ISOXAZOLINE DERIVATIVES AS ANTI-DEPRESSANTS

The invention concerns substituted isoxazolines derivatives having anti-depressant activity and/or anxiolytic activity and/or body weight control activity, processes for their preparation, pharmaceutical compositions comprising them and their use as a medicine, in particular for the treatment of depression, anxiety, stress-related disorders associated with depression and/or anxiety and disorders of body weight including anorexia nervosa and bulimia.

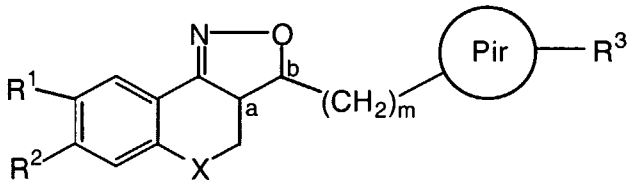
The invention also relates to novel combination of substituted isoxazolines derivatives having anti-depressant activity and/or anxiolytic activity and/or body weight control activity with antidepressants, anxiolytics and/or antipsychotics.

Tetrahydronaphtalene and indane derivatives showing anti-depressant activity are known from EP-361 577 B1. These compounds are typical monoamine reuptake blockers with additional α_2-adrenoceptor antagonist activity and they show anti-depressant activity without being sedative.

The problems associated with the compounds according to the state of the art is that the compounds cause considerable side-effects, such as nausea, excitation, an increased heart rate and a reduced sexual function. Furthermore, it requires a long time, in particular 3-4 weeks, before the response starts.

The purpose of the present invention is to provide novel compounds derivatives having anti-depressant and/or anxiolytic and/or body weight control activity, in particular compounds that do not exhibit the aforementioned disadvantages.

The present invention relates to novel isoxazoline derivatives according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, wherein :

X is CH_2, N-R^7, S or O ;

R^7 is selected from the group of hydrogen, alkyl, phenyl, phenylalkyl, alkylcarbonyl, alkyloxycarbonyl and mono- and dialkylaminocarbonyl, the phenyl and alkyl groups being optionally substituted with one or more halo atoms;

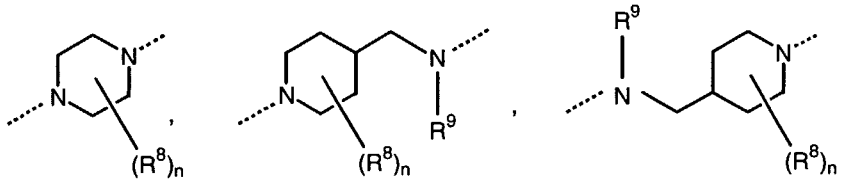
R^1 and R^2 are each, independently from each other, selected from the group of hydrogen, hydroxy, cyano, halo, OSO_2H, OSO_2CH_3, phenyl, phenylalkyl, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkylthio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenyl-carbonyloxy and mono-and dialkylaminoalkyloxy, the alkyl and aryl radicals being optionally substituted with one or more hydroxy or halo atoms or amino groups ; or

R^1 and R^2 may be taken together to form a bivalent radical -R^1-R^2- selected from the group of -CH_2-CH_2-O-, -O-CH_2-CH_2-, -O-CH_2-O-, -CH_2-O-CH_2- and -O-CH_2-CH_2-O- ;

a and b are asymmetric centers ;

$(CH_2)_m$ is a straight hydrocarbon chain of m carbon atoms, m being an integer ranging from 1 to 4 ;

Pir is an optionally substituted radical according to any one of Formula (IIa), (IIB or (IIc)



(II)

(a) (b) (c)

wherein :

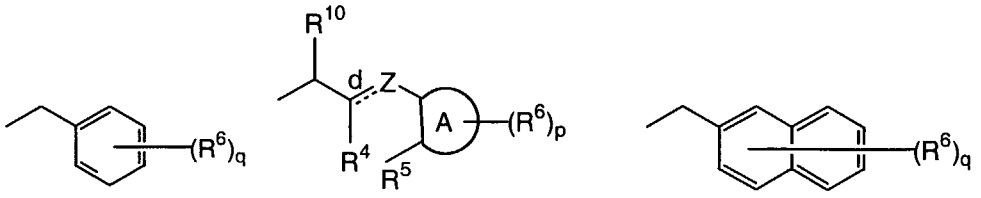
each R^8 is independently from each other, selected from the group of hydrogen, hydroxy, amino, nitro, cyano, halo and alkyl ;

n is an integer ranging from 1 to 5 ;

R^9 is selected from the group of hydrogen, alkyl and formyl ; and

R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system together with an optionally substituted and partially or completely hydrogenated hydrocarbon chain of 1 to 6 atoms long with which said ring system is attached to the Pir radical and of which may contain one or more heteroatoms selected from the group of O, N and S.

More in particular, the invention relates to compounds according to Formula (I) wherein R^3 is a radical according to any one of Formula (IIIa), (IIIb) and (IIIc)



(III)

(a) (b) (c)

wherein :

d is a single bond while Z is a bivalent radical selected from the group of $-CH_2-$, -C(=O)-, -CH(OH)-, -C(=N-OH)-, –CH(alkyl)-, -O-, -S-, -S(=O), -NH- and –SH-; or d is a double bond while Z is a trivalent radical of formula =CH- or =C(alkyl)-;

A is a 5- or 6-membered aromatic homocyclic or heterocyclic ring, selected from the group of phenyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, oxadiazolyl and isoxazolyl ;

p is an integer ranging from 0 to 4 ;

q is an integer ranging from 0 to 7 ;

R^4 is selected from the group of hydrogen, alkyl, phenyl, biphenyl, naphthyl, halo and cyano, the alkyl and aryl radicals being optionally substituted with one or more hydroxy or halo atoms or amino groups ;

R^5 is equal to R^4 ; or

R^4 and R^5 may be taken together to form a bivalent radical $-R^4-R^5-$ selected from the group of $-CH_2-$, =CH-, $-CH_2-CH_2-$, -CH=CH- , -O-, -NH-, =N-, -S-, $-CH_2N(-alkyl)-$, -CH=N-, $-CH_2O-$ and $-OCH_2-$;

each R^6 is independently from each other, selected from the group of hydrogen, hydroxy, amino, nitro, cyano, halo, carboxyl, alkyl, phenyl, alkyloxy, phenyloxy, alkylcarbonyloxy, alkyloxycarbonyl, alkylthio, mono- and dialkylamino, alkylcarbonylamino, mono- and dialkylaminocarbonyl, mono- and dialkylaminocarbonyloxy, mono- and dialkylaminoalkyloxy, the alkyl and aryl radicals being optionally substituted with one or more hydroxy or halo atoms or amino groups ; or

two vicinal radicals R^6 may be taken together to form a bivalent radical $-R^6-R^6-$ selected from the group of $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-O-CH_2-C(=O)-$, $-O-CH_2-O-$, $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-O-$, -CH=CH-CH=CH-, -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-C(=O)-$ and $-CH_2-CH_2-CH_2-CH_2-$; and

R^{10} is selected from the group of hydrogen, alkyl, phenylalkyl and phenyl.

Preferably, the invention relates to those compounds wherein X=O or NH ; R^1 and R^2 are both alkyloxy ; m = 1 ; Pir is a radical according to Formula (IIa) wherein R^8 is hydrogen and n = 4 ; R^3 is a radical according to Formula (IIIb) wherein Z is =CH-, d is a double bond, A is a phenyl ring, R^4 is an alkyl and R^{10} is hydrogen.

More preferably, the invention relates to compounds where X=O, R^1 and R^2 are both methoxy ; m = 1 ; Pir is a radical according to Formula (IIa) wherein R^8 is hydrogen and n = 4 ; R^3 is a radical according to Formula (IIIb) wherein Z is =CH-, d is a double bond, A is a phenyl ring, R^4 is methyl and R^{10} is hydrogen

In the framework of this application, alkyl defines straight or branched saturated hydrocarbon radicals having from 1 to 6 carbon atoms, for example methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl ; or alkyl defines cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms, for example cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Halo is generic to fluoro, chloro, bromo and iodo. Alkyl radicals being optionally substituted with one or more halo atoms are for example polyhaloalkyl radicals, for example difluoromethyl and trifluoromethyl.

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicyclic acid, p-aminosalicylic acid and pamoic acid.

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hybramine salts, and salts

with amino acids, for example arginine and lysine.

Conversely, said salts forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

The N-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called N-oxide, particularly those N-oxides wherein one or more nitrogens of the piperazinyl radical are N-oxidized.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of Formula (I) are obviously intended to be embraced within the scope of this invention.

Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R*,R*]* or [*R*,S*]*, where R* is always specified as the reference center and [*R*,R**] indicates centers with the same chirality and [*R*,S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the

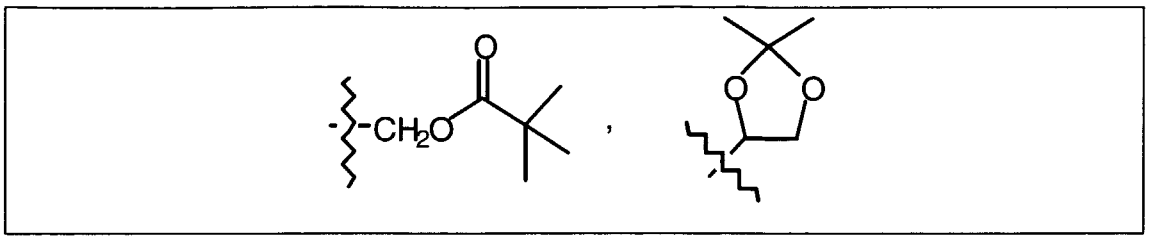
molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R**,*S**]. If "α" and "β" are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds of Formula(I)) relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

Compounds of Formula (I) and some of the intermediates have at least two stereogenic centers in their structure, respectively denoted a and b in Formula (I). Due to the synthetic pathway followed for the synthesis of the tricyclic system, the configuration of those two asymmetric centers a and b is predetermined, so that the relative configuration of center a is S* and of center b is R*.

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs,* 1985, **29**, pp. 455-473.

Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, having an acid group which is esterified or amidated. Included

in such esterified acid groups are groups of the formula $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups :



Amidated groups include groups of the formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl.

Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds according to the invention have surprisingly been shown to have selective serotonine (5-HT) reuptake inhibitor activity in combination with additional

α_2-adrenoceptor antagonist activity and show a strong anti-depressant and/or anxiolytic activity and/or a body weight control activity without being sedative. Also, in view of their selective serotonine (5-HT) reuptake inhibitor as well as α_2-adrenoceptor antagonist activity, compounds according to the invention are also suitable for treatment and/or prophylaxis in diseases where either one of the activities alone or the combination of said activities may be of therapeutic use. In particular, the compounds according to the invention may be suitable for treatment and/or prophylaxis in the following diseases :

- Central nervous system disorders, including :
  - Mood disorders, including particularly major depressive disorder, depression with or without psychotic features, catatonic features, melancholic features, atypical features of postpartum onset and, in the case of recurrent episodes, with or without seasonal pattern, dysthymic disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, recurrent brief depressive disorder, mixed affective disorder, bipolar disorder not otherwise specified, mood disorder due to a general medical condition, substance-induced mood disorder, mood disorder not otherwise specified, seasonal affective disorder and premenstrual dysphoric disorders.
  - Anxiety disorders, including panic attack, agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified.
  - Stress-related disorders associated with depression and/or anxiety, including acute stress reaction, adjustment disorders (brief depressive reaction, prolonged depressive reaction, mixed anxiety and depressive reaction, adjustment disorder with predominant disturbance of other emotions, adjustment disorder with predominant disturbance of conduct, adjustment disorder with mixed disturbance of emotions and conduct, adjustment disorders with other specified predominant symptoms) and other reactions to severe stress.

- Dementia, amnesic disorders and cognitive disorders not otherwise specified, especially dementia caused by degenerative disorders, lesions, trauma, infections, vascular disorders, toxins, anoxia, vitamin deficiency or endocrinic disorders, or amnesic disorders caused by alcohol or other causes of thiamin deficiency, bilateral temporal lobe damage due to Herpes simplex encephalitis and other limbic encephalitis, neuronal loss secondary to anoxia / hypoglycemia / severe convulsions and surgery, degenerative disorders, vascular disorders or pathology around ventricle III.
- Cognitive disorders due to cognitive impairment resulting from other medical conditions.
- Personality disorders, including paranoid personality disorder, schizoid personality disorder, schizotypical personality disorder, antisocial personality disorder, borderline personality disorder, histrionic personality disorder, narcissistic personality disorder, avoidant personality disorder, dependent personality disorder, obsessive-compulsive personality disorder and personality disorder not otherwise specified.
- Schizoaffective disorders resulting from various causes, including schizoaffective disorders of the manic type, of the depressive type, of mixed type, paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, substance-induced psychotic disorder and psychotic disorder not otherwise specified.
- Akinesia, akinetic-rigid syndromes, dyskinesia and medication-induced parkinsonism, Gilles de la Tourette syndrome and its symptoms, tremor, chorea, myoclonus, tics and dystonia.
- Attention-deficit / hyperactivity disorder (ADHD).
- Parkinson's disease, drug-induced Parkinsonism, post-encephalitic Parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification.
- Dementia of the Alzheimer's type, with early or late onset, with depressed mood.

- Behavioral disturbances and conduct disorders in dementia and the mentally retarded, including restlessness and agitation.
- Extra-pyramidal movement disorders.
- Down's syndrome.
- Akathisia.
- Eating Disorders, including anorexia nervosa, atypical anorexia nervosa, bulimia nervosa, atypical bulimia nervosa, overeating associated with other psychological disturbances, vomiting associated with other psychological disturbances and non-specified eating disorders.
- AIDS-associated dementia.

- Chronic pain conditions, including neuropathic pain, inflammatory pain, cancer pain and post-operative pain following surgery, including dental surgery. These indications might also include acute pain, skeletal muscle pain, low back pain, upper extremity pain, fibromyalgia and myofascial pain syndromes, orofascial pain, abdominal pain, phantom pain; tic douloureux and atypical face pain, nerve root damage and arachnoiditis, geriatric pain, central pain and inflammatory pain.
- Neurodegenerative diseases; including Alzheimer's disease, Huntington's chorea, Creutzfeld-Jacob disease, Pick's disease, demyelinating disorders, such as multiple sclerosis and ALS, other neuropathies and neuralgia, multiple sclerosis, amyotropical lateral sclerosis, stroke and head trauma.
- Addiction disorders, including :
  - Substance dependence or abuse with or without physiological dependence, particularly where the substance is alcohol, amphetamines, amphetamine-like substances, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, phencyclidine-like compounds, sedative-hypnotics, benzodiazepines and/or other substances, particularly useful for treating withdrawal from the above substances and alcohol withdrawal delirium.
  - Mood disorders induced particularly by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics, anxiolitics and other substances.
  - Anxiety disorders induced particularly by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine,

sedatives, hypnotics, anxiolitics and other substances and adjustment disorders with anxiety.

- Smoking cessation.
- Body weight control, including obesity.
- Sleep disorders and disturbances, including :
  - Dyssomnias and/or parasomnias as primary sleep disorders, sleep disorders related to another mental disorder, sleep disorder due to a general medical condition and substance-induced sleep disorder.
  - Circadian rhythms disorders.
  - Improving the quality of sleep.
- Sexual dysfunction, including sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorders, sexual dysfunction due to a general medical condition, substance-induced sexual dysfunction and sexual dysfunction not otherwise specified.

The present invention thus also relates to compounds of Formula (I) as defined hereinabove, the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof, as well as the pro-drugs thereof for use as a medicine. Further, the present invention also relates to the use of a compound of Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof , the N-oxide form thereof as well as the pro-drugs thereof for the manufacture of a medicament for treating depression, anxiety and body weight disorders or more generally any one of the diseases mentioned above.

The compounds according to the invention may also be suitable as add-on treatment and/or prophylaxis in the above listed diseases in combination with antidepressants, anxiolytics and/or antipsychotics which are currently available or in development or which will become available in the future, to improve efficacy and/or onset of action. This is evaluated in rodent models in which antidepressants, anxiolytics and/or antipsychotics are shown to be active. For example, compounds are evaluated in combination with antidepressants, anxiolytics and/or antipsychotics for attenuation of

stress-induced hyperthermia.

The invention therefore also relates to a pharmaceutical composition comprising the compounds according to the invention and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics as well as to the use of such a composition for the manufacture of a medicament to improve efficacy and/or onset of action in the treatment of depression and/or anxiety.

In vitro receptor and neurotransmitter transporter binding and signal-transduction studies can be used to evaluate the α_2-adrenoceptor antagonism activity and serotonine (5-HT) reuptake inhibitor activity of the present compounds. As indices for central penetration and potency to block the α_2-adrenoceptors and serotonin transporters, respectively, *ex vivo* α_2-adrenoceptor and serotonin transporter occupancy can be used. As indices of α_2-adrenoceptor antagonism *in vivo*, the reversal of the loss of righting reflex, observed in rats after subcutaneous injection or oral dosage of the compound before intravenous medetomidine administration in rats can be used (medetomidine-test). As indices of serotonine (5-HT) reuptake inhibition activity, the inhibition of head-twitches and excitation in rats, observed after subcutaneous injection or oral dosage of the compound before subcutaneous p-chloroamphetamine administration in rats can be used (pCA-test).

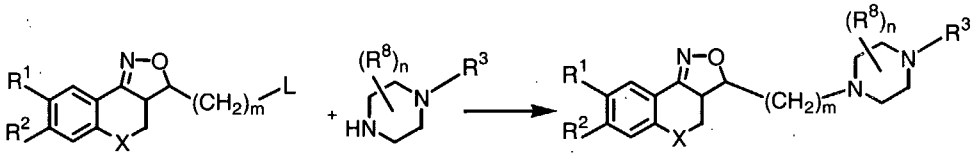
The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds of the invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for

administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

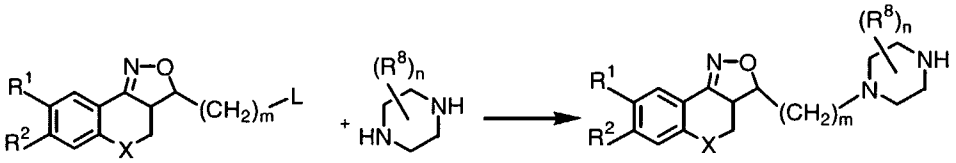
In particular, the compounds according to Formula (I) with a Pir-radical according to Formula (IIa) can be prepared by a nucleophilic substitution reaction with a substituted piperazine according to Formula (V) on an intermediate of Formula (IV). These reactions may be carried out in a reaction inert solvent such as dioxane, methylisobutylketone or N,N'-dimethylformamide, in the presence of a suitable base such as potassium carbonate, sodium carbonate or triethylamine, or even without a base, using in this latter case excess of reagent of Formula (V). Convenient reaction temperatures range between 100°C and 150°C.



(IV) (V) (VI)

In compound (IV), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy.

The compounds according to Formula (I) with a Pir-radical according to Formula (IIa) can also be prepared by a 2-step reaction scheme in which an intermediate of Formula (IV) is first reacted with a substituted piperazine according to Formula (VII) after which the R^3-radical is introduced into the molecule. Reaction conditions are similar to those described above for compounds of Formula (VI).

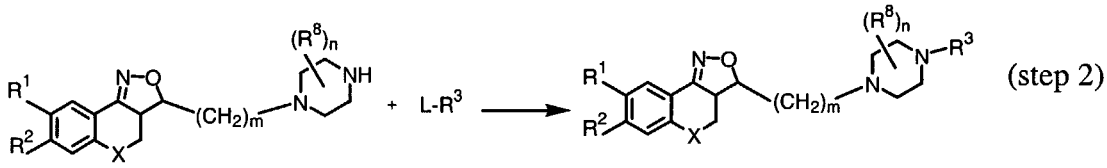


(step 1)

(IV) (VII) (VIII)

In compound (IV), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy.

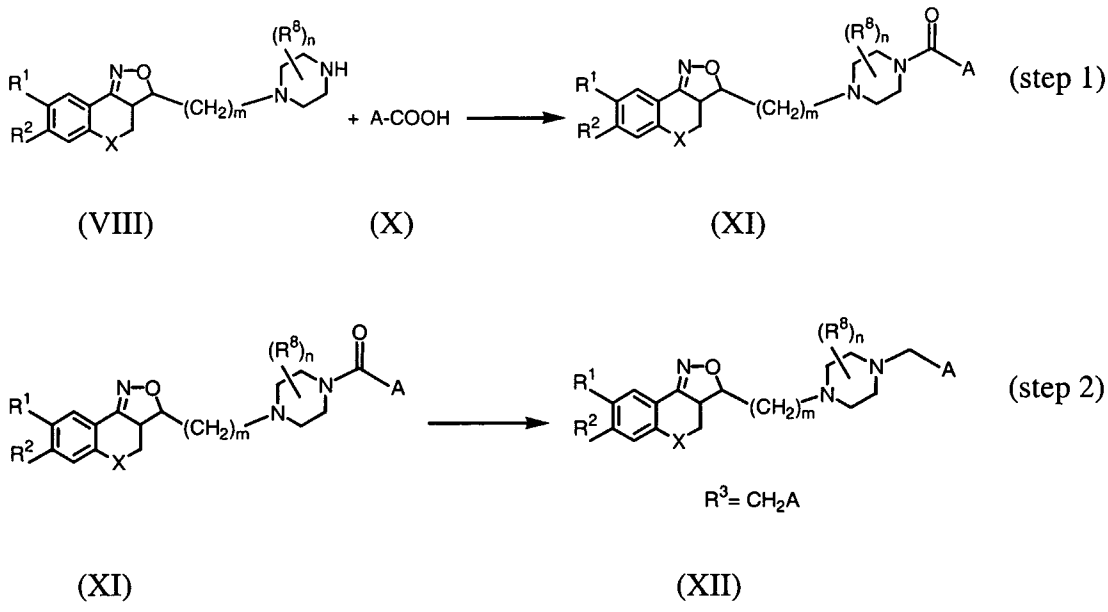
In intermediate compound (VII), one of the nitrogen function may also be protected, e.g. by a tert-butyloxycarbonyl-group.



