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(54) Title: 5-PHENYL-5,6,7,8-HYDROQUINOLINE TACHYKININ RECEPTOR ANTAGONISTS

(57) Abstract: The present invention is directed to certain 5-phenyl-5,6,7,8-hydroquinoline compounds which are useful as neurokinin-1 (NK-1) receptor antagonists, and inhibitors of tachykinin and in particular substance P. The invention is also concerned with pharmaceutical formulations comprising these compounds as active ingredients and the use of the compounds and their formulations in the treatment of certain disorders, including emesis, urinary incontinence, depression, and anxiety.

TITLE OF THE INVENTION

5-PHENYL-5,6,7,8-HYDROQUINOLINE TACHYKININ RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

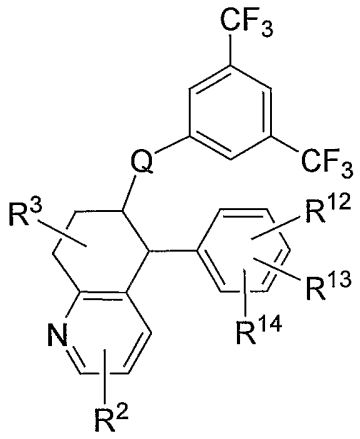
Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The tachykinins are distinguished by a conserved carboxyl-terminal sequence. In addition to substance P, the known mammalian tachykinins include neurokinin A and neurokinin B. The current nomenclature designates the receptors for substance P, neurokinin A, and neurokinin B as neurokinin-1 (NK-1), neurokinin-2 (NK-2), and neurokinin-3 (NK-3), respectively. Tachykinin, and in particular substance P, antagonists are useful in the treatment of of clinical conditions which are characterized by the presence of an excess of tachykinin, in particular substance P, activity, including disorders of the central nervous system, nociception and pain, gastrointestinal disorders, disorders of bladder function and respiratory diseases. Attempts have been made to provide antagonists for the receptors of substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases mentioned above.

SUMMARY OF THE INVENTION

The present invention is directed to certain quinoline compounds which are useful as neurokinin-1 (NK-1) receptor antagonists, and inhibitors of tachykinin and in particular substance P. The invention is also concerned with pharmaceutical formulations comprising these compounds as active ingredients and the use of the compounds and their formulations in the treatment of certain disorders, including emesis, urinary incontinence, depression, and anxiety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

and N-oxides thereof,

wherein:

Q is selected from the group consisting of:

(1) -O-CH_2-,

(2) -O-CH(CH_3)-,

(3) -O-CH(CH_2OH)-,

(4) -O-(CO)-, and

(5) -O-(C=CH_2)-;

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) halo,

(g) -NR^9R^{10}, wherein R^9 and R^{10} are independently selected from:

(I) hydrogen,

(II) C_{1-6} alkyl,

(III) phenyl,

(IV) (C_{1-6} alkyl)-phenyl,
(V) (C_{1-6} alkyl)-hydroxy, and
(VI) (C_{1-6} alkyl)-(C_{1-4} alkoxy),
or where $-NR^9R^{10}$ forms a morpholine, piperidine or quinuclidine ring

(h) $-NR^9-COR^{11}$, wherein R^{11} is independently selected from:
(I) hydrogen,
(II) C_{1-6} alkyl,
(III) phenyl,
(IV) (C_{1-6} alkyl)-phenyl,
(V) (C_{1-6} alkyl)-hydroxy, and
(VI) (C_{1-6} alkyl)-(C_{1-4} alkoxy),

(j) $-NR^9-CO_2R^{11}$,

(k) $-CO-NR^9R^{10}$,

(l) $-COR^{11}$,

(m) $-CO_2R^{11}$,

(3) hydroxy,
(4) C_{1-6}alkoxy,
(5) oxo,
(6) halo,
(7) -CN,
(8) $-CF_3$,
(9) $-NR^9R^{10}$,
(10) $-NR^9-COR^{11}$,
(11) $-NR^9-CO_2R^{11}$,
(12) $-CO-NR^9-COR^{11}$,
(13) $-COR^{11}$,
(14) $-O-(CO)R^{11}$,
(15) $-CO_2R^{11}$,
(16) -imidazolyl, and
(17) -triazolyl;

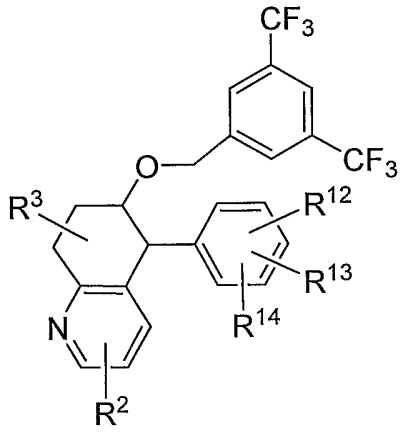
R^{12}, R^{13} and R^{14} are independently selected from the group consisting of:

(1) hydrogen,
(2) halo, and

(3) C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

An embodiment of the present invention includes compounds of the formula Ia:

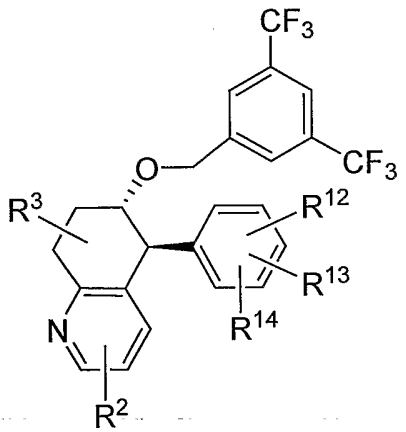


Ia

and N-oxides thereof, wherein R^2, R^3, R^{12}, R^{13} and R^{14} are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

Within this embodiment, the present invention includes compounds of the formula Ia':

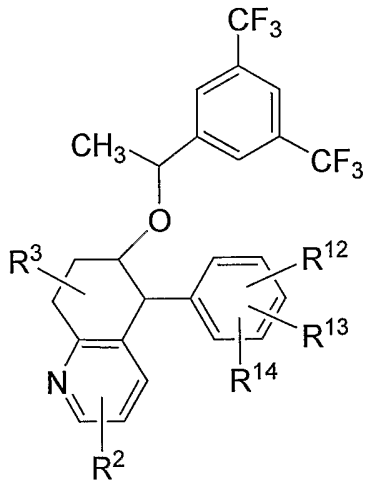


Ia'

and N-oxides thereof, wherein R^2, R^3, R^{12}, R^{13} and R^{14} are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

An embodiment of the present invention includes compounds of the formula Ib:

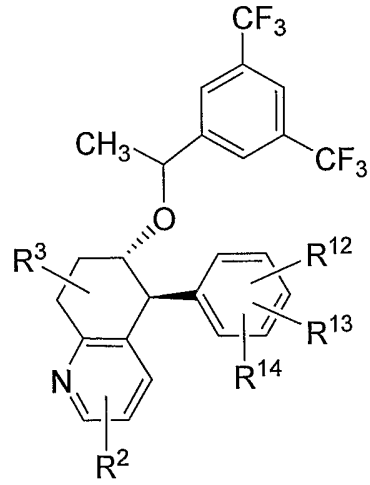


Ib

and N-oxides thereof, wherein R^2, R^3, R^{12}, R^{13} and R^{14} are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

Within this embodiment, the present invention includes compounds of the formula Ib':



Ib'

and N-oxides thereof, wherein R^2, R^3, R^{12}, R^{13} and R^{14} are defined herein;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

An embodiment of the present invention includes compounds wherein R^2 is selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more of the substituents selected from:

(a) morpholinyl,
(b) $-NH_2$,
(c) $-NH(C_{1-6}$ alkyl),
(d) $-N(C_{1-6}$ alkyl)$(C_{1-6}$ alkyl),
(e) hydroxy,
(f) $-CO_2(C_{1-6}$ alkyl),
(g) $-NHCO(C_{1-6}$ alkyl),
(h) $-CO_2H$, and
(i) triazolyl,

(3) hydroxy,
(4) halo,
(5) $-CO_2(C_{1-6}$ alkyl),
(6) $-CO_2H$, and
(7) -CN.

Within this embodiment, the present invention includes compounds wherein R^2 is hydrogen.

Within this embodiment, the present invention includes compounds wherein R^2 is methyl.

An embodiment of the present invention includes compounds wherein R^3 is hydrogen.

An embodiment of the present invention includes compounds wherein R^3 is fluoro.

An embodiment of the present invention includes compounds wherein R^{12} is fluoro, R^{13} is hydrogen or methyl, and R^{14} is hydrogen.

An embodiment of the present invention includes compounds wherein R^{12} is 4-fluoro, R^{13} is hydrogen and R^{14} is hydrogen.

An embodiment of the present invention includes compounds wherein R^{12} is 4-fluoro, R^{13} is 2-methyl and R^{14} is hydrogen..

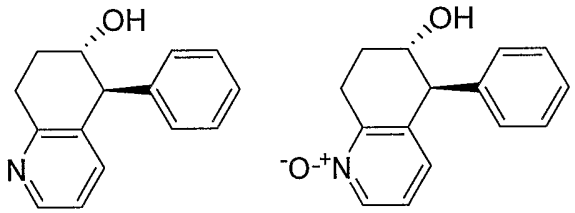
An embodiment of the present invention includes compounds wherein the compound is present as an N-oxide on the pyridyl ring.

Specific embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the Examples herein and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of

the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without preferred stereochemistry. The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

There are several acceptable methods of naming the compounds discussed herein.



A B

For example, the above compound A can be named as "(5*S*,6*S*)-5-phenyl-5,6,7,8-tetrahydroquinolin-6-ol." The above compound B can be named as "(5*S*,6*S*)-5-phenyl-5,6,7,8-tetrahydroquinolin-6-ol 1-oxide" or alternatively "(5*S*,6*S*)-5-phenyl-5,6,7,8-tetrahydroquinolin-6-ol N-oxide." The core structures A and B may be generally referred to as tetrahydroquinoline, or hydroquinoline and tetrahydroquinoline 1-oxide, tetrahydroquinoline N-oxide, hydroquinoline 1-oxide or hydroquinoline N-oxide compounds, respectively.

