cl}$	
O	Cl	
O	Cl	
O	Cl	
O	Cl	
O	Cl	
O	Cl	

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X
OR⁸
Cl

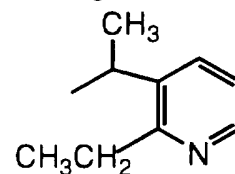
O

Cl



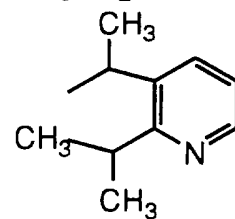
O

Cl



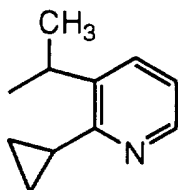
O

Cl



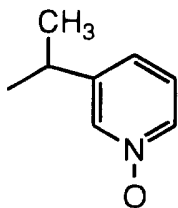
O

Cl

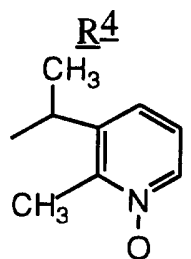
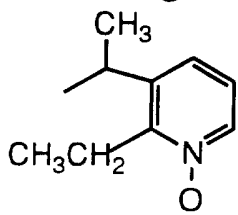
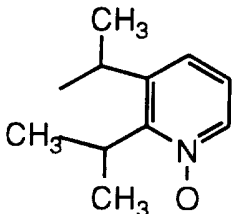
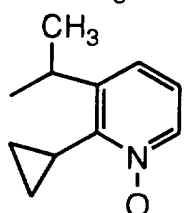
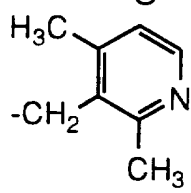
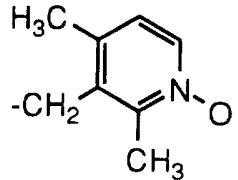


O

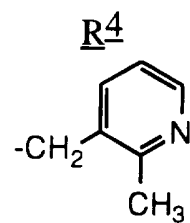
Cl



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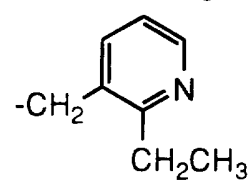
$\frac{\underline{X}}{O}$	$\frac{\underline{R^8}}{Cl}$	
O	Cl	
O	Cl	
O	Cl	
O	Br	
O	Br	

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 $\frac{X}{O}$ $\frac{R^8}{Br}$ 

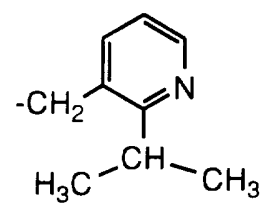
O

Br



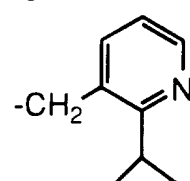
O

Br



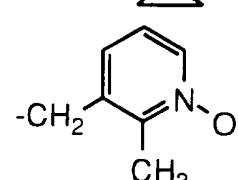
O

Br



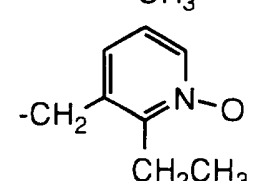
O

Br



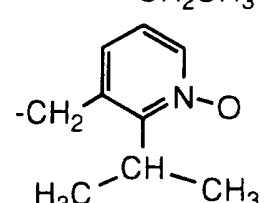
O

Br

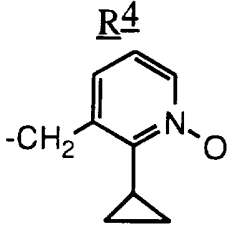
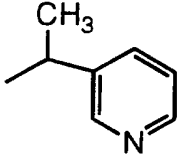
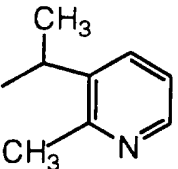
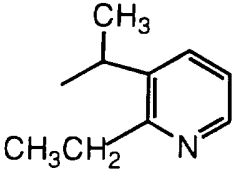
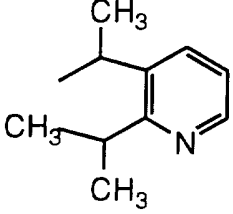
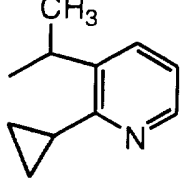
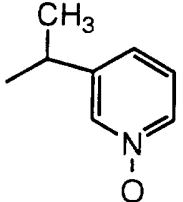


O

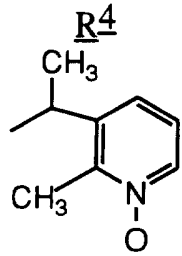
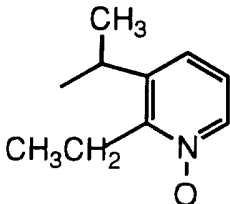
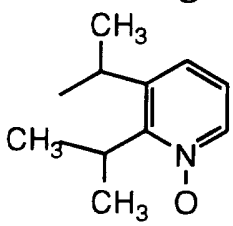
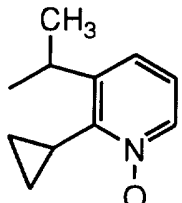
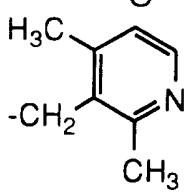
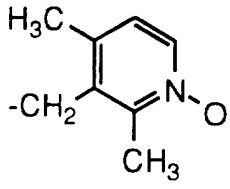
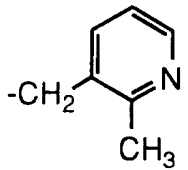
Br



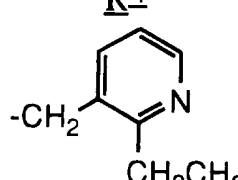
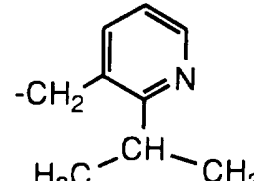
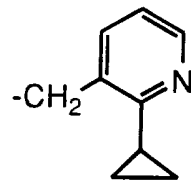
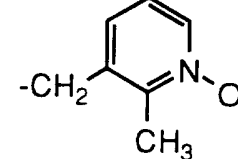
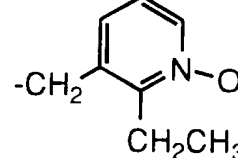
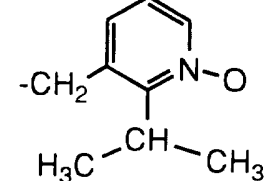
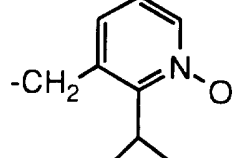
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<u>X</u> O	<u>R⁸</u> Br	
O	Br	
O	Br	
O	Br	
O	Br	
O	Br	
O	Br	

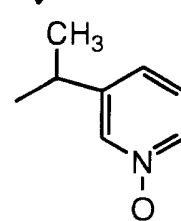
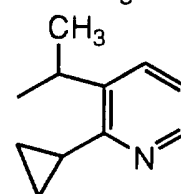
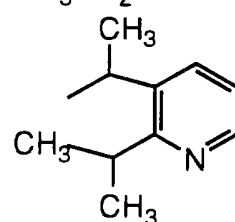
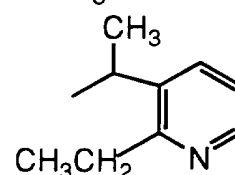
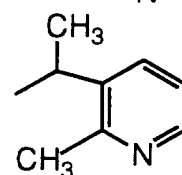
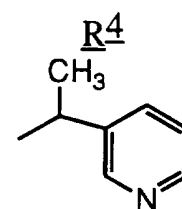
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$\frac{\underline{X}}{O}$	$\frac{\underline{R^8}}{Br}$	
O	Br	
O	Br	
O	Br	
CH2	CH3	
CH2	CH3	
CH2	CH3	

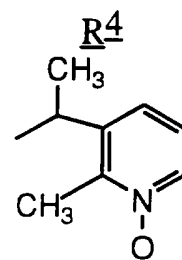
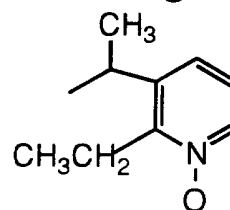
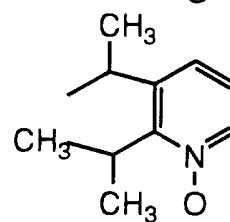
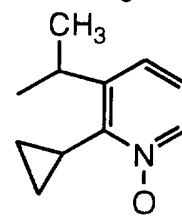
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$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{CH}_3}$	$\frac{\underline{R^4}}{\text{CH}_2\text{CH}_3}$ 
CH_2	CH_3	
CH_2	CH_3	
CH_2	CH_3	
CH_2	CH_3	
CH_2	CH_3	
CH_2	CH_3	

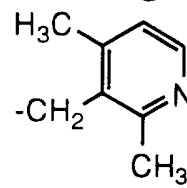
- 156 -

 $\frac{\underline{X}}{\text{CH}_2}$ $\frac{\underline{R^8}}{\text{CH}_3}$ CH_2 CH_3 CH_2 CH_3 CH_2 CH_3 CH_2 CH_3 CH_2 CH_3 

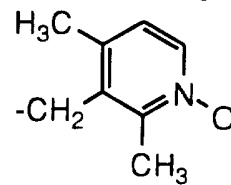
- 157 -

 $\underline{X}$
CH₂ $\underline{R^8}$
CH₃CH₂CH₃CH₂CH₃CH₂CH₃CH₂

F

CH₂

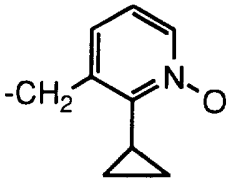
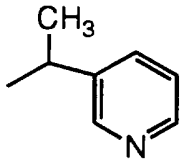
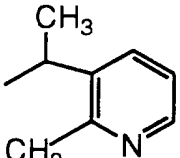
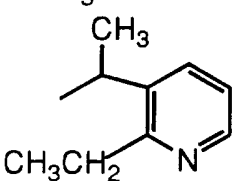
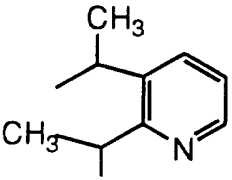
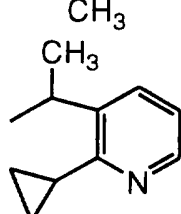
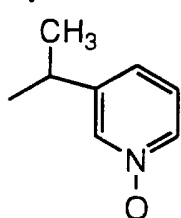
F



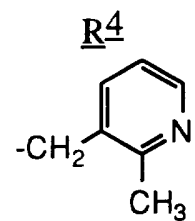
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$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{F}}$	$\frac{\underline{R^4}}{\text{-CH}_2\text{-C}_5\text{H}_4\text{N-CH}_3}$
CH_2	F	$\text{-CH}_2\text{-C}_5\text{H}_4\text{N-CH}_2\text{CH}_3$
CH_2	F	$\text{-CH}_2\text{-C}_5\text{H}_4\text{N-CH(CH}_3)_2$
CH_2	F	$\text{-CH}_2\text{-C}_5\text{H}_4\text{N-Cyclopropyl}$
CH_2	F	$\text{-CH}_2\text{-C}_5\text{H}_4\text{N(CH}_3\text{)-NO}$
CH_2	F	$\text{-CH}_2\text{-C}_5\text{H}_4\text{N(CH}_3\text{)-NO-CH}_2\text{CH}_3$
CH_2	F	$\text{-CH}_2\text{-C}_5\text{H}_4\text{N(CH}_3\text{)-NO-CH(CH}_3)_2$

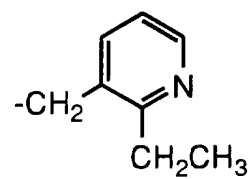
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$\frac{X}{CH_2}$	$\frac{R^8}{F}$	$\frac{R^4}{-CH_2}$ 
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	

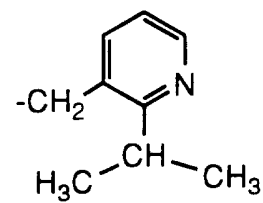
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 $\underline{X}$
CH₂ $\underline{R^8}$
ClCH₂