(VIII) (IX) (VI)

In compound (IX), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy. Also R^3-CHO may be used as compound (IX).

The compounds according to Formula (I) with a Pir-radical according to Formula (IIa) can also be prepared by a 2-step reaction scheme in which an intermediate of Formula (VIII) is reacted with an acid according to Formula (X), followed by a subsequent reduction of the carbonyl-function of intermediate (XI). Reactions of step 1 may be carried out in a reaction inert solvent, such as chloroform, dichloromethane, tetrahydrofuran, dimethylformamide or a mixture thereof, using any of methods known to a person skilled in the art using condensation reagents such as 1,1'-carbonyldiimidazole, N,N'-dicyclohexylcarbodiimide or by previous transformation of carboxylic acid of Formula (X) into its corresponding acid chloride. Reactions shown in step 2 can be performed using a suitable reducing agent, such as lithium-aluminum hydride or aluminum hydride, in a suitable solvent, for example tetrahydrofuran. Generally, these reactions are run at a temperature ranging between –20°C and room temperature.



(VIII) (X) (XI)

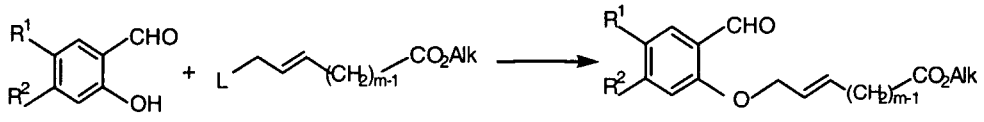
(XI) (XII)

In intermediate compounds (XI) and (XII), the A-group represents an optionally substituted aromatic homocyclic or heterocyclic ring system including a partially or completely hydrogenated hydrocarbon chain of maximum 5 atoms long of which one or more carbon atoms may be replaced by one or more atoms selected from the group of oxygen, nitrogen and sulphur, with which the ring system is attached to the Pir radical that has been defined above.

The substituents R^1 and R^2 may be changed or interconverted into each other by methods well known in the art, such as demethylation, acylation, esterification, amination and amidation.

The starting materials and some of the intermediates are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of Formula (IV) in which X=O may be prepared according to the following reaction scheme (Scheme 1) :

Scheme 1

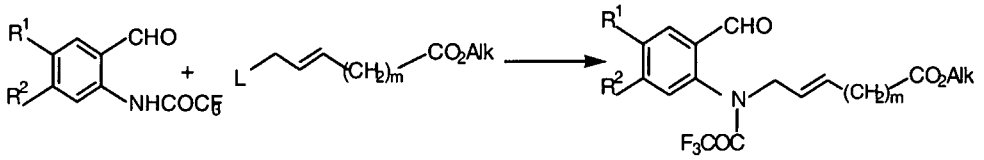


(step 1a)

(XIII) (XIV) (XV)

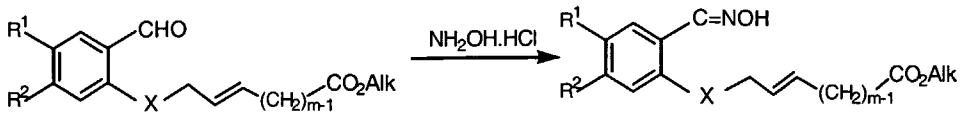
In intermediate compound (XIV), L represents any suitable reactive leaving group, in particular halo, such as chloro, bromo or iodo or sulfonyloxy, such as methylsulphonyloxy or 4-methylbenzenesulfonyloxy. Furthermore, Alk in intermediate compound (XIV) represents any C_{1-6} alkyl-group, in particular an ethyl-group and m is defined as in Formula (I).

Intermediates according to Formula (IV) in which X=NH may also be prepared in an equivalent manner according to above step 1, provided that the intermediate compound (XIII) is replaced by its amine-analog (XVI), preferably with the amine group protected with e.g. a $COCF_3$- group. The alkylation step may be carried out in a reaction inert solvent, for example, tetrahydrofuran or dimethylformamide, in the presence of a strong base, such as sodium or potassium hydride, and the addition of a crown-ether, such as 18-crown-6 or 15-crown-5. Convenient reaction temperatures range between room temperature and 60°C.



(step 1b)

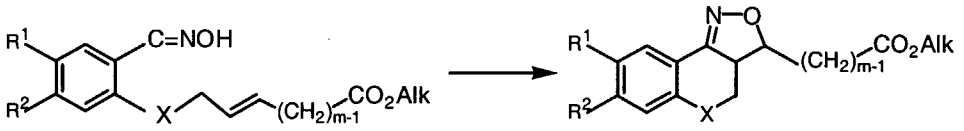
(XVI) (XIV) (XVII)



(step 2)

(XVII) (XVIII)

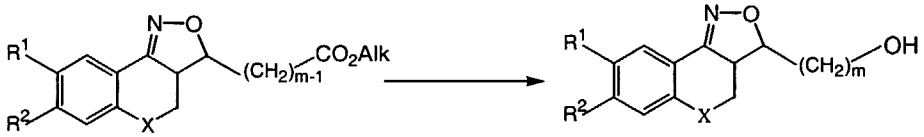
Intermediates of Formula (XVII) are converted to oximes of Formula (XVIII) using art-known techniques, such as using hydroxylamine hydrochloride in the presence of $NaHCO_3$ or pyridine in a reaction inert solvent, for example ethanol. Intermediate (XVIII) is oxidized to its nitril oxide and undergoes *in situ* an intramolecular cycloaddition, yielding compound of Formula (XIX). This oxidation can be carried out using a sodium hypochlorite solution in the presence of triethylamine in an inert solvent such as dichloromethane at room temperature. Oxidation can also be performed using Chloramine-T (*N*-chloro-4-methyl-benzenesulfonamide, sodium salt), stirring and heating in a solvent such as refluxing ethanol. At this stage the two stereocenters a and b of Formula (I) are formed.



(step 3)

(XVIII) (XIX)

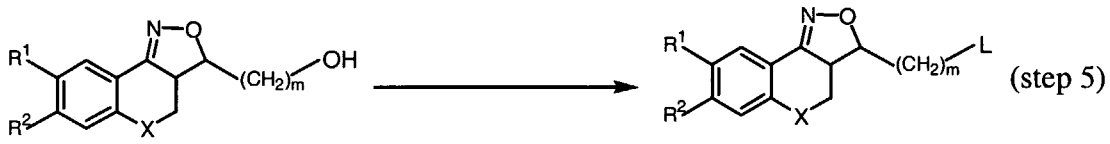
Preparation of a compound of Formula (XX) can be achieved using procedures known in the art, for instance by reduction of the carbonyl compound of Formula (XIX) in the presence of a suitable reducing agent, for example, sodiumborohydride in a suitable solvent, such as water, an alcohol, tetrahydrofuran or a mixture thereof, generally at room temperature.



(step 4)

(XIX) (XX)

Intermediate of Formula (IV) can be prepared from intermediate of Formula (XX) using standard techniques. Thus, reaction with methanesulfonyl chloride or 4-methylbenzenesulfonyl chloride in the presence of a base, such as triethylamine, in a reaction inert solvent, for example dichloromethane, at reaction temperatures ranging between 0°C and room temperature, yields the corresponding sulfonyloxy derivative intermediate (IV). The corresponding halo-derivative can also be prepared, e.g. treating intermediate of Formula (XX) with triphenylphosphine, in the presence of tetrachloromethane, in a reaction inert solvent, such as tetrahydrofuran, stirring and refluxing the mixture.



(step 5)

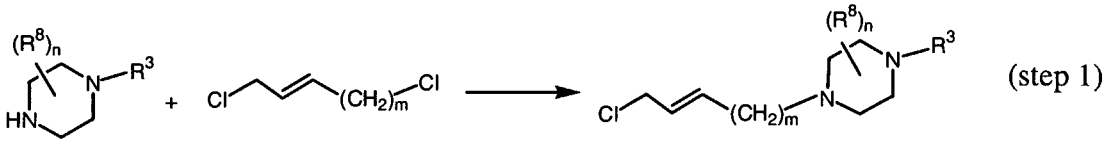
(XX) (IV)

It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC. Typically, intermediate compounds (IV) and final compounds according to Formula (I) may be separated into their enantiomeric forms.

Compounds according to the invention in which $X=CH_2$ may be prepared according to the following reaction scheme (Scheme 2) in which an intermediary compound according to Formula (V) is first N-alkylated with a dihaloderivative of Formula (XX) using standard techniques, in the presence or absence of a base and in an inert reaction solvent, such as chloroform, dichloromethane or 1,2-dichloroethane, and at reaction temperatures ranging between room temperature and 80°C, yielding an intermediate of

Formula (XXI). An aldehyde of Formula (XXII) was reacted with *tert*-butylamine in an aprotic solvent such as toluene, stirring and heating at reflux temperature with removal of water using a standard device, such as a Dean-Stark water separator, yielding an imine of Formula (XXIV). C-alkylation of intermediary compound of Formula (XXIV) with intermediate of Formula (XXI) can be achieved in the presence of an alkyl-lithium derivative, such as *n*-butyllithium, under an inert atmosphere and in a dry inert solvent, such as tetrahydrofuran, at low temperatures ranging between –78°C and 0°C, yielding an intermediate of Formula (XXV). The intermediate compound of Formula (XXVI) may be prepared by reaction of compound of Formula (XXV) with hydroxylamine, in the presence of a base such as sodium bicarbonate, in a solvent such as a lower alkyl-alcohol like ethanol, generally at room temperature. Finally, the oxidation of the oxime derivative of Formula (XXVI) to its nitril oxide and subsequent *in situ* cycloaddition to give compound of Formula (XXVII), may be achieved by similar standard techniques such as those described above for intermediate of Formula (XVIII) to give compounds of Formula (XIX).

