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5 FLUOROALKOXYBENZYLAMINO DERIVATIVES OF NITROGEN CONTAINING
HETEROCYCLES

Background of the Invention

The present invention relates to novel fluoroalkoxybenzylamino derivatives of nitrogen containing
10 heterocycles, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention of inflammatory and central nervous system disorders, as well as several other disorders. The pharmaceutically active compounds of this invention are
15 substance P receptor antagonists. This invention also relates to novel intermediates used in the synthesis of such substance P receptor antagonists.

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter
20 being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is
25 illustrated by D. F. Veber et al. in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission
30 of pain or migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases
35 such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract such as ulcerative colitis and Crohn's disease, etc. (see D. Regoli in "Trends in Cluster Headache," edited by F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)).

40 In the recent past, some attempts have been made to provide antagonists for substance P and other tachykinin



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optionally substituted with from one to three fluorine atoms;

X^2 and X^3 are independently selected from hydrogen, halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6) -

10 alkylamino, di- (C_1-C_6) alkylamino, $\overset{\text{O}}{\parallel}\text{-C-NH-}(C_1-C_6)\text{alkyl}$,

15 (C_1-C_6) alkyl- $\overset{\text{O}}{\parallel}\text{-C-NH-}(C_1-C_6)$ alkyl, hydroxy (C_1-C_4) alkyl,

(C_1-C_4) alkoxy (C_1-C_4) alkyl, $\overset{\text{O}}{\parallel}\text{-NHCH}$ and $\overset{\text{O}}{\parallel}\text{-NHC-}(C_1-C_6)$ alkyl; and
20 Q is a group of the formula

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wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to
 5 three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

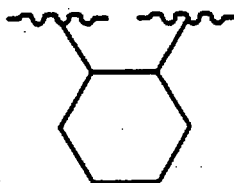
R^{13} is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_3-C_7) cycloalkyl, and the radicals named
 10 in the definition of R^1 ;

R^2 is hydrogen or (C_1-C_6) alkyl;

R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from
 15 halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_1$, wherein 1 is an integer from one to three, or Y is a group of the formula

20



(J)

;

25

Z is oxygen, sulfur, amino, (C_1-C_3) alkylamino or $(CH_2)_n$, wherein n is zero, one or two;

o is two or three;

30

p is zero or one;

R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10})
 35 alkoxy optionally substituted with from one to three fluorine atoms, carboxy, (C_1-C_3) alkoxy-carbonyl and benzyloxycarbonyl;

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(C_1-C_6) -alkylamino, (C_1-C_6) alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-
 5 (C_1-C_6) alkyl, (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-C(=O)-
 10 (C_1-C_6) alkyl-O-, (C_1-C_6) alkyl-C(=O)-, (C_1-C_6) alkyl-C(=O)-
 15 (C_1-C_6) alkyl-, di- (C_1-C_6) alkylamino, -CNH-C(=O)- (C_1-C_6) alkyl, (C_1-C_6) -
 (C_1-C_6) alkyl-C(=O)-NH- (C_1-C_6) alkyl, -NHCH(=O) and -NHC(=O)- (C_1-C_6) alkyl; and
 20 wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^7 is hydrogen, phenyl or (C_1-C_6) alkyl;

or R^6 and R^7 , together with the carbon to which they are
 25 attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^8 and R^9 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, hydroxy- $(C_1-$
 30 $C_6)$ alkyl, (C_1-C_6) alkoxy- (C_1-C_6) alkyl, (C_1-C_6) alkylamino, di- (C_1-C_6) alkylamino, (C_1-C_6) alkoxy,

(C_1-C_6) alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)- (C_1-C_6) alkyl,
 35 (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-C(=O)- (C_1-C_6) alkyl-O-,
 40 (C_1-C_6) alkyl-C(=O)-, (C_1-C_6) alkyl-C(=O)- (C_1-C_6) alkyl-, and the radicals set forth in the definition of R^6 ;
 45

R^{10} is $NHCR^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6 , R^8 and R^9 ;



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maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

5 The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or
10 combinations thereof.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

Preferred compounds of the formula I are those wherein
15 R¹, R⁴, R⁵ and R⁷ are phenyl, R² is hydrogen, R³ is phenyl optionally substituted with chlorine, fluorine, (C₁-C₆) alkyl optionally substituted with from one to three fluorine atoms or (C₁-C₆) alkoxy optionally substituted with from one to three fluorine atoms, m is 0 and n is 3 or 4.

20 Specific preferred compounds of the formula I are:

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine;

(2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

25 (2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine;

(2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

30 2-(diphenylmethyl)-N-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine;

35 (2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine;

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- 3-(2-methoxy-5-trifluoromethoxybenzyl) amino-2-phenylhomopiperidine;
- 2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl) aminopyrrolidine;
- 5 2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl) aminohomopiperidine;
- 3-[2,5-bis-(2,2,2-trifluoroethoxy) benzyl] amino-2-phenylpiperidine;
- 2-phenyl-3-(3-trifluoromethoxybenzyl) aminopiperidine;
- 10 2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl) aminopiperidine;
- 1-(5,6-difluorohexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl) amino-2-phenylpiperidine;
- 1-(6-hydroxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl) amino-2-phenylpiperidine;
- 15 3-phenyl-4-(2-methoxy-5-trifluoromethoxybenzyl) amino-2-azabicyclo[3.3.0]octane;
- 4-benzhydryl-5-(2-methoxy-5-trifluoromethoxybenzyl) amino-3-azabicyclo[4.1.0]heptane;
- 20 4-(2-methoxy-5-trifluoromethoxybenzyl) amino-3-phenyl-2-azabicyclo[4.4.0]decane;
- 2-phenyl-3-(2-methoxy-5-trifluoromethoxybenzyl) aminoquinuclidine;
- 8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.0^{4,9}]decan-7-amine;
- 25 9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-10-azatricyclo[4.4.1.0^{5,10}]undecan-8-amine;
- 9-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-3-thia-10-azatricyclo[4.4.1.0^{5,10}]undecan-8-amine;
- 30 8-benzhydryl-N-(2-methoxy-5-trifluoromethoxybenzyl)-9-azatricyclo[4.3.1.0^{4,9}]decan-7-amine;
- 5,6-pentamethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl) aminoquinuclidine;
- 5,6-trimethylene-2-benzhydryl-3-(2-methoxy-5-trifluoromethoxybenzyl) aminoquinuclidine;
- 35 9-benzhydryl-N-((2-methoxy-5-trifluoromethoxyphenyl)-methyl)-3-oxa-10-azatricyclo[4.4.1.0^{5,10}]undecan-3-amine;



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I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of
5 treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, allergies such as eczema
10 and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis, reflex sympathetic dystrophy such
15 as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to
20 immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in
25 treating or preventing such condition.

The present invention also relates to a pharmaceutical composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of the formula I, or a
30 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal
35 a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

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The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a

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compounds of the formula I are the tritium and C^{14} isotopes thereof.