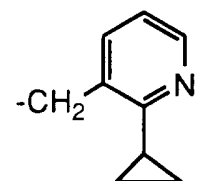
Cl

CH₂

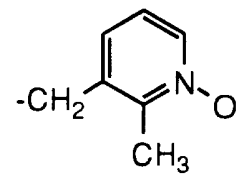
Cl

CH₂

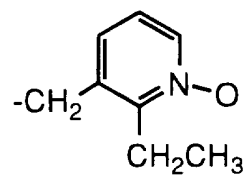
Cl

CH₂

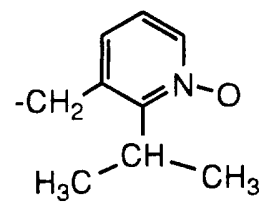
Cl

CH₂

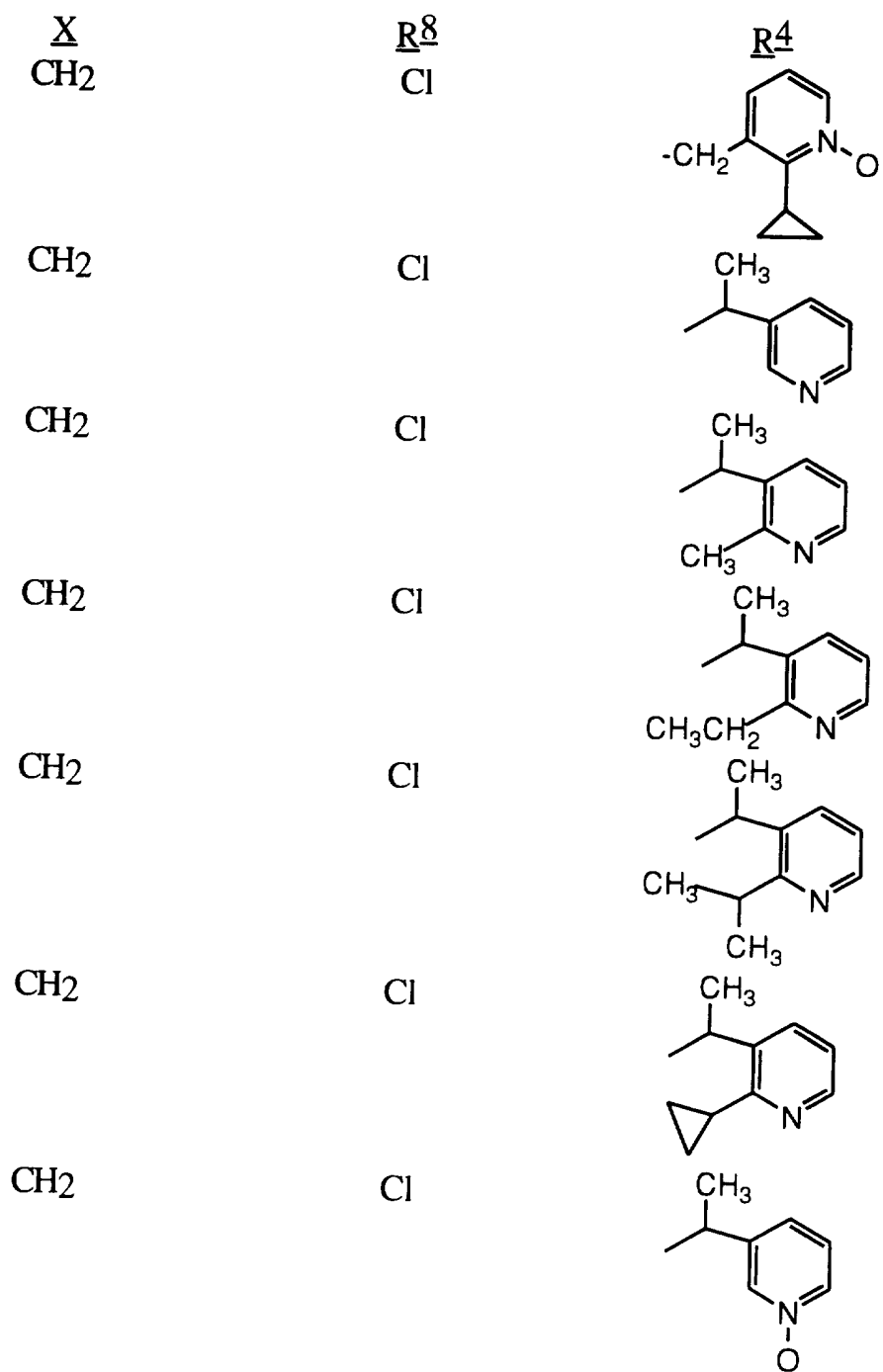
Cl

CH₂

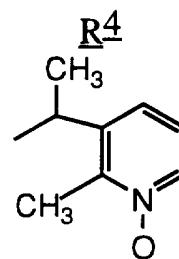
Cl



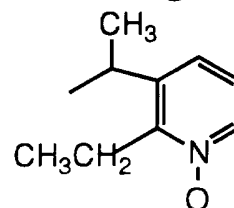
- 162 -



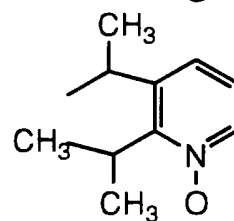
- 163 -

 $\underline{X}$
CH₂ $\underline{R^8}$
ClCH₂

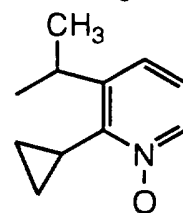
Cl

CH₂

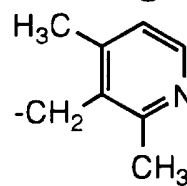
Cl

CH₂

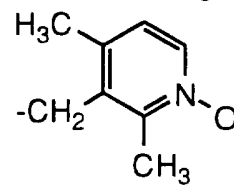
Cl

CH₂

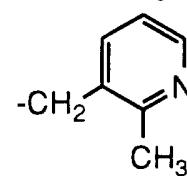
Br

CH₂

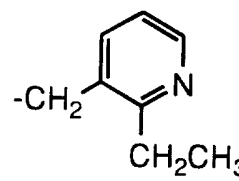
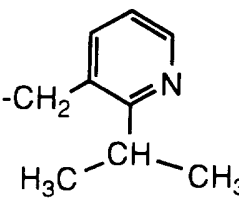
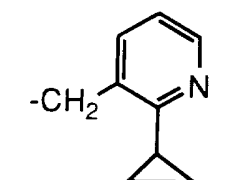
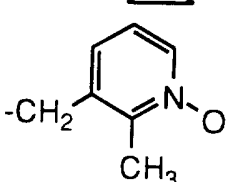
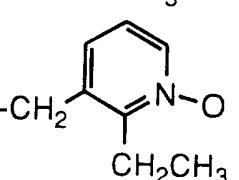
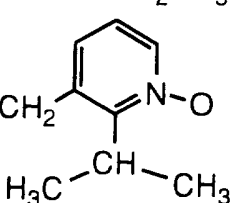
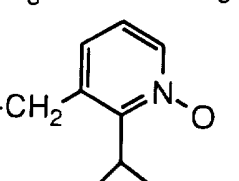
Br

CH₂

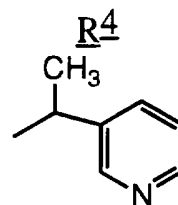
Br



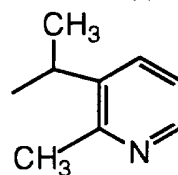
- 164 -

$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{Br}}$	$\underline{R^4}$ 
CH_2	Br	
CH_2	Br	
CH_2	Br	
CH_2	Br	
CH_2	Br	
CH_2	Br	

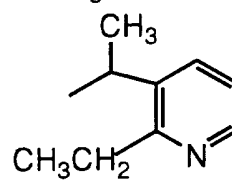
- 165 -

 $\underline{X}$
CH₂ $\underline{R^8}$
BrCH₂

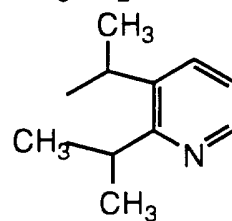
Br

CH₂

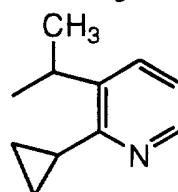
Br

CH₂

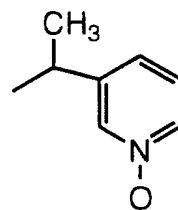
Br

CH₂

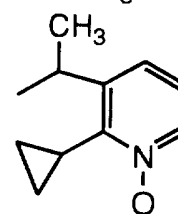
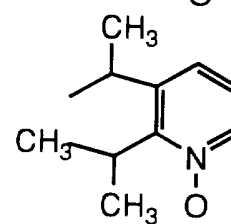
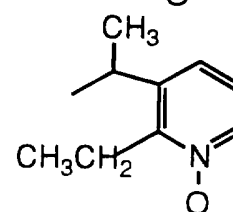
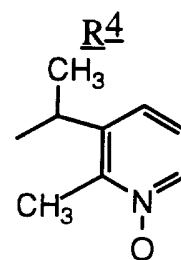
Br

CH₂

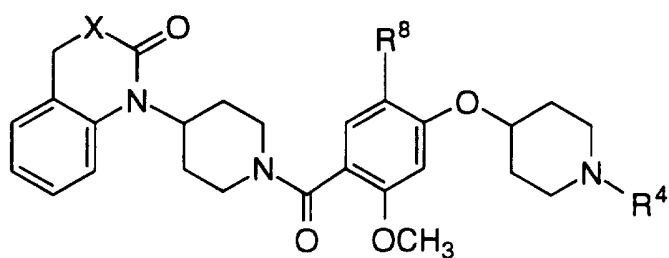
Br



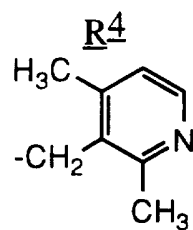
- 166 -

 $\frac{\underline{X}}{\text{CH}_2}$ $\frac{\underline{R^8}}{\text{Br}}$ CH_2 Br CH_2 Br CH_2 Br 

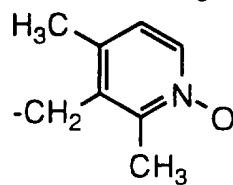
- 167 -

TABLE 11X

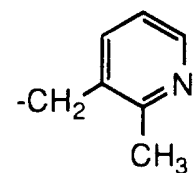
O

R⁸CH₃

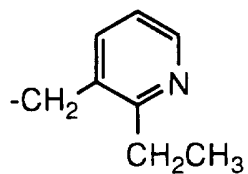
O

CH₃

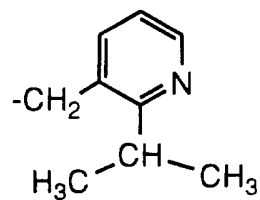
O

CH₃

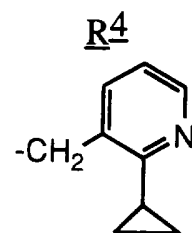
O

CH₃

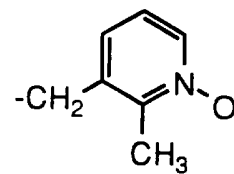
O

CH₃

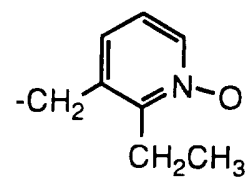
- 168 -

 $\frac{\underline{X}}{O}$ $\frac{\underline{R^8}}{CH_3}$ 

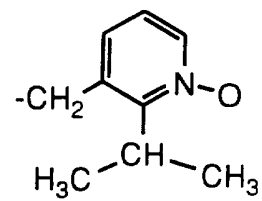
O

CH₃

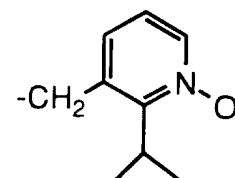
O

CH₃

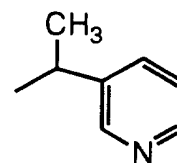
O

CH₃

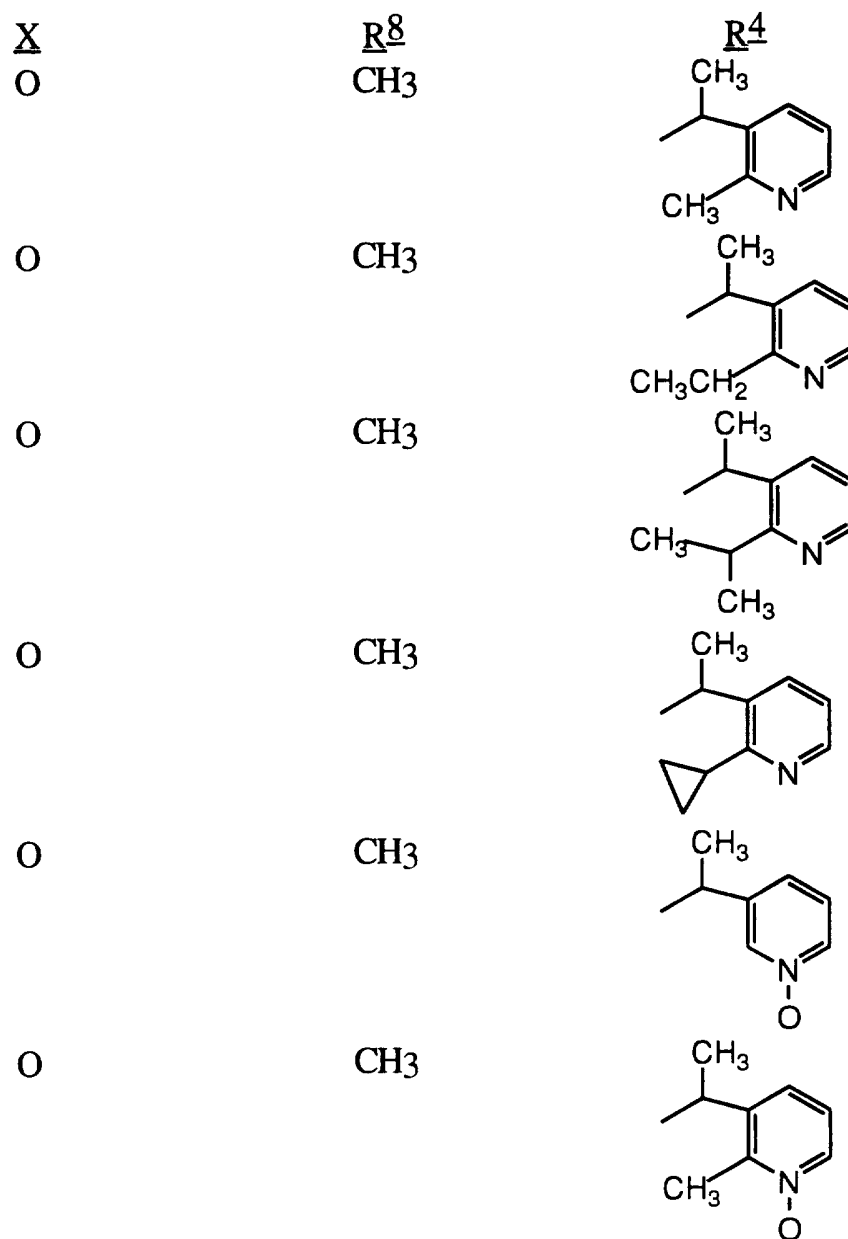
O

CH₃

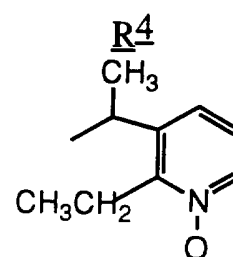
O

CH₃

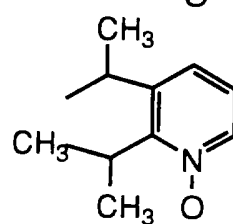
- 169 -



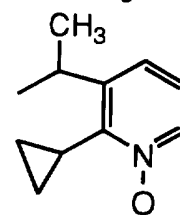
- 170 -

 $\frac{X}{O}$ $\frac{R^8}{CH_3}$ 

O

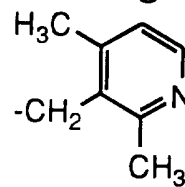
CH₃

O

CH₃

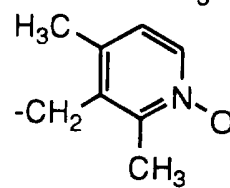
O

F



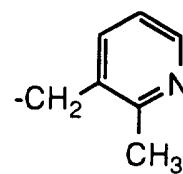
O

F

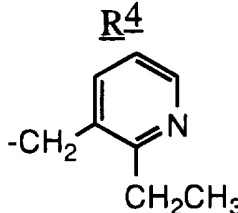
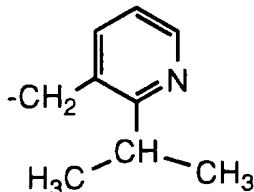
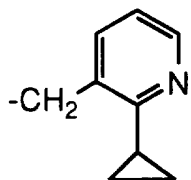
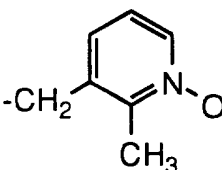
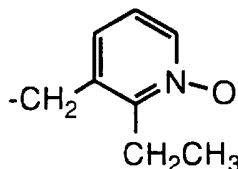
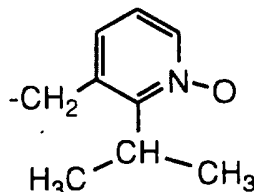


O

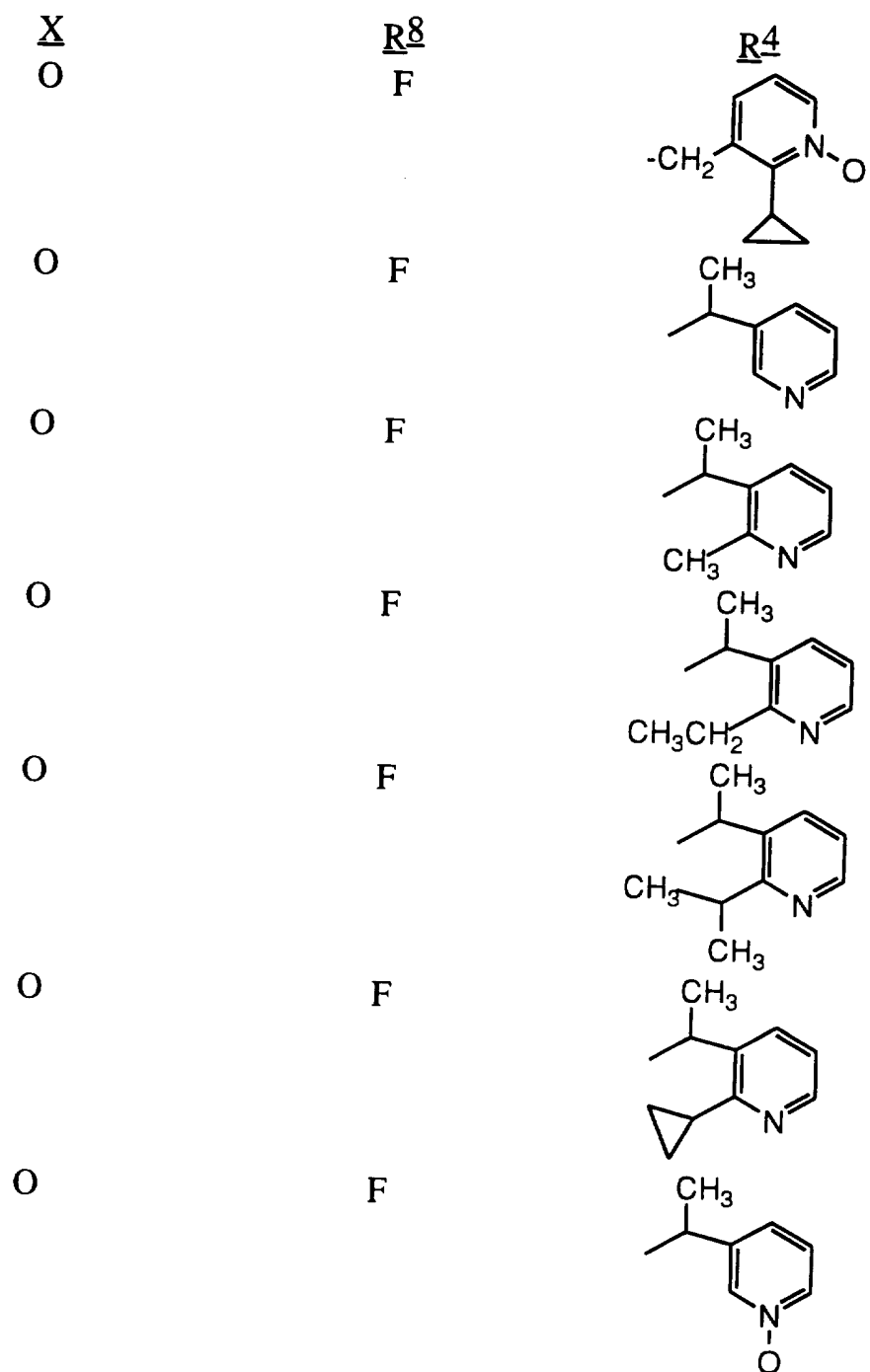
F



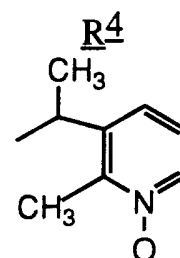
- 171 -

<u>X</u>	<u>R⁸</u>	<u>R⁴</u>
O	F	
O	F	
O	F	
O	F	
O	F	
O	F	

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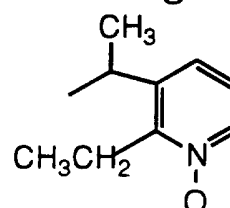