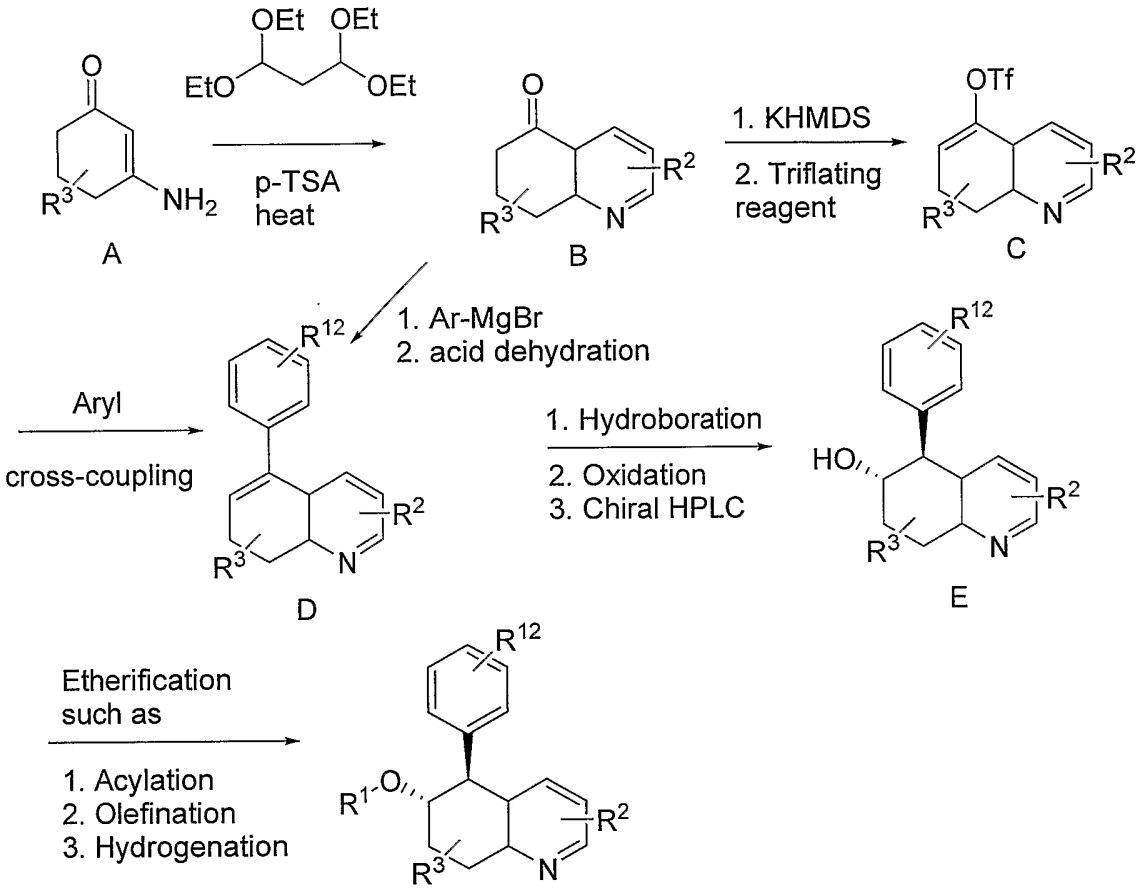
As appreciated by those of skill in the art, halo or halogen as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C_{1-6}, as in C_{1-6}alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_{1-6}alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are benzenesulfonic, citric, hydrobromic, hydrochloric, maleic, fumaric, succinic and tartaric acids. It will be understood that, as used herein, references to the compounds of the present invention are meant to also include the pharmaceutically acceptable salts.

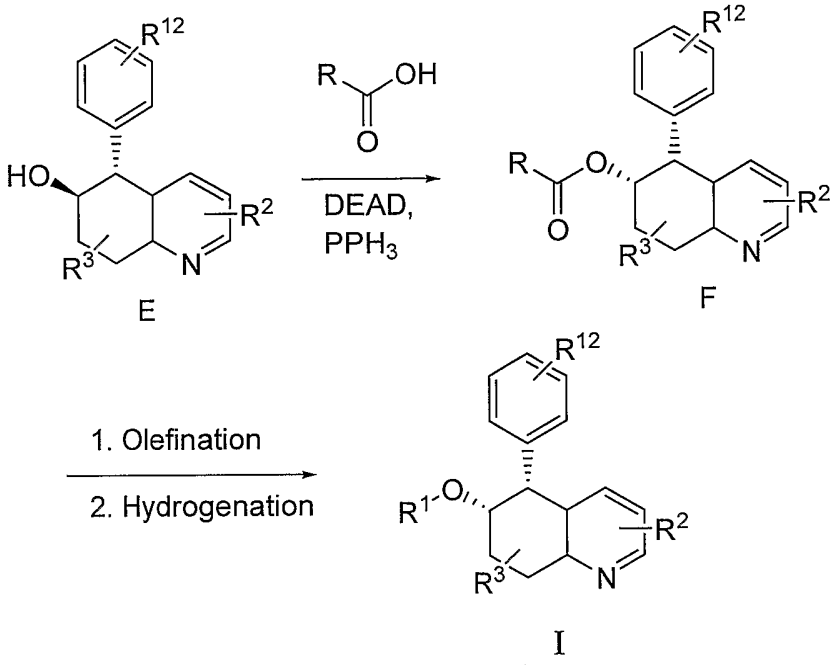
Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

General reaction sequences to prepare the compounds of the present invention are outlined in the schemes below. The substituted 3-aminocyclohex-2-enones A may react with 1,1,3,3-tetarethoxypropane in the presence of an acid catalyst and heating in appropriate solvent to provide the 5-

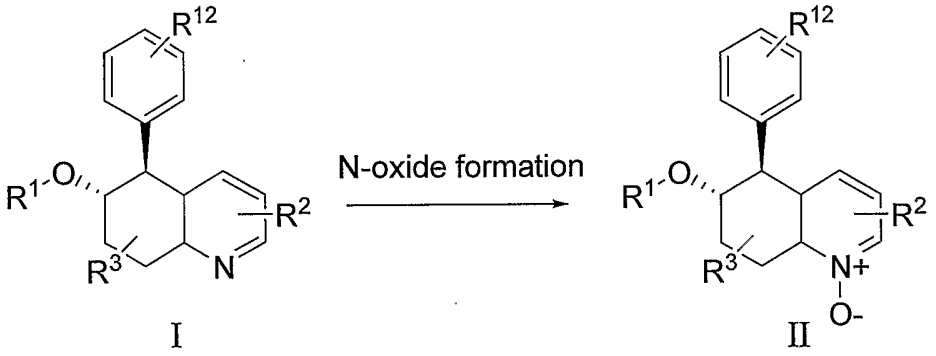
oxoquinolines B. The 5-oxo quinolines may be converted to the 5-vinyl triflate (trifluormethanesulfonate) C by reaction with a strong base such as potassium bistrimethylsilylamide (KHMDS) followed by quenching with a triflating reagent such as trifluoromethanesulfonic anhydride or 2-[N,N-bis(trifluoromethylsulfonylamino)]-5-chloropyridine. Resulting triflates C may be reacted with aryl metal reagents such as aryl boronic acids or aryl stannanes to provide the 5-aryl-7,8-dihydroquinoline intermediates D. Alternatively, the heteroaryl ketones B may be reacted with aryl metal reagents such as aryllithium, cerium or magnesium reagents and the resulting crude aryl alcohols dehydrated in the presence of acid such as methanesulfonic acid to provide the intermediates of general structure D. The olefin of intermediates D may be hydroborated with reagents known to the skilled in the art and the intermediate organoboranes oxidized with hydrogen peroxide and base to provide the racemic *trans*-7-hydroxy-8-arylquinoline intermediates. These racemic intermediates may be further functionalized without separation of enantiomers by the reactions outlined below. The alcohols may be separated however, by chiral HPLC, to provide single enantiomers of the *trans*-6-hydroxy-5-arylquinoline intermediates E (only one enantiomer shown). The 6-hydroxyl group may be converted to ethers by a variety of reactions know to those skilled in the art such as "Williamson" ether synthesis, reaction with a trichloroacetimidate under acid conditions or by the sequence of reactions shown in the scheme. The alcohol may acylated to form an ester. The resulting ester may be reacted with titanium olefination reagents such as the "Tebbe" reagent. The intermediate enol ether may then be hydrogenated to provide the 6-ether compounds of the present invention of the generalized structure I (wherein R^1 is the Q-((3,5-bis-trifluoro-methyl)phenyl) group and wherein R^{12} includes R^{12}, R^{13} and R^{14}).



The *cis* 5-aryl-6-hydroxyquinoline compounds may be prepared as outlined below. The chiral (or racemic) *trans* alcohols E may be reacted with an appropriate acid in the presences of an azodicarboxylate such diethylazodicarboxylate (DEAD) and a phosphine such as triphenylphosphine to provide the resulting ester F with inversion of stereochemistry. The intermediate ester F may be olefinated with the "Tebbe" reagent to provide the enol ether. Hydrogenation of the enolether will provide compounds of the general structure I of cis relative stereochemistry at the 5- and 6-positions.



The compounds of the present invention of general structure I may be converted to N-oxide compounds of generalized structure II of the present invention by reaction with a variety of oxidizing reagents such as a peracid such as m-CPBA in either the *cis*- or *trans*-series (only *trans* shown).



These generalized compounds I and II may serve as intermediates and may be further substituted or functionalized by reactions know to those skilled in the art and described in detail in the experimentals contained herein.

The compounds of the present invention are useful in the prevention and treatment of a wide variety of clinical conditions which are characterized by the presence of an excess of tachykinin, in particular substance P, activity. Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for

example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central

nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis. Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neurogangliobiastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia, frequent urination and urinary incontinence, including the prevention or treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. The compounds of

the present invention are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of the present invention are particularly useful in the prevention or treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. For example, the compounds of the present invention are of use optionally in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate or highly emetogenic cancer chemotherapy, including high-dose cisplatin. Most especially, the compounds of the present invention are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents, including those routinely used in cancer chemotherapy, and emesis induced by other pharmacological agents, for example, rolipram. Examples of such chemotherapeutic agents include alkylating agents, for example, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics. Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine, streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172]. A further aspect of the present invention comprises the use of a compound of the present invention for achieving a chronobiologic (circadian rhythm phase-shifting) effect and alleviating circadian rhythm disorders in a mammal. The present invention is further directed to the use of a compound of the present invention for blocking the phase-shifting effects of light in a mammal.

The present invention is further directed to the use of a compound of the present invention or a pharmaceutically acceptable salt thereof, for enhancing or improving sleep quality as well as preventing and treating sleep disorders and sleep disturbances in a mammal. In particular, the present invention provides a method for enhancing or improving sleep quality by increasing sleep efficiency and augmenting sleep maintenance. In addition, the present invention provides a method for preventing and treating sleep disorders and sleep disturbances in a mammal which comprising the administration of a compound of the present invention or a pharmaceutically acceptable salt thereof. The present invention is useful for the treatment of sleep disorders, including Disorders of Initiating and Maintaining Sleep

(insomnias) ("DIMS") which can arise from psychophysiological causes, as a consequence of psychiatric disorders (particularly related to anxiety), from drugs and alcohol use and abuse (particularly during withdrawal stages), childhood onset DIMS, nocturnal myoclonus, fibromyalgia, muscle pain, sleep apnea and restless legs and non specific REM disturbances as seen in ageing.

The particularly preferred embodiments of the instant invention are the treatment of emesis, urinary incontinence, depression or anxiety by administration of the compounds of the present invention to a subject (human or companion animal) in need of such treatment.

The present invention is directed to a method for the manufacture of a medicament for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a mammal comprising combining a compound of the present invention with a pharmaceutical carrier or diluent. The present invention is further directed to a method for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins in a mammal comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of the present invention or a composition comprising a compound of the present invention. As used herein, the term "treatment" or "to treat" refers to the administration of the compounds of the present invention to reduce, ameliorate, or eliminate either the symptoms or underlying cause of the noted disease conditions, in a subject (human or animal) that suffers from that condition or displays clinical indicators thereof. The term "prevention" or "to prevent" refers to the administration of the compounds of the present invention to reduce, ameliorate, or eliminate the risk or likelihood of occurrence of the noted disease conditions, in a subject (human or animal) susceptible or predisposed to that condition.

The compounds of this invention are useful for antagonizing tachykinins, in particular substance P in the treatment of gastrointestinal disorders, central nervous system disorders, inflammatory diseases, pain or migraine and asthma in a mammal in need of such treatment. This activity can be demonstrated by the following assays.

Receptor Expression in COS: To express the cloned human neurokinin-1 receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 ul of transfection buffer (135 mM NaCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 2.4 mM K_2HPO_4, 0.6 mM KH_2PO_4, 10 mM glucose, 10 mM HEPES pH 7.4) at 260 V and 950 uF using the IBI GENEZAPPER (IBI, New Haven, CT). The

cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY) in 5% CO_2 at 37°C for three days before the assay.