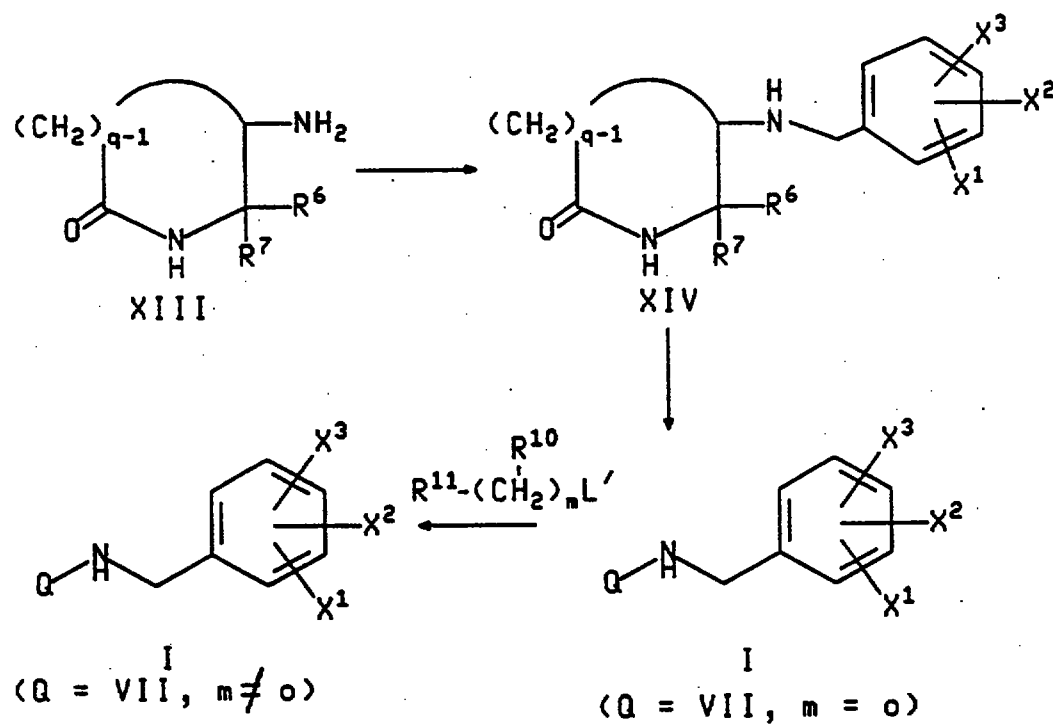
Detailed Description of the Invention

The compounds of the formula I may be prepared as
5 described in the following reaction schemes and discussion.
Unless otherwise indicated, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 ,
 R^{10} , R^{11} , R^{12} , R^{13} , X, Z, Q, Y, m, n, o, p, q, x, y, and z in
the reaction schemes and discussion that follow are defined
as above.

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Scheme 2

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Compounds of the formula I may be prepared by the methods illustrated in schemes 1 and 2.

Referring to scheme 1, compounds of the formula X may be subjected to hydrolytic removal of the methoxybenzyl group using a strong mineral acid such as hydrochloric, hydrobromic or hydroiodic acid, at a temperature from about room temperature to about the reflux temperature of the acid. Preferably, the reaction is conducted in hydrobromic acid at the reflux temperature. This reaction, which yields the corresponding compounds of formula XI, is usually carried out for a period of about 2 hours.

For those compounds of the formula X wherein Q is a group of the formula VII or VIII, it is preferable to remove the methoxybenzyl group by treating them with hydrogen in the presence of a metal containing catalyst such as platinum or palladium. Generally, this reaction is conducted in a reaction inert solvent such as acetic acid or a lower alcohol, at a temperature from about 0°C to about 50°C. (These compounds may also, alternatively, be treated with a dissolving metal such as lithium or sodium in ammonia at a temperature from about -30°C to about -78°C, or with a formate salt in the presence of palladium or with cyclohexane in the presence of palladium). Preferably, such compounds are treated with hydrogen in the presence of palladium on carbon in a mixture of methanol/ethanol in water or methanol/ethanol containing hydrochloric acid at a temperature of about 25°C.

The resulting compounds of the formula XI may be converted to the corresponding compounds of the formula I by reaction with the appropriate compound of the formula XII (as depicted in scheme 1). This reaction is typically carried out in the presence of a reducing agent such as sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, hydrogen and a metal catalyst, zinc and hydrochloric acid, borane dimethylsulfide or formic acid at a temperature from about -60°C to about 50°C. Suitable reaction inert solvents for this reaction include lower

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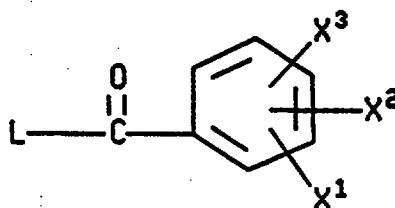


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wherein L is a leaving group (e.g., chloro, bromo, iodo, tosylate or mesylate). This reaction is generally carried out in a reaction inert solvent such as dichloromethane or THF, preferably dichloromethane, at a temperature from about 5 0°C to about 60°C, preferably at about 25°C.

Compounds of the formula XI may also be converted to the corresponding compounds of the formula I by reacting them with the appropriate compound of the formula

10



15 wherein L is defined as above or is imidazole, and then reducing the resulting amide. This reaction is typically carried out in an inert solvent such as THF or dichloromethane at a temperature from about -20°C to about 60°C, preferably in dichloromethane at about 0°C. Reduction 20 of the resulting amide is accomplished by treatment with a reducing agent such as borane dimethylsulfide complex, lithium aluminum hydride or diisobutylaluminum hydride in an inert solvent such as ethyl ether or THF. The reaction temperature may range from about 0°C to about the reflux 25 temperature of the solvent. Preferably, the reduction is accomplished using borane dimethylsulfide complex in THF at about 60°C.

When Q is a group of the formula II, the starting 30 materials of the formula X may be prepared as described in United States Patent Application Serial No. 566,338, filed July 20, 1990 and assigned to Pfizer Inc. This application is incorporated herein in its entirety.

When Q is a group of the formula III, the starting 35 materials of the formula X may be prepared as described in United States Patent Application Serial No. 532,525, filed June 1, 1990 and the PCT patent application claiming

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50°C. Methanol is the preferred solvent and about 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be from about 4 to about 5.

Reduction of the compound of formula XIV yields a
5 compound of the formula I wherein Q is a group of the formula VII and m is zero. Suitable reducing agents include borane dimethylsulfide in THF, lithium aluminum hydride, borane in THF and sodium borohydride-titanium (IV) chloride. Best results are obtained by using borane dimethylsulfide in
10 THF. The reaction may be carried out at temperatures from about room temperature to about 150°C, and is preferably carried out at the reflux temperature of the solvent.

The compounds of formula I so formed may be converted to a compound of the formula I wherein Q is a group of the
15 formula VII and m is other than zero having the same stereochemistry by reacting them with the appropriate compound of the formula $R^{10}-(CH_2)_m-L'$, wherein L' is halo, mesylate or tosylate and wherein one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced by a
20 carbon-carbon double bond or a carbon-carbon triple bond, and wherein one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^{11} . This reaction is typically carried out in the presence of a base such as triethylamine or potassium t-butoxide, in a polar solvent such as methylene
25 chloride or dichloroethane, and at a temperature from about room temperature to about 150°C. Preferably, the reaction is carried out at the reflux temperature in methylene chloride in the presence of triethylamine.

The starting materials of the formula XIII may be
30 prepared as described in United States Patent Application Serial No. 619,361, filed November 28 1990 and assigned to Pfizer Inc. This application is incorporated herein in its entirety.

Scheme 3 illustrates an alternate method of making
35 compounds of the formula I wherein Q is a group of the formula VIII.

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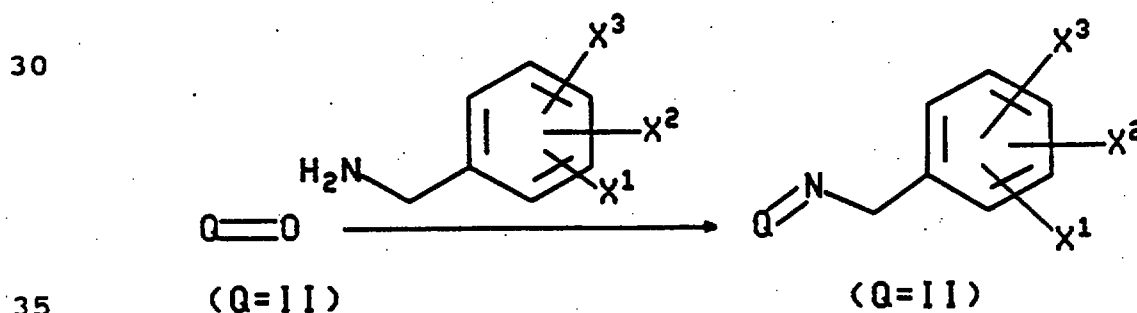
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(e.g., 10% palladium on charcoal). Usually, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room temperature to about 150°C for about 0.5 to about 24 hours. Preferably, the reaction is conducted in ethanol at room temperature for about 3 to about 24 hours.