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X
OR⁸
F

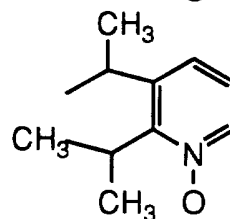
O

F



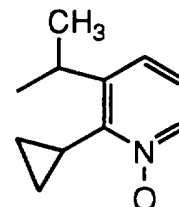
O

F



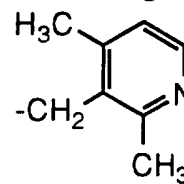
O

F



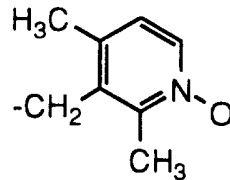
O

Cl

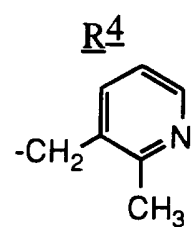


O

Cl

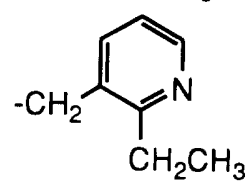


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 $\frac{X}{O}$ $\frac{R^8}{Cl}$ 

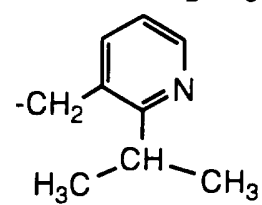
O

Cl



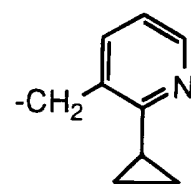
O

Cl



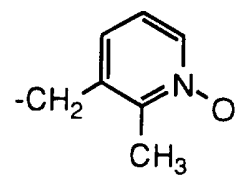
O

Cl



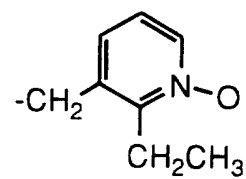
O

Cl

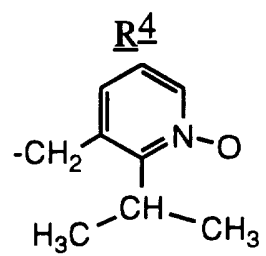


O

Cl

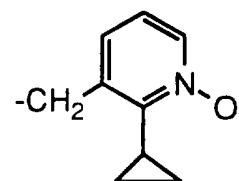


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X
OR⁸
Cl

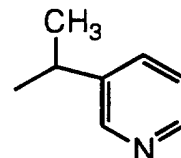
O

Cl



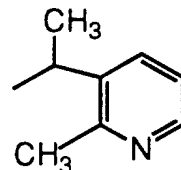
O

Cl



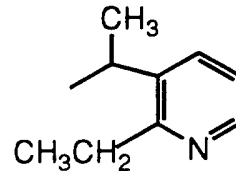
O

Cl



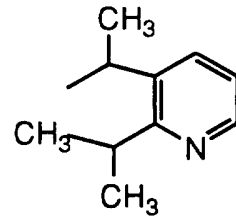
O

Cl

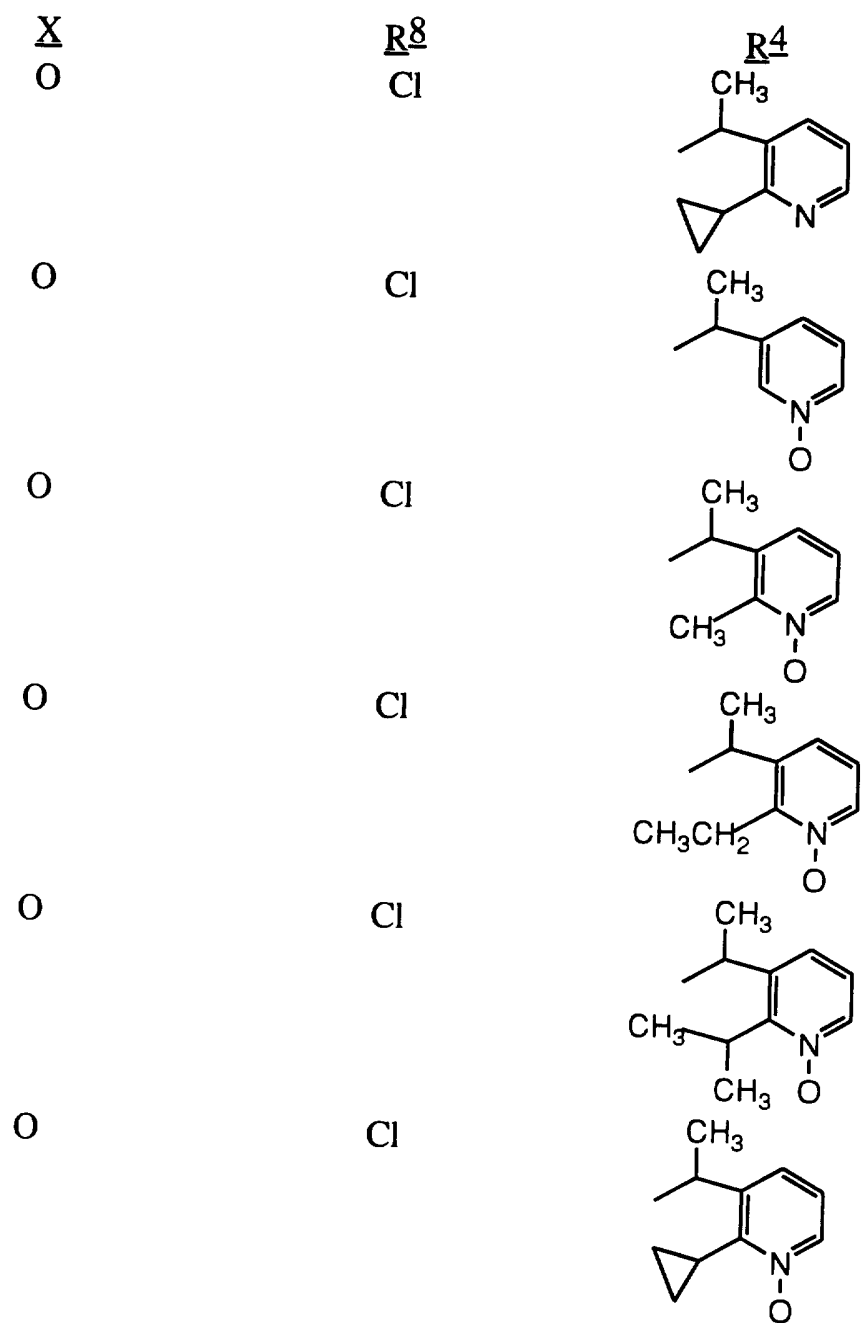


O

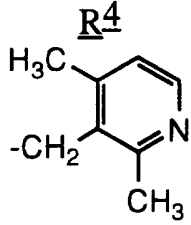
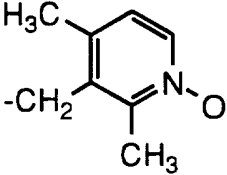
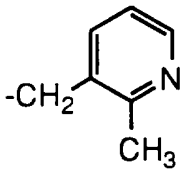
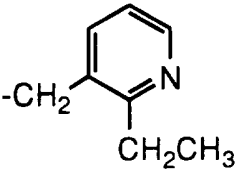
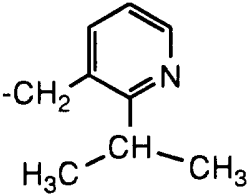
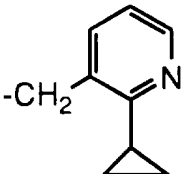
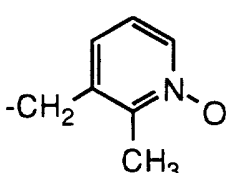
Cl



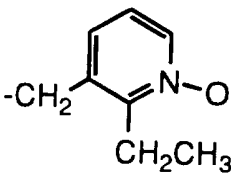
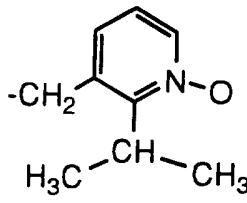
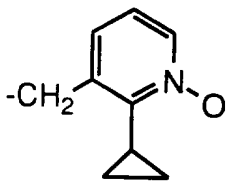
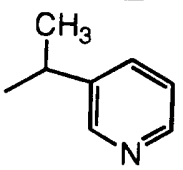
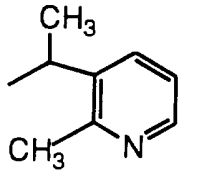
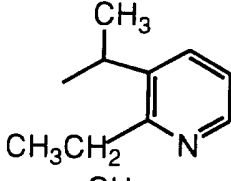
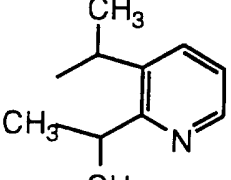
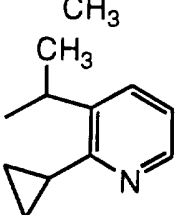
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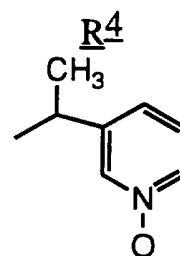
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$\frac{X}{O}$	$\frac{R^8}{Br}$	 <chem>Cc1cc(C)cc(C)nc1C</chem>
O	Br	 <chem>Cc1cc(C)cc(C)nc1C</chem>
O	Br	 <chem>Cc1cc(C)cc(C)nc1C</chem>
O	Br	 <chem>CCc1cc(C)cc(C)nc1C</chem>
O	Br	 <chem>CC(C)Cc1cc(C)cc(C)nc1C</chem>
O	Br	 <chem>C1CC1Cc2cc(C)cc(C)nc2C</chem>
O	Br	 <chem>Cc1cc(C)cc(C)nc1C</chem>

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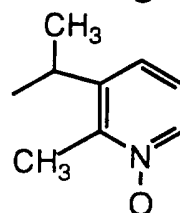
$\frac{X}{O}$	$\frac{R^8}{Br}$	R^4 
O	Br	
O	Br	
O	Br	
O	Br	
O	Br	
O	Br	
O	Br	

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 $\frac{X}{O}$ $\frac{R^8}{Br}$ 

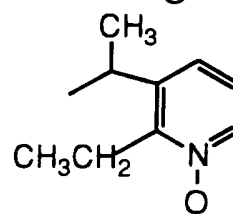
O

Br



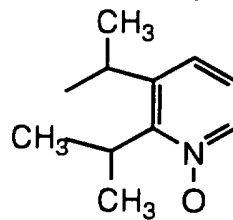
O

Br

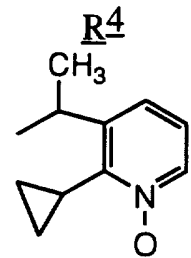
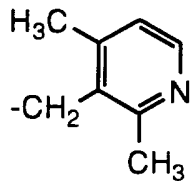
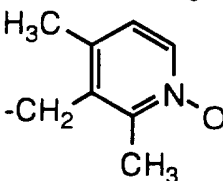
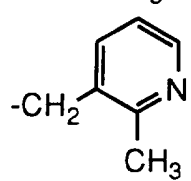
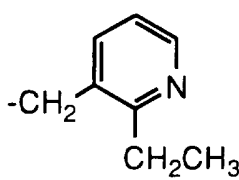
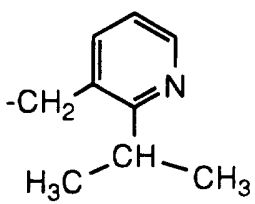
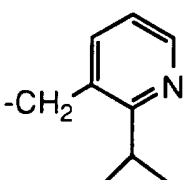


O

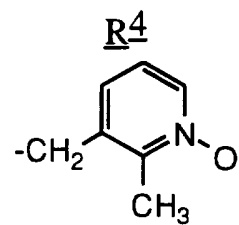
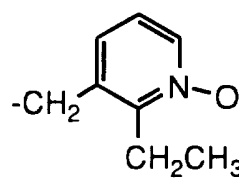
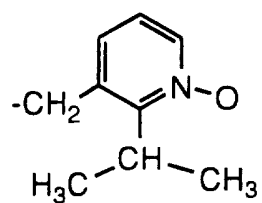
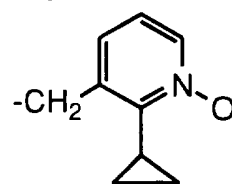
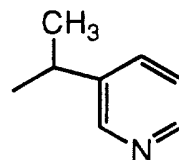
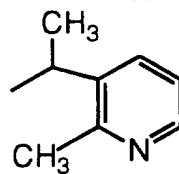
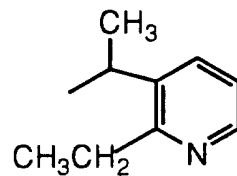
Br