Stable Expression in CHO: To establish a stable cell line expressing the cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of 20 ug of the plasmid DNA into CHO cells was achieved by electroporation in 800 ul of transfection buffer suplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 uF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10 % fetal calf serum, 100 U/ml pennicilin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS), 0.7 mg/ml G418 (GIBCO)] in 5% CO_2 at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

Assay Protocol using COS or CHO: The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ^{125}I-substance P (^{125}I-SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavallette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl, 0.04 mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200 ul of the cell suspension would give rise to about 10,000 cpm of specific ^{125}I-SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200 ul of cells were added to a tube containing 20 ul of 1.5 to 2.5 nM of ^{125}I-SP and 20 ul of unlabeled substance P or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1 % polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM $MnCl_2$, 150 mM NaCl) three times and its radioactivity was determined by gamma counter. The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP_3. CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 0.025 uCi/ml of ^{3}H-myoinositol by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 0.1 mM with or without the test compound, and incubation is continued at 37°C for 15 min. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 min of incubation at 37°C, the media is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and extracted with $CHCl_3$/methanol (1:1). The aqueous phase is applied to a 1 ml

Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid. The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid and quantitated by beta counter. In particular, the intrinsic tachykinin receptor antagonist activities of the compounds of the present invention may be demonstrated by these assays. The compounds of the following examples have activity in the aforementioned assays in the range of 0.05 nM to 10 μM. The activity of the present compounds may also be demonstrated by the assay disclosed by Lei, et al., British J. Pharmacol., 105, 261-262 (1992).

According to a further or alternative aspect, the present invention provides a compound of the present invention for use as a composition that may be administered to a subject in need of a reduction of the amount of tachykinin or substance P in their body.

The term "composition" as used herein is intended to encompass a product comprising specified ingredients in predetermined amounts or proportions, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. This term in relation to pharmaceutical compositions is intended to encompass a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid;

binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives.

Pharmaceutical compositions of the present compounds may be in the form of a sterile injectable aqueous or oleagenous suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may also be formulated for administered by inhalation. The compounds of the present invention may also be administered by a transdermal patch by methods known in the art.

The compositions containing compounds of the present invention may be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. The term "unit dosage form" is taken to mean a single dose wherein all active and inactive ingredients are combined in a suitable system, such that the patient or person adminstering the drug to the patient can open a single container or package with the entire dose contained therein, and does not have to mix any components together from two or more containers or packages. Typical examples of unit dosage forms are tablets or capsules for oral administration, single dose vials for injection, or suppositories for rectal administration. This list of unit dosage forms is not intended to be limiting in any way, but merely to represent typical examples in the pharmacy arts of unit dosage forms. The compositions containing compounds of the present invention may also be presented as a kit, whereby two or more components, which may be active or inactive ingredients, carriers, diluents, and the like, are provided with instructions for preparation of the actual dosage form by the patient or person administering the drug to the patient. Such kits may be provided with all necessary materials and ingredients contained therein, or they may contain instructions for using or making materials or components that must be obtained independently by the patient or person administering the drug to the patient.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment in a form that can be introduced into that individuals body in a therapeutically useful form and therapeutically effective amount, including, but not limited to: oral dosage forms, such as tablets, capsules, syrups, suspensions, and the like; injectable dosage forms, such as IV, IM, or IP, and the like; transdermal dosage forms, including creams, jellies, powders, or patches; buccal dosage forms; inhalation powders, sprays, suspensions, and the like; and rectal suppositories. The term "therapeutically effective amount" refers to a sufficient quantity of the compounds of the present invention, in a suitable composition, and in a suitable dosage form to treat or prevent the noted disease conditions.

The compounds of the present invention may be administered in combination with another substance that has a complimentary effect to the tachykinin and substance P inhibitors of the present invention. Accordingly, in the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially $5HT_3$ receptor antagonists, such as ondansetron, granisetron, tropisetron, palenosetron and zatisetron, a corticosteroid, such as dexamethasone, or $GABA_B$ receptor agonists, such as baclofen. Likewise, for the prevention or treatment of migraine a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or $5HT_1$ agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents, such as norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), α-adrenoreceptor antagonists, atypical anti-depressants, benzodiazepines, $5\text{-}HT_{1A}$ agonists or antagonists, especially $5\text{-}HT_{1A}$ partial agonists, corticotropin releasing factor (CRF) antagonists, and pharmaceutically acceptable salts thereof. For the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction with other anorectic agents. It will be appreciated that for the treatment or prevention of pain or nociception or inflammatory diseases, a compound of the present invention may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an

NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent.

It will be appreciated that when using any combination described herein, both the compound of the present invention and the other active agent(s) will be administered to a patient, within a reasonable period of time. The compounds may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms which are taken simultaneously. The term "combination" also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, one active component may be administered as a tablet and then, within a reasonable period of time, the second active component may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a "fast dissolving oral formulation" is meant, an oral delivery form which when placed on the tongue of a patient, dissolves within about 10 seconds. By "reasonable period of time" is meant a time period that is not in excess of about 1 hour. That is, for example, if the first active component is provided as a tablet, then within one hour, the second active component should be administered, either in the same type of dosage form, or another dosage form which provides effective delivery of the medicament.

The compounds of this invention may be administered to patients (humans and animals, including companion animals, such as dogs, cats and horses) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level of the compounds of the present invention, or pharmaceutically acceptable salts thereof, is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day. The dosage range will generally be about 0.5 to 1000 mg per patient per day, which may be administered in single or multiple doses. Preferably, the dosage range will be about 0.5 mg to 500 mg per patient per day; more preferably about 0.5 mg to 200 mg per patient per day; and even more preferably about 5 mg to 50 mg per patient per day. Specific dosages of the compounds of the present invention, or pharmaceutically acceptable salts thereof, for administration include 1 mg, 5 mg, 10 mg, 30 mg, 100 mg, and 500 mg. Pharmaceutical compositions of the present invention may be provided in a formulation comprising about 0.5 mg to 1000 mg active ingredient; more preferably comprising

about 0.5 mg to 500 mg active ingredient; or 0.5 mg to 250 mg active ingredient; or 1 mg to 100 mg active ingredient. Specific pharmaceutical compositions for treatment or prevention of excess tachykinins comprise about 1 mg, 5 mg, 10 mg, 30 mg, 100 mg, and 500 mg of active ingredient.

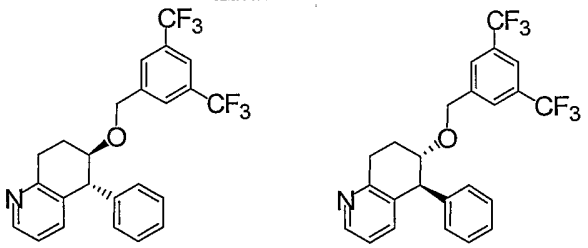
Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein. All NMR spectra were obtained on instrumentation at a field strength of 400 or 500 MHz in either $CDCl_3$ or CD_3OD with reported chemical shifts as δ. The HPLC/MS analyses were obtained using an Agilent 1100 Series HPLC in combination with a Waters Micromass ZQ mass spectrometer. The HPLC RP column was a Waters Exterra MS-C18 (5 μm) 3.0x50 mm column eluting with a 10–100% acetonitrile/water (both containing 0.05% TFA) gradient over 3.75 min with a run time of 5.50 min. UV monitoring was done at 210 nM. Retention times (Rt) are reported in minutes based on the MS data. The reported m/e value was usually the parent molecular ion, except when the 100% ion was not the parent ion as also indicated. Preparative chiral HPLC was done with the indicated Chiracel 25x250 mm columns eluting at 9 mL per min with the indicated percent isopropanol/heptanes solvent mixture. Retention times (Rt) are reported in minutes based on the UV chromatogram monitored at 210 or 254 nm.

PREPARATION OF INTERMEDIATE

2-methyl-7,8-dihydroquinolin-5(6*H*)-one

To a solution of 6.2 g (56.1 mmol) 3-aminocyclohex-2-en-1-one and 4.82g (67.3mmol) 3-butyne-1-one in dry DMF under nitrogen atmosphere was heated at 100 °C for 2 hr then at 150 °C for 4 hr. The volatiles were removed under vacuum to give an oil. This material was purified by column chromatography on silica gel eluting with hexanes/EtOAc (1/1) then EtOAc (100%) afford the title compound. ^{1}H-NMR ($CDCl_3$): δ: . LC-MS: $(MH)^+$.

EXAMPLE 1



Racemic-(5,6-*trans*)-6-{[3,5-bis(trifluoromethyl)benzyl]oxy}-5-phenyl-5,6,7,8-tetrahydroquinoline

Step A: 7,8-Dihydroquinolin-5(6*H*)-one

To a solution of 10.12 g (0.14 mmol) 3-aminocyclohex-2-en-1-one and 22 mL 1,1,3,3-tetraethoxypropane in 40 mL dry DMF under nitrogen atmosphere was added 0.5 g (cat.) p-toluenesulfonic acid. The reaction mixture was heated at 140 °C for 18 hr. The volatiles were removed under vacuum and the residue distilled under vacuum to give an oil. This material was further purified by column chromatography on silica gel eluting with hexanes/EtOAc (3/1) then EtOAc (100%) afford 1.75 g of the title compound. LC-MS: $(MH)^+$: 148.2.

Step B: 7,8-Dihydroquinolin-5-yl trifluoromethanesulfonate

To a solution of 1.75 g (12 mmol) of 7,8-dihydroquinolin-5(6*H*)-one (step A) in dry THF, under nitrogen atmosphere at -78 °C was added dropwise 30.53 mL (1.3 equiv.) of a 0.5 M solution of KHMDS in THF. The reaction mixture was stirred at -78 °C to RT over in THF, 2-[N,N-bis(trifluoromethylsulfonylamino)]-5-chloropyridine (5.1 g, 13 mmol) in 30 mL THF was added dropwise. The resulting solution was stirred at RT for 16 hr. and the solvent was removed under vacuum. The residue was dissolved in $CHCl_3$, and the resulting mixture was washed with 2 N aq. NaOH, dried over $MgSO_4$ drying agent, filtered and the solvent evaporated under vacuum. This material was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95/5) to afford 2.25 g of the title compound that was used for the next step without purification.

Step C: 5-Phenyl-7,8-dihydroquinoline

A mixture of 2.25 g (8.1 mmol) 7,8-dihydroquinolin-5-yl trifluoromethanesulfonate (step B), 1 .95g (16.0 mmol) phenylboronic acid, 0.7 g LiCl, 0.2 g (cat.) tetrakis(triphenylphosphine)Pd(0), 7 mL Na_2CO_3 (2 M), 2 mL ethanol in solvent toluene under nitrogen atmosphere was heated at reflux for 16 hr. The reaction mixture was cooled to RT, diluted with EtOAc, transferred to a separatory funnel and the organic layer separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexanes/EtOAc (1/1) to afford 1.1 g of the title compound. 8.35 (1 H, m), 7.21-7.42 (m, 6 H), 7.07 (1 H, m), 6.15 (1 H, m), 3.12 (2 H, t), 2.37 (2 H, m). MS $(MH)^+$: 208.1.