Schema 2



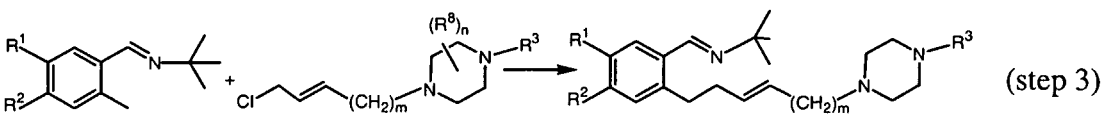
(step 1)

(V) (XX) (XXI)



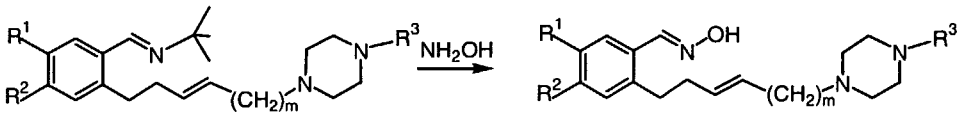
(step 2)

(XXII) (XXIII) (XXIV)



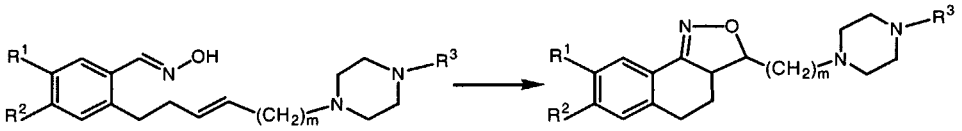
(step 3)

(XXIV) (XXI) (XXV)



(step 4)

(XXV) (XXVI)



(step 5)

(XXVI) (XXVII)

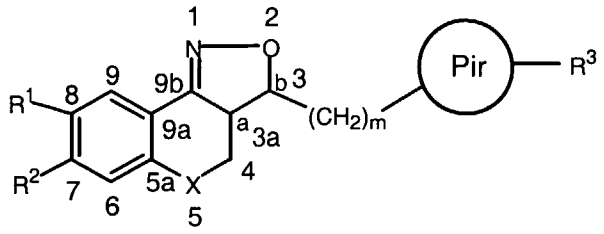
It is evident that the reaction steps disclosed above may be adapted to the specific reaction products. The reaction steps disclosed may be performed in any way known to the skilled person, including in solution or as solid phase reactions, the latter during which the reaction products are bound to a resin material and are - in a final cleavage step - released from the resin material. Examples of such embodiments and adaptations have been disclosed by way of the Examples further in this application.

The compound 3,3a,4,5-tetrahydronaphto[1,2-c]isoxazole-3-acetic acid (Formula (IV) wherein each of R^1 and R^2 are H, m=0, X=CH_2 and L=COOH) and has been disclosed in Synthetic Communications, 27(16), 2733-2742 (1997) as an intermediate for the syntheses of anti-inflammatory, analgesic and antipyretic compounds and is excluded from patent protection.

The following examples illustrate the present invention without being limited thereto.

Experimental part

The carbon ring numbering system for the compounds according to Formula (I) used in this application is as follows :



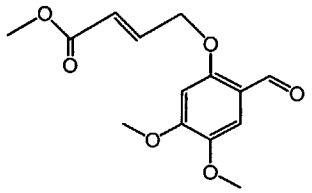
Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction. The stereogenic centers a and b in Formula (I) have respectively the ring numbers 3a and 3.

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropyl ether, and "THF" is defined as tetrahydrofurane.

A. Preparation of the intermediate compounds

Example A1.a

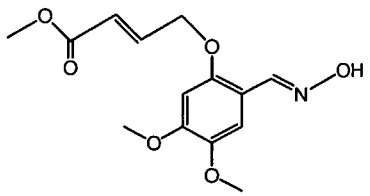
Preparation of intermediate1



A solution of 4-bromo-2-butenoic acid methyl ester (0.1647 mol) in DMF (50 ml) was added dropwise to a mixture of 2-hydroxy-4,5-dimethoxy-benzaldehyde (0.0823 mol) and K_2CO_3 (0.1647 mol) in DMF (200 ml). The reaction mixture was stirred for 2 hours at room temperature, filtered and the filtrate was evaporated to dryness. The residue was washed in a 10% aqueous NaOH solution, then extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated. The residue was washed with diethyl ether, then dried. Yielding: 20 g of intermediate 1 (87%).

Example A1.b

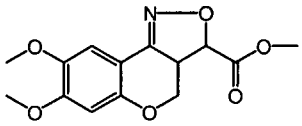
Preparation of intermediate 2



Hydroxylamine (0.045 mol) was added to a solution of intermediate 1 (0.041 mol) in ethanol (150 ml). Pyridine (57 ml) was added. The reaction mixture was stirred for 2 hours at room temperature, then poured out into water and acidified with concentrated HCl. This mixture was extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated. Yielding: 11.7 g (96%, crude yield). A sample (2 g) was purified by high-performance liquid chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was washed with diethyl ether, then dried. Yielding: 0.9 g intermediate 2 .

Example A1.c

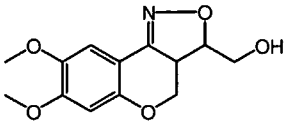
Preparation of intermediate 3



NaOCl, 5% (130 ml) was added dropwise to a mixture of intermediate 2 (0.037 mol) and Et_3N (1 ml) in CH_2Cl_2 (220 ml). The reaction mixture was stirred for 4 hours at room temperature, then washed with water, dried (Na_2SO_4), filtered, and the filtrate was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/2-propanone 100/0 and 95/5). The desired fractions were collected and the solvent was evaporated. Yielding: 5.8 g (54%, used in next traction step without further purification). A sample (2 g) was recrystallised from EtOAc. The precipitate was filtered off and dried. Yielding: 1.7 g of intermediate 3.

Example A1.d

Preparation of intermediate 4

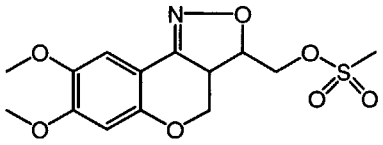


$NaBH_4$ (0.043 mol) was added portionwise to a solution of intermediate 3 (0.017 mol) in THF (50 ml) and H_2O (5 ml), stirred and cooled on an ice-bath. The resulting reaction mixture was stirred for 2 hours at room temperature. 2-Propanone was added while stirring for 30 min. The reaction mixture was washed with water and extracted with CH_2Cl_2. The separated organic layer was washed with brine, dried (Na_2SO_4),

filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5) and by high-performance liquid chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. A sample (1.8 g) was treated with diethyl ether, then dried. Yielding: 1.2 g of intermediate 4 (59%).

Example A1.e

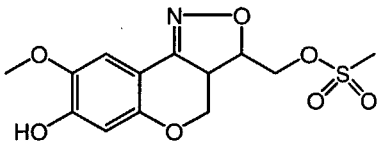
Preparation of intermediate 5



Et_3N (0.016 mol) was added to a solution of intermediate 4 (prepared according to A3) (0.0109 mol) in CH_2Cl_2 (60 ml). The mixture was cooled in an ice-bath. Methanesulfonyl chloride (0.012 mol) was added and the resulting reaction mixture was stirred for 30 min. Then, the mixture was washed with water, dried (Na_2SO_4), filtered and the solvent was evaporated. Yielding: 3.5 g of intermediate 5 (82%, used in next reaction step without further purification).

Example A1.f

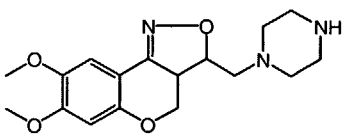
Preparation of intermediate 6



Reaction under N_2 atmosphere. BBr_3 (0.04368 mol) was added dropwise to a stirred solution of intermediate 5 (prepared according to A1.e) (0.00873 mol) in CH_2Cl_2 (100 ml), cooled to -78 °C. The reaction mixture was allowed to warm to -40 °C and stirring was continued for 2 hours at -40 °C. Then, the mixture was poured out into ice-water and extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. The residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3), then by HPLC (eluent: CH_2Cl_2/CH_3OH 99.5/0.5 to 90/10). Two product fraction groups were collected and their solvent was evaporated. Yield: 0.750 g of intermediate 6 (26%).

Example A1.g

Preparation of intermediate 7

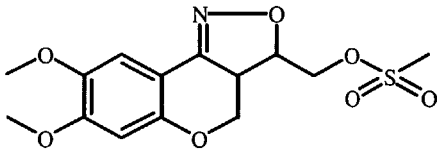


A mixture of intermediate 5 (prepared according A1d) (0.0422 mol) and piperazine (0.1267 mol) in 1,4-dioxane (15 ml) was stirred for 2 hours at 100 °C. The solvent was

evaporated. The residue was washed with water and extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. Yielding: 13 g of intermediate 7 (NMR: 85%).

Example A1.h

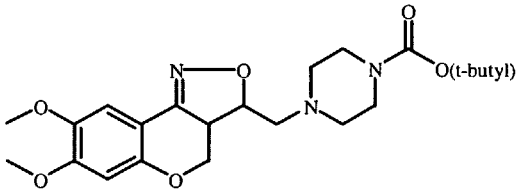
Preparation of intermediate 8



Intermediate 5 (prepared according to A1.e) (200 g, 0.58 mol) was separated into its enantiomers by chiral column chromatography over column LC110-2 with stationary phase CHIRALPAK-AD (2000 g, packing pressure: 45 bar, detector range: 2.56, wavelength: 240nm, temperature: 30 °C; injection solution: 200 g in 8.4 L CH_3CN; then, 19.6 L methanol (+ 2% ethanol) was added, then filtered; injection-volume: 700 ml; eluent: CH_3OH/CH_3CN 70/30 v/v). Two product fraction groups were collected and their solvent was evaporated. Yield: 95 g of intermediate 8 .

Example A1.i

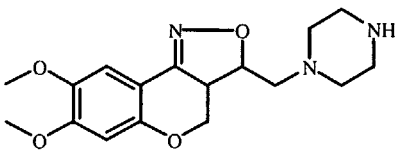
Preparation of intermediate 9



A mixture of intermediate 8 (prepared according A1.h) (0.0728 mol) and 1-(tert-butyloxycarbonyl)piperazine (0.087 mol) in dioxane (500ml) was stirred and refluxed for 48 hours. The solvent was evaporated and CH_2Cl_2 was added. H_2O and NaOH (50%) were added also and the mixture was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuum. Yield intermediate 9

Example A1.j

Preparation of intermediate 10

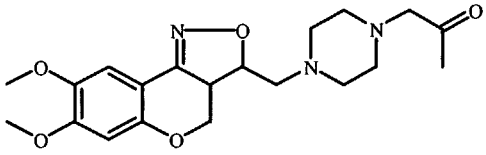


A mixture of intermediate 9 (0.00318 mol) and 2,2,2-trifluoroacetic acid (189ml) in CH_2Cl_2 (500ml) was stirred for 1 hour at room temperature. The solvent was evaporated and the residue was dissolved in CH_2Cl_2. NaOH (50%)was added and the

mixture was extracted. The separated organic layer was dried($MgSO_4$), filtered and the solvent was evaporated in vacuum. The residue was purified by short column chromatography over silica gel (eluent : CH_2Cl_2/(MeOH/NH_3) 100/0;95/5). The pure fractions were collected and the solvent was evaporated. Yield : 14.32g of intermediate 10 (59%).