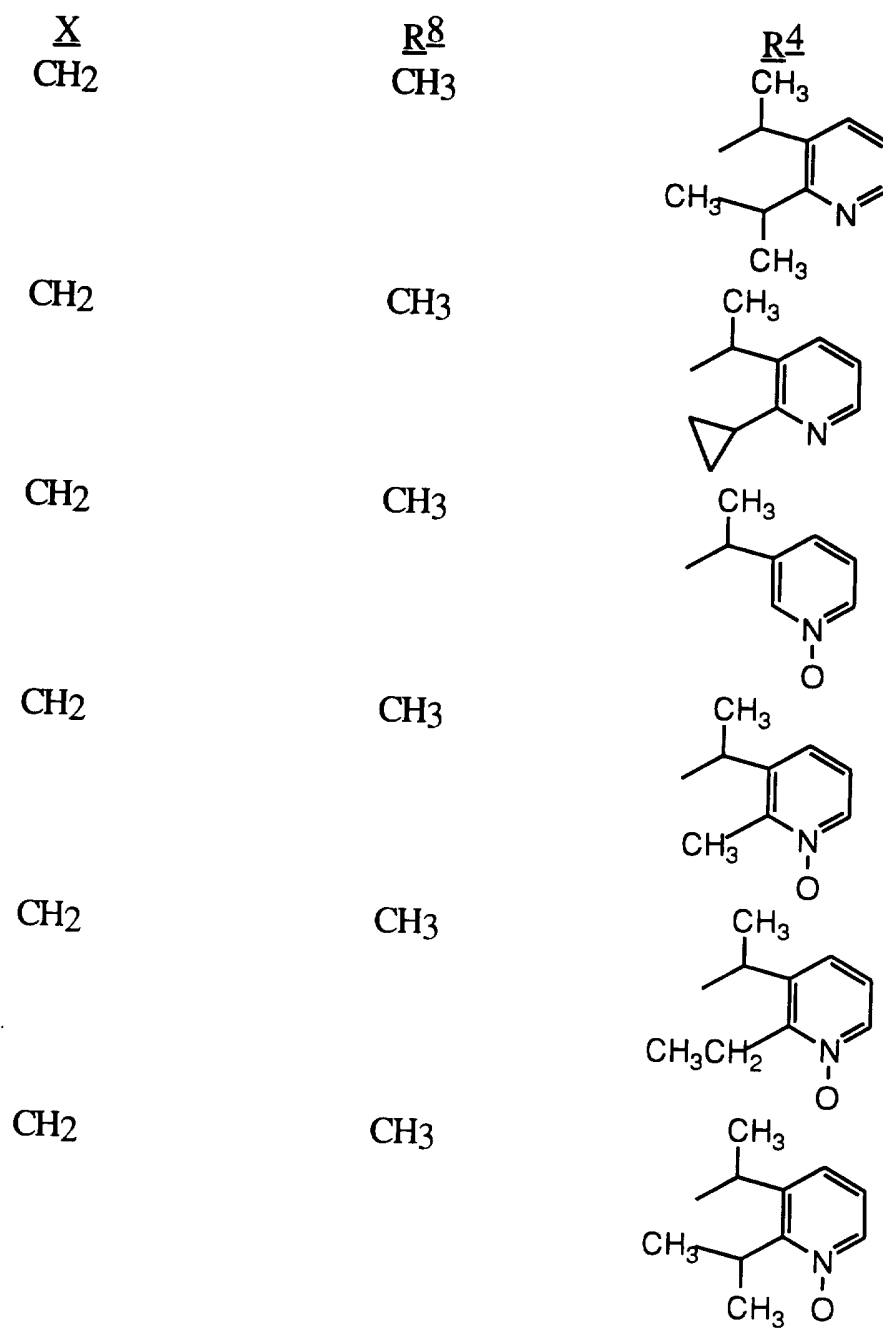
- 180 -

$\frac{\underline{X}}{O}$	$\frac{\underline{R^8}}{Br}$	
CH ₂	CH ₃	
CH ₂	CH ₃	
CH ₂	CH ₃	
CH ₂	CH ₃	
CH ₂	CH ₃	
CH ₂	CH ₃	

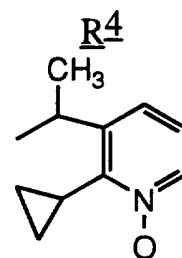
- 181 -

 $\underline{X}$
CH₂ $\underline{R^8}$
CH₃CH₂CH₃CH₂CH₃CH₂CH₃CH₂CH₃CH₂CH₃CH₂CH₃

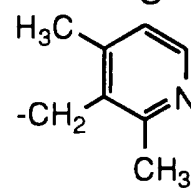
- 182 -



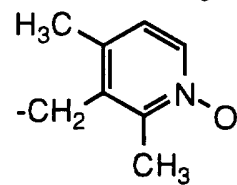
- 183 -

 $\underline{X}$
CH₂ $\underline{R^8}$
CH₃CH₂

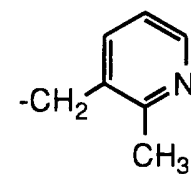
F

CH₂

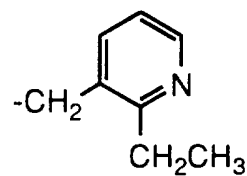
F

CH₂

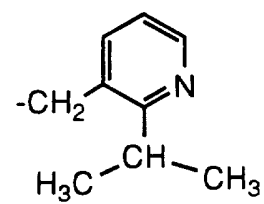
F

CH₂

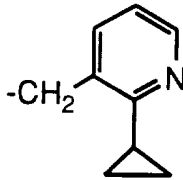
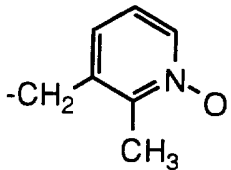
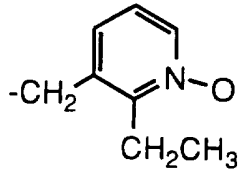
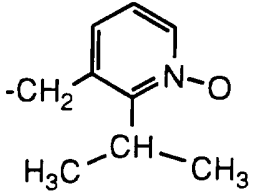
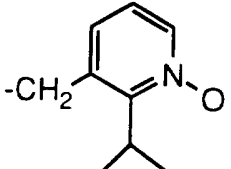
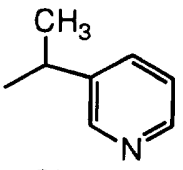
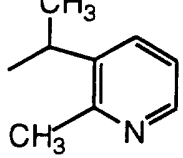
F

CH₂

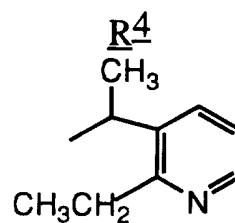
F



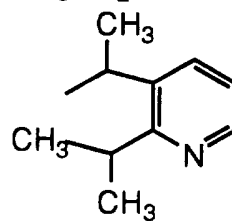
- 184 -

$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{F}}$	$\frac{\underline{R^4}}{\text{F}}$
CH_2	F	
CH_2	F	
CH_2	F	
CH_2	F	
CH_2	F	
CH_2	F	
CH_2	F	

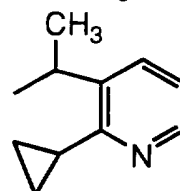
- 185 -

 $\frac{X}{CH_2}$ $\frac{R^8}{F}$  CH_2

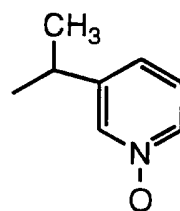
F

 CH_2

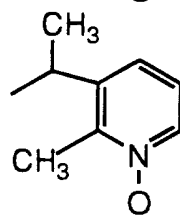
F

 CH_2

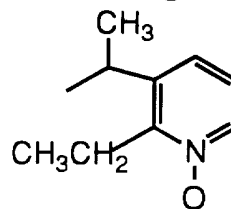
F

 CH_2

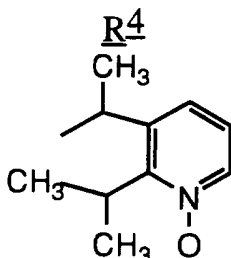
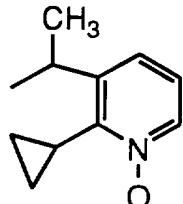
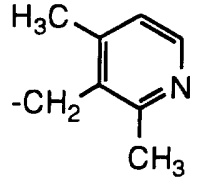
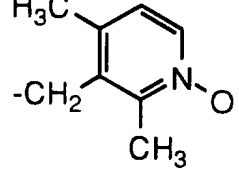
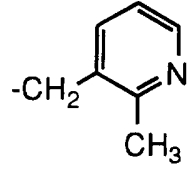
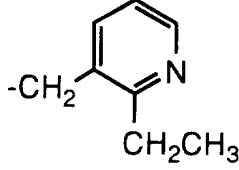
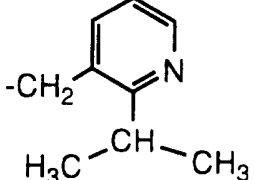
F

 CH_2

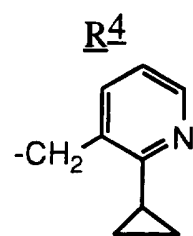
F



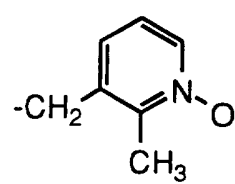
- 186 -

$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{F}}$	
CH_2	F	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	

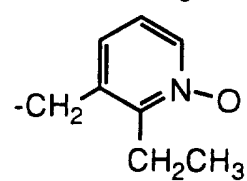
- 187 -

 $\underline{X}$
CH₂ $\underline{R^8}$
ClCH₂

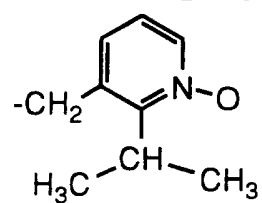
Cl

CH₂

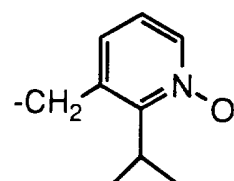
Cl

CH₂

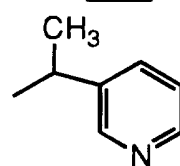
Cl

CH₂

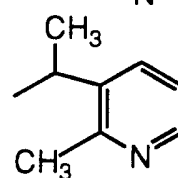
Cl

CH₂

Cl

CH₂

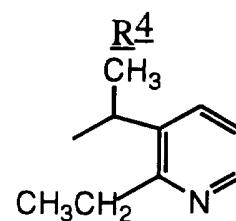
Cl



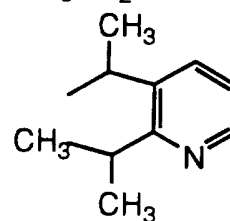
- 188 -

 $\frac{\underline{X}}{\text{CH}_2}$ $\frac{\underline{R^8}}{\text{Cl}}$ CH_2

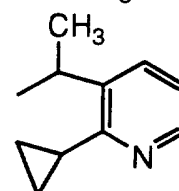
Cl

 CH_2

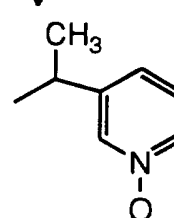
Cl

 CH_2

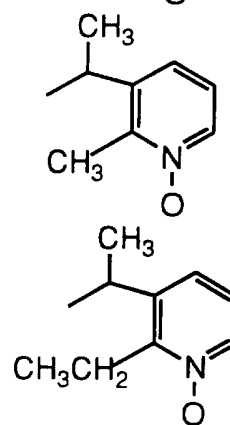
Cl

 CH_2

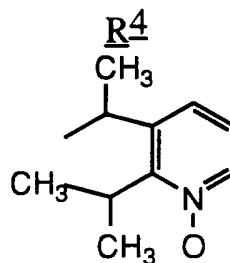
Cl

 CH_2

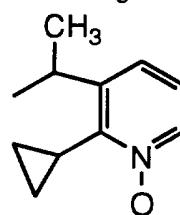
Cl



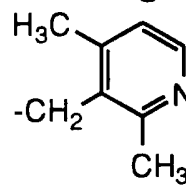
- 189 -

 $\frac{X}{CH_2}$ $\frac{R^8}{Cl}$  CH_2

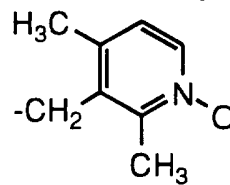
Cl

 CH_2

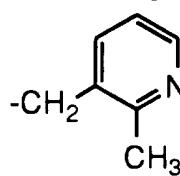
Br

 CH_2

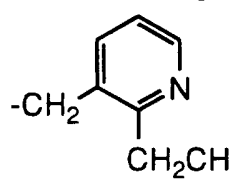
Br

 CH_2

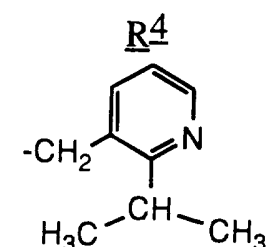
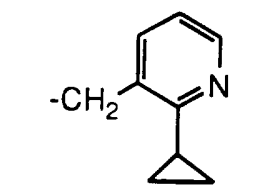
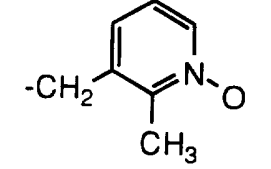
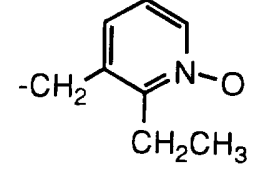
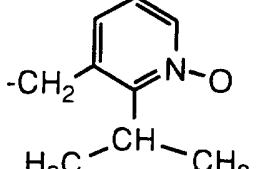
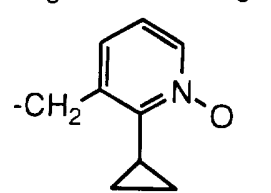
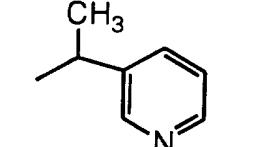
Br

 CH_2

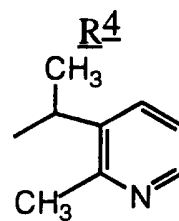
Br



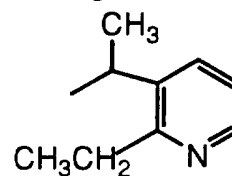
- 190 -

$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{Br}}$	
CH_2	Br	
CH_2	Br	
CH_2	Br	
CH_2	Br	
CH_2	Br	
CH_2	Br	

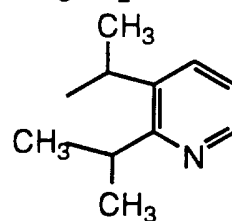
- 191 -

 $\frac{X}{CH_2}$ $\frac{R^8}{Br}$  CH_2

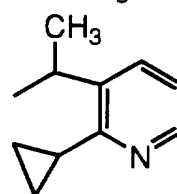
Br

 CH_2

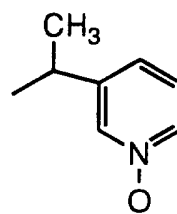
Br

 CH_2

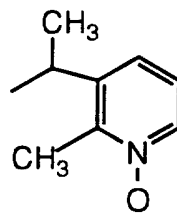
Br

 CH_2

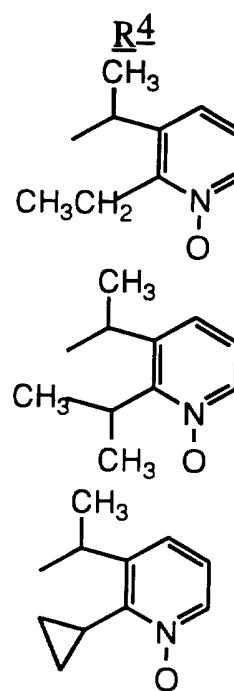
Br

 CH_2

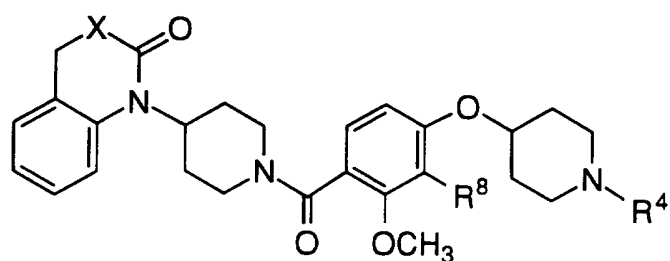
Br



- 192 -

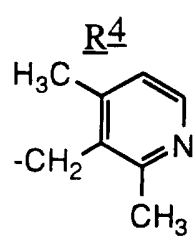
 $\frac{\underline{X}}{\text{CH}_2}$ $\frac{\underline{R^8}}{\text{Br}}$ CH_2 Br CH_2 Br 