The compounds of the formula I prepared by the foregoing procedure may be converted into compounds that are identical but for the fact that m is not equal to zero using the procedure described above for preparing compounds of the formula I wherein Q is a group of the formula VII and m is not equal to zero.

The starting materials of the formula XV may be prepared as described in United States Patent application Serial No. 590,423, filed September 28, 1990 and assigned to Pfizer Inc. This application is incorporated herein in its entirety.

Compounds of Formula I wherein Q is a group of the formula II and there is a double bond between Q and the adjacent nitrogen are prepared as shown below by condensation of Q=O (Q of formula II) with the appropriate benzylamine. The condensation is typically carried out in a nonhydroxylic solvent such as benzene, toluene or THF using an acid such as methanesulfonic acid or p-toluenesulfonic acid at a temperature from about 20°C to the reflux temperature of the solvent. Preferably, the reaction is carried out using camphorsulfonic acid in toluene at reflux.



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Those compounds of the formula I which are also acidic in nature, e.g., where R¹ is carboxyphenyl, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of formula I and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the treatment and prevention of a wide variety of clinical conditions the treatment or prevention of which are effected or facilitated by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, gastroesophageal reflux disease, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and



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carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water,



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of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty-minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of bacitracin, 4 µg/ml of leupeptin, 2 µg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100 µl of the test compound made up to a concentration of 1 µM, followed by the addition of 100 µl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 µl of the tissue preparation produced as described above. The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC₅₀ values are calculated by using standard statistical methods.

The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders may be determined by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs. Such a study may be carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs with

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B. 2-(Diphenylmethyl)-N-((2-difluoromethoxy)-phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine

To a 25 mL round-bottomed flask equipped with a nitrogen inlet were added 500 mg (1.71 mmol) 2-
5 diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine (prepared according to the method of Warawa, et al., J. Med. Chem., 17, 497 (1974)), 8.5 mL methanol, 383 mg (2.23 mmol) 2-(difluoromethoxy)-benzaldehyde, and 216 mg (3.42 mmol) sodium cyanoborohydride. The reaction was stirred at room
10 temperature for 30 hours, partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated. To remove the last traces of unreacted amine, the mixture was treated with sodium triacetoxyborohydride in acetic acid at room
15 temperature for 16 hours, then worked up with aqueous sodium hydroxide and methylene chloride. The residue was crystallized from isopropanol to afford a white solid, m.p. 144-147°C, 206 mg (27%).

^1H NMR (δ , CDCl_3): 1.27 (m, 1H), 1.4-1.8 (m, 2H), 1.90
20 (m, 1H), 2.05 (m, 1H), 2.63 (m, 1H), 2.78 (m, 2H), 2.88 (m, 1H), 3.19 (m, 1H), 3.45 (AB_q , $J_{\text{AB}}=13.5$, $\Delta\nu=105.5$, 2H), 3.72 (dd, $J=8$, 12, 1H), 4.43 (d, $J=12$, 1H), 6.31 (t, $J=7.4$ (H-F), 1H), 6.55 and 7.0-7.4 (m, 14H).

^{13}C -NMR (CDCl_3): 20.0, 24.9, 25.4, 42.0, 45.8, 49.4,
25 49.5, 55.0, 61.8, 116.3, 119.0, 125.4, 126.0, 126.5, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 128.6, 129.1, 129.2,
- 130.0, 131.6, 143.2, 145.2, 149.3.

IR (cm^{-1} , neat): 2940 (C-H), 1599 (C=C).

MS (%): 449 (<1, parent+1), 291 (51), 281 (100), 84
30 (66), 49 (69).

Anal. Calc'd for $\text{C}_{28}\text{H}_{30}\text{F}_2\text{N}_2\text{O}$: C 74.98, H 6.74, N 6.25.
Found: C 74.72, H 6.70, N 6.23.



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B. (2S,3S)-2-Phenyl-3-[2-(2,2,2-trifluoroethoxy)-benzyl]aminopiperidine hydrochloride

Under a nitrogen atmosphere in a round-bottom flask were placed 112 mg (0.63 mmol) of (2S, 3S)-3-amino-2-phenylpiperidine, 155 mg (0.76 mmol) of the aldehyde prepared in step A above and ca. 2 mL of acetic acid, and the solution was stirred at room temperature for 1 hour. To the system were added 294 mg (1.39 mmol) of sodium triacetoxymethylborohydride in portions, and the mixture was stirred at room temperature overnight. The mixture was concentrated with a rotary evaporator and partitioned between 1M aqueous sodium hydroxide (NaOH) and methylene chloride (CH₂Cl₂). The layers were separated, and the aqueous phase was extracted with three portions of CH₂Cl₂. The combined organic fractions were extracted with three portions of 2N aqueous HCl, the extracts were made basic with 2N aqueous NaOH, and the mixture was extracted with four portions of CH₂Cl₂. These CH₂Cl₂ extracts were dried (Na₂SO₄) and concentrated. The resulting oil was dissolved in ca. 2 mL ethyl acetate and treated with ether saturated with hydrogen chloride (HCl). The resulting white solid (73 mg, m.p. > 275°C) was collected. This material was converted to its free base by partitioning between 1N aqueous NaOH and CH₂Cl₂. The free base (58 mg) was purified by flash column chromatography eluting with chloroform (CHCl₃) followed by 1:19 methanol/CHCl₃ to obtain 32 mg of oil. Conversion of the free base to the corresponding hydrochloride salt as described above afforded 17 mg of the title compound, m.p. > 275°C.

¹H NMR (free base, CDCl₃) δ 1.44 (m, 1H), 1.63 (m, 1H), 1.88 (m, 1H), 2.1 (m, 1H), 2.80 (m, 2H), 3.26 (m, 1H), 3.38 (d, 1H, J=15), 3.66 (d, 1H, J=15), 3.88 (s, 1H), 4.08 (m, 2H), 6.68 (d, 1H, J=6), 6.90 (m, 1H), 6.98 (d, 1H, J=6), 7.16 (m, 1H), 7.26 (m, 5H).

HRMS Calc'd for C₂₀H₂₄F₃N₂O₃ (parent + 1): 365.1835.
Found: 365. 1980.

This Sheet Has Been Replaced



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¹H NMR (CDCl₃) δ 3.94 (s, 3H), 7.00 (d, 1H, J=9), 7.38 (dd, 1H, J=3, 9), 7.66 (d, 1H, J=3), 10.4 (s, 1H). Mass spectrum m/z: 220 (parent).

B. (2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)-
5 amino-2-phenylpiperidine hydrochloride salt

Under a nitrogen atmosphere in a round-bottom flask were placed 525 mg (2.4 mmol) of 2-methoxy-5-trifluoromethoxybenzaldehyde, 350 mg (2.0 mmol) of (2S, 3S)-3-amino-2-phenylpiperidine and 5 mL of acetic acid. The
10 reaction mixture was stirred at room temperature for 3 days and concentrated with a rotary evaporator. The residue was partitioned between 1N aqueous sodium hydroxide and chloroform (CHCl₃) and the mixture was extracted with three portions of chloroform. The combined chloroform extracts
15 were extracted with three portions of 1N aqueous hydrochloric acid. The combined HCl extracts were made basic with concentrated aqueous sodium hydroxide and extracted with four portions of chloroform. The chloroform extracts were dried (Na₂SO₄) and concentrated with a rotary
20 evaporator to obtain 760 mg of an oil. The oil was dissolved in ethyl acetate, and ether saturated with hydrogen chloride (HCl) was added to the solution. The resulting white solid was collected by suction filtration and washed with ether to obtain 600 mg of the title
25 compound, m.p. > 250°C.