Step D: Racemic (*trans*)-5-phenyl-5,6,7,8-tetrahydroquinolin-6-ol

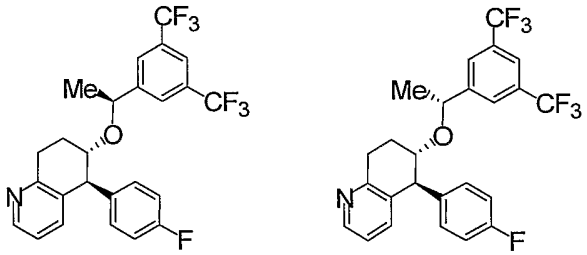
A solution of 10 mL (84.0 mmol) of 2,3-dimethyl-2-butene in 100 mL dry THF under nitrogen atmosphere at 0 °C was treated with 42 mL of a 2.0 M solution of borane-dimethylsulfide complex in THF. The resulting mixture was stirred at 0 °C for 1 hr at which time was added a solution of

1.1g (5.3 mmol) 5-phenyl-7,8-dihydroquinoline (step C) in THF. The resulting mixture was heated at 60 °C for 16 hr. The reaction mixture was cooled in an ice bath and carefully treated with a mixture of 20 mL of 35% aq. H_2O_2 and 40 mL 5 N aq. NaOH. After stirring vigorously for 16 hr, the reaction mixture was extracted with EtOAc, dried over drying agent and the solvent evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexanes/EtOH (1/1) then EtOAc/MeOH (9/1) to afford 0.41 g of the title compound. ^{1}H-NMR ($CDCl_3$): δ 8,40 (1 H, d, J = 5), 7.38-7.30 (3 H, m), 7.18 (2 H, d), 7.12 (1 H, d), 7.00 (1 H, m). MS $(MH)^+$: 226.1.

Step E: Racemic-(5,6-*trans*)-6-{[3,5-Bis(trifluoromethyl)benzyl]oxy}-5-phenyl-5,6,7,8-tetrahydroquinoline

In a round bottom flask was added 0.1 g (excess) 60% sodium hydride dispersion in dry DMF under nitrogen atmosphere at 0 °C. To the resulting mixture was added a solution of 0.05 g (0.25 mmol) racemic (*trans*)-5-phenyl-5,6,7,8-tetrahydroquinolin-6-ol (step D) in 5 mL dry DMF. The resulting mixture was stirred at 0 °C for 0.5 hr then 0.35 g (1.1 mmol) of 3,5-bis(trifluoromethyl)benzylbromide was added by syringe. The reaction mixture was stirred 0 °C for 0.5 hr and quenched by the addition water. The reaction mixture was extracted with EtOAc, dried over drying agent and the solvent evaporated under vacuum. The residue was purified by prep TLC on silica gel eluting with hexanes/EtOAc (1/1) to afford 0.067 g of the title compound. MS $(MH)^+$: 451.9.

EXAMPLE 2



Racemic-(5,6-*trans*)-6-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

Step A: 5-(4-Fluorophenyl)-7,8-dihydroquinoline

The title compound was prepared from 7,8-dihydroquinolin-5-yl trifluoromethanesulfonate (Example 1, step B), and 4-fluorophenylboronic acid according to the procedure for Example 1, step C. ^{1}H-NMR ($CDCl_3$): δ 8.37 (1 H, d), 7.29 (3 H, m), 7.10 (3 H, m), 6.15 (1 H, t), 3.11 (2 H, t), 2.60 (2 H, m). MS $(MH)^+$: 226.1.

Step B: Racemic (*trans*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol

The title compound was prepared from 5-(4-fluorophenyl)-7,8-dihydroquinoline (step A) according to the procedure of Example 1, step D. ^{1}H-NMR ($CDCl_3$): δ 8.43 (1 H, d), 7.18-7.0 (6 H, m), 4.11 (1 H, m), 4.02 (1 H, d), 3.21 (2 H, m), 2.31 (1 H, m), 2.05 (1 H, m). MS $(MH)^+$: 244.1.

Step C: Racemic 5,6-(*trans*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl 3,5-bis(trifluoromethyl)benzoate

To a solution of 0.41g (1.65 mmol) of the intermediate of step B in dry methylene chloride under nitrogen atmosphere at RT was added 0.58 g (1.1 equiv.) of 3,5-bis(trifluoromethyl)benzoic acid, 0.28 g DMAP and 0.45 g (1.4 equiv) EDC. The resulting mixture was stirred at RT for 2 hr then transferred to a separatory funnel, washed with sat. aq. $NaHCO_3$, aq. $KHSO_4$, and brine. The combined organic layers dried over magnesium sulfate, filtered and the solvent evaporated under vacuum to afford 0.41 g of the crude title compounds which were used without further purification. ^{1}H-NMR ($CDCl_3$): δ 8.52 (1 H, d), 8.38 (2 H, s), 8.05 (1 H, s), 7.23-7.00 (6 H, m), 5.50 (1 H, m), 4.47 (1 H, d), 3.30 (2 H, m), 2.38 (1 H, m), 2.22 (1 H, m). MS $(MH)^+$: 484.3.

Step D: Racemic 5,6-(*trans*)-6-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

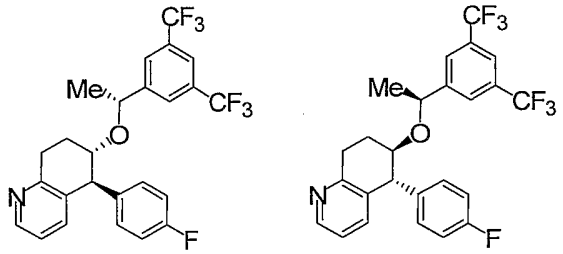
To a solution of 0.41 g (0.76 mmol) of the intermediate of step C in dry THF under nitrogen atmosphere at 0 °C was added 2 mL (1.2 equiv) of a 0.5 M solution of Tebbe reagent in toluene. The resulting mixture was stirred at 0 °C for 0.5 hr then carefully quenched by the dropwise addition of 0.5 mL water, then 0.5 mL of 5.0 N aq. NaOH. The resulting suspension was diluted with ethyl acetate, stirred at RT for 0.5 hr and the solids filtered. The resulting filtrate stirred with 0.5 mL of 5.0 N aq. NaOH for 16 hr and the solids filtered through a pad of filter aid. The solvent was evaporated under vacuum to give the crude title compounds which were used without further purification. ^{1}H-NMR ($CDCl_3$): δ: 8.50 (1 H, d), 7.82 (2 H, s), 7.79 (1 H, s), 7.22-7.02 (6 H, m), 4.89 (1 H, d), 4.60 (1 H, m), 4.51 (1 H, d), 4.45 (1 H, d), 3.25 (2 H, m), 2.46 (1 H, m), 2.20 (1 H, m).

Step E: Racemic-(5,6-*trans*)-6-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

The intermediate of step D was hydrogenated at 50 PSI hydrogen over 10% by weight of 10%Pd-C in ethanol for 16 hr at RT. The catalyst was filtered and the solvent of the filtrate was evaporated under vacuum to give the crude title compounds which were purified by prep TLC eluting with EtOAc/hexanes (1/3) to afford the two diastereomers. The less polar isomer, ^{1}H-NMR ($CDCl_3$): δ 8.41 (1 H, m), 7.80 (1 H, s), 7.73 (2 H, s), 7.17-7.00 (6 H, m), 4.42 (1 H, m), 4.18 (1 H, d), 3.70 (1 H, m),

3.17 (1 H, m), 3.02 (1 H, m), 2.05 (1 H, m), 1.90 (1 H, m), 1.18 (3 H, d). MS $(MH)^+$ 484.2. The more polar isomer, ^{1}H-NMR ($CDCl_3$): δ 8.40 (1 H, m), 7.73 (1 H, s), 7.48 (2 H, s), 7.07 (1 H, m), 7.00 (1 H, m), 6.88 (4 H, m), 4.67 (1 H, m), 4.08 (1 H, d), 3.62 (1 H, m), 3.20 (1 H, m), 3.08 (1 H, m), 2.28 (1 H, m), 2.02 (1 H, m), 1.45 (3 H, d). MS $(MH)^+$: 482.2.

EXAMPLE 3

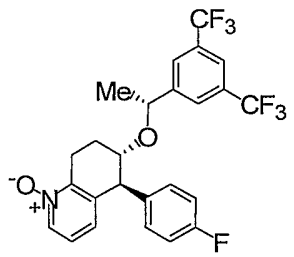


(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline and (5*R*,6*R*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

Step A: (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline and (5*R*,6*R*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

Starting with 0.2 g of the racemic mixture of the more polar diastereomer of intermediate of Example 2, step E was separated by chiral HPLC using CHIRACEL OD column eluting with hexanes/EtOH (94/6) to afford the first eluting isomer (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (R_t = 10.91 min) and the second eluting isomer (5*R*,6*R*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (R_t = 21.9 min).

EXAMPLE 4



(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

Step A: (5*S*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol and (5*R*,6*R*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol

11.6g of racemic (*trans*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol (Example 2, step B) was separated by preparative chromatography on CHIRACEL OD column eluting with isooctane/IPA (8/2) to afford 6.06 g of the first eluting enantiomer (5*S*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol and 5.55 g of the second eluting isomer (5*R*,6*R*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol. LC-MS: $(MH)^+$: 500.4.

Step B: (5*S*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl 3,5-bis(trifluoromethyl)benzoate

The title compound was prepared from the first eluting enantiomer (5*S*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol of step A according to the procedure of Example 2, step C.

Step C: (5*S*,6*S*)-6-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

The title compound was prepared from the intermediate of step B according to the procedure of Example 2, step D.

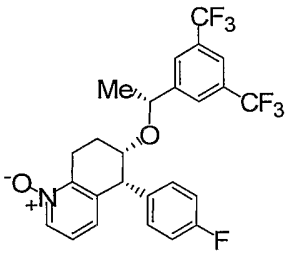
Step D: (5*S*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline and (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

The title compounds were prepared from the intermediate of step C according to the procedure of Example 2, step E. The less polar (the major) isomer, (5*S*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline, ^{1}H-NMR ($CDCl_3$): δ 8.41 (1 H, m), 7.80 (1 H, s), 7.73 (2 H, s), 7.17-7.00 (6 H, m), 4.42 (1 H, m), 4.18 (1 H, d), 3.70 (1 H, m), 3.17 (1 H, m), 3.02 (1 H, m), 2.05 (1 H, m), 1.90 (1 H, m), 1.18 (3 H, d). LC-MS: $(MH)^+$ 484.3. he more polar (minor) isomer, (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline ^{1}H-NMR ($CDCl_3$): δ 8.40 (1 H, m), 7.73 (1 H, s), 7.48 (2 H, s), 7.07 (1 H, m), 7.00 (1 H, m), 6.88 (4 H, m), 4.67 (1 H, m), 4.08 (1 H, d), 3.62 (1 H, m), 3.20 (1 H, m), 3.08 (1 H, m), 2.28 (1 H, m), 2.02 (1 H, m), 1.45 (3 H, d). LC-MS: $(MH)^+$ 484.3.

Step E: (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

To a solution of 2.32 g (4.8 mmol) of (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (more polar isomer of step D) in dry $CHCl_3$ was added 3 equiv. of m-CPBA. The resulting mixture was stirred at RT for 3 hr then 2 N aq. NaOH was added. The resulting mixture was stirred at RT for 1 hr then was extracted with methylene chloride. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum. The crude product was crystallized from hexanes/EtOAc to give the title compound. ^{1}H-NMR ($CDCl_3$): δ : ppm. 7.68 (1 H, s), 7.23 (2 H, s), 7.02 (2 H, m), 6.87 (2 H, m), 4.45 (1 H, m), 3.27 (1 H,), 2.78-2.65 (2 H, m), 2.57 (2 H, m), 2.45-2.30 (3 H, m), 2.23-2.12 (2 H, m), 1.98 (1 H, m), 1.83-1.68 (2 H, m), 1.30 (3 H, d) MS $(MH)^+$: 500.3.