- 193 -

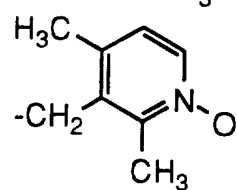
TABLE 12

X
O

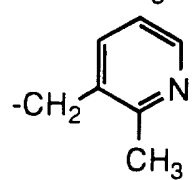
R⁸
CH₃



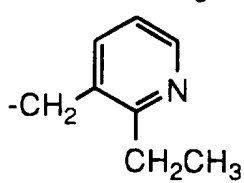
O

CH₃

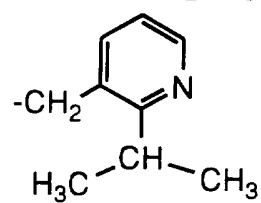
O

CH₃

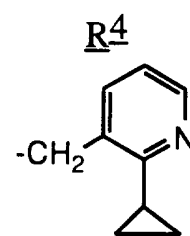
O

CH₃

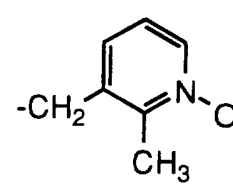
O

CH₃

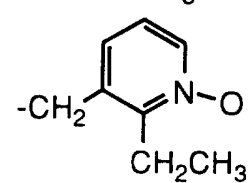
- 194 -

 $\frac{X}{O}$ $\frac{R^8}{CH_3}$ 

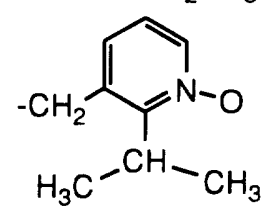
O

CH₃

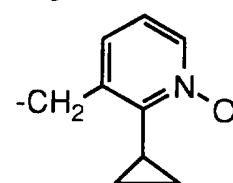
O

CH₃

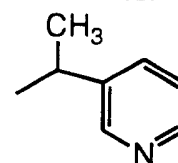
O

CH₃

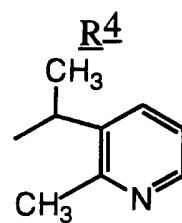
O

CH₃

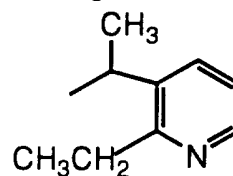
O

CH₃

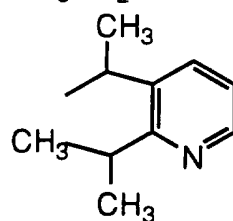
- 195 -

X
OR⁸
CH₃

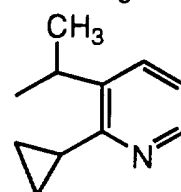
O

CH₃

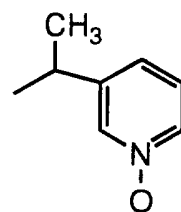
O

CH₃

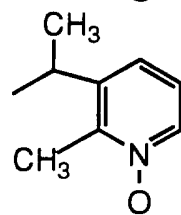
O

CH₃

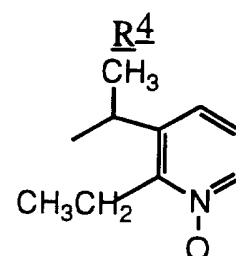
O

CH₃

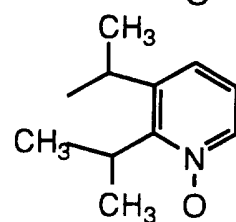
O

CH₃

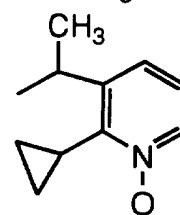
- 196 -

 $\frac{\underline{X}}{O}$
 $\frac{\underline{R^8}}{CH_3}$


O

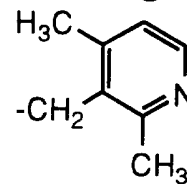
CH₃

O

CH₃

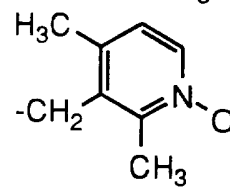
O

F



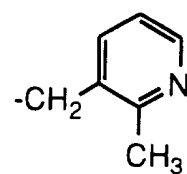
O

F

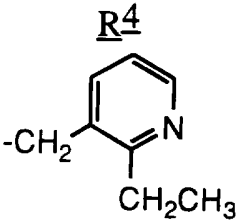
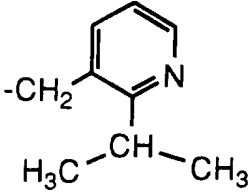
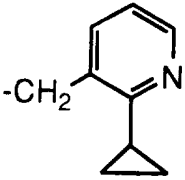
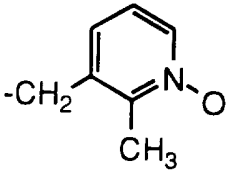
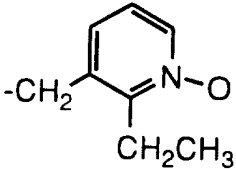
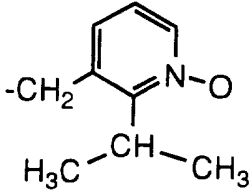
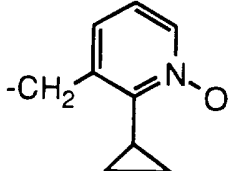


O

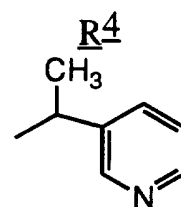
F



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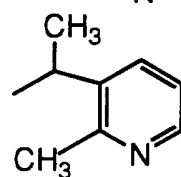
$\frac{X}{O}$	$\frac{R^8}{F}$	
O	F	
O	F	
O	F	
O	F	
O	F	
O	F	

- 198 -

X
OR⁸
F

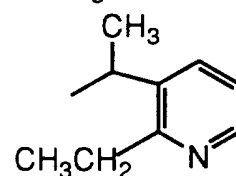
O

F



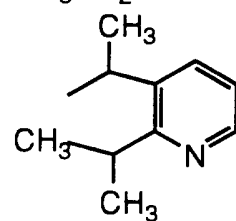
O

F



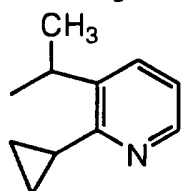
O

F



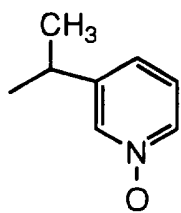
O

F

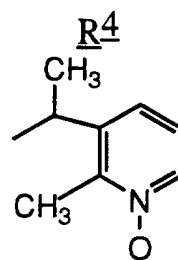


O

F

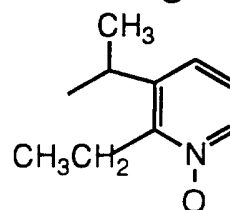


- 199 -

X
OR⁸
F

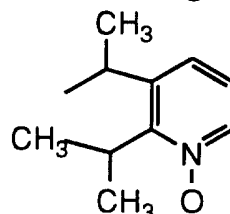
O

F



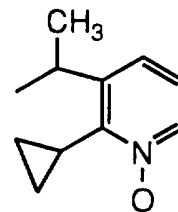
O

F



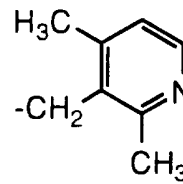
O

F



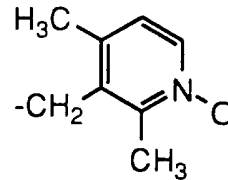
O

Cl

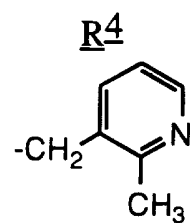


O

Cl

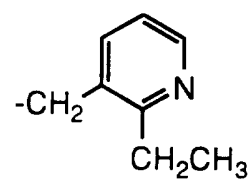


- 200 -

 $\frac{X}{O}$ $\frac{R^8}{Cl}$ 

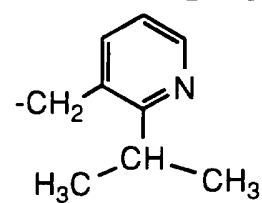
O

Cl



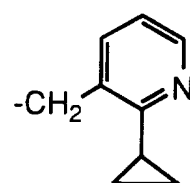
O

Cl



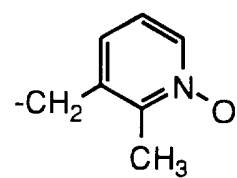
O

Cl



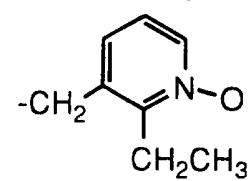
O

Cl



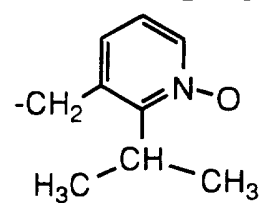
O

Cl



O

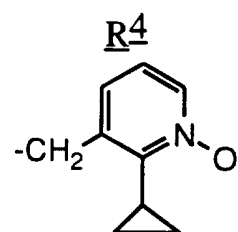
Cl



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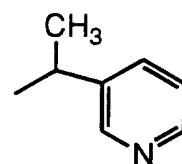
X
O

R⁸
Cl



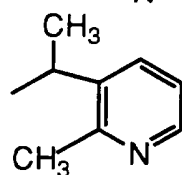
O

Cl



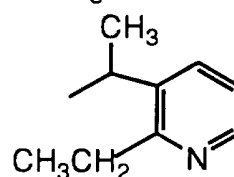
O

Cl



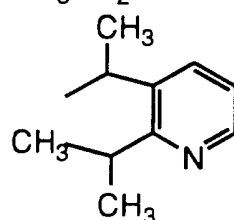
O

Cl



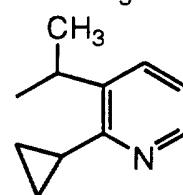
O

Cl



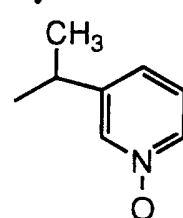
O

Cl

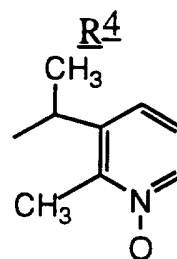


O

Cl

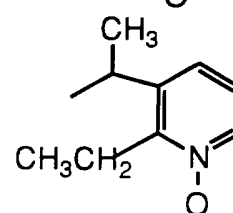


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X
OR⁸
Cl

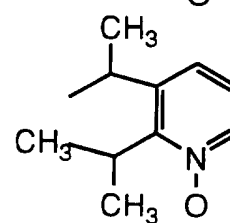
O

Cl



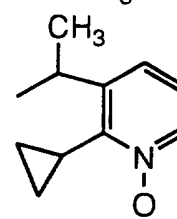
O

Cl



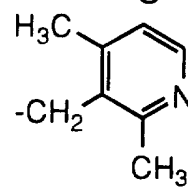
O

Cl



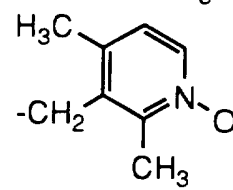
O

Br

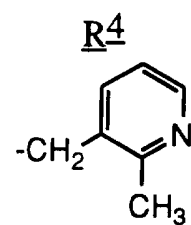


O

Br

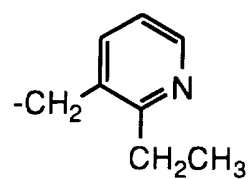


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 $\frac{X}{O}$ $\frac{R^8}{Br}$ 

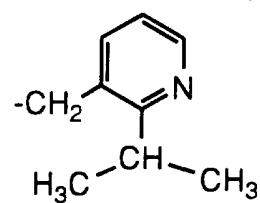
O

Br



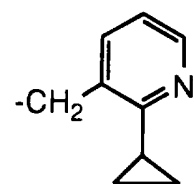
O

Br



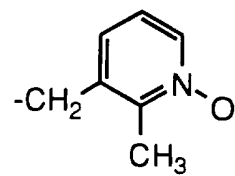
O

Br



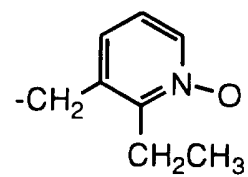
O

Br



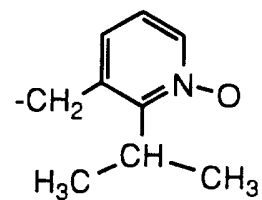
O

Br

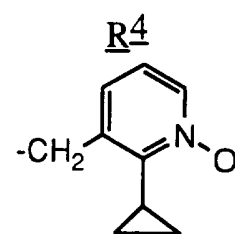


O

Br

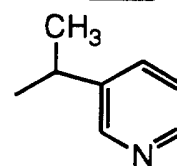


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X
OR⁸
Br

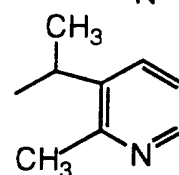
O

Br



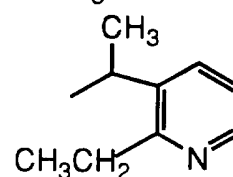
O

Br



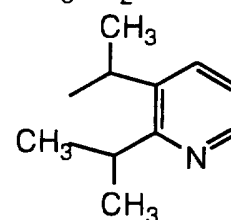
O

Br



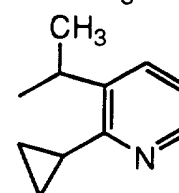
O

Br



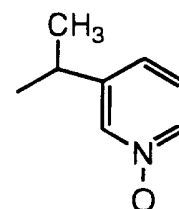
O

Br

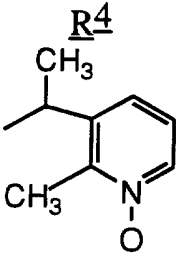
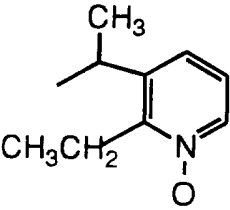
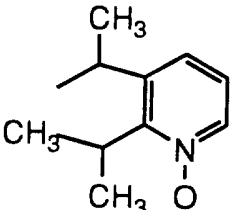
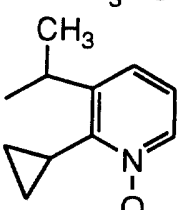
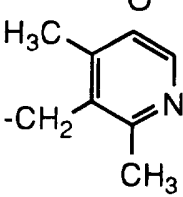
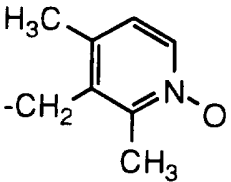