Example A1.k

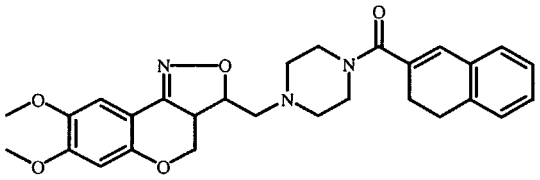
Preparation of intermediate 11



A mixture of intermediate 10 (0.00599 mol), 1-Chloro-2-propanone (0.00599 mol) and K_2CO_3 (0.01199 mol) in DMF (200 ml) was stirred for 24 hours at room temperature. The solvent was evaporated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. Yield: (quantitative yield) of intermediate 11 .

Example A1.l

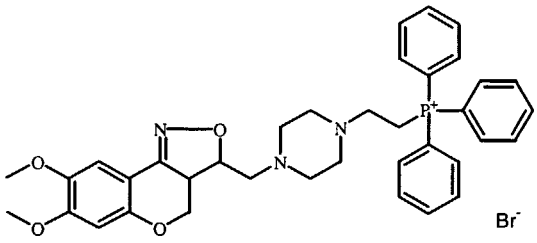
Preparation of intermediate 12



Reaction under N_2 atmosphere. A mixture of 3,4-Dihydro-2-naphthalenecarboxylic acid (0.0043 mol) and 1,1'-carbonylbis[1H-imidazole] (0.0047 mol) in CH_2Cl_2, dry was stirred for one hour at room temperature. A solution of intermediate 7 (prepared according to A1.g) (0.0043 mol) in CH_2Cl_2, dry was added and the resulting reaction solution was stirred for ± 24 hours at room temperature. The solution was washed with water, then extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. Yield: 0.4 g of intermediate 12 (22%).

Example A1.m

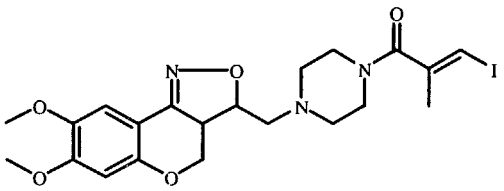
Preparation of intermediate 13



Ethenyltriphenylphosphonium bromide (0.0025 mol) was added to a solution of intermediate 7 (prepared according A1.g) (0.003 mol) in CH_2Cl_2 (20 ml). The reaction mixture was stirred for 4 hours at room temperature. The solvent was evaporated under reduced pressure. Yield: 2.2 g of intermediate 13 , used in next reaction step, without further purification.

Example A1.n

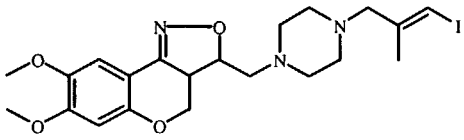
Preparation of intermediate 14



To a solution of (E)-3-iodo-2-methylpropenoic acid (0.009 mol) in CH_2Cl_2, dry (100ml) at room temperature under N_2 flow, 1,1'-carbonylbis[1H-imidazole] (0.0099 mol) was added. The mixture was stirred for 1 hour, then intermediate 7 (prepared according to A1.g) (0.009 mol) was added. The reaction mixture was stirred at room temperature for 16 hours, washed with H_2O and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue (white foam) was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 99/1). The pure fractions were collected and the solvent was evaporated. Yield : 3.82g of intermediate 14 (white solid, 81%).

Example A1.o

Preparation of intermediate 15



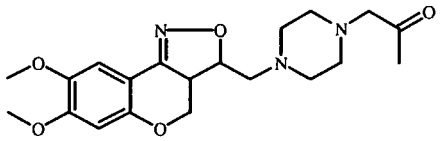
[3α(E),3A α]

A solution of $LiAlH_4$, 1.0 M/THF (0.00848 mol) in THF (100ml) was stirred and refluxed under N_2 flow at -20°C. $AlCl_3$ (0.0093 mol) was added in one portion and the

resulting mixture was stirred at -20°C for 10 minutes. A solution of intermediate 14 (prepared according to A1.n) (0.0077 mol) in THF (100ml) was added dropwise and the resulting mixture was stirred at -20°C for 1 hour. A saturated NH_4Cl-solution 20% was added dropwise at -10°C and the reaction mixture was allowed to warm to room temperature. H_2O was added to the suspension and was extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was treated with Et_2O and dried. Yield : 3.73g of intermediate 15 (white solid, 94%).

Example A1.p

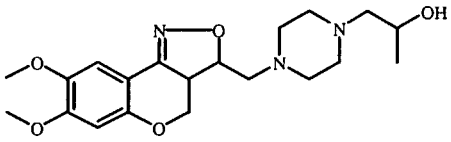
Preparation of intermediate 16



A mixture of intermediate 7 (prepared according A1.g) (0.015 mol), 1-chloro-2-propanone (0.015 mol) and K_2CO_3 (0.030 mol) in CH_3CN (60 ml) was stirred for 24 hours at room temperature. The solvent was evaporated. The residue was partitioned between water and CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. Yield: 4.79 g of intermediate 16 (82%).

Example A1.q

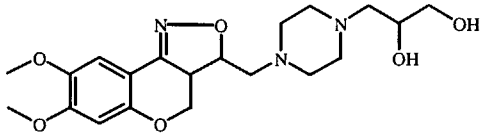
Preparation of intermediate 17



$NaBH_4$ (0.0128 mol) was added portionwise to a solution of intermediate 16 (prepared according A1.p) (0.0051 mol) and H_2O (3.2 ml) in THF (40.5 ml), at 0 °C. The reaction mixture was stirred overnight at room temperature, then treated with a 10% aqueous NH_4Cl solution. This mixture was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The desired fractions were collected and the solvent was evaporated. Yield: 1.6 g of intermediate 17 (80%).

Example A1.r

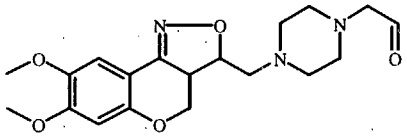
Preparation of intermediate 18



Intermediate 7 (prepared according A1.g) (0.03 mol) was dissolved in CH_3CN (200 ml) and K_2CO_3 (0.27 ml) was added. Oxiranemethanol (0.27 mol) was added and the reaction mixture was stirred over the weekend at 60°C. The solvent was evaporated in vacuo. The residue was partitioned between water and CH_2Cl_2. The organic layer was separated, dried (Na2SO4), filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparatory HPLC ((1) eluent: CH_2Cl_2/(CH3OH/NH_3) 95/5, then (2) eluent: CH_2Cl_2/CH_3OH 90/10). The product fractions were collected and the solvent was evaporated. Yield: 7.5 g (61%) of pure intermediate 18 and 3.5 g of a mixture of starting material/target compound 1/1.

Example A1.s

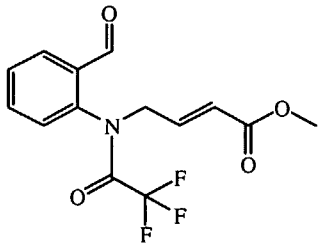
Preparation of intermediate 19



Intermediate 18 (prepared according A1.r) (0.0012 mol) was dissolved in CH_2Cl_2 (20 ml). A solution of periodic acid sodium salt (0.0024 mol) in $NaHCO_3/H_2O$ (q.s.) was added and the resulting reaction mixture was stirred vigorously for 2 hours. The mixture was partitioned between water and CH_2Cl_2. The separated organic layer was washed with brine, dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. Yield: 0.430 g of intermediate 19 (quantitative yield; used in next reaction step, without further purification).

Example A2.a

Preparation of intermediate 20

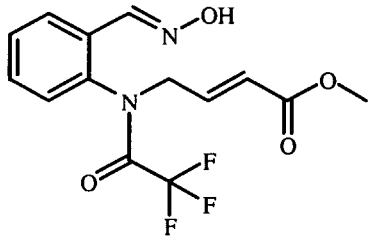


Reaction under N2 atmosphere. A solution of 2,2,2-trifluoro-N-(2-formylphenyl)-acetamide, (0.1869 mol) in DMF (375 ml) was added dropwise to NaH (0.2055 mol) in DMF (375 ml). The mixture was stirred for 30 min. at room temperature. A solution of 4-Bromo-3-butenoic acid methyl ester (0.2803 mol) in DMF (200 ml) was added dropwise. Then, 18-crown-6 (catalytic quantity) was added. The resulting reaction

mixture was stirred for 2 hours at 60 °C, then overnight at room temperature. The solvent was evaporated. The residue was washed in water and extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue was purified by open column chromatography over silica gel (eluent: CH_2Cl_2/hexane 90/10, 100/0 and with CH_2Cl_2/2-propanone 96/4, 90/10 and 80/20). The pure fractions were collected and the solvent was evaporated. Yielding: 44.37 g of intermediate 20 (75%, used in next reaction step, without further purification).

Example A2.b

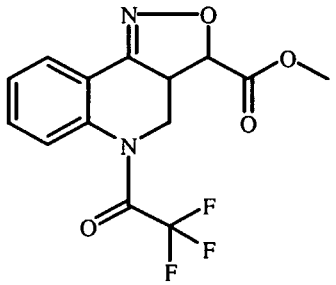
Preparation of intermediate 21



Hydroxylamine (0.169 mol) and pyridine (0.211 mol) were added to a solution of intermediate 20 (prepared according to A2.a) (0.1407 mol) in ethanol (450 ml) and the resulting reaction mixture was stirred for 3 hours at room temperature. The mixture was washed with a 10% citric acid solution, then extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. Yielding: 45.76 g of intermediate 21 (98%, used in next reaction step, without further purification).

Example A2.c

Preparation of intermediate 22

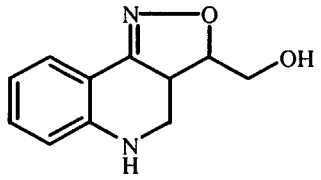


A mixture of intermediate 21 (prepared according to A2.b) (0.0658 mol) and N-chloro-4-methyl-benzenesulfonamide, sodium salt (0.0658 mol) in ethanol (500 ml) was stirred and refluxed for 2 hours. The mixture was concentrated in vacuo, filtered over dicalite, and the filtrate was washed with water and brine, then extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue was purified by open column chromatography over silica gel (eluent: CH_2Cl_2/2-propanone 100/0, 96/4, 90/10 and 80/20). The desired fractions were collected and the solvent was evaporated. The residue (syrup) was crystallized from

hexane, then washed with DIPE, and dried. Yielding: 12.32 g of intermediate 22 (57%).