¹H NMR (free base, CDCl₃) δ 1.36 (s, 1H), 1.54 (m, 1H), 1.86 (m, 1H), 2.06 (m, 1H), 2.76 (m, 2H), 3.22 (m, 1H), 3.32 (d, 1H, J=15), 3.48 (s, 3H), 3.58 (d, 1H, J=15), 3.85 (d, 1H, J=3), 6.57 (d, 1H, J=9), 6.80 (d, 1H, J=3), 6.92 (dd, 1H, J=3, 9), 7.22 (m, 5H).
30

HRMS Calc'd for C₂₀H₂₃F₃N₂O₂: 380.1711. Found: 380.1704.

Anal. Calc'd for C₂₀H₂₃F₃N₂O₂•2HCl•0.2H₂O: C 52.57, H 5.60, N 6.13. Found: C 52.58, H 5.40, N 5.97.





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EXAMPLE 6(2S,3S)-2-Phenyl-3-(2-trifluoromethoxybenzyl)amino-piperidine hydrochloride salt

Under a nitrogen atmosphere in a round-bottom flask
5 were placed 3.0 mL (23 mmol) of trifluoromethoxybenzene and
25 mL of benzene. The system was cooled in ice/acetone
bath, and 4.1 mL (45 mmol) of α,α -dichloromethylmethyl ether
was added to the stirring solution. To the system was added
6.13 g (46 mmol) of aluminum chloride (AlCl_3) in portions.
10 After this addition was complete, the reaction mixture was
allowed to warm gradually to room temperature and stirred at
room temperature overnight. The reaction mixture was poured
slowly into water and extracted with three portions of
dichloromethane. The combined organic fractions were washed
15 with water, dried (Na_2SO_4) and concentrated with a rotary
evaporator to obtain 3.7 g of oil. This material,
containing a mixture of 4- and 2-
trifluoromethoxybenzaldehyde, was subjected to flash column
chromatography (160 g of silica gel) using 1:49 ethyl
20 acetate/hexanes as the eluant to obtain 500 mg of material
enriched in 2-trifluoromethoxy-benzaldehyde.

Under a nitrogen atmosphere in a round-bottom flask
were placed 155 mg (0.88 mmol) of (2S,3S)-3-amino-2-
phenylpiperidine, the aldehyde obtained above and 2 mL of
25 acetic acid. To the system were added 370 mg (1.8 mmol) of
sodium triacetoxyborohydride and the mixture was stirred at
room temperature overnight. The mixture was concentrated
and the residue was partitioned between 1N aqueous sodium
hydroxide and dichloromethane and extracted with three
30 portions of dichloromethane. The combined organic fractions
were extracted with three portions of 1N HCl. The acid
extracts were made basic with 1N aqueous NaOH and extracted
with three portions of dichloromethane. The dichloromethane
extracts were dried and concentrated to afford 190 mg of
35 oil, which was subjected to flash column chromatography (5
g of silica gel) using 1:9 methanol/chloroform as the eluant
to obtain 95 mg of the free base of the title compound. The



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B. (2S,3S)-3-(2-Hydroxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine Hydrochloride

The title compound was prepared in a manner similar to the compound of Example 4 by replacing 2-methoxy-5-trifluoromethoxybenzaldehyde with 2-hydroxy-5-trifluoromethoxybenzaldehyde.

¹H NMR (free base, CDCl₃) δ 1.60 (m, 3H), 2.04 (m, 1H), 2.76 (m, 1H), 2.88 (m, 1H), 3.18 (m, 1H), 3.42 (s, 2H), 3.90 (m, 1H), 6.52 (m, 1H), 6.64 (d, 1H, J=9), 6.89 (m, 1H), 7.30 (m, 5H).

HRMS calc'd for C₁₉H₂₁F₃N₂O₂: 366.1545. Found: 366.1562.

Anal. calc'd for C₁₉H₂₁F₃N₂O₂•2HCl•1/3H₂O: C, 51.25; H, 4.90; N, 6.29. Found: C, 51.30; H, 4.75; N, 6.22.

EXAMPLE 8

15 (2S,3S)-3-(5-Chloro-2-(2,2,2-trifluoroethoxy)benzyl)-amino-2-phenylpiperidine Hydrochloride

A. 5-Chloro-2-(2,2,2-trifluoroethoxy)benzaldehyde

Under a nitrogen atmosphere, in a round-bottom flask were placed 880 mg (22 mmol) of 60% sodium hydride (NaH) and 12 ml of N,N-dimethylformamide. To the system were added 2.9 ml (4 g, 40 mmol) of 2,2,2-trifluoroethanol via syringe over a period of 15 minutes and the mixture was stirred at room temperature for 20 minutes. To the system were added 1.72 g (10 mmol) of 2,5-dichlorobenzonitrile, and the mixture was heated at 90°C for three days. The mixture was cooled to room temperature, poured into 50 ml of 2M aqueous HCl and extracted with three portions of ether. The combined organic fractions were dried (Na₂SO₄) and concentrated to afford 2.5 g of a solid. The crude material was purified by flash column chromatography using 1:49 ethyl acetate/hexanes as the eluant to obtain 1.4 g of 5-chloro-2-(2,2,2-trifluoroethoxy)benzonitrile as a white solid.

M.p. 61-62°C.

Under a nitrogen atmosphere, in a round-bottom flask equipped with a reflux condenser were placed 400 mg (1.7 mmol) of the above nitrile and 10 ml of formic acid. To the system were added ca. 500 mg of Raney nickel and the

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Anal. calc'd for $C_{19}H_{21}F_3N_2O \cdot 2HCl$: C, 53.91; H, 5.48; N, 6.62. Found: C, 53.84; H, 5.07; N, 6.59.

The title compounds of Examples 10-23 and 26 were prepared in a manner similar to the procedure described in Example 4, by replacing 2-methoxy-5-trifluoromethoxybenzaldehyde with the appropriate aldehyde. Reaction sequences for the preparation of the requisite aldehydes are set forth in Table 1 below.

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TABLE 1
Preparation of Compounds of the Formula XII

$-C_6H_2X_1X_2X_3$	Starting Material	Reaction* Sequence
2-difluoromethoxy-5-isopropylphenyl	4-isopropylphenol	a, j
2-difluoromethoxy-5-nitrophenyl	2-hydroxy-5-nitrobenzaldehyde	j
5-dimethylamino-2-(2,2,2-trifluoroethoxy)phenyl	2-chloro-5-nitrobenzonitrile	d, l, e
5-acetamido-2-(2,2,2-trifluoroethoxy)phenyl	5-nitro-2-(2,2,2-trifluoroethoxy)-benzonitrile	m, c, e
2-difluoromethoxy-5-ethylphenyl	4-ethyl-methoxybenzene	a, f, j
5-chloro-2-difluoromethoxyphenyl	5-chloro-2-hydroxybenzaldehyde	j
2-trifluoromethoxyphenyl	-	commercial
2-methoxy-5-trifluoromethoxyphenyl	4-trifluoromethoxyphenol	b, a
2-difluoromethoxy-5-methylphenyl	5-methyl-2-methoxybenzaldehyde	f, j





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Anal. calc'd for $C_{23}H_{29}F_3N_2O \cdot 2HCl \cdot 1/3H_2O$: C, 56.92; H, 6.56; N, 5.77. Found: C, 56.99; H, 6.41; N, 6.03.

EXAMPLE 12

(2S,3S)-3-[5-Isopropyl-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine hydrochloride

M.P. > 280°C.