O

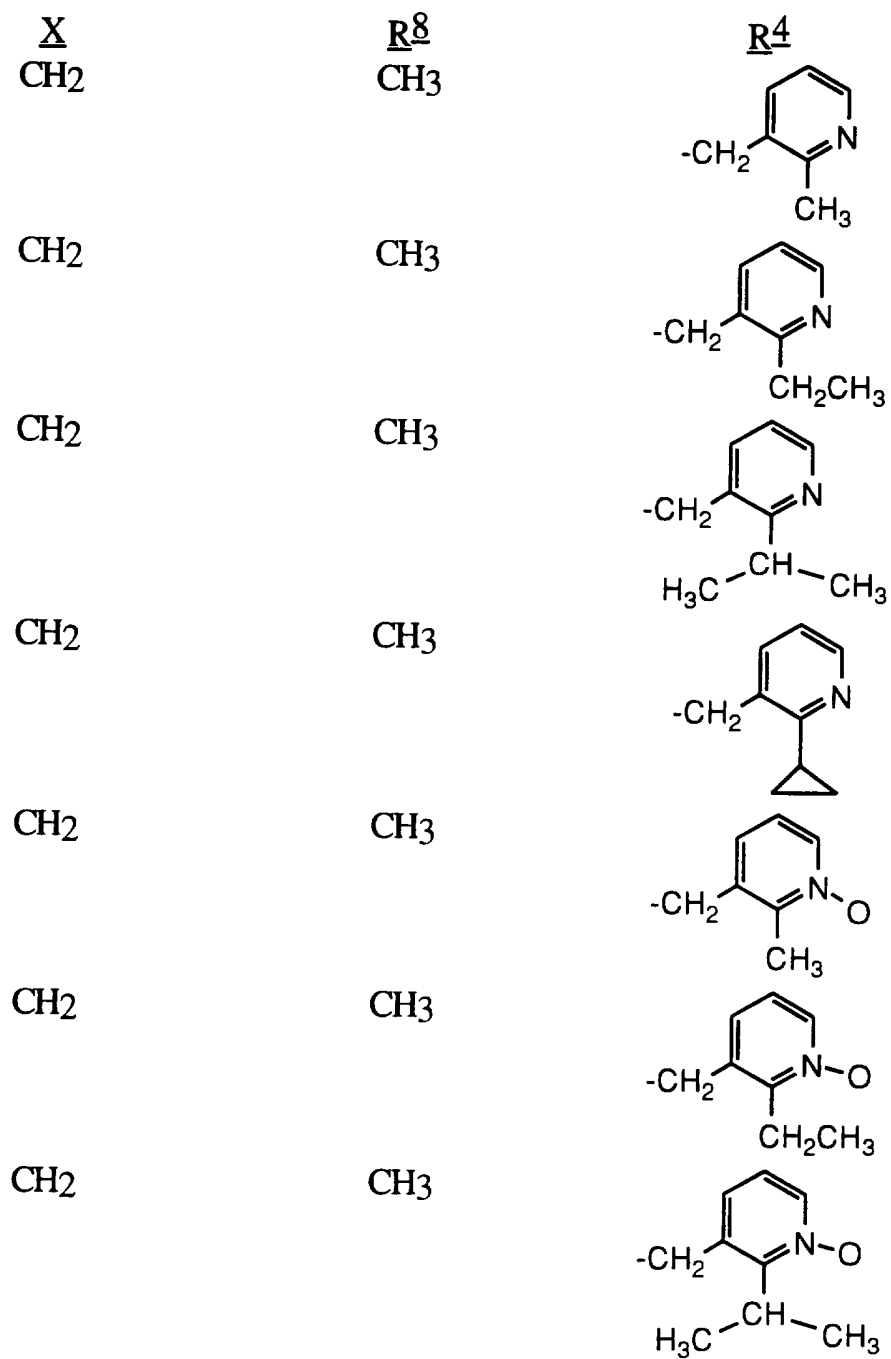
Br



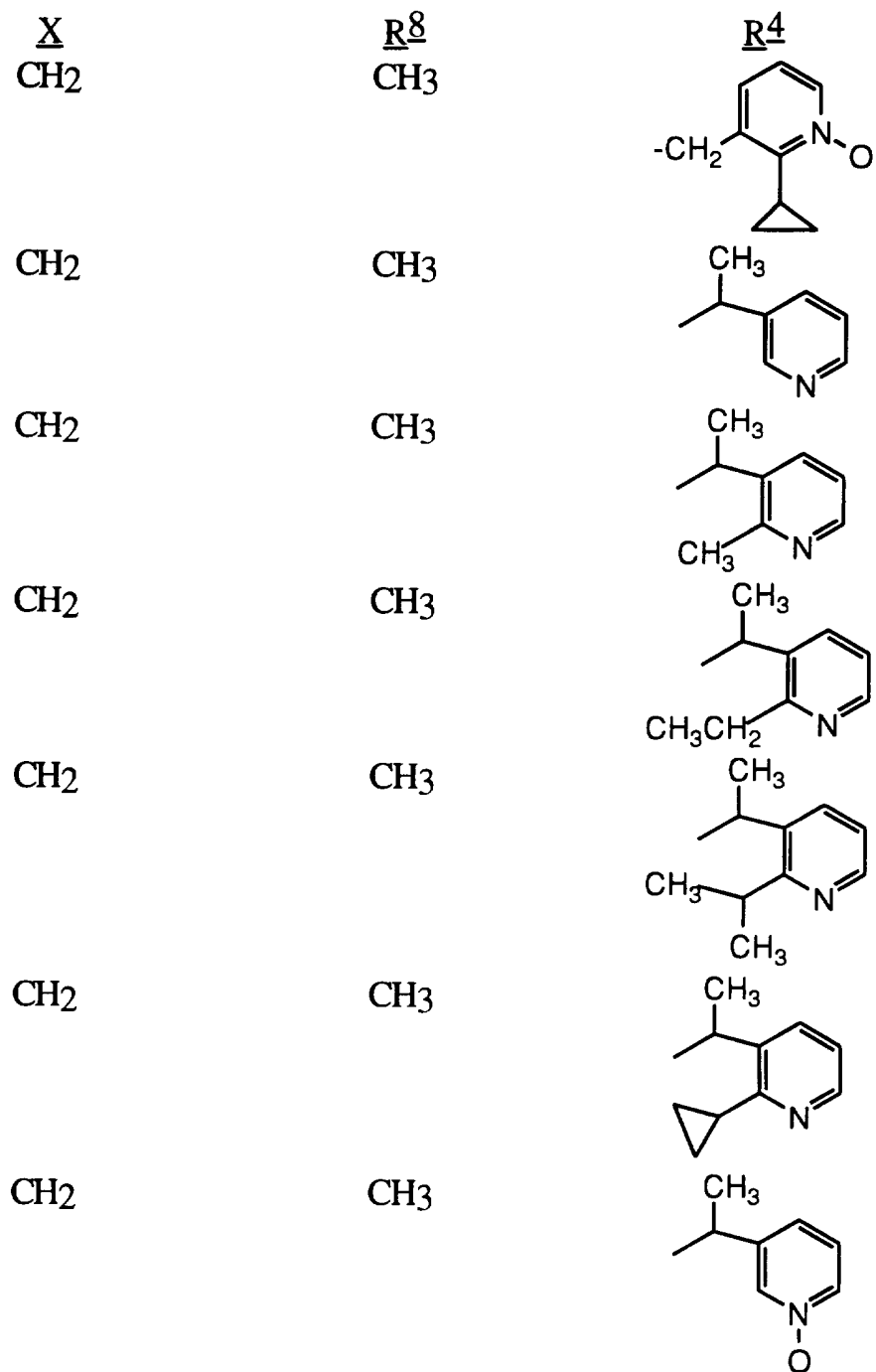
- 205 -

$\frac{X}{O}$	$\frac{R^8}{Br}$	
O	Br	
O	Br	
O	Br	
CH ₂	CH ₃	
CH ₂	CH ₃	

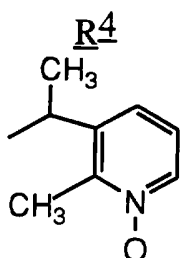
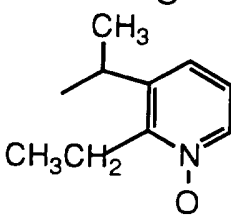
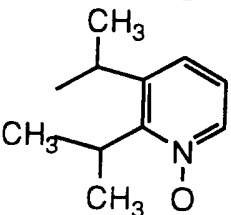
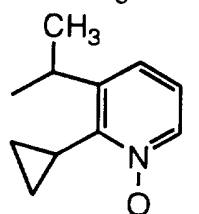
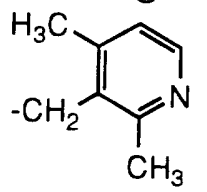
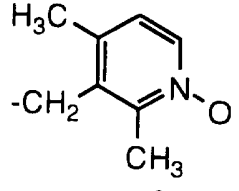
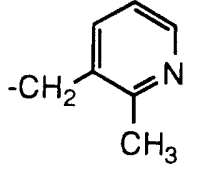
- 206 -



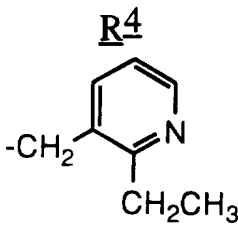
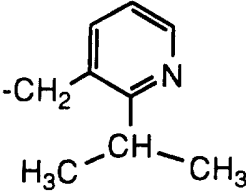
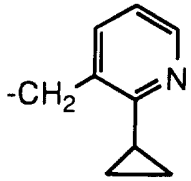
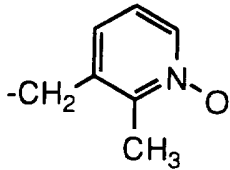
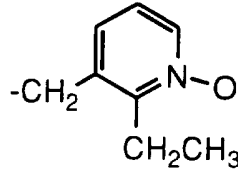
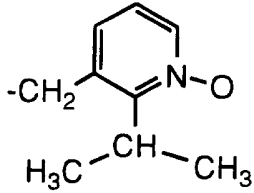
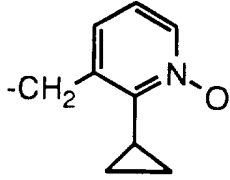
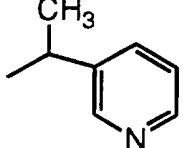
- 207 -



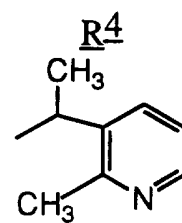
- 208 -

$\underline{X}$ CH ₂	$\underline{R^8}$ CH ₃	
CH ₂	CH ₃	
CH ₂	CH ₃	
CH ₂	CH ₃	
CH ₂	F	
CH ₂	F	
CH ₂	F	

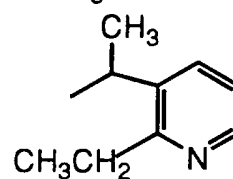
- 209 -

$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{F}}$	$\frac{\underline{R^4}}{\text{F}}$
		
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	
CH ₂	F	

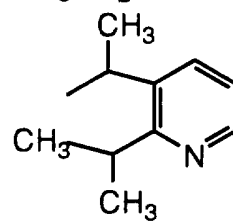
- 210 -

 $\underline{X}$
CH₂ $\underline{R^8}$
FCH₂

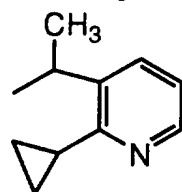
F

CH₂

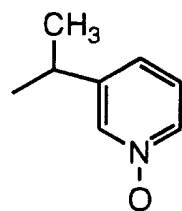
F

CH₂

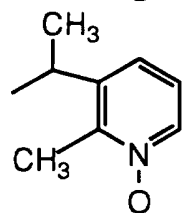
F

CH₂

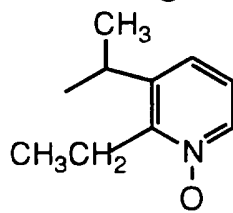
F

CH₂

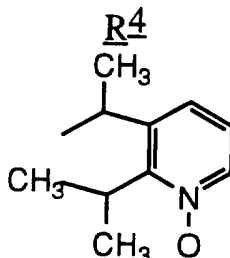
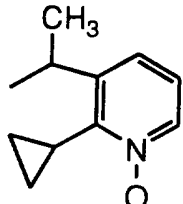
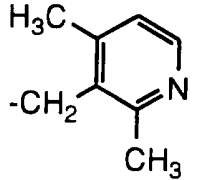
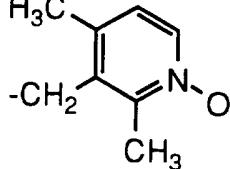
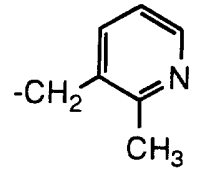
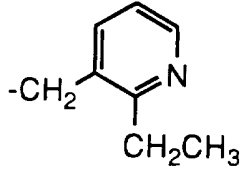
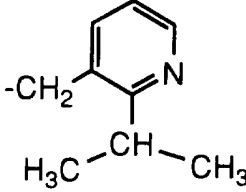
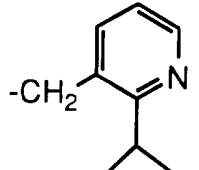
F

CH₂

F

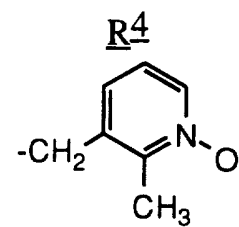


- 211 -

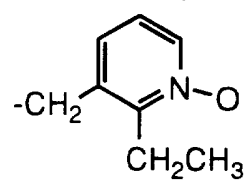
$\frac{\underline{X}}{\text{CH}_2}$	$\frac{\underline{R^8}}{\text{F}}$	
CH_2	F	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	
CH_2	Cl	

- 212 -

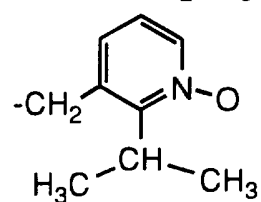
$$\begin{array}{c} \underline{\text{X}} \\ \text{CH}_2 \end{array}$$

$$\begin{array}{c} \underline{\text{R}^8} \\ \text{Cl} \end{array}$$


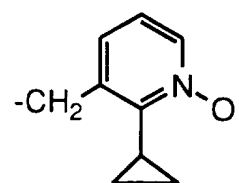
$$\text{CH}_2$$

$$\text{Cl}$$


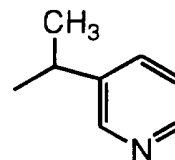
$$\text{CH}_2$$

$$\text{Cl}$$


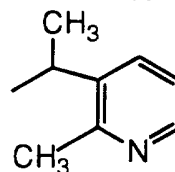
$$\text{CH}_2$$

$$\text{Cl}$$


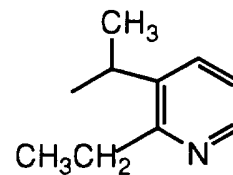
$$\text{CH}_2$$

$$\text{Cl}$$


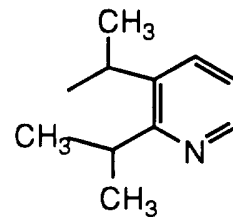
$$\text{CH}_2$$

$$\text{Cl}$$


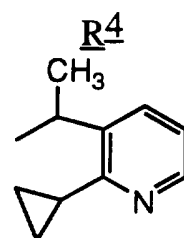
$$\text{CH}_2$$

$$\text{Cl}$$


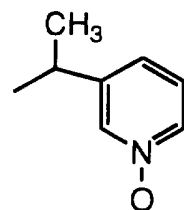
$$\text{CH}_2$$

$$\text{Cl}$$


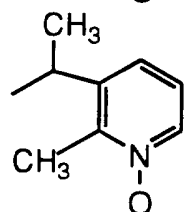
- 213 -

 $\frac{\underline{X}}{\text{CH}_2}$
 $\frac{\underline{R^8}}{\text{Cl}}$
CH₂

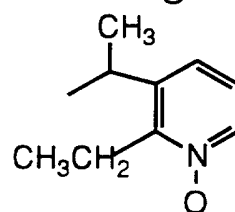
Cl

CH₂

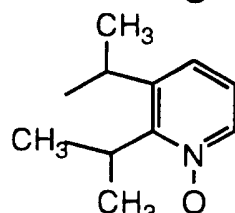
Cl

CH₂

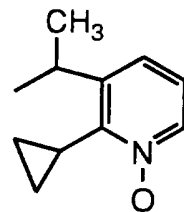
Cl

CH₂

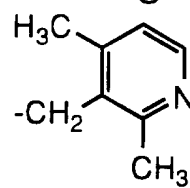
Cl

CH₂

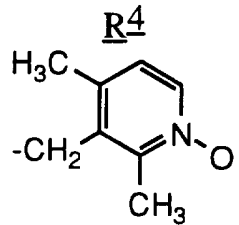
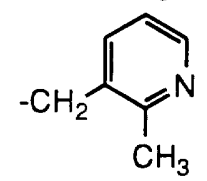
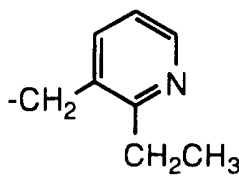
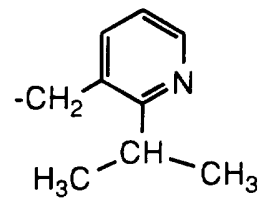
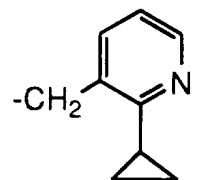
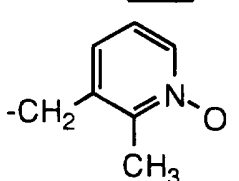
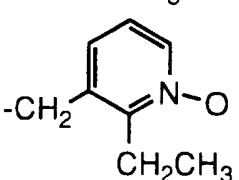
Cl