EXAMPLE 5



(5*R*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

Step A: (5*R*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl 3,5-bis(trifluoromethyl)benzoate

To a solution of 1.5 g (6.17 mmol) of the second eluting isomer (5*R*,6*R*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol (Example 4, step A) in dry THF under nitrogen atmosphere at RT was added 1.91 g (1.2 equiv) 3,5-bis(trifluoromethyl)benzoic acid, 1.94 g (1.2 equiv) triphenylphosphine then, dropwise by syringe, 1.4 mL (1.3 equiv) of DEAD. The reaction mixture was stirred at RT for 16 hr and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel eluting with EtOAc to afford 4.0 g of the title compound. MS $(MH)^+$: 484.1.

Step B: (5*R*,6*S*)-6-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

The title compound was prepared from the intermediate of step A according to the procedure of Example 2, step D. ^{1}H-NMR ($CDCl_3$): δ 8.53 (1 H, d), 7.80 (2 H, s), 7.34 (1 H, d), 7.14-6.97 (6 H, m), 4.97 (1 H, d), 4.81 (1 H, m), 4.64 (1 H, d), 4.53 (1 H, d), 3.31 (1 H, m), 3.17 (1 H, m), 2.34 (1 H, m), 2.21 (1 H, m).

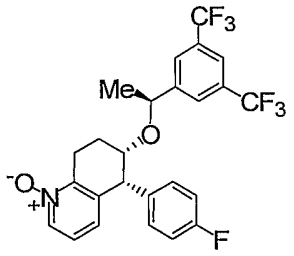
Step C: (5*R*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline and (5*R*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

The title compounds were prepared from the intermediate of step B according to the procedure of Example 2, step E. The less polar (the major) isomer, (5*R*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline, ^{1}H-NMR ($CDCl_3$): δ 8.48 (1 H, d), 7.81 (1 H, s), 7.71 (2 H, s), 7.30-7.09 (6 H, m), 4.49 (1 H, q), 4.40 (1 H, d), 3.94 (1 H, m), 3.25 (1 H, m), 2.97 (1 H, m), 1.92 (2 H, m), 1.30 (3 H, d). LC-MS: $(MH)^+$: 484.3. The more polar (minor) isomer, (5*R*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline. ^{1}H-NMR ($CDCl_3$): δ: 8.47 (1 H, d), 7.74 (1 H, s), 7.38 (2 H, s), 7.22-7.00 (6 H, m), 4.73 (1 H, q), 4.21 (1 H, m), 3.75 (1 H, m), 3.34 (1 H, m), 3.04 (1 H, m), 2.42 (1 H, m), 2.02 (1 H, m), 1.42 (3 H, d). MS $(MH)^+$: 484.3.

Step D: (5*R*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

The title compound was prepared from (5*R*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (more polar isomer of step C) according to the procedure of Example 4, step E. ^{1}H-NMR ($CDCl_3$): δ 7.68 (1 H, s), 7.23 (2 H, s), 7.02 (2 H, m), 6.87 (2 H, m), 4.45 (1 H, m), 3.27 (1 H,), 2.78-2.65 (2 H, m), 2.57 (2 H, m), 2.45-2.30 (3 H, m), 2.23-2.12 (2 H, m), 1.98 (1 H, m), 1.83-1.68 (2 H, m), 1.30 (3 H, d) MS: $(MH)^+$: 500.3.

EXAMPLE 6

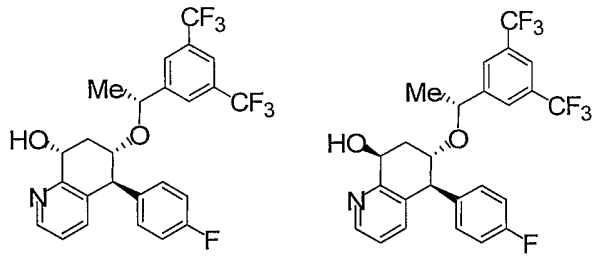


(5*R*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

Step A: (5*R*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

The title compound was prepared from (5*R*,6*S*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (less polar isomer of Example 5, step C) according to the procedure of Example 4, step E. MS $(MH)^+$: 500.1.

EXAMPLE 7



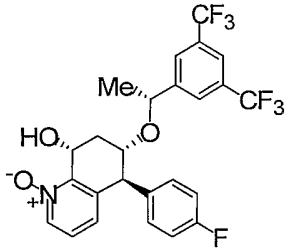
(5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol and(5*S*,6*S*,8*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol

Step A: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol and(5*S*,6*S*,8*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)-phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol

To a solution of 20 mg (0.04 mmol) (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide (Example 4, Step E) in 2.5 mL dry DMF under nitrogen atmosphere at RT was added 1 mL trifluoroacetic anhydride. The reaction mixture was stirred at RT for 2 days and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed with 2 N aq. NaOH. The organic layer was dried over drying agent, filtered and the solvent removed under vacuum. The residue was purified by prep TLC eluting with hexanes/EtOAc (1/1) to afford a less polar diastereomer and a more polar diastereomer. Less polar diastereomer: ^{1}H-NMR ($CDCl_3$): δ 8.48 (1 H, bs), 7.70 (1 H, s), 7.53 (2 H, s), 7.10 (2 H, bs), 6.92 (4 H, bs), 4.85 (1 H, m), 4.68 (1 H, m), 4.35 (1 H, bs), 4.13 (1 H, d), 3.70 (1 H, t), 2.87 (1 H, d). MS $(MH)^+$: 500.4. More polar diastereomer: ^{1}H-NMR ($CDCl_3$): δ 8.50 (1 H, bs), 7.87 (1 H, s), 7.58 (2 H, s),

7.15 (2 H, s), 6.92 (4 H, m), 5.10 (1 H, m), 4.72 (1 H, m), 4.12 (1 H, d), 3.98 (1 H, bs), 3.90 (1 H, bs), 2.37 (1 H, m), 2.15 (1 H, m), 1.48 (3 H, d). MS $(MH)^+$: 500.5.

EXAMPLE 8



(5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol 1-oxide

Step A: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-yl acetate

To a solution of 90 mg (0.18 mmol) of (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol (less polar diastereomer, Example 7) in dry CH_2Cl_2 under nitrogen atmosphere at RT was added 0.075mL (0.54 mmol) TEA, 0.040 mL (3 equiv) acetyl chloride and a catalytic amount of DMAP. The resulting mixture was stirred at RT for 16 hr then quenched with sat. aq. $NaHCO_3$. The resulting mixture was stirred at RT for 15 min then was extracted with chloroform. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum. The residue was purified by prep TLC eluting with hexanes/EtOAc (1/1) to afford the title compound. MS $(MH)^+$: 551.8.

Step B: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-8-yl acetate

The title compound was prepared from the intermediate of step A according to the procedure of Example 4, Step E. MS $(MH)^+$: 557.9.

Step C: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol 1-oxide

To a solution of (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-8-yl acetate (intermediate step B) in THF/water (5/1) was added 5 equiv of LiOH. The resulting mixture was stirred at RT for 3 hr. The solvent was removed

under vacuum and the residue was purified by reverse phase HPLC to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.37 (1 H, bs), 7.85 (1 H, s), 7.43 (2 H, s), 7.33 (1 H, m), 7.07 (1 H, d), 6.95 (2 H, t), 6.85 (2 H, m), 5.37 (1 H, bs), 4.65 (1 H, q), 4.19 (1 H, d), 3.65 (1 H, m), 2.68 (1 H, m), 2.22 (1 H, m), 1.43 (3 H, d). MS $(MH)^+$: 516.0.

An alternate procedure is as follows:

Step A: (5*S*,6*S*)-8-benzylidene-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

A mixture of 10 g (20.7 mmol) of (5*R*,6*R*)-6-{(1*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (more polar diastereomer (Example 2) 1.5 g benzaldehyde and 3.0 g of acetic anhydride was heated at 170 °C for 16 hr. The resulting mixture was cooled to RT and purified by column chromatography on silica gel eluting with hexanes/EtOAc (9/1) to afford 1.1 g the title compound as a mixture double bond isomers. MS $(MH)^+$: 571.9.

Step B: (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-6,7-dihydroquinolin-8(5*H*)-one

A solution of the intermediate of step A in methanol cooled in a dry ice/acetonitrile bath was treated with ozone until the solution became blue in color. The excess ozone was removed by a nitrogen stream and excess dimethylsulfide was added. The cooling bath was removed and the reaction mixture was stirred at RT for 17 hr. The solvent was evaporated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/hexanes (1/1) to give 0.62 g of the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.80 (1 H, d), 7.80 (1 H, s), 7.52 (2 H, s), 7.42 (1 H, m), 7.37 (1 H, m), 6.98 (2 H, m), 6.90 (2 H, m), 4.65 (1 H, q), 4.37 (1 H, d), 4.00 (1 H, m), 3.20 (1 H, dd), 3.00 (1 H, m), 1.42 (3 H, d). MS $(MH)^+$: 498.3.

Step C: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol

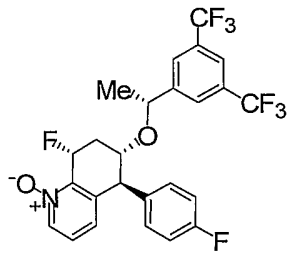
To a solution of 120 mg (0.24 mmol) (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-6,7-dihydroquinolin-8(5*H*)-one (Step B) in methanol under nitrogen atmosphere cooled in an ice bath was added excess $NaBH_4$. The reaction mixture was stirred at 0 °C for 30 min. and the solvent was removed under vacuum. The residue was dissolved in EtOAc and washed with brine. The organic layer was dried over drying agent, filtered and the solvent removed under vacuum. The residue was purified by prep TLC eluting with hexanes/EtOAc

(2/3) to afford 120 mg of the title compound as a single diastereomer.^{1}H-NMR ($CDCl_3$): δ 8.48 (1 H, bs), 7.70 (1 H, s), 7.53 (2 H, s), 7.10 (2 H, bs), 6.92 (4 H, bs), 4.85 (1 H, m), 4.68 (1 H, m), 4.35 (1 H, bs), 4.13 (1 H, d), 3.70 (1 H, t), 2.87 (1 H, d). MS $(MH)^+$: 500.0.

Step D: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol 1-oxide

To a solution of 120 mg (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol (intermediate step C) in 10 mL CH_2Cl_2 at RT was added 2.5 mL of 35% aq. H_2O_2 followed by a catalytic amount $MeReO_3$. The resulting mixture was vigourously stirred at RT for 2 hr. The layers were separated and the aqueous layer extracted several times with CH_2Cl_2. The combined organic layers was washed with brine, dried over drying agent and filtered. The solvent was removed under vacuum and the residue was purified by reverse phase HPLC (using the condition for LC-MS: 1% TFA H_2O-AcCN 10%-90% gradient) to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.37 (1 H, bs), 7.85 (1 H, s), 7.43 (2 H, s), 7.33 (1 H, m), 7.07 (1 H, d), 6.95 (2 H, t), 6.85 (2 H, m), 5.37 (1 H, bs), 4.65 (1 H, q), 4.19 (1 H, d), 3.65 (1 H, m), 2.68 (1 H, m), 2.22 (1 H, m), 1.43 (3 H, d). MS, $(MH)^+$: 516.0.

EXAMPLE 9



(5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-8-fluoro-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

Step A: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-8-fluoro-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

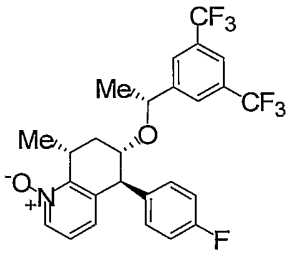
To a solution of 90 mg (0.18 mmol) of (5*S*,6*S*,8*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol (more polar diastereomer, Example 7) in dry CH_2Cl_2 under nitrogen atmosphere at -78 °C was added by syringe 0.037 mL (1.2 equiv) bis(2-methoxyethyl)amino-sulfur trifluoride. The resulting mixture was stirred -78 °C for 1 hr then quenched with sat. aq. $NaHCO_3$ at -78 °C. The resulting mixture was warmed to RT for 15min

then was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum to afford the title compound which was used without further purification. MS $(MH)^+$: 502.0.