Example A2.d

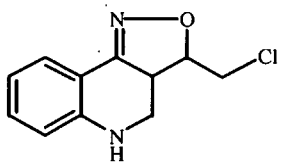
Preparation of intermediate 23



$NaBH_4$ (0.0289 mol) was added portionwise to a mixture of intermediate 22 (prepared according to A2.c) (0.0116 mol) in THF (81 ml) and H_2O (6.8 ml), stirred and cooled on an ice-bath. The resulting reaction mixture was stirred overnight at room temperature. The mixture was treated with a saturated aqueous NH_4Cl solution, then extracted with EtOAc. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was washed with CH_2Cl_2, then recrystallized from EtOAc. The precipitate was filtered off and dried. Yielding: 0.9 g of intermediate 23 (38%).

Example A2.e

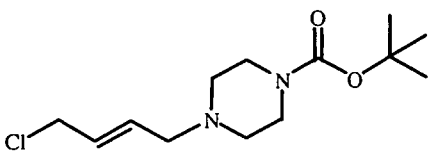
Preparation of intermediate 24



A mixture of intermediate 23 (prepared according A2.d) (0.001468 mol) and triphenylphosphine (0.001909 mol) in tetrachloromethane (30 ml) and THF (20 ml) was stirred and refluxed for 3 hours. The solvent was evaporated till dryness. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/hexane 90/10, then 100/0). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from methanol. The precipitate was filtered off and dried. Yielding: 2.6 g of intermediate 24 (79%).

Example A3.a

Preparation of intermediate 25

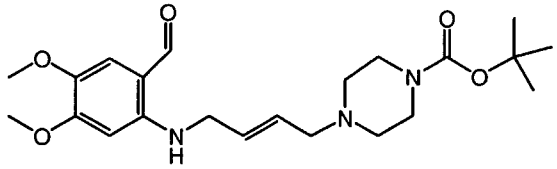


1,1-Dimethylethyl 1-piperazinecarboxylate (0.02 mol) was added portionwise to a solution of 1,4-dichloro-2-butene (0.025 mol) in $CHCl_3$ (60 ml). The reaction mixture was stirred for 24 hours at room temperature, then stirred and refluxed for 24 hours.

The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc). The pure fractions were collected and the solvent was evaporated. Yielding: 2.2 g of intermediate 25 (40%).

Example A3.b

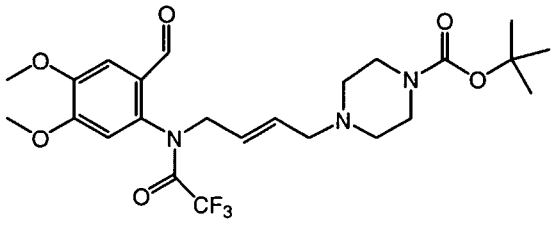
Preparation of intermediate 26



Reaction was carried out under N_2 flow. A mixture of NaH, 60% (0.0579 mol) and 18-crown-6 (cat.quant.) in THF (25ml) was cooled. A mixture of 2-Amino-4,5-dimethoxybenzaldehyde (0.0579 mol) in THF (50ml) was added portionwise. The reaction was stirred at room temperature for 30 min. A mixture of intermediate 25 (prepared according to A3.a) (0.0386 mol) in THF (50ml) was added portionwise. The mixture was stirred at room temperature for 3 days and then treated with NH_4Cl (10%). The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated till dryness. The residue was purified by short open column chromatography (eluent: CH_2Cl_2/CH_3OH 99/1 and 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 5.5g of intermediate 26 (23%).

Example A3.c

Preparation of intermediate 27

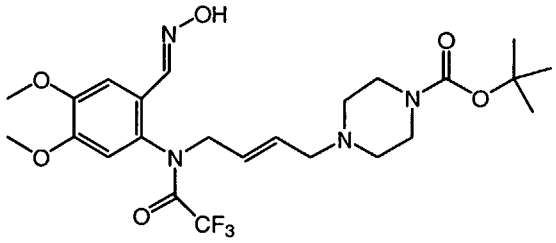


The reaction was carried out under N_2 flow. A mixture of intermediate 26 (prepared according A2.b) (0.02 mol) in THF (80ml) and 18-crown-6 (cat.quant.) were added portionwise to a mixture of NaH, 60% (0.03 mol) in THF (20ml). The mixture was stirred at room temperature for 20 min. trifluoroacetic acid anhydride (0.022 mol) was added portionwise. The mixture was stirred at room temperature for 3 hours, treated with a solution of NH_4Cl (20%) and then extracted with CH_2Cl_2 and the solvent was evaporated till dryness. The residue was purified by short column chromatography over

silica gel (CH_2Cl_2/CH_3OH 99/1 and 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 5.3g of intermediate 27 (58%).

Example A3.d

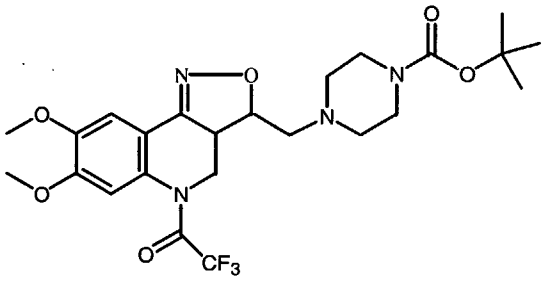
Preparation of intermediate 28



A mixture of intermediate 27 (prepared according to A3.c) (0.0115 mol), hydroxylamine (0.0126 mol) and $NaHCO_3$ (0.023 mol) in ethanol, abs. (60ml) was stirred at room temperature for 24 hours, filtered off and the solvent was evaporated till dryness. Yield: 5.8g of intermediate 28 (95%).

Example A3.e

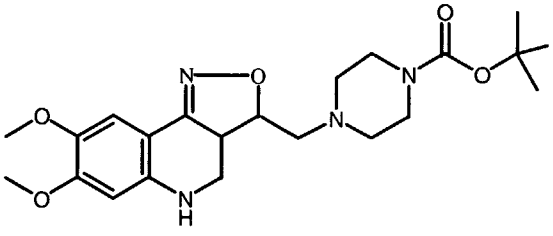
Preparation of intermediate 29



1-chloro-2,5-Pyrrolidinedione (0.0272 mol) was added portionwise to a solution of intermediate 28 (prepared according to A3.d) (0.0109 mol) in CH_2Cl_2 (100ml). The mixture was stirred at room temperature for 2 hours. Et_3N (0.0272 mol) was added dropwise. The mixture was stirred at room temperature overnight, quenched with a K_2CO_3 10% solution, then extracted and the solvent was evaporated till dryness. Yield: of intermediate 29 .

Example A3.f

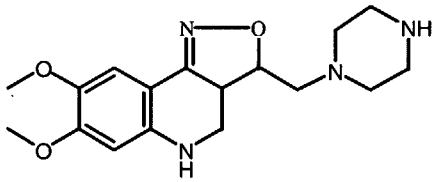
Preparation of intermediate 30



A mixture of intermediate 29 (prepared according to A3.e) (0.0109 mol) and LiOH (0.0119 mol) in H_2O (17.5ml) and 1,4-dioxane (70ml) was stirred at room temperature for 3 hours. The mixture was treated with a NaOH (2N) solution and then extracted with CH_2Cl_2. The solvent was evaporated till dryness. The residue was purified by short open column chromatography (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 2.07g of intermediate 30 (45%).

Example A3.g

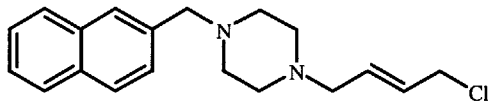
Preparation of intermediate 31



Trifluoroacetic acid (7.9ml) was added dropwise to a solution of intermediate 30 (0.0047 mol) in CH_2Cl_2 (33ml). The mixture was stirred at room temperature for 3 hours, cooled and basified with a 50% NaOH solution. The mixture was extracted and the solvent was evaporated till dryness. Yield: 1.6g of compound 31 (100%).

Example A4.a

Preparation of intermediate 32

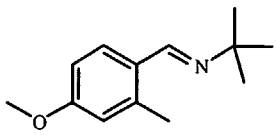


E

1,4-dichloro-2-butene (0.03 mol) was added to a mixture of 1-(2-naphthylmethyl)piperazine (0.025 mol) and $NaHCO_3$ (0.025 mol) in CH_2Cl_2 (75 ml). The reaction mixture was stirred for 24 hours at room temperature. The solid was filtered off, washed with more CH_2Cl_2 and the organic solution was washed with a 10% Na_2CO_3 solution, dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc/2-propanone). The pure fractions were collected and the solvent was evaporated. Yield: 3.4 g of intermediate 32 (43%).

Example A4.b

Preparation of intermediate 33

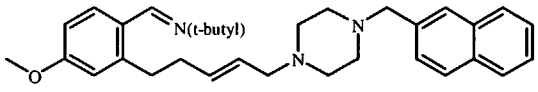


A solution of NS (0.0546 mol) and tert-Butylamine (0.0983 mol) in toluene (75 ml) was stirred and refluxed for 24 hours using a Dean-Stark water separator. The solvent

was evaporated. The residue was purified by distillation (bp at 0.5 mm Hg: 75 °C). Yielding: 8.1 g of intermediate 33 (72%).

Example A4.c

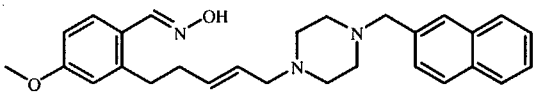
Preparation of intermediate 34



Reaction under N_2 atmosphere. n-BuLi (0.014 mol) was added dropwise to a solution of intermediate 33 (prepared according A4.a) (0.0125 mol) and 2,2,6,6-tetramethylpiperidine (0.0012 mol) in THF, dry (25 ml), stirred at -78 °C. The mixture was stirred for 3 hours at -10 °C. A solution of intermediate 32 (prepared according A4.b) (0.0083 mol) in THF, dry (25 ml) was added portionwise at -10 °C. The reaction mixture was stirred for 24 hours at room temperature, then quenched with NH_4Cl (10%) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was evaporated. Yielding: 5.6 g of intermediate 34 (100%)

Example A4.d

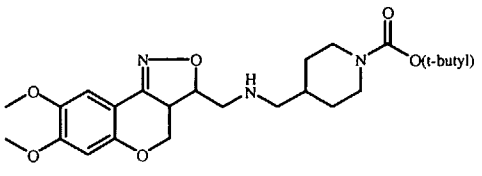
Preparation of intermediate 35



$NaHCO_3$ (0.015 mol) and hydroxylamine (0.0125 mol) were added to a solution of intermediate 34 (prepared according A4.c) (0.0083 mol) in ethanol, abs. (50 ml). The reaction mixture was stirred for 24 hours at room temperature. CH_2Cl_2 was added and the solid was filtered off and washed with CH_2Cl_2. The solvent was evaporated. The residue was taken up into CH_2Cl_2 and washed with 10% Na_2CO_3 and with brine. The organic layer was separated, dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc/2-propanone). The desired fractions were collected and the solvent was evaporated. Yielding: 0.9 g of intermediate 35 (24%).