1H NMR (free base; $CDCl_3$) δ 1.12 (m, 6H), 1.4 (m, 1H), 1.62 (m, 1H), 1.82 (m, 1H), 2.08 (m, 1H), 2.76 (m, 3H), 3.22 (m, 1H), 3.30 (d, 1H, J=15), 3.38 (d, 1H, J=15), 3.82 (d, 1H, J=3), 4.02 (m, 2H), 6.56 (d, 1H, J=10), 6.78 (d, 1H, J=3), 6.94 (m, 1H), 7.24 (m, 5H).

HRMS calc'd for $C_{23}H_{30}F_3N_2O$ (M+1): 407.2303. Found: 407.2287.

Anal. calc'd for $C_{23}H_{29}F_3N_2O \cdot 2HCl \cdot 1/2H_2O$: C, 56.55, H, 6.60; N, 5.70. Found: C, 56.17; H, 6.39; N, 5.77.

EXAMPLE 13

(2S,3S)-3-[5-Dimethylamino-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine hydrochloride.

M.P. 250-252°C.

1H NMR (free base; $CDCl_3$) δ 1.40 (m, 1H), 1.60 (m, 1H), 1.86 (m, 1H), 2.10 (m, 1H), 2.82 (m, 8H), 3.22 (m, 1H), 3.34 (d, 1H, J=15), 3.58 (d, 1H, J=15), 3.88 (d, 1H, J=3), 4.00 (m, 2H), 6.42 (d, 1H, J=3), 6.50 (m, 1H), 6.64 (d, 1H, J=10), 7.30 (m, 5H).

HRMS calc'd for $C_{22}H_{28}F_3N_3O$: 407.2178. Found: 407.2179.

EXAMPLE 14

(2S,3S)-3-(2-Difluoromethoxy-5-N,N-dimethylamino-benzyl)amino-2-phenylpiperidine hydrochloride

M.P. 243-245°C (dec).

1H NMR (free base; $CDCl_3$) δ 1.44 (m, 1H), 1.72 (m, 2H), 2.10 (m, 1H), 2.84 (m, 8H), 3.21 (m, 1H), 3.28 (d, 1H, J=15), 3.55 (d, 1H, J=15), 3.88 (d, 1H, J=3), 6.08 (t, 1H, J=72), 6.36 (d, 1H, J=3), 6.46 (dd, 1H, J=3,9), 6.86 (d, 1H, J=9), 7.28 (m, 5H).

HRMS calc'd for $C_{21}H_{27}F_2N_3O$: 375.2122. Found: 375.2138.

Anal. calc'd for $C_{21}H_{27}F_2N_3O \cdot 3HCl \cdot 1/2H_2O$: C, 51.07; H, 6.44; N, 8.51. Found: C, 50.71; H, 6.08; N, 8.28.



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(d, 1H, J=15), 3.54 (d, 1H, J=15), 3.87 (d, 1H, J=2), 6.15 (t, 1H, J=72), 6.94 (m, 3H), 7.26 (m, 5H).

HRMS calc'd for $C_{20}H_{21}F_5N_2O_2$: 416.1523. Found: 416.1501.

Anal. calc'd for $C_{20}H_{21}F_5N_2O_2 \cdot 2HCl \cdot 1/3H_2O$: C, 48.50; H, 4.81; N, 5.65. Found: C, 48.45; H, 4.57; N, 5.66.

EXAMPLE 19

(2S,3S)-3-(2-Ethoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

M.P. > 275°C (dec).

10 1H NMR (free base; $CDCl_3$) δ 1.13 (t, 3H, J=6), 1.38 (m, 1H), 1.70 (m, 2H), 2.06 (m, 1H), 2.74 (m, 2H), 3.22 (m, 1H), 3.30 (d, 1H, J=15), 3.68 (m, 3H), 3.84 (br s, 1H), 6.55 (d, 1H, J=9), 6.79 (br s, 1H), 6.90 (m, 1H), 7.2 (m, 5H).

HRMS calc'd for $C_{21}H_{25}F_3N_2O_2$: 394.1868. Found: 394.1875.

15 Anal. calc'd for $C_{21}H_{25}F_3N_2O_2 \cdot 2HCl$: C, 53.97; H, 5.82; N, 6.00. Found: C, 53.85; H, 5.79; N, 5.95.

EXAMPLE 20

(2S,3S)-3-(2-Difluoromethoxy-5-nitrobenzyl)amino-2-phenylpiperidine hydrochloride

20 1H NMR (free base; $CDCl_3$) δ 1.50 (m, 1H), 1.66 (m, 1H), 1.98 (m, 2H), 2.82 (m, 2H), 3.28 (m, 1H), 3.42 (d, 1H, J=15), 3.64 (d, 1H, J=15), 3.95 (d, 1H, J=2), 6.30 (t, 1H, J=72), 7.08 (d, 1H, J=8), 7.30 (m, 5H), 8.04 (m, 2H).

FAB HRMS calc'd for $C_{19}H_{21}F_2N_3O_3(M+1)$: 378.1629. Found:
25 378.1597.

EXAMPLE 21

(2S,3S)-3-(2-Difluoromethoxy-5-isopropylbenzyl)amino-2-phenylpiperidine hydrochloride

M.P. 245-247°C (dec).

30 1H NMR (free base; $CDCl_3$) δ 1.19 (2d, 6H, J=7), 1.50 (m, 1H), 1.75 (m, 2H), 2.12 (m, 1H), 2.83 (m, 3H), 3.25 (m, 1H), 3.35 (d, 1H, J=14), 3.60 (d, 1H, J=14), 3.90 (d, 1H, J=3), 6.20 (t, 1H, J=75), 6.90 (m, 2H), 7.00 (m, 1H), 7.30 (m, 5H).

35 HRMS calc'd for $C_{22}H_{28}F_2N_2O$: 374.2170. Found: 374.2207.

Anal. calc'd for $C_{22}H_{28}F_2N_2O \cdot 2HCl \cdot 1/3H_2O$: C, 58.28; H, 6.67; N, 6.18. Found: C, 58.17; H, 6.52; N, 6.17.



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In a round bottom flask were placed 20 g (66 mmol) of the product obtained above, 13 g of KOH and 100 mL of ethanol, and the mixture was stirred at room temperature for 90 minutes. To the system was added ca. 35 mL of 33% sulfuric acid/ethanol. The mixture was poured into 150 mL of water and extracted with three 100 mL portions of CHCl₃. The combined extracts were washed with water, dried (Na₂SO₄) and concentrated. The crude material was purified by column chromatography (300 g of silica gel) using ethyl acetate followed by 1:99 methanol/ethyl acetate as the eluant to obtain 5.8 g of cis-5-nitro-6-(3-trifluoromethoxyphenyl)-piperidin-2-one which contained ca. 12% of the corresponding trans-isomer. This material was purified by a second chromatography to obtain 4.6 g of the cis-product.

15 B. cis-5-Amino-6-(3-trifluoromethoxyphenyl)piperidin-2-one

Under a nitrogen atmosphere, in a three-neck round-bottom flask equipped with a thermometer and a mechanical stirrer, were placed this cis-material and a mixture of THF (200 mL), methanol (50 mL) and water (5 mL). To this stirring solution was added aluminum amalgam (prepared by washing 4.1 g of aluminum foil strips with ether and dipping in 2% aqueous HgCl₂ for 30-45 seconds and washing with ether), and the mixture was stirred at room temperature overnight. The mixture was filtered through a pad of diatomaceous earth and the pad washed with THF. The filtrate was concentrated, dissolved in ethyl acetate and treated with 30 mL of ether saturated with HCl. Concentration afforded 3.7 g of crude cis-5-amino-6-(3-trifluoromethoxyphenyl)piperidin-2-one as a waxy solid, m.p. 126-130°C.