CH₂

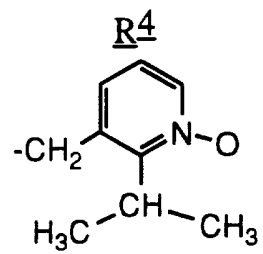
Br



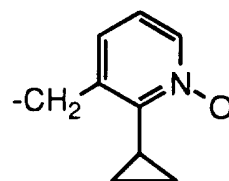
- 214 -

$\underline{X}$ CH ₂	$\underline{R^8}$ Br	$\underline{R^4}$ 
CH ₂	Br	
CH ₂	Br	
CH ₂	Br	
CH ₂	Br	
CH ₂	Br	
CH ₂	Br	

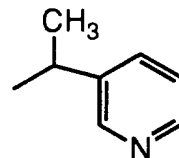
- 215 -

 $\frac{X}{CH_2}$ $\frac{R^8}{Br}$ CH₂

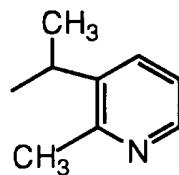
Br

CH₂

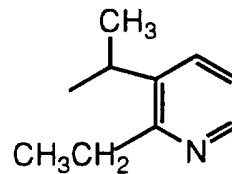
Br

CH₂

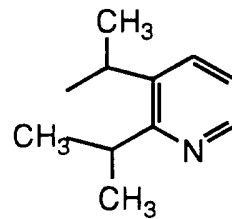
Br

CH₂

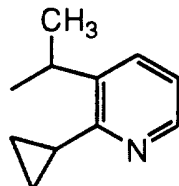
Br

CH₂

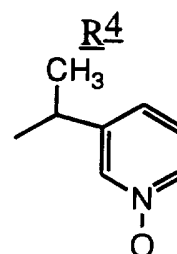
Br

CH₂

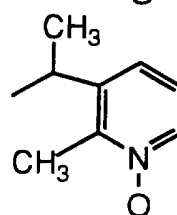
Br



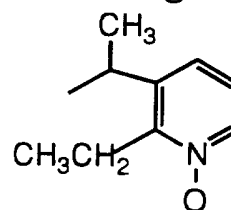
- 216 -

 $\frac{X}{CH_2}$ $\frac{R^8}{Br}$  CH_2

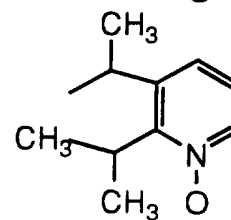
Br

 CH_2

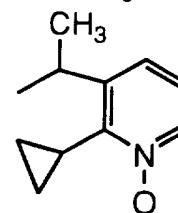
Br

 CH_2

Br

 CH_2

Br



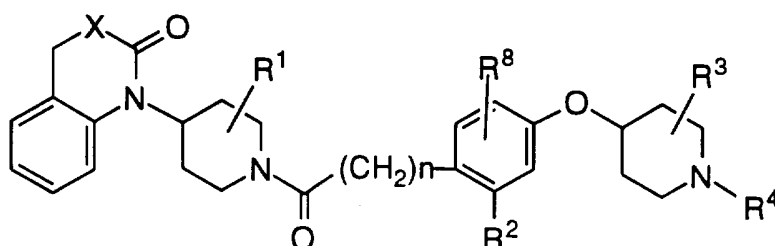
- 217 -

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

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WHAT IS CLAIMED IS:

1. A compound of the formula



5 wherein

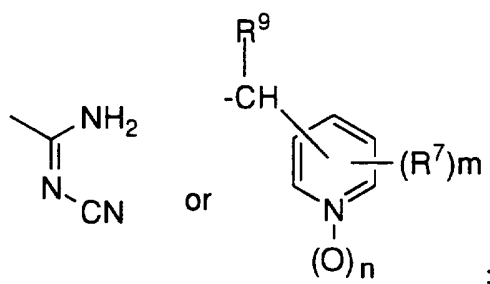
X is selected from CH₂ or O;

10 R¹ is selected from hydrogen, mono- or di-C₁₋₅ alkyl, C₁₋₅ alkoxy-substituted C₁₋₅ alkyl, CO₂H or CONH₂;

R² is selected from hydrogen or C₁₋₅ alkoxy;

15 R³ is selected from hydrogen, C₁₋₅ alkyl, di-, tri- or tetra-methyl, C₁₋₅ alkoxy-substituted C₁₋₅ alkyl, hydroxy-substituted C₁₋₅ alkyl, C₁₋₅ alkoxycarbonyl, CO₂H or CONH₂;

R⁴ is selected from hydrogen, C₁₋₅ alkoxycarbonyl, C₁₋₁₀ alkyl, C₃₋₈ cycloalkyl-substituted C₁₋₅ alkyl, COR⁵, SO₂R⁶,



20

R⁵ is selected from C₁₋₁₀ alkyl or NHCOR⁶;

- 219 -

R⁶ is C₁₋₁₀ alkyl;

R⁷ is selected from hydrogen, halogen, amino, mono- or di-C₁₋₅ alkylamino, C₁₋₁₀ alkyl or C₃₋₈ cycloalkyl;

5

R⁸ is selected from hydrogen, C₁₋₅ alkyl or halogen;

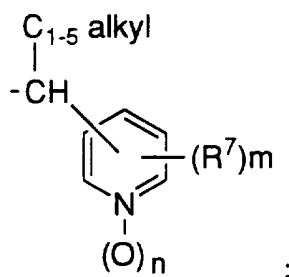
R⁹ is selected from hydrogen and C₁₋₅ alkyl;

10 n is an integer of from 0 to 1; and
m is an integer of from 1 to 3;

provided that when R¹ and R³ are both simultaneously hydrogen: then
(a) R⁸ is C₁₋₅ alkyl or halogen, and R² is C₁₋₅ alkoxy, or

15

(b) R⁴ is



and the pharmaceutically acceptable salts thereof.

20

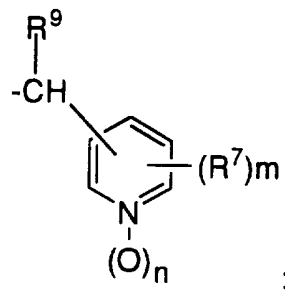
2. The compound of Claim 1, wherein

R¹ is selected from hydrogen, C₁₋₅ alkyl or CONH₂;

25 R³ is selected from hydrogen, C₁₋₅ alkyl, C₁₋₅ alkoxy-substituted
C₁₋₅ alkyl, C₁₋₅ alkoxycarbonyl, CO₂H or CONH₂;

R⁴ is selected from hydrogen, C₁₋₅ alkyl, C₃₋₈ cycloalkyl-substituted
C₁₋₅ alkyl, COR⁵, SO₂R⁶ or

- 220 -



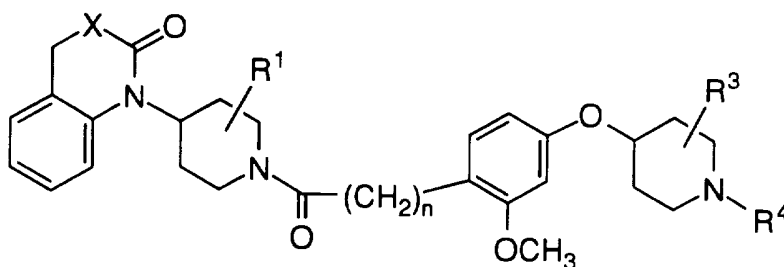
R^5 is C₁₋₅ alkyl;

5 R^6 is C₁₋₅ alkyl;

R^7 is selected from hydrogen, chlorine, amino, mono- or di-C₁₋₅ alkylamino, C₁₋₅ alkyl or C₃₋₈ cycloalkyl; and

10 m is an integer of from 1 to 2.

3. The compound of Claim 2, of the formula



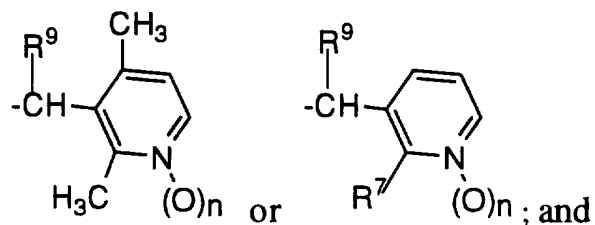
wherein

15

R^3 is selected from hydrogen, C₁₋₅ alkyl, CH_2OCH_3 , C₁₋₅ alkoxy carbonyl, CO_2H or $CONH_2$;

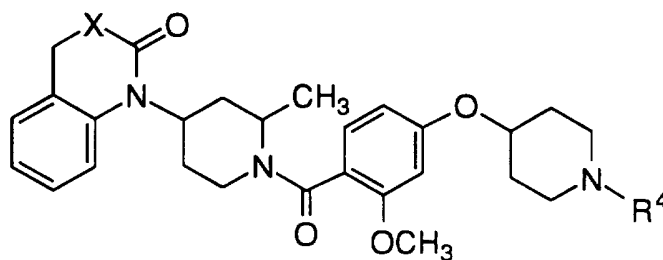
20 R^4 is selected from hydrogen, methyl, ethyl, isopropyl, CH_2 -cyclopropyl, $COCH_3$, SO_2CH_3 ,

- 221 -



R^7 is selected from hydrogen, methyl, ethyl, isopropyl or cyclopropyl.

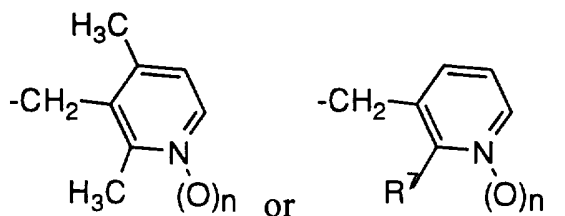
- 5 4. The compound of Claim 3 wherein X is O.
5. The compound of Claim 3 wherein X is CH_2 .
6. The compound of Claim 3, of the formula



10

wherein

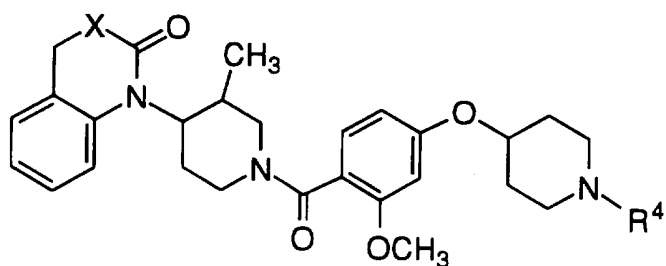
R^4 is selected from hydrogen, isopropyl, COCH_3 , SO_2CH_3 ,



15

7. The compound of Claim 3, of the formula

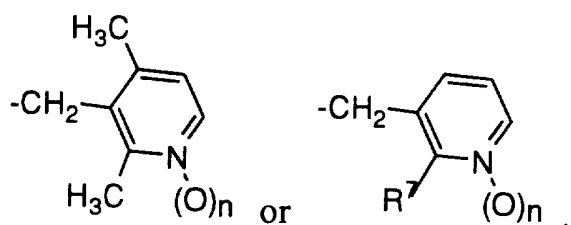
- 222 -



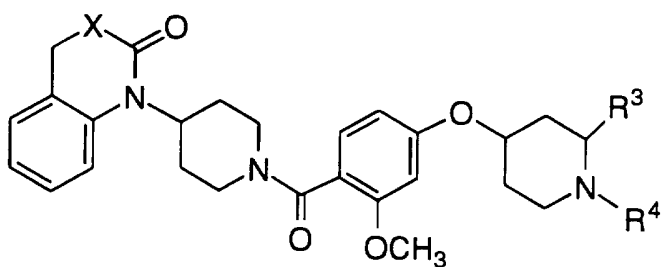
wherein

R⁴ is selected from hydrogen, isopropyl, COCH₃, SO₂CH₃,

5



8. The compound of Claim 3, of the formula



wherein

10

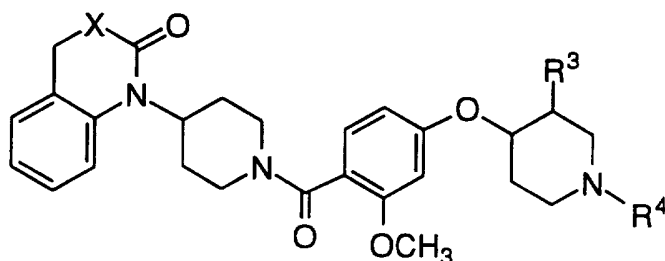
R³ is selected from C₁-5 alkyl, CH₂OCH₃, CO₂CH₂CH₃, CO₂H or CONH₂.

15

9. The compound of Claim 8, wherein R³ is C₁-5 alkyl.

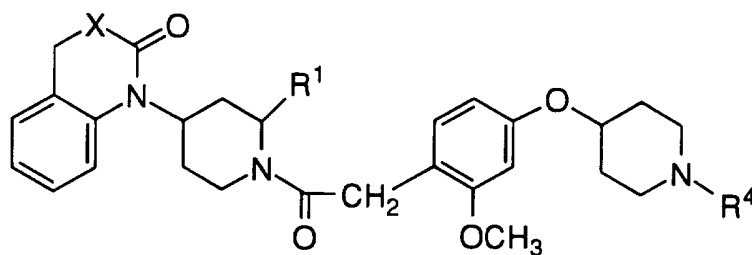
10. The compound of Claim 3, of the formula

- 223 -



wherein R^3 is C₁-5 alkyl.

11. The compound of Claim 3, of the formula



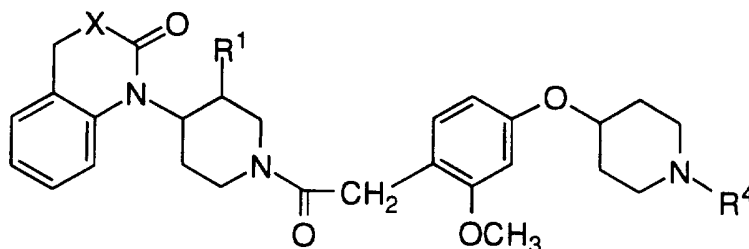
5

wherein

R^1 is selected from methyl or CONH₂; and

10 R^4 is selected from hydrogen, methyl, ethyl, isopropyl, CH₂-cyclopropyl, COCH₃ or SO₂CH₃.

12. The compound of Claim 3, of the formula



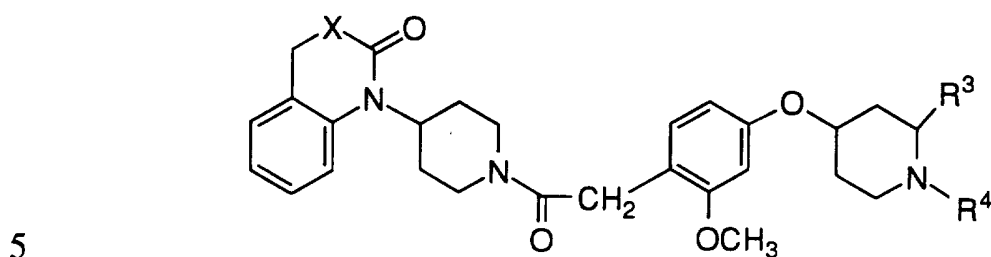
15 wherein

R^1 is C₁-5 alkyl; and

- 224 -

R^4 is selected from hydrogen, methyl, ethyl, isopropyl, CH_2 -cyclopropyl, COCH_3 or SO_2CH_3 .

13. The compound of Claim 3 of the formula

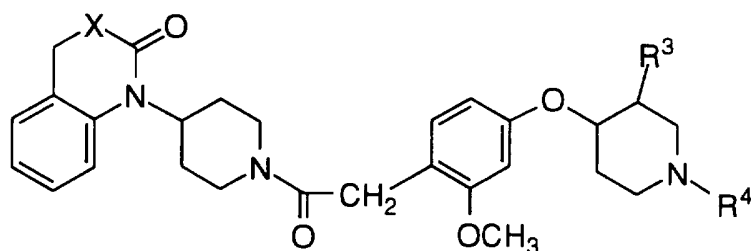


wherein

R^3 is selected from C_{1-5} alkyl, CH_2OCH_3 , C_{1-5} alkoxy carbonyl, CO_2H or CONH_2 .