Example A5.a

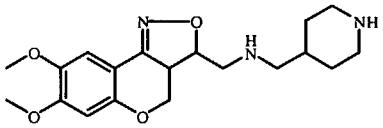
Preparation of compound 36



A mixture of A (0.029 mol) and intermediate5 (prepared according to A1.e) (0.0058 mol) in 1,4-dioxane (5 ml) was stirred for 6 hours at 100 °C. The solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2 - 97/3). The product fractions were collected and the solvent was evaporated. Yield: 3.3 g of intermediate 36

Example A5.b

Preparation of compound 37

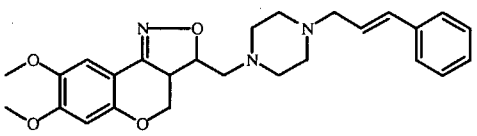


Trifluoroacetic acid (11.7 ml) was added dropwise to a solution of intermediate 36 (prepared according to A5.f) (0.0071 mol) in $CHCl_3$ (50 ml) and the resulting reaction mixture was stirred for 3 hours at ± 10 °C. The reaction mixture was cooled, then further alkalized with 50% NaOH. This mixture was extracted and the extract's solvent was evaporated. Yield: 2.5 g of intermediate 37 (quantitative yield; used in next reaction step, without further purification).

B. Preparation of the final compounds

Example B1.a

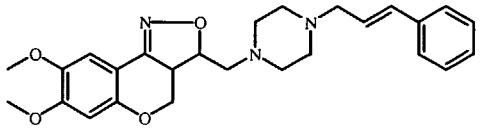
Preparation of compound 1



A mixture of intermediate5 (prepared according to A1.e) (0.0291 mol) and 1-(3-phenyl-2-propenyl)-piperazine, (0.0582 mol) was heated for 2 hours at 100 °C. The crude reaction mixture was washed with water and extracted with CH_2Cl2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5) and by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 80/20). The pure fractions were collected and the solvent was evaporated. This fraction was separated into its optical enantiomers by chiral column chromatography over Chiralpak AD (eluent: C_2H_5OH/CH_3CN 90/10). The (B)-enantiomeric fractions were collected and the solvent was evaporated. The residue was dissolved in methanol and converted into the hydrochloric acid salt (1:2). The precipitate was filtered off and dried. Yielding: 2.47 g of compound 1 .

Example B1.b

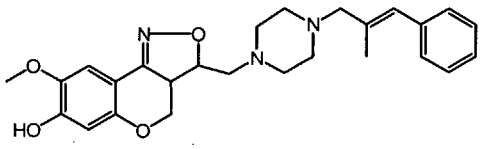
Preparation of compound 2



A mixture of intermediate 5 (prepared according to A1.e) (0.0044 mol) and (3-phenyl-2-propenyl)-piperazine (0.0087 mol) was stirred for 2 hours at 100 °C. The reaction mixture was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5), then by high-performance liquid chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 96/4). The pure fractions were collected and the solvent was evaporated. The residue (1.4 g) was treated with diethyl ether, then dried. Yielding: 1.2 g of compound 2 (60%).

Example B1.c

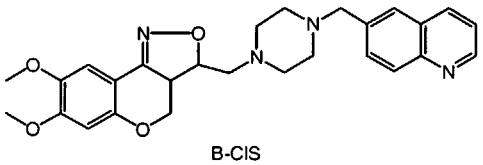
Preparation of compound 3



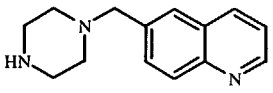
A mixture of intermediate 6 (0.00227 mol), (E) 1-(2-methyl-3-phenyl-2-propenyl)piperazine (0.00273 mol) and $NaHCO_3$ (0.00455 mol) in dioxane (30 ml) was stirred and refluxed for 48 hours. The solvent was evaporated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1), then by HPLC (eluent: CH_2Cl_2/CH_3OH 99.5/0.5 to 98/2). The desired fractions were collected and the solvent was evaporated. Yield: 0.17 g of compound 3 .

Example B1.d

Preparation of compound 4



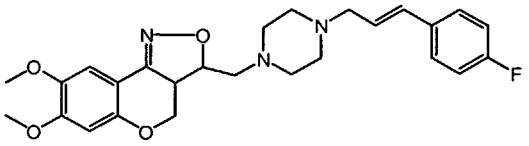
B-CIS

A mixture of intermediate 8 (prepared according to A1.h) (0.0058 mol) and  (0.0116 mol) in dioxane (10ml) was stirred and refluxed for 8 hours, then stirred overnight at room temperature, then stirred and refluxed for 18 hours. The mixture was treated with H_2O and extracted with CH_2Cl_2. The solvent of the separated organic layer was evaporated. The residue was purified by short open column chromatography (eluent : CH_2Cl_2/MeOH 97/3). The desired fractions were

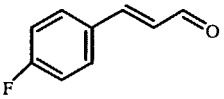
collected and the solvent was evaporated. The residue was treated with diethyl ether, then dried. Yield : 0.9g of compound 4 (33%).

Example B1.e

Preparation of compound 5



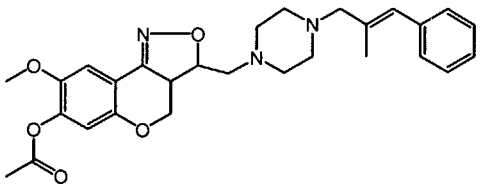
A mixture of intermediate 10 (prepared according to A1.i) (0.0029 mol),



(0.0058 mol), AcOH (0.48g) and $(AcO)_3BHNa$ (0.4g) in 1,2-dichloroethane (20ml) was stirred and refluxed overnight. The mixture was treated with H_2O and extracted. The solvent of the separated organic layer was evaporated. The residue was purified by short column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 97/3). The desired fractions were collected and the solvent was evaporated. The residue was treated with diethyl ether, then dried. Yield : 1.07g of compound 5 (82%).

Example B1.f

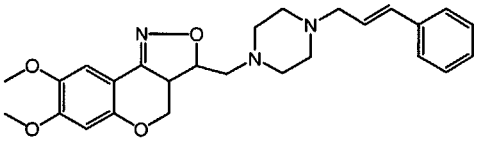
Preparation of compound 6



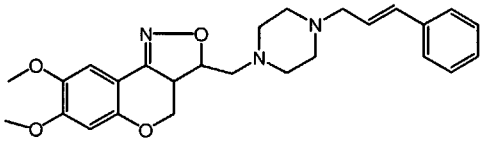
A mixture of compound 3 (prepared according ex. B1) (0.00020 mol), acetylchloride (0.00024 mol) and Et_3N (0.00061 mol) in chloroform (10 ml) was stirred at room temperature for 2 hours. Water was added and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by CC-TLC on Chromatotron (eluent: CH_2Cl_2/CH_3OH 97/3; then 99/1). The desired fractions were collected and the solvent was evaporated. Yield: 0.022 g of compound 6 .

Example B1.g

Preparation of compound 7



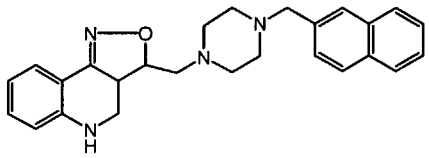
Preparation of compound 8



Compound 2 (prepared according B1.b) (0.0022 mol) was separated and purified into its optical enantiomers by chiral column chromatography over Chiralpak AD (eluent: C_2H_5OH/CH_3CN 90/10). Two fraction groups were collected and their solvent was evaporated. Yielding: ± 1.5 g of fraction 1 (LCI purity: > 99.5%) and ± 1.5 g of fraction 2 (LCI purity: > 99.5%). Fraction 1 was crystallized by treatment with hexane, stirring overnight. The precipitate was filtered off and dried. Yielding: 1.08 g of compound compound 7 (grease solid). Fraction 2 was crystallized by treatment with EtOAc, stirring overnight. The precipitate was filtered off and dried. Yielding: 0.54 g of 8 (grease solid).

Example B2.a

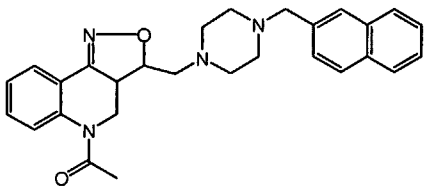
Preparation of compound 9



A mixture of intermediate 24 (prepared according A2.e) (0.0022 mol), 1-(2-naphthalenylmethyl)-piperazine, (0.0044 mol) and KI (catalytic quantity) in 1,4-dioxane (2.5 ml) was stirred and refluxed overnight. The reaction mixture was washed with water and this mixture was extracted with CH_2Cl_2. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2), then by HPLC (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 96/4). The pure fractions were collected and the solvent was evaporated. The residue was treated with DIPE, filtered off and dried. Yield: 0.3 g of compound 9 (30%).

Example B2.b

Preparation of compound 10

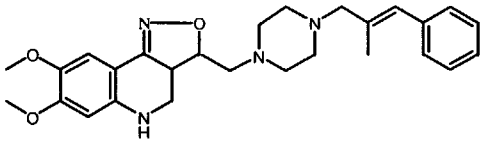


Reaction under N_2 atmosphere. A solution of compound 9 (prepared according to B2.a) (0.0012 mol) in THF, dry (3 ml) and 18-crown-6 (catalytic quantity) was slowly added to a solution of NaH, 60% (0.0018 mol) in THF, dry (2 ml). The reaction mixture was stirred for 30 min at room temperature. acetylchloride (0.0013 mol) was added dropwise and the reaction mixture was stirred for 3 hours at room temperature.

The reaction mixture was treated with aqueous NH_4Cl and extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2), then by HPLC (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 0.26 g of compound 10 (52%).

Example B3a

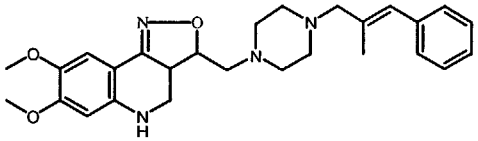
Preparation of compound 11



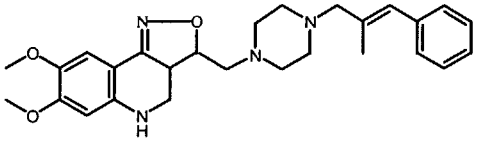
A mixture of intermediate 31 (prepared according A3.g) (0.0045 mol), (E)- (3-chloro-2-methyl-1-propenyl)-benzene (0.0037 mol) and K_2CO_3 (0.0037 mol) in DMF (15 ml) was stirred at 70°C for 2 hours. The mixture was washed with water and then extracted with CH_2Cl_2 . The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The desired fractions were collected and the solvent was evaporated. The residue was purified again by HPLC (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 98/2). The pure fractions were collected and the solvent was evaporated. The residue was treated with DIPE. The precipitate was filtered off and dried. Yield: 0.34 g of compound 11 (20%).