C. cis-3-(5-t-Butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine hydrochloride

Under a nitrogen atmosphere, in a round-bottom flask were placed 0.38 g (1.4 mmol) of the amine obtained above, 6 mL of acetic acid and 0.32 g (1.66 mmol) of 5-t-butyl-2-methoxybenzaldehyde. The mixture was stirred for 45

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EXAMPLE 25cis-2-(3,5-Dibromophenyl)-3-(2-methoxy-5-trifluoro-methoxybenzyl)aminopiperidine

The title compound was prepared by a procedure similar to that described in Example 25, with the exception that the nitro substituent of the product of the initial reaction [6-(3,5-dibromophenyl)-5-nitropiperidin-2-one] was converted to an amino group by sequential oxidative cleavage (O_3 , KO^+Bu), oxime formation (H_2NOH) and Raney nickel-catalyzed reduction. The final product can be resolved by treatment with (R)-(-)-mandelic acid in isopropanol. Two recrystallizations of the solid isolated from this procedure (isopropanol), followed by treatment with saturated aqueous sodium bicarbonate affords the (2S,3S)-enantiomer; $[\alpha]_D$ (mandelate salt): +4.11° (MeOH, $c=0.51$).

1H NMR ($CDCl_3$) δ 1.36 (m, 1H), 1.50 (m, 1H), 1.80 (m, 1H), 2.04 (m, 1H), 2.70 (m, 2H), 3.18 (m, 1H), 3.30 (d, 1H, $J=18$), 3.57 (s, 3H), 3.66 (d, 1H, $J=18$), 3.75 (m, 1H), 6.63 (d, 1H, $J=9$), 6.86 (d, 1H, $J=3$), 6.97 (dd, 1H, $J=6, 9$), 7.32 (m, 2H), 7.48 (s, 1H).

EXAMPLE 26(2S-3S)-3-(2-Difluoromethoxy-5-methylbenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 4.

M.P. >275°C.

1H NMR (free-base, $CDCl_3$) δ 1.44 (m, 1H), 1.6 (m, 1H), 1.84 (m, 1H), 2.10 (m, 1H), 2.20 (s, 3H), 2.80 (m, 2H), 3.22 (m, 1H), 3.34 (d, 1H, $J=15$), 3.58 (d, 1H, $J=15$), 3.90 (d, 1H, $J=3$), 6.10 (t, 1H, $J=72$), 6.84 (m, 2H), 7.26 (m, 5H).

HRMS calc'd for $C_{20}H_{24}F_2N_2O$: 347.1929 (M+1). Found: 347.1911.

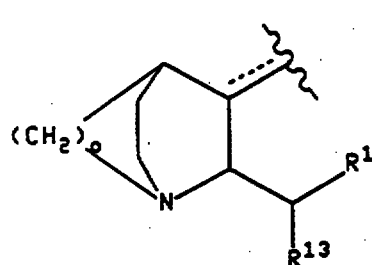
Anal. calc'd for $C_{20}H_{24}F_2N_2O \cdot 2HCl \cdot 0.25H_2O$: C, 56.67; H, 6.30; N, 6.61. Found: C, 56.81; H, 6.16; N, 6.50.

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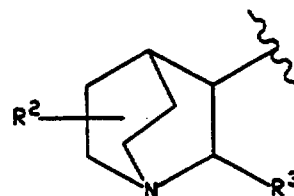


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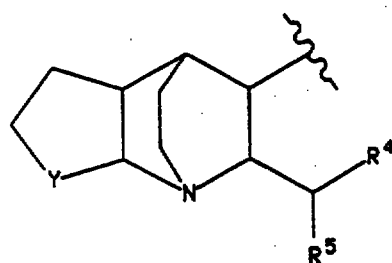
-57-



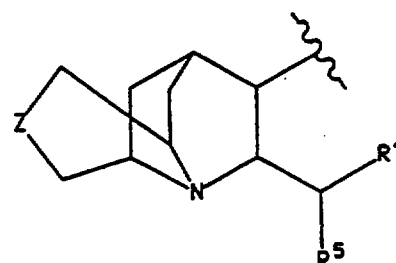
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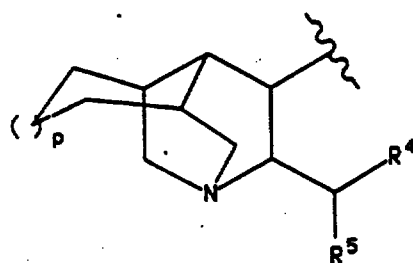
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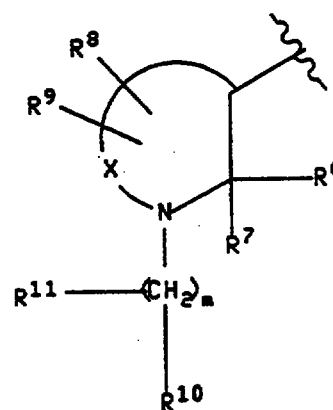
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V

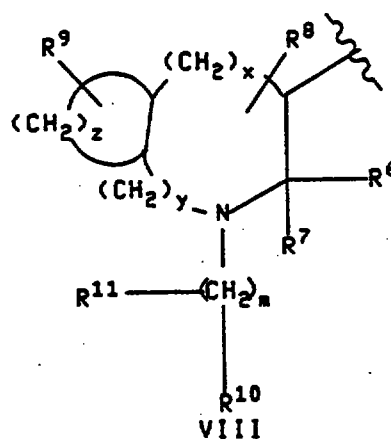


VI



VII

OR



VIII



* C L M S *



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R^5 is thienyl, biphenyl or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

each of the two dashed lines in formula I and the dashed line in formula II represent an optional double bond that may optionally exist when Q is a group of the formula II;

10 X is $(CH_2)_q$, wherein q is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_q$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^8 , and wherein any one of
15 the carbon atoms of said $(CH_2)_q$ may optionally be substituted with R^9 ;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon
20 triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^{11} ;

R^6 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen
25 or sulfur; aryl selected from biphenyl, phenyl, indanyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and
30 the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to
35 three fluorine atoms, amino, hydroxy- (C_1-C_6) alkyl, (C_1-C_6) alkoxy- (C_1-C_6) alkyl,



* C L M S *



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O

R^{10} is $NH\overset{\parallel}{C}R^{12}$, $NHCH_2R^{12}$, $NHSO_2R^{12}$ or one of the radicals set forth in any of the definitions of R^6 , R^8 and R^9 ;

5 R^{11} is oximino ($=NOH$) or one of the radicals set forth in any of the definitions of R^6 , R^8 and R^9 ; and

R^{12} is (C_1-C_6) alkyl, hydrogen, phenyl (C_1-C_6) alkyl or phenyl optionally substituted with (C_1-C_6) alkyl;

with the proviso that (a) when m is 0, R^{11} is absent,
10 (b) neither R^8 , R^9 , R^{10} nor R^{11} can form, together with the carbon to which it is attached, a ring with R^7 , (c) when Q is a group of the formula VIII, R^8 and R^9 cannot be attached to the same carbon atom, (d) when R^8 and R^9 are attached to the same carbon atom, then either each of R^8 and R^9 is
15 independently selected from hydrogen, fluoro, (C_1-C_6) alkyl, hydroxy- (C_1-C_6) alkyl and (C_1-C_6) alkoxy- (C_1-C_6) alkyl, or R^8 and R^9 , together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are
20 attached, (e) the nitrogen of formula I can not be double bonded to both Q and the substituted benzyl group to which it is attached, (f) when Q is a group of the formula VII and q is 2 and either R^8 or R^9 is 5-hydroxy- (C_1-C_6) alkyl or 5- (C_1-C_6) alkoxy- (C_1-C_6) alkyl, then the other of R^8 and R^9 is either
25 5- (C_1-C_6) alkyl or hydrogen; (g) when Q is a group of the formula VII and q is 2, then neither R^8 nor R^9 is 4-hydroxy- (C_1-C_6) alkyl or 4- (C_1-C_6) alkoxy- (C_1-C_6) alkyl, and (h) when neither X^1 , X^2 nor X^3 is a fluorinated alkoxy group, at least one of R^1 , R^3 , R^4 , R^5 , R^6 , R^7 and R^{13} is an aryl group
30 substituted with a fluorinated alkoxy group;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein Q is a group of the formula II wherein o is two or three and each of R^1 and R^{13} is phenyl or substituted phenyl.