10

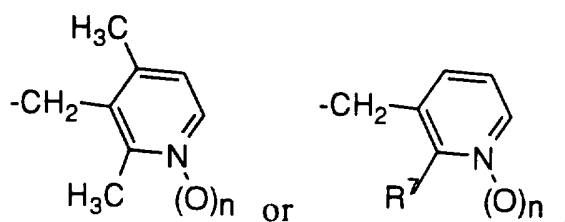
14. The compound of Claim 3 of the formula



wherein

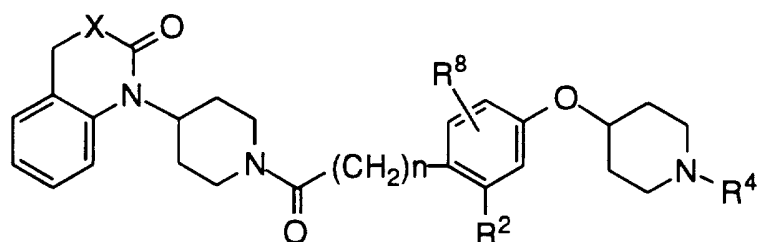
15 R^3 is C_{1-5} alkyl; and

R^4 is selected from hydrogen, isopropyl, COCH_3 , SO_2CH_3 ,



- 225 -

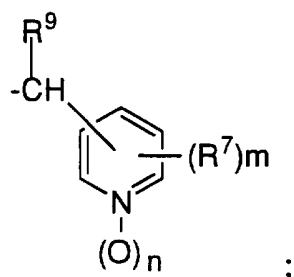
15. The compound of Claim 2 of the formula



wherein

5

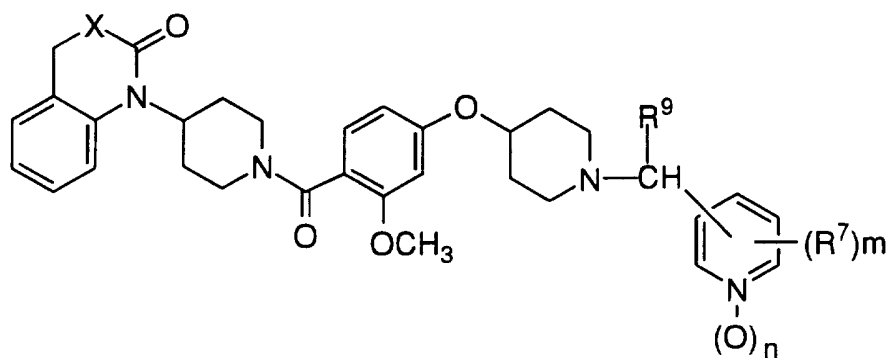
R⁴ is



10 R⁷ is selected from hydrogen, chlorine, amino, mono- or di-C₁₋₅ alkylamino, C₁₋₅ alkyl or C₃₋₈ cycloalkyl; and

R⁹ is C₁₋₅ alkyl.

16. The compound of Claim 15, of the formula



15

wherein

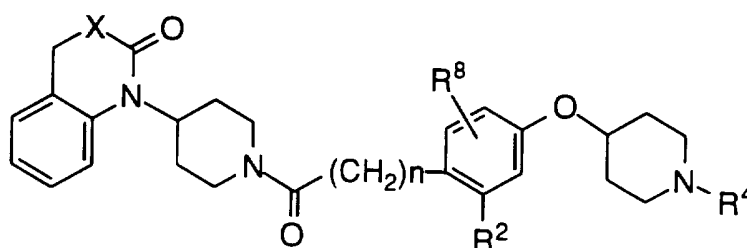
- 226 -

R^7 is selected from hydrogen, C₁-5 alkyl or C₃-8 cycloalkyl; and

R^9 is methyl.

5

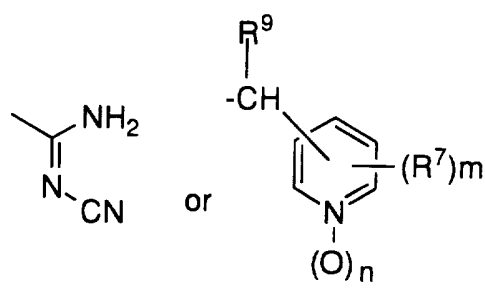
17. The compound of Claim 1, of the formula



wherein

10 R^2 is C₁-5 alkoxy;

R^4 is selected from C₁-3 alkoxy carbonyl, C₁-10 alkyl, C₃-8 cycloalkyl-substituted C₁-5 alkyl, COR⁵, SO₂R⁶,

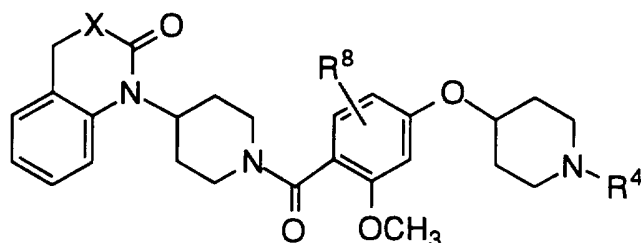


15 R^5 is selected from C₂-10 alkyl or NHCOR⁶; and

R^8 is selected from C₁-5 alkyl or halogen.

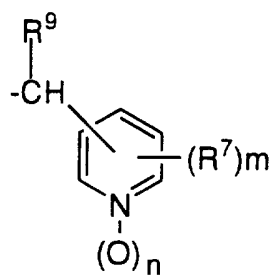
18. The compound of Claim 17, of the formula

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wherein

R⁴ is



5

;

R⁷ is selected from hydrogen, C₁₋₅ alkyl or C₃₋₈ cycloalkyl;

R⁸ is selected from methyl, fluorine, chlorine or bromine; and

10 R⁹ is selected from hydrogen or methyl.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmacologically effective amount of a compound as claimed in Claim 1.

15

20. A method of eliciting an oxytocin antagonizing effect in a mammal, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in Claim 1.

20

21. A method of treating preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in

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Claim 1.

22. A method of stopping labor preparatory to cesarian
delivery in a mammal in need thereof, comprising the step of
5 administering to said mammal a pharmacologically effective amount of
a compound as claimed in Claim 1.

23. A method of treating dysmenorrhea in a mammal in
need thereof, comprising the step of administering to said mammal a
10 pharmacologically effective amount of a compound as claimed in
Claim 1.

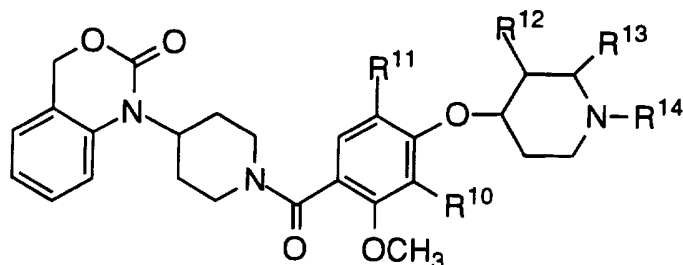
24. A method of increasing fertility and embryonic
survival in a farm animal, comprising administering to the farm animal
15 a pharmacologically effective amount of a compound as claimed in
Claim 1.

25. A method for improving survival of a farm animal
neonate comprising controlling timing of parturition to effect delivery
20 of the neonate during daylight hours by administering to a farm animal
which is expected to deliver the neonate within 24 hours a
pharmacologically effective amount of a compound as claimed in
Claim 1.

25 26. A method of controlling the timing of estrus in a
farm animal, comprising administering to the farm animal a pharmaco-
logically effective amount of a compound as claimed in Claim 1.

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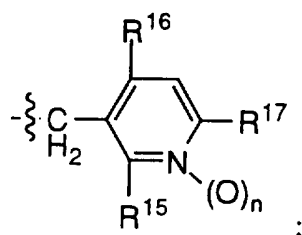
27. A compound of the formula



wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen or C₁-6 alkyl;

5 R^{12} and R^{13} are each independently selected from hydrogen, C₁-6 alkyl or CO₂-C₁-6 alkyl;

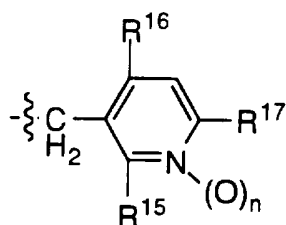
R^{14} is selected from hydrogen, CO-C₁-6 alkyl, CO₂-C₁-6 alkyl or



10 R^{15} , R^{16} and R^{17} are each independently selected from hydrogen or C₁-6 alkyl; and

n is integer from zero to one;

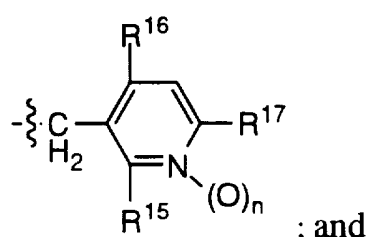
provided that when R^{10} , R^{11} , R^{12} and R^{13} are all simultaneously hydrogen, then R^{14} is



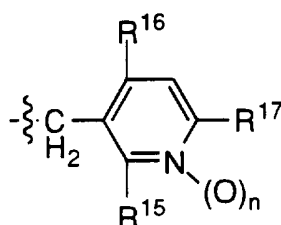
15 wherein R^{15} , R^{16} and R^{17} are each independently C₁-6 alkyl; and the pharmaceutically acceptable salts thereof.

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28. The compound of Claim 27, wherein
- R¹⁰ is selected from hydrogen or methyl;
- R¹¹ is selected from hydrogen, bromine or fluorine;
- R¹² is selected from hydrogen or methyl;
- 5 R¹³ is selected from hydrogen or CO₂CH₃;
- R¹⁴ is selected from hydrogen, COCH₃, CO₂C(CH₃)₃ or

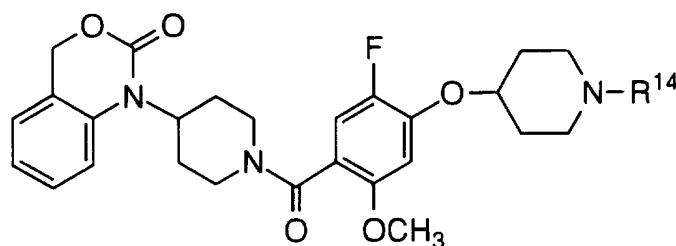


- R¹⁵, R¹⁶ and R¹⁷ are each independently selected from hydrogen, methyl, ethyl or 2-propyl;
- 10 provided that when R¹⁰, R¹¹, R¹² and R¹³ are all simultaneously hydrogen, then R¹⁴ is



- wherein R¹⁵, R¹⁶ and R¹⁷ are each independently selected from methyl, ethyl or 2-propyl;
- 15 and the pharmaceutically acceptable salts thereof.

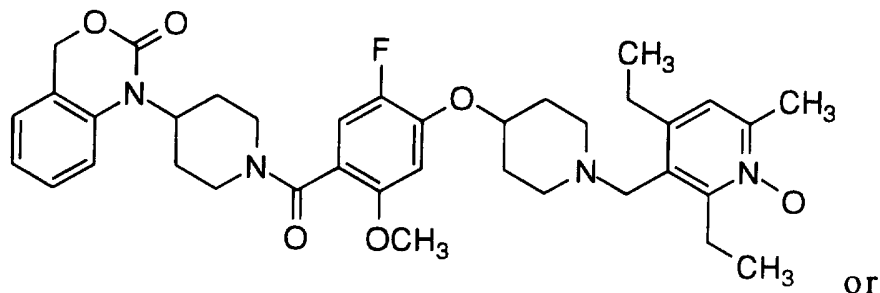
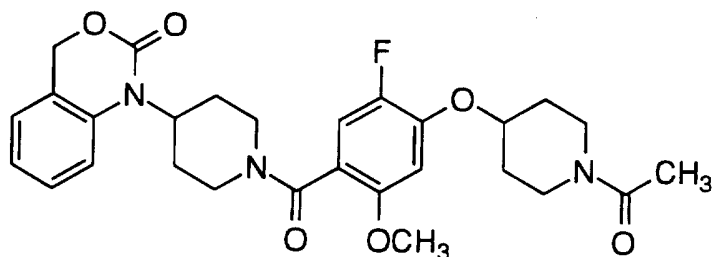
29. The compound of Claim 28, of the formula



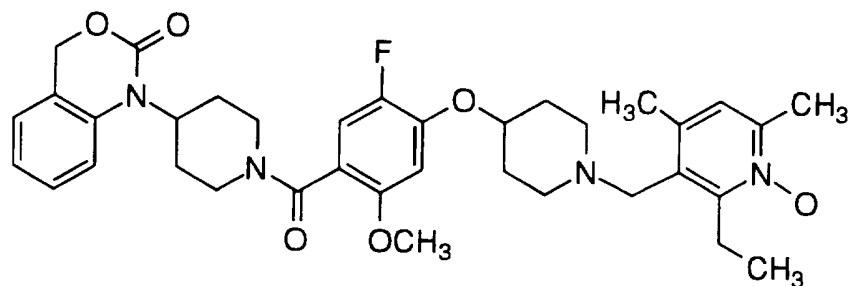
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and the pharmaceutically acceptable salts thereof.

30. The compound of Claim 29, selected from



or



and the pharmaceutically acceptable salts thereof.

31. A pharmaceutical composition comprising a
10 pharmaceutically acceptable carrier and a pharmacologically effective
amount of a compound as claimed in Claim 27.

32. A method of eliciting an oxytocin antagonizing effect
in a mammal, comprising the step of administering to said mammal a
15 pharmacologically effective amount of a compound as claimed in
Claim 27.

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33. A method of treating preterm labor in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in
5 Claim 27.

34. A method of stopping labor preparatory to cesarian delivery in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of
10 a compound as claimed in Claim 27.

35. A method of treating dysmenorrhea in a mammal in need thereof, comprising the step of administering to said mammal a pharmacologically effective amount of a compound as claimed in
15 Claim 27.

36. A method of increasing fertility and embryonic survival in a farm animal, comprising administering to the farm animal a pharmacologically effective amount of a compound as claimed in
20 Claim 27.

37. A method for improving survival of a farm animal neonate comprising controlling timing of parturition to effect delivery of the neonate during daylight hours by administering to a farm animal
25 which is expected to deliver the neonate within 24 hours a pharmacologically effective amount of a compound as claimed in Claim 27.

38. A method of controlling the timing of estrus in a
30 farm animal, comprising administering to the farm animal a pharmacologically effective amount of a compound as claimed in Claim 27.

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39. The use of the compound of Claim 27 in the preparation of a medicament for the treatment of preterm labor, dysmenorrhea or stoppage of labor prior to cesarian delivery in a mammal in need thereof.

5

40. A drug which is useful for treating preterm labor, dysmenorrhea or stopping labor prior to cesarian delivery in a mammal in need thereof, the effective ingredient of the said drug being the compound of Claim 27.

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00250**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/535, 31/47; C07D 265/18, 215/58.

US CL : 514/230.8, 312; 544/92; 546/158.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/230.8, 312; 544/92; 546/158.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Chemical Abstracts On-Line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO,A, 95/02405 (MERCK & CO.) 26 JANUARY 1995, especially pages 25-29.	1-40
X P	Journal of Medicinal Chemistry, Volume 38, Number 23, issued 1995, Williams et al., "1-[1-[4-[(N-Acetyl-4-piperidinyloxy)-2-methoxybenzoyl]benzoyl]piperidin-4-yl]-4H-3,1-benzoxazin-2(1H)-one (L-371,257): a new, orally bioavailable, non-peptide oxytocin antagonist," pages 4634-4636, see especially pages 4634-4636.	1-40

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	
A document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	*Z* document member of the same patent family

Date of the actual completion of the international search 22 MARCH 1996	Date of mailing of the international search report 13 MAY 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MATTHEW V. GRUMLING Telephone No. (703) 308-1235