Step B: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-8-fluoro-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide

The title compound was prepared from the intermediate of step A according to the procedure of Example 4, Step E. ^{1}H-NMR ($CDCl_3$): δ 8.53 (1 H, d), 7.85 (1 H, s), 7.80 (2 H, s), 7.30 (1 H, d), 6.95 (3 H, m), 6.75 (2 H, m), 6.21 (1 H, dt), 4.85 (1 H, q), 4.40 (1 H, s), 3.65 (1 H, bs), 2.63 (1 H, m), 2.00 (1 H, m), 1.43 93 H, d). MS $(MH)^+$: 518.0.

EXAMPLE 10



(5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-8-methyl-5,6,7,8-tetrahydroquinoline 1-oxide

Step A: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-8-methyl-5,6,7,8-tetrahydroquinoline and (5*S*,6*S*,8*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-8-methyl-5,6,7,8-tetrahydroquinoline

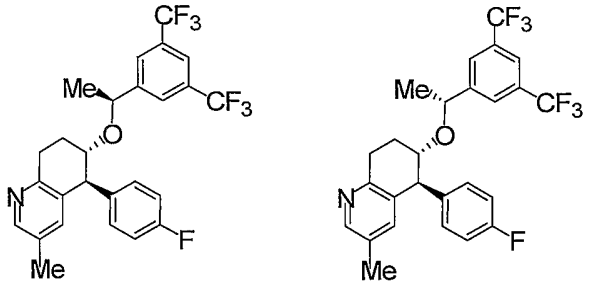
To a solution of 76 mg (0.16 mmol) of (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (the first eluting isomer, Example 3, step A) in dry THF under nitrogen atmosphere at 0 °C was added by syringe 0.22 mL (1.5 equiv) a 1.5 M solution of LDA in THF. The resulting mixture was stirred 0 °C for 1 hr then 0.1 mL of methyliodide was added by syringe. The resulting mixture was stirred 0 °C for 2 hr quenched with water. The resulting mixture was warmed to RT for 15 min then was extracted with ether. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was

evaporated under vacuum. The crude title compounds were purified by prep TLC eluting with EtOAc/hexanes (1/3) to afford the two diastereomers. The less polar (*R*) isomer, ^{1}H-NMR ($CDCl_3$): δ 8.45 (1 H, s), 7.70 (1 H, s), 7.55 (2 H, s), 7.00-6.86 (6 H, m), 4.63 (1 H, q), 4.10 (1 H, d), 3.65 (1 H, m), 3.18 (1 H, m), 2.55 (1 H, m), 1.77 (1 H, q), 1.78 (3 H, d), 1.45 (3 H, d). MS $(MH)^+$: 514.0. The more polar (*S*) isomer, ^{1}H-NMR ($CDCl_3$): δ 8.50 (1 H, d), 7.75 (1 H, s), 7.53 (2 H, s), 7.07 (1 H, m), 7.02 (1 H, m), 6.95-6.85 (4 H, m), 4.68 (1 H, q), 4.08 (1 H, d), 3.73 (1 H, m), 3.35 (1 H, m), 2.17 (1 H, m), 2.05 (1 H, m), 1.53 (3 H, d), 1.47 (3 H, d). MS $(MH)^+$: 498.0.

Step B: (5*S*,6*S*,8*R*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-8-methyl-5,6,7,8-tetrahydroquinoline 1-oxide

The title compound was prepared from the less polar intermediate of step A according to the procedure of Example 4, Step E. ^{1}H-NMR ($CDCl_3$): δ 8.65 (1 H, d), 7.86 (1 H, s), 7.70 (2 H, s), 7.40 (2 H, m), 6.95 (2 H, d), 6.87 (2 H, m), 4.75 (1 H, q), 4.27 (1 H, d), 3.85 (1 H, m), 3.70 (1 H, m), 2.27 (1 H, m), 2.05 (1 H, m), 1.75 (3 H, d), 1.50 (3 H, m). MS $(MH)^+$: 514.0.

EXAMPLE 11



Racemic-(5,6-*trans*)-6-{1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-3-methyl-5,6,7,8-tetrahydroquinoline

Step A: Ethyl 5-{[(trifluoromethyl)sulfonyl]oxy}-7,8-dihydroquinoline-3-carboxylate

The title compound was prepared from ethyl 5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (S. Torii, I. Tsutomu, M. Kubota, *Synthesis* **1986**, 400-403.) according to the procedure for Example 1, step B. ^{1}H-NMR ($CDCl_3$): δ: 9.08 (1 H, s), 8.20 (1 H, s), 6.22 (1 H, t), 4.46 (2 H, q), 3.19 (2 H, t), 2.74 (2 H, m), 1.47 (3 H, t).

Step B: Ethyl 5-(4-fluorophenyl)-7,8-dihydroquinoline-3-carboxylate

The title compound was prepared from ethyl 5-{[(trifluoromethyl)sulfonyl]oxy}-7,8-dihydroquinoline-3-carboxylate (intermediate step A) and 4-fluorophenylboronic acid according to the procedure for Example 1, step C. ^{1}H-NMR ($CDCl_3$): δ: 8.97 (1 H, s), 7.83 (1 H, s), 7.30 (2 H, m), 7.12 (2 H, m), 6.20 (1 H, t), 4.37 (2 H, q), 3.15 (2 H, t), 2.61 (2 H, m), 1.38 (3 H, t).

Step C: [5-(4-Fluorophenyl)-7,8-dihydroquinolin-3-yl]methanol

To a solution of 0.5 g (1.7mmol) ethyl 5-(4-fluorophenyl)-7,8-dihydroquinoline-3-carboxylate in dry ether under nitrogen atmosphere at 0 °C was added by syringe 5 mL (~3.0 equiv) of a 1.0 M solution of $LiAlH_4$ in ether. The reaction mixture was stirred at 0 °C for 0.5 hr then quenched carefully by the addition of ~1 mL water. The ether solution was decanted and dried over drying agent, filtered and the solvent removed under vacuum to afford the title compound which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ: 8.32 (1 H, s), 7.52 (1 H, m), 7.30 (2 H, m), 7.13 (2 H, m), 6.17 (1 H, t), 4.62 (2 H, s), 3.08 (2 H, t), 2.59 (2 H, m).

Step D: 3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-7,8-dihydroquinoline

To a solution of 4 g (16mmol) [5-(4-fluorophenyl)-7,8-dihydroquinolin-3-yl]methanol in 50 mL dry DMF under nitrogen atmosphere at RT was added 3.1 g (1.3 equiv) *tert*-butyl(chloro)dimethylsilane and 2.2 g (2 equiv) imidazole. The reaction mixture was stirred at RT for 16 hr. The reactionmixture was diluted with 200 mL ether and 100 mL water. The layers were separated and the ether layer was washed with water (3x). The aqueous wash was back extracted with 50 mL ether. The combined ether layers were washed with brine, dried over drying agent and filtered. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography on silica gel eluting with EtOAc/hexanes (1/3) to give 2.2 g of the title compound. ^{1}H-NMR ($CDCl_3$): δ 8.30 (1 H, s), 7.30 (2 H, m), 7.23 (1 H, s), 7.09 (2 H, m), 6.13 (1 H, t), 4.62 (2 H, s), 3.05 (2 H, t), 2.58 (2 H, m), 0.87 (6 H, s), 0.10 (9 H, s). MS $(MH)^+$: 370.0.

Step E: Racemic (*trans*)-(5,6)-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-ol

The title compound was prepared from 3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-7,8-dihydroquinoline (intermediate step D) according to the procedure of Example 1, step D. MS $(MH)^+$ 388.1.

Step F: Racemic 5,6-(*trans*)-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl 3,5-bis(trifluoromethyl)benzoate

To a solution of 1 g (2.6 mmol) of the intermediate of step E in 40mL dry methylene chloride under nitrogen atmosphere at RT was added 0.5 mL (1.3 equiv) TEA, 0.6 mL (1.2 equiv)) of 3,5-bis(trifluoromethyl)benzoyl chloride and a catalytic amount of DMAP. The resulting mixture was stirred at RT for 16 hr then quenched sat. aq. $NaHCO_3$. The mixture was transferred to a separatory funnel and extracted with methylene chloride. The combined organic layers were dried over drying agent, filtered and the solvent evaporated under vacuum to afford the crude title compounds which were used without further purification.

Step G: Racemic 5,6-(*trans*)-6-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline

The title compound was prepared from racemic 5,6-(*trans*)-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl 3,5-bis(trifluoromethyl)benzoate (intermediate of step F) according to the procedure of Example 2, step D. ^{1}H-NMR ($CDCl_3$): δ 8.41 (1 H, s), 8.13-8.04 (3 H, m), 7.90-7.80 (4 H, m), 7.29 (1 H, s), 4.84 (1 H, s), 4.45 (1 H, s), 4.11 (1 H, m), 3.83 (1 H, m), 2.74 (2 H, s), 2.13 (2 H, m), 1.67 (2 H, m), 1.34-1.23 (15 H, m).

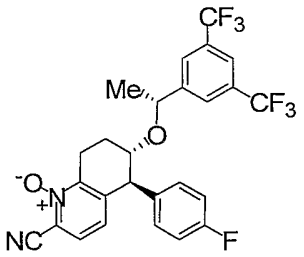
Step H: Racemic (5,6-*trans*)-6-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-3-methyl-5,6,7,8-tetrahydroquinoline

The crude title compounds were prepared from racemic 5,6-(*trans*)-6-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (intermediate of step G) according to the procedure of Example 2, step E. The diastereomers were purified by prep TLC eluting with EtOAc/hexanes (1/1) to afford the two diastereomers. The less polar isomer, MS $(MH)^+$: 498.1. The more polar isomer, ^{1}H-NMR ($CDCl_3$): δ: 8.25 (1 H, s), 7.75 (1 H, s), 7.50 (2 H, s), 6.93-6.86 (5 H, m), 4.69 (1 H, q), 4.07 (1 H, d), 3.61 (1 H, m), 3.18 (1 H, m), 3.03 (1 H, m), 2.25 (1 H, m), 2.19 (3 H, s), 2.0 (1 H, m), 1.46 (3 H, d). MS $(MH)^+$:498.1.

Step I: Racemic (5,6-*trans*)-6-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-3-methyl-5,6,7,8-tetrahydroquinoline 1-oxide

The title compound was prepared the more polar isomer of the intermediate of step H according to the procedure of Example 4, step E. MS $(MH)^+$:514.1.

EXAMPLE 12



(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carbonitrile 1-oxide

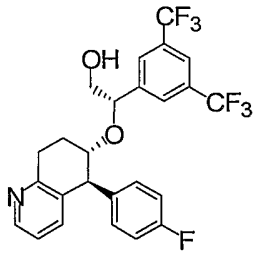
Step A: (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carbonitrile

To a solution of 1.13 g (2.3 mmol) of (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide (Example 4) in dry methylene chloride under nitrogen atmosphere was added by syringe 0.29 mL (2.76 mmol, 1.2 equiv) of N,N-dimethylcarbamoyl chloride. The resulting mixture was stirred for 10 min. then 0.6 mL of trimethylsilyl cyanide was added by syringe. The resulting mixture was stirred for 72 hr, then quenched with 5 N aq. NaOH. The resulting mixture was extracted with methylene chloride. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum to afford the crude title compound which was used without further purification. MS $(MH)^+$: 508.9.