35 3. A compound according to claim 1 wherein Q is a group of the formula III, R^2 is hydrogen and R^3 is phenyl or substituted phenyl.





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15. A compound according to claim 1, wherein said compound is (2S,3S)-1-(5,6-dimethoxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine.

16. A compound according to claim 1, wherein said compound is (2S,3S)-2-phenyl-3-(2-trifluoromethoxybenzyl)-aminopiperidine.

17. A compound according to claim 1, wherein said compound is (2S,3S)-3-[5-chloro-2-(2,2,2-trifluoroethoxy)-benzyl]amino-2-phenylpiperidine.

18. A compound according to claim 1, wherein said compound is (2S,3S)-3-(5-tert-butyl-2-trifluoromethoxybenzyl)amino-2-phenylpiperidine.

19. A compound according to claim 1, wherein said compound is 3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine.

20. A compound according to claim 1, wherein said compound is 3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl)piperidine.

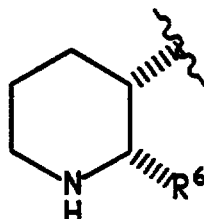
21. A compound according to claim 1, wherein said compound is 3-(2-difluoromethoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine.

22. A compound according to claim 1, wherein X^1 is 5-trifluoromethoxy, X^2 is hydrogen and X^3 is 2-methoxy.

23. A compound according to claim 1 wherein X^1 is 2-trifluoromethoxy and each of X^2 and X^3 is hydrogen.

24. A compound according to claim 1, wherein X^1 is 2-(2,2,2-trifluoroethoxy) and each of X^2 and X^3 is hydrogen.

25. A compound according to claim 1 wherein Q is a group of the formula



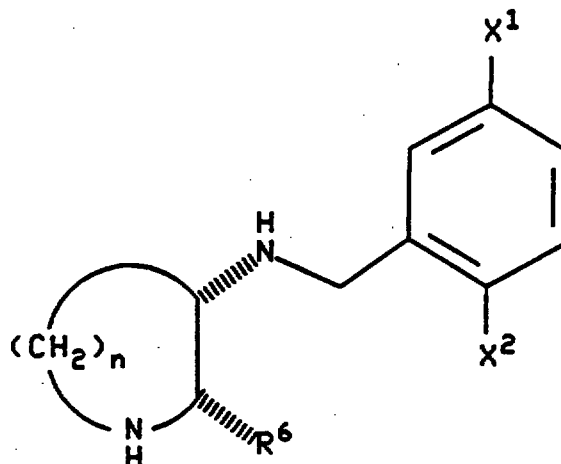
wherein X^1 is 2-trifluoromethoxy, 2-methoxy or 2-(2,2,2-trifluoroethoxy), X^2 is 5-halo, 5-(C₁-C₆) alkyl, or 5-(C₁-C₆)



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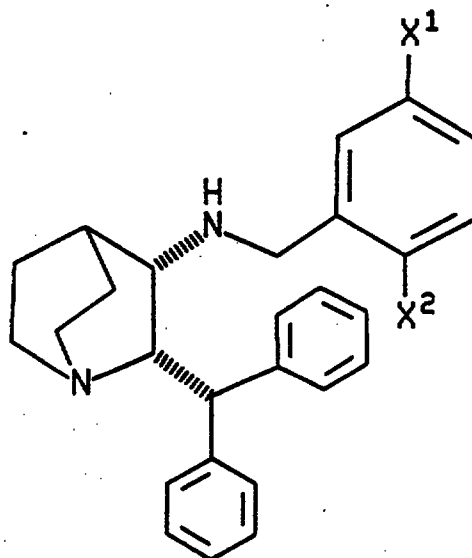


wherein n is an integer from 2 to 4, X^1 is OCF_3 or OCHF_2 , X^2 is $(\text{C}_1\text{-C}_4)$ alkoxy, and R^6 is phenyl optionally substituted with a substituent selected from $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxy, fluorine and chlorine.

29. A compound according to claim 1 having the formula

20

25



wherein X^1 is $(\text{C}_1\text{-C}_4)$ alkyl or hydrogen, X^2 is OCF_3 or OCHF_2 , and one or both of the phenyl moieties of the benzhydryl group may be optionally substituted with a substituent selected from $(\text{C}_1\text{-C}_4)$ alkyl, $(\text{C}_1\text{-C}_4)$ alkoxy, fluorine and chlorine.

35

30. A compound according to claim 1 having the formula





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neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claim 1 effective in preventing or treating such condition
5 and a pharmaceutically acceptable carrier.

35. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases anxiety, colitis, depression or dysthymic disorders, psychosis, pain, gastroesophageal reflux disease, allergies,
10 chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to
15 immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in preventing or treating such condition.

20 36. A pharmaceutical composition for antagonizing the effects of substance P in a mammal, comprising a substance P antagonizing effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

37. A method of antagonizing the effects of substance
25 P in a mammal, comprising administering to said mammal a substance P antagonizing effective amount of a compound according to claim 1.

38. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or
30 prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

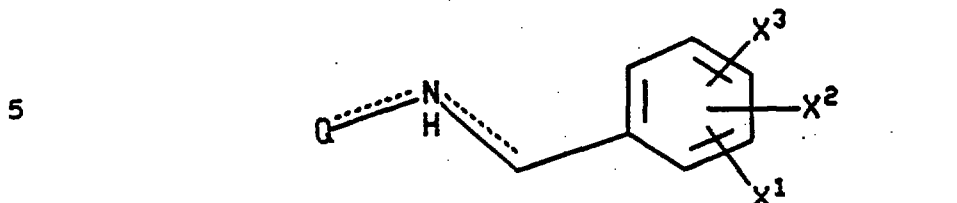
35 39. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated



* C L N S *

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45. A process for preparing a compound having the formula



wherein X^1 is hydrogen, (C_1-C_{10}) alkoxy optionally substituted
10 with from one to three fluorine atoms or (C_1-C_{10}) alkyl
optionally substituted with from one to three fluorine
atoms;

X^2 and X^3 are independently selected from halo,
hydrogen, nitro, (C_1-C_{10}) alkyl optionally substituted with
15 from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally
substituted with from one to three fluorine atoms,
trifluoromethyl, hydroxy, phenyl, cyano, amino, (C_1-C_6) -

20 alkylamino, di- (C_1-C_6) alkylamino, $-\overset{\overset{O}{\parallel}}{C}-NH-(C_1-C_6)alkyl$,

$\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl-NH-(C_1-C_6)alkyl$, hydroxy $(C_1-C_4)alkyl$, $(C_1-$
25

$C_4)alkoxy(C_1-C_4)alkyl$, $-NH\overset{\overset{O}{\parallel}}{C}H$ and $-NH\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$; and
30 Q is a group of the formula

35

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wherein R^1 is a radical selected from furyl, thienyl, pyridyl, indolyl, biphenyl and phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to
 5 three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms, carboxy, benzyloxycarbonyl and (C_1-C_3) alkoxy-carbonyl;

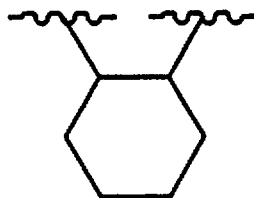
R^{13} is selected from (C_3-C_4) branched alkyl, (C_5-C_6) branched alkenyl, (C_5-C_7) cycloalkyl, and the radicals named
 10 in the definition of R^1 ;