Step B: 5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carbonitrile 1-oxide

The title compound was prepared from the intermediate of step A according to the procedure of Example 4, Step E. MS $(MH)^+$: 525.0.

EXAMPLE 13

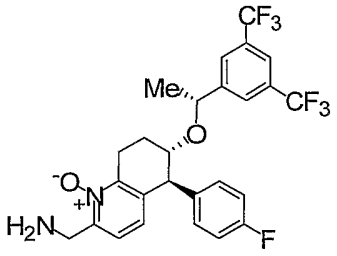


(2*S*)-2-[3,5-bis(Trifluoromethyl)phenyl]-2-{[(5*S*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl]oxy}ethanol

Step A: (2*S*)-2-[3,5-bis(Trifluoromethyl)phenyl]-2-{[(5*S*,6*S*)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl]oxy}ethanol

To a solution of 120 mg (0.25 mmol) of (5*S*,6*S*)-6-({1-[3,5-bis(trifluoromethyl)phenyl]vinyl}oxy)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline (Example 4, step C) was hydroborated in THF at rt for 16 hr. The resulting mixture was with 5 N aq. NaOH and 30% aq. H_2O_2 then stirred at RT 16 hours. The resulting mixture was extracted with methylene chloride. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum to afford the crude title compounds which were purified by prep TLC eluting with hexanes/EtOAC (1:1) to give an ~1:1 mixture of two isomers. Isomer 1: ^{1}H-NMR ($CDCl_3$): δ 8.45 (1 h, bs), 7.80 (1 H, s), 7.52 (2 H, s), 7.05 (2 H, m), 6.92 (4 H, m), 4.75 (1 H, t), 4.15 (1 H, d), 3.75 (1 H, m), 5.67 (2 H, bs), 3.17 (1 H, dt), 3.12 (1 H, m), 2.15 (1 H, m), 2.07 (1 H, m). LC-MS $(MH)^+$: 500.0. Isomer 2: ^{1}H-NMR ($CDCl_3$): δ 8.75 (1 H, 7.80 (1 H, m), 7.52 (2 H, m), 7.20 (2 H, m), 7.11 (1 H, d), 6.85 (2 H, m), 4.53 (1 H, m), 4.36 (1 H, d), 3.87 (1 H, m), 3.73 (2 H, m), 3.50 (1 H, m), 3.30 (1 H, m), 2.05 (2 H, m). MS $(MH)^+$: 500.0.

EXAMPLE 14



{[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine hydrochloride

Step A: {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine

To a solution of 0.1 g (0.19 mmol) of (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carbonitrile (Example 12, step A) in dry toluene under nitrogen atmosphere at -58 °C was added by syringe 0.5 mL (0.5 mmol, 2.63 equiv) of 1 M solution of DiBAL-H in toluene. The resulting mixture was stirred for 10

min. then the cooling bath was removed. The resulting mixture was warmed to RT then quenched with 5 N aq. NaOH. The resulting mixture was extracted with methylene chloride. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum. The residue was purified by prep TLC eluting with CH_2Cl_2 / 2 N NH_3 in MeOH (9/1) to afford the title compound. MS $(MH)^+$: 513.0.

Step B: *tert*-butyl {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]methyl}carbamate

To a solution of {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bistrifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine (Step A) in dry methylene chloride under nitrogen atmosphere at RT was added by 2 equiv of di-tert-butyl dicarbonate. The resulting mixture was stirred at RT for 2 hr then the solvent was evaporated under vacuum. The residue was purified by prep TLC eluting with hexanes/EtOAc (4/1) to afford the title compound. ^{1}H-NMR ($CDCl_3$): δ: 7.75 (1 H, s), 7.49 (2 H, s), 7.07-6.97 (2 H, m), 6.89 (4 H, m), 5.52 (1 H, s), 4.69 (1 H, q), 4.40 (2 H, s), 4.08 (1 H, d), 3.61 (1 H, m), 3.19 (1 H, m), 3.04 (1 H, m), 2.28 (1 H, m), 2.0 (1 H, m), 1.50 (9 H, s), 1.25 (3 H, d)

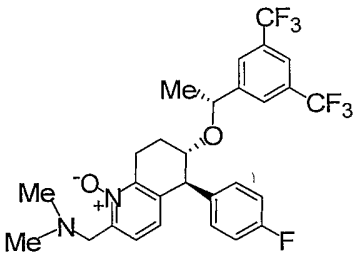
Step C: *tert*-Butyl {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}carbamate

The title compound was prepared from the intermediate of step B according to the procedure of Example 4, Step E. ^{1}H-NMR ($CDCl_3$): δ: 7.78 (1 H, s), 7.56 (2 H, s), 7.18 (1 H, m), 6.92 (2 H, m), 6.83 (2 H, m), 6.72 (1 H, d), 5.87 (1 H, s), 4.69 (1 H, q), 4.50 (2 H, d), 4.09 (1 H, d), 3.60 (1 H, m), 3.24 (1 H, m), 3.09 (1 H, m), 2.18 (1 H, m), 2.05 (1 H, m), 1.45 (9 H, s), 1.25 (3 H, d).

Step D: {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine hydrochloride

The *tert*-butyl {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}carbamate (Step C) was dissolved in several mL of 4 N HCl in dioxane and stirred at RT for 48 hr. The solvent was removed under vacuum to afford the title compound as the hydrochloride salt. MS $(MH)^+$ 529.0.

EXAMPLE 15

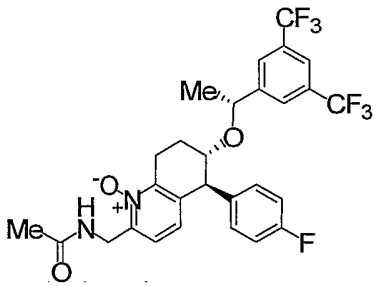


{[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}dimethylamine

Step A: {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}dimethylamine

To a solution of ~0.010 g (0.02 mmol) of {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine hydrochloride (Example 14) in several mLs of methanol under nitrogen atmosphere at - RT was added 40 mg (~15 equiv) of 37% aq. formaldehyde, 10 mg KOAc, and 9 mg $NaCNBH_3$. The resulting mixture was stirred for several hr. then solvent was evaporated under vacuum. The residue was taken up in EtOAc and the solids filtered. The solvent of the filtrate was evaporated under vacuum and the residue was purified by prep TLC eluting with EtOAc/MeOH (9/1) to afford the title compound. MS $(MH)^+$: 557.1.

EXAMPLE 16



N-{[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}acetamide

Step A: *N*-{[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]methyl}acetamide

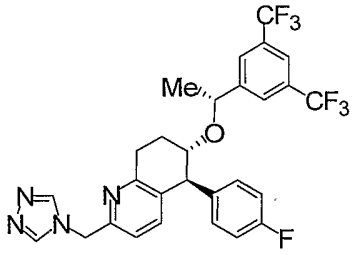
To a solution of ~10mg {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bistTrifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine (Example 14, Step A) in dry methylene

chloride under nitrogen atmosphere at RT was added ~4 mg TEA and ~3 mg acetyl chloride. The resulting mixture was stirred at RT for 20 min, quenched with a few drops of 2 N aq. NaOH, then the solvent was evaporated under vacuum. The residue was purified by prep TLC eluting with EtOAc to afford the title compound. MS: $(MH)^+$: 555.0.

Step B: *N*-{[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}acetamide

The title compound was prepared from the intermediate of step A according to the procedure of Example 4, Step E. MS $(MH)^+$ 571.4.

EXAMPLE 17

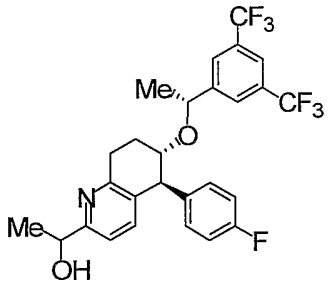


(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-2-(4*H*-1,2,4-triazol-4-ylmethyl)-5,6,7,8-tetrahydroquinoline

Step A: (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-2-(4*H*-1,2,4-triazol-4-ylmethyl)-5,6,7,8-tetrahydroquinoline

To a solution of ~30 mg {[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bistrifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine (Example 14, Step A) in dry toluene under nitrogen atmosphere at RT was added 17 mg *N'*-[(1*E*)-(dimethylamino)methylene]-*N*,*N*-dimethylhydrazonoformamide and ~3 mg PTSA. The resulting mixture was heated at reflux for 16 hr then the solvent was evaporated under vacuum. The residue was purified by prep TLC eluting with $EtOAc/CH_3CN/CH_3OH/H_2O$ (7.5/0.5/0.5/0.5) to afford the title compound. MS $(MH)^+$: 565.2.

EXAMPLE 18



1-[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]ethanol

Step A: 1-[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]ethanone

To a solution of 0.1 g (0.19 mmol) of (5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carbonitrile (Example 12, step A) in dry ether/THF (1/1) under nitrogen atmosphere at -10 °C was added by syringe 0.155 mL (0.22 mmol, 1.1 equiv) of 1.4 M solution of methylmagnesium bromide in toluene/THF. The resulting mixture was warmed to RT and stirred for 2 hr. then quenched with 2 N aq. HCl. The resulting mixture was extracted with ether. The combined extracts were washed with brine, dried over drying agent, filtered and the solvent was evaporated under vacuum. The residue was purified by prep TLC eluting with hexanes/EtOAc (1/1) to afford the title compound. LC-MS: $(MH)^+$ 526.13.

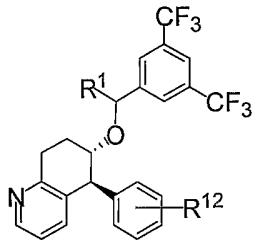
Step B: 1-[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]ethanol

To a solution of ~30 mg 1-[(5*S*,6*S*)-6-{(1*R*)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]ethanone (Step A) in methanol under nitrogen atmosphere at RT was added ~8 equiv. solid $NaBH_4$. The resulting mixture was stirred at RT for 0.5 hr then quenched with 5 N aq. NaOH then the solvent was evaporated under vacuum. The residue was taken up in EtOAc and the solids filtered through filter aid. The filtrate was washed with water, dried over drying agent and filtered. The solvent was evaporated under vacuum to afford the title compound. MS $(MH)^+$: 528.2.

TABLE 1

The compounds in Table 1 were synthesized using the foregoing methodology, but substituting the appropriately substituted reagent as described in the foregoing examples. The requisite

starting materials were commercialy available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

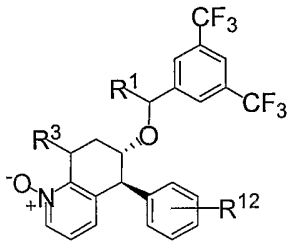


5

Ex. #	R^1	R^{12}	parent ion (MH^+) *m/z*
19		H	464.2
20		H	466.2
21		H	466.0
22		H	466.1
23		2-Me, 4-F	498.3
24		2-Me, 4-F	498.3
25		2-Me, 4-F	498.3

TABLE 2

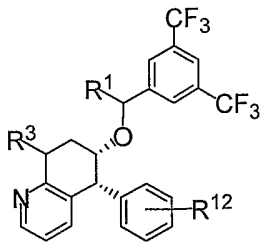
The compounds in Table 2 were synthesized using the foregoing methodology, but substituting the appropriately substituted reagent as described in the foregoing examples. The requisite starting materials were commercialy available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.



Ex. #	R^1	R^{12}	R^3	parent ion (MH^+) *m/z*
26	H	H	H	468.2
27		2-Me, 4-F	H	514.2
28		F		518.0

TABLE 3

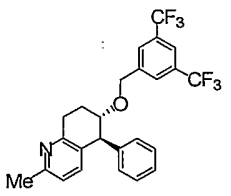
The compounds in Table 3 were synthesized using the foregoing methodology, but substituting the appropriately substituted reagent as described in the foregoing examples. The requisite starting materials were commercialy available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

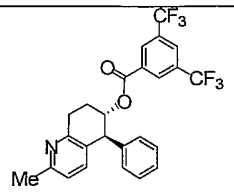
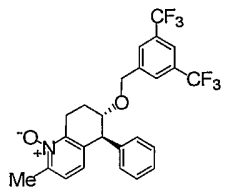
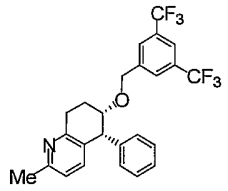
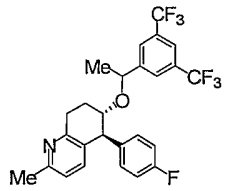
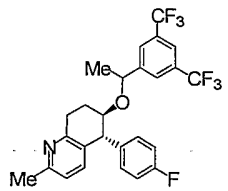
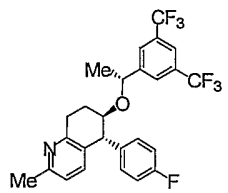


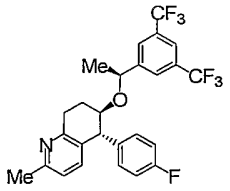
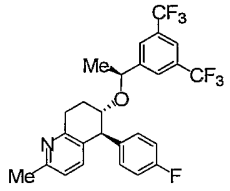
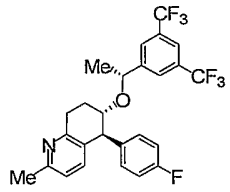
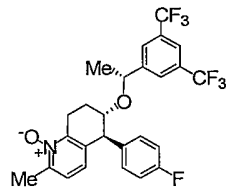
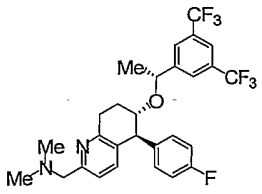
Ex. #	R^1	R^{12}	R^3	parent ion (MH^+) *m/z*
29		4-F	-OH	500.1
30		4-F	-OH	500.1
31		4-F		502.0

TABLE 4

The compounds in Table 4 were synthesized using the foregoing methodology, but substituting the appropriately substituted reagent as described in the foregoing examples. The requisite starting materials were commercialy available, described in the literature or readily synthesized by one skilled in the art of organic synthesis without undue experimentation.

Ex. #	Compound	parent ion (MH^+) *m/z*
32		466.4

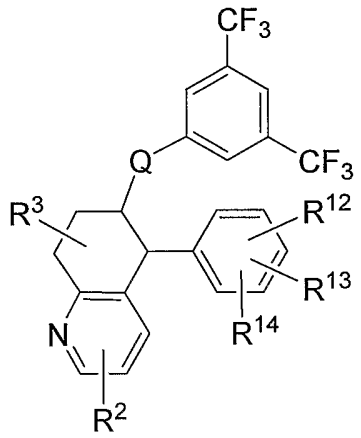
33		480.0
34		482.4
35		466.3
36		498.1
37		498.1
38		498.1

39		498.1
40		498.1
41		498.1
42		514.1
43		541.2

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

and N-oxides thereof,

wherein:

Q is selected from the group consisting of:

(1) -O-CH_2-,

(2) -O-CH(CH_3)-,

(3) -O-CH(CH_2OH)-,

(4) -O-(CO)-, and

(5) -O-(C=CH_2)-;

R^2 and R^3 are independently selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl-C_{1-3} alkoxy,

(e) phenyl,

(f) halo,

(g) -NR^9R^{10}, wherein R^9 and R^{10} are independently selected from:

(I) hydrogen,
(II) C_{1-6} alkyl,
(III) phenyl,
(IV) (C_{1-6} alkyl)-phenyl,
(V) (C_{1-6} alkyl)-hydroxy, and
(VI) (C_{1-6} alkyl)-(C_{1-4} alkoxy),
or where $-NR^9R^{10}$ forms a morpholine, piperidine or quinuclidine ring

(h) $-NR^9-COR^{11}$, wherein R^{11} is independently selected from:
(I) hydrogen,
(II) C_{1-6} alkyl,
(III) phenyl,
(IV) (C_{1-6} alkyl)-phenyl,
(V) (C_{1-6} alkyl)-hydroxy, and
(VI) (C_{1-6} alkyl)-(C_{1-4} alkoxy),

(j) $-NR^9-CO_2R^{11}$,
(k) $-CO-NR^9R^{10}$,
(l) $-COR^{11}$,
(m) $-CO_2R^{11}$,

(3) hydroxy,
(4) C_{1-6}alkoxy,
(5) oxo,
(6) halo,
(7) -CN,
(8) $-CF_3$,
(9) $-NR^9R^{10}$,
(10) $-NR^9-COR^{11}$,
(11) $-NR^9-CO_2R^{11}$,
(12) $-CO-NR^9-COR^{11}$,
(13) $-COR^{11}$,
(14) $-O-(CO)R^{11}$,
(15) $-CO_2R^{11}$,
(16) -imidazolyl, and
(17) -triazolyl;

R^{12}, R^{13} and R^{14} are independently selected from the group consisting of:

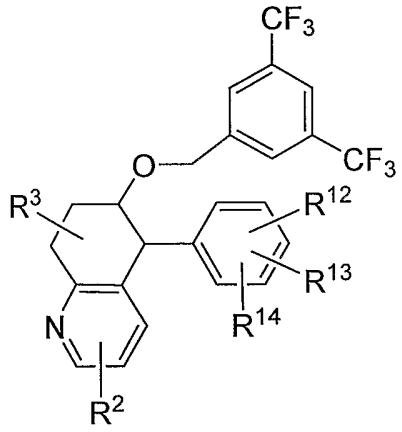
(1) hydrogen,

(2) halo, and

(3) C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

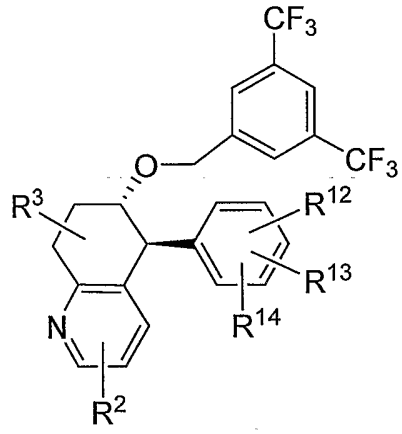
2. The compound of Claim 1 of the formula Ia:



Ia

and N-oxides thereof, and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

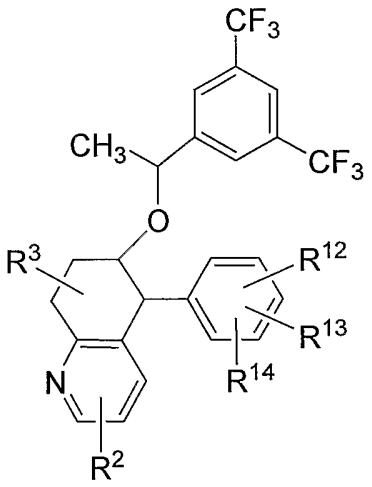
3. The compound of Claim 2 of the formula Ia':



Ia'

and N-oxides thereof, and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

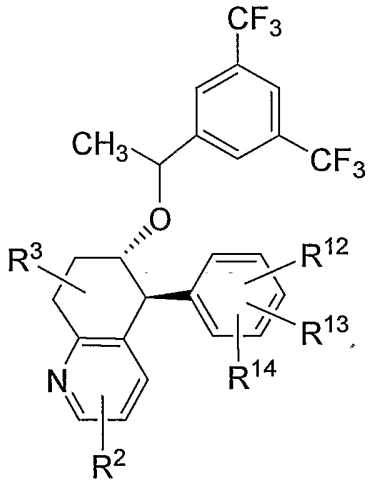
4. The compound of Claim 1 of the formula Ib:



Ib

and N-oxides thereof, and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

5. The compound of Claim 4 of the formula Ib':



Ib'

and N-oxides thereof, and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

6. The compound of Claim 1 wherein R^2 is selected from the group consisting of:

(1) hydrogen,

(2) C_{1-6} alkyl, which is unsubstituted or substituted with one or more of the substituents selected from:

(a) morpholinyl,

(b) $-NH_2$,

(c) $-NH(C_{1-6}$ alkyl),

(d) $-N(C_{1-6}$ alkyl)$(C_{1-6}$ alkyl),

(e) hydroxy,

(f) $-CO_2(C_{1-6}$ alkyl),

(g) $-NHCO(C_{1-6}$ alkyl),

(h) $-CO_2H$, and

(i) triazolyl,

(3) hydroxy,

(4) halo,

(5) $-CO_2(C_{1-6}$ alkyl),

(6) $-CO_2H$, and

(7) -CN.

7. The compound of Claim 6 wherein R^2 is hydrogen.

8. The compound of Claim 6 wherein R^2 is methyl.

9. The compound of Claim 1 wherein R^3 is hydrogen.

10. The compound of Claim 1 wherein R^3 is fluoro.

11. The compound of Claim 1 wherein R^{12} is fluoro, R^{13} is hydrogen or methyl, and R^{14} is hydrogen.

12. The compound of Claim 11 wherein R^{12} is 4-fluoro, R^{13} is hydrogen and R^{14} is hydrogen.

13. The compound of Claim 11 wherein R^{12} is 4-fluoro, R^{13} is 2-methyl and R^{14} is hydrogen..

14. The compound of Claim 1 wherein the compound is present as an N-oxide on the pyridyl ring.

15. A compound which is selected from the group consisting of:
(5,6-trans)-6-{[3,5-bis(trifluoromethyl)benzyl]oxy}-5-phenyl-5,6,7,8-tetrahydroquinoline;
(5,6-trans)-6-{1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline;
(5S,6S)-6-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline;
(5R,6R)-6-{(1S)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline;
(5S,6S)-6-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide;
(5R,6S)-6-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide;
(5R,6S)-6-{(1S)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide;
(5S,6S,8R)-6-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol;
(5S,6S,8S)-6-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol;
(5S,6S,8R)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-8-ol 1-oxide;
(5S,6S,8R)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-8-fluoro-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline 1-oxide;
(5S,6S,8R)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-8-methyl-5,6,7,8-tetrahydroquinoline 1-oxide;
Racemic-(5,6-trans)-6-{1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-3-methyl-5,6,7,8-tetrahydroquinoline;
(5S,6S)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-2-carbonitrile 1-oxide;

(2S)-2-[3,5-bis(Trifluoromethyl)phenyl]-2-{[(5S,6S)-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-6-yl]oxy}ethanol;
{[(5S,6S)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}amine;
{[(5S,6S)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}dimethylamine;
N-{[(5S,6S)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-1-oxido-5,6,7,8-tetrahydroquinolin-2-yl]methyl}acetamide;
(5S,6S)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-2-(4H-1,2,4-triazol-4-ylmethyl)-5,6,7,8-tetrahydroquinoline;
1-[(5S,6S)-6-{(1R)-1-[3,5-bis(Trifluoromethyl)phenyl]ethoxy}-5-(4-fluorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl]ethanol;
and pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

17. A method for the manufacture of a medicament for antagonizing the effect of substance P at its receptor site or for the blockade of neurokinin-1 receptors in a mammal comprising combining a compound of the present invention or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.

18. A method for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins in a mammal comprising combining a compound of the present invention or a pharmaceutically acceptable salt thereof with a pharmaceutical carrier or diluent.