R^2 is hydrogen or (C_1-C_6) alkyl;

R^3 is phenyl, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl or furyl, and R^3 may optionally be substituted with from one to three substituents independently selected from
 15 halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_{10}) alkoxy optionally substituted with from one to three fluorine atoms;

Y is $(CH_2)_1$, wherein 1 is an integer from one to three, or Y is a group of the formula

20



(J)

;

25

Z is oxygen, sulfur, amino, (C_1-C_3) alkylamino or $(CH_2)_n$, wherein n is zero, one or two;

o is two or three;

p is zero or one;

30

R^4 is furyl, thienyl, pyridyl, indolyl, biphenyl, or phenyl optionally substituted with one or two substituents independently selected from halo, (C_1-C_{10}) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_{10}) alkoxy optionally substituted with from one to three
 35 fluorine atoms, carboxy, (C_1-C_3) alkoxy-carbonyl and benzyloxycarbonyl;





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(C_1-C_6) -alkylamino, (C_1-C_6) alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)-
 5 (C_1-C_6) alkyl, (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-C(=O)-
 10 (C_1-C_6) alkyl-O-, (C_1-C_6) alkyl-C(=O)-, (C_1-C_6) alkyl-C(=O)-
 15 (C_1-C_6) alkyl-, di- (C_1-C_6) alkylamino, -C(=O)NH- (C_1-C_6) alkyl, (C_1-C_6) -
 (C_1-C_6) alkyl-C(=O)NH- (C_1-C_6) alkyl, -NHCH(=O) and -NHC(=O)- (C_1-C_6) alkyl; and
 20 wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^7 is hydrogen, phenyl or (C_1-C_6) alkyl;

or R^6 and R^7 , together with the carbon to which they are
 attached, form a saturated carbocyclic ring having from 3 to
 25 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

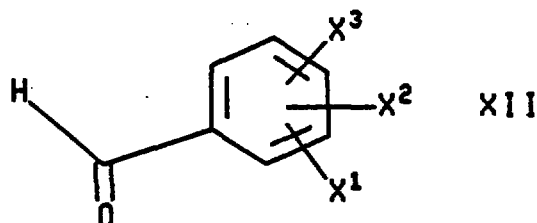
R^8 and R^9 are each independently selected from hydrogen,
 hydroxy, halo, amino, oxo (=O), nitrile, hydroxy- (C_1-C_6) -
 alkyl, (C_1-C_6) alkoxy- (C_1-C_6) alkyl, (C_1-C_6) alkylamino,
 30 di- (C_1-C_6) alkylamino, (C_1-C_6) alkoxy,

(C_1-C_6) alkyl-O-C(=O)-, (C_1-C_6) alkyl-O-C(=O)- (C_1-C_6) alkyl,
 35 (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-C(=O)- (C_1-C_6) alkyl-O-,
 40 (C_1-C_6) alkyl-C(=O)-, (C_1-C_6) alkyl-C(=O)- (C_1-C_6) alkyl-, and the radicals
 set forth in the definition of R^6 ;



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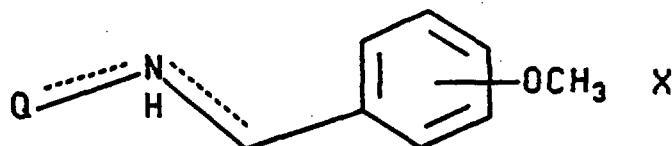
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wherein X^1 , X^2 and X^3 are defined as above, in the presence of a reducing agent.

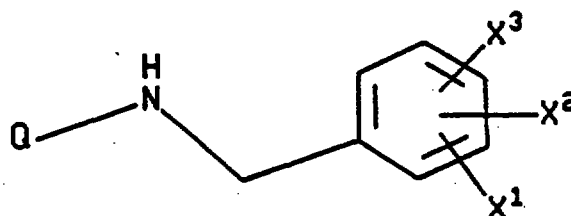
46. A process according to claim 45, wherein said
10 compound of the formula $Q-NH_2$ is obtained by subjecting a compound of the formula



15

wherein Q is defined as in claim 45, to hydrolytic removal of the methoxybenzyl group.

20 47. A process for preparing a compound of the formula



25

wherein Q is a group of the formula VIII, as defined in claim 45, and wherein X^1 , X^2 and X^3 are defined as in claim 45 and m is zero, comprising reacting a compound of the formula

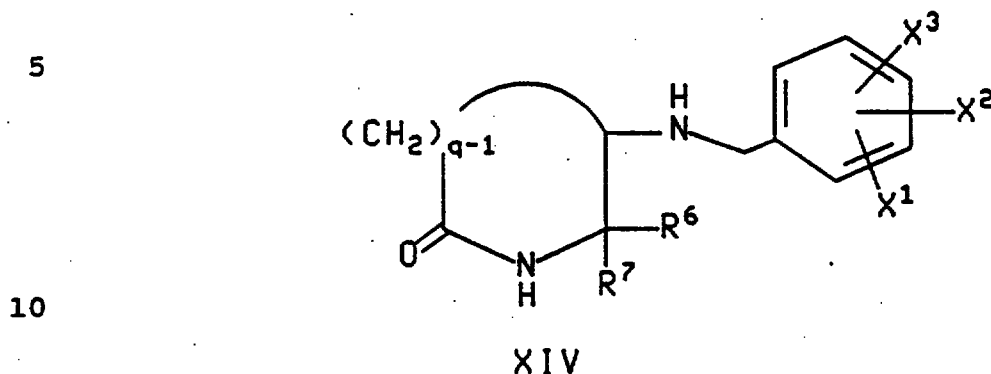
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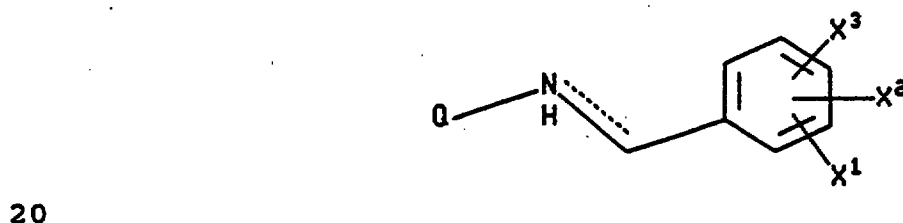
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wherein Q is a group of the formula VII, as defined in claim 45, and wherein X^1 , X^2 , and X^3 are defined as in claim 45, comprising reacting a compound of the formula

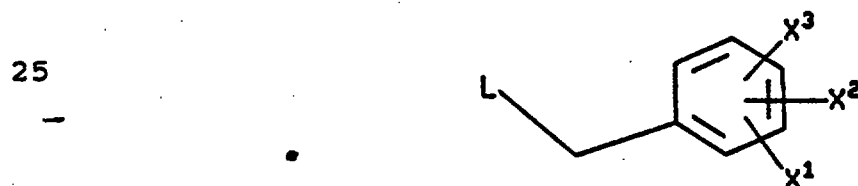


wherein X^1 , X^2 , X^3 , R^6 , R^7 and q are defined as in claim 45, with a reducing agent.

15 50. A process for preparing a compound of the formula



wherein Q, X^1 , X^2 and X^3 are defined as in claim 45, comprising reacting a compound of the formula $Q-NH_2$, wherein Q is defined as in claim 45, with a compound of the formula



wherein L is a leaving group.

30 51. A process for preparing a compound of the formula I, as defined in claim 45, wherein Q is a group of the formula II and there exists a double bond between Q and the adjacent nitrogen, comprising reacting a compound of the formula $Q=O$, wherein Q is defined as above, with the

35 appropriate benzylamine of the formula



* C L M S *