Example B3.b

Preparation of compound 12



Preparation of compound 13

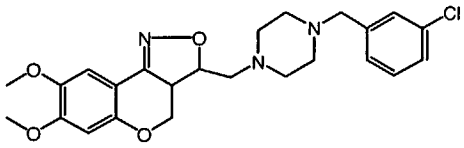


Compound 11 (prepared according to B3.a) (0.00605 mol) was purified by high-performance liquid chromatography over Chiralcel OJ (eluent : hexane/MeOH/EtOH 20/24/56). The desired fractions were collected and the solvent was evaporated. Yield : fractions A and B. Fraction A was purified by high-performance liquid chromatography over RP BDS C18 (eluent : (0.5%NH_4OAc in H_2O/CH_3CN(90/10))/MeOH 70/30). The pure fractions were collected and the organic solvent was evaporated. The aqueous layer was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue

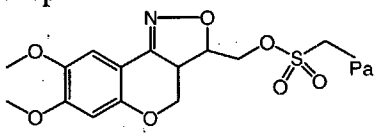
was stirred in hexane and the precipitate was filtered off. Yield : 0.69g of compound 12 . Fraction B was purified by high-performance liquid chromatography over RP BDS C18 (eluent : (0.5%NH_4OAc in H_2O/CH_3CN(90/10))/MeOH 70/30). The pure fractions were collected and the organic solvent was evaporated. The aqueous layer was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was stirred in hexane and the precipitate was filtered off. Yield : 0.67g of compound 13 .

Example 4

Preparation of compound 14



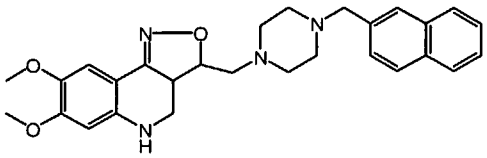
Reaction done in solid phase using a Quest 210 synthesizer (Argonaut Technologies, San Carlos, USA). N,N-Diisopropylethylamine (0.0036 mol) was added to a suspension of



(0.0006 mol) in acetonitrile (4 ml). 1-(2-Chlorophenylmethyl)piperazine (0.0012 mol) was added and the resulting reaction mixture was stirred for 20 hours at 80 °C. Then, each reaction vessel was filtrated and the filtrate was evaporated. The residue was HPLC purified. The pure fractions were collected and the solvent was evaporated. Yield: 0.102 g of compound 14

Example B5.a

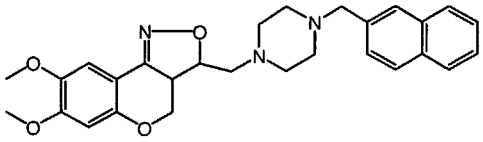
Preparation of compound 15



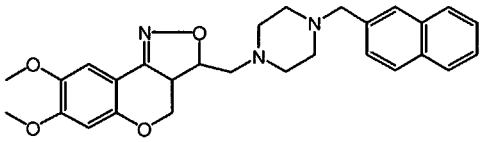
A mixture of intermediate 7 (prepared according A1.g) (0.0036 mol), 2-(bromomethyl)naphthalene (0.0055 mol) and K_2CO_3 (0.0055 mol) in MIK (15 ml) was stirred for ± 24 hours at 100 °C. The crude reaction mixture was washed with water, then extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by high-performance liquid chromatography over silica gel (2 x) ((I) eluent: CH_2Cl_2/CH_3OH 95/5; (II) eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 98/2). The pure fractions were collected and the solvent was evaporated. Yielding: 0.2 g of compound 15 (11%).

Example B5.b

Preparation of compound 16



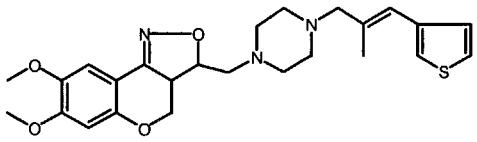
Preparation of compound 17



Compound 15 (prepared according B5.a) (0.0106 mol) was separated into its enantiomers by column chromatography (eluent: hexane/C_2H_5OH gradient 30/70 to 0/100; column: CHIRALPAK AD 1000 Å 20 μm DIACEL). Two pure fractions were collected and their solvents were evaporated. The residue was dissolved in CH_3OH and converted into the hydrochloric acid salt (1:2). The precipitate was filtered off and dried. Yielding: 2.08g of compound 16 (36%) and 2.19g of compound 17 (38%).

Example B6

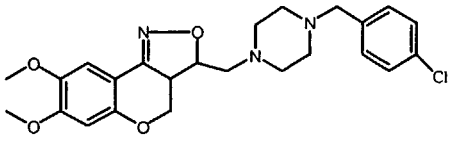
Preparation of compound 18



A mixture of intermediate 7 (prepared according to A1.g) (0.0045 mol), 2-methyl-3-(3-thienyl)-2-propenal (0.00675 mol), $NaBH(OAc)_3$ (0.00675 mol) and HOAc (2 drops) in 1,2-dichloroethaan (30 ml) was stirred overnight at room temperature. A saturated aqueous NH_4Cl solution was added and this mixture was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3), then by HPLC (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1 to 98/2). The product fractions were collected and the solvent was evaporated. Yield: 0.965 g of compound 18 (46%; containing also 3% of the (Z) isomer!).

Example B7

Preparation of compound 19

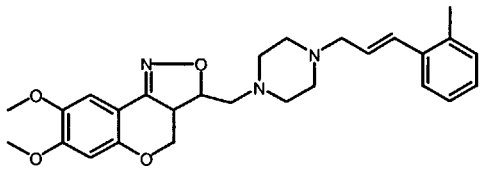


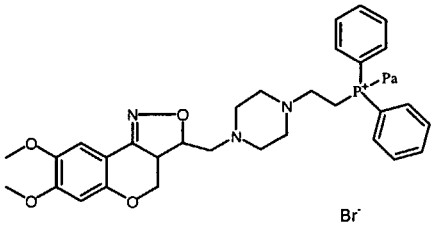
A mixture of intermediate 10 (prepared according to A1.j) (0.003 mol), 4-chlorobenzaldehyde (0.0045 mol) and $(AcO)_3BHNa$ (0.0045 mol) in 1,2-dichloroethane (30ml) was stirred and refluxed for 2 hours at room temperature. A saturated aqueous NH_4Cl-solution was added and the mixture was extracted with

CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated in vacuum. The residue was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2/(MeOH/NH_3) 97/3). The desired fractions were collected and the solvent was evaporated. The residue was precipitated from DIPE. Yield : 1.180g of compound 19 (57%).

Example B8

Preparation of compound 20

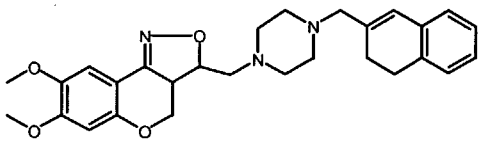


A mixture of  (0.00036 mol),

2-methylbenzaldehyde (0.00108 mol) and $NaOCH_3$, 30% in CH_3OH (0.00108 mol) in CH_3OH, dry (8 ml) was stirred for 16 hours at 65 °C (Reaction done in solid phase using a Quest 210 synthesizer (Argonaut Technologies, San Carlos, USA)). The mixtures were filtered and the filtrate was HPLC purified (eluent: CH_2Cl_2/(CH_3OH/NH_3) 98/2). The desired fractions were collected and the solvent was evaporated. Yield: 0.032 g of compound 20.

Example B9

Preparation of compound 21



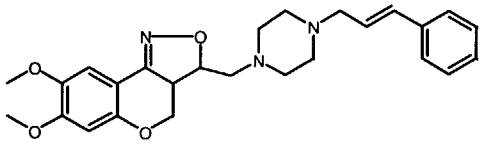
CIS

Reaction under N_2 atmosphere. Solution $LiAlH_4$, 1 M/THF (0.8 ml) was stirred at -20 °C. $AlCl_3$ (0.0009 mol) was added in one portion. The resulting solution was stirred for 10 min at -20 °C. A solution of intermediate 12 (prepared according to A1.l) (0.0008 mol) in THF, dry (5 ml) was added dropwise and the resulting reaction mixture was stirred for one hour at -20 °C. Then, a saturated aqueous NH_4Cl solution was added carefully. The reaction mixture was washed with water, then extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was treated with ether. The residue (0.13 g) was purified by

CC-TLC Chromatotron (eluent: CH_2Cl_2/CH_3OH 97/3). The pure fractions were collected and the solvent was evaporated. Yield: 0.09 g of compound 21 (30%).

Example B10

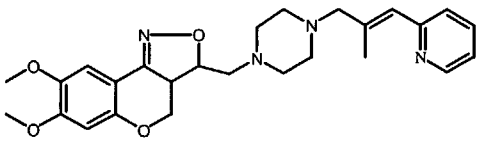
Preparation of compound 22



Reaction under N_2 flow. A mixture of intermediate 13 (prepared according to A1.m) (0.001 mol) in CH_3OH, dry (20 ml) was stirred at room temperature. $NaOCH_3$, 30% in CH_3OH (0.002 mol) was added. 5-Indanecarboxaldehyde (0.002 mol) was added and the resulting reaction mixture was stirred and refluxed for 16 hours. The reaction mixture was allowed to cool to room temperature. 20% NH_4Cl was added and this mixture was extracted with CH_2Cl_2. The separated organic layer was washed with water, with brine, dried (Na_2SO_4), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by short open column chromatography and CC-TLC (eluent: CH_2Cl_2/CH_3OH 98/2). The product fractions were collected and the solvent was evaporated. Yield: 0.035 g of compound 22 (7.2%, light-brown solid).

Example B11

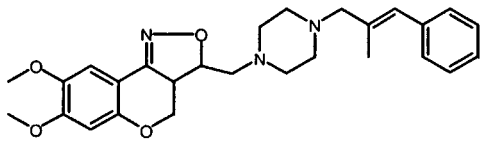
Preparation of compound 23



A mixture of intermediate 15 (prepared according to A1.o) (0.00136 mol), 2-(trimethylstannyl)pyridine (0.0027 mol) and $Pd(PPh_3)_4$ (0.00013 mol) in toluene (20ml) was heated to 100°C. The reaction mixture was stirred for 16 hours and was allowed to cool to room temperature. H_2O was added and the mixture was extracted with CH_2Cl_2. The separated organic layer was collected, washed with H_2O and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by short open column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 98/2). The pure fraction was collected and the solvent was evaporated. The resulting residue was purified by CC-TLC on Chromatotron (eluent : CH_2CL_2/MeOH 98/2). The pure fraction was collected and the solvent was evaporated. Yield : 0.044g of compound 23 (light brown solid, 7%).

Example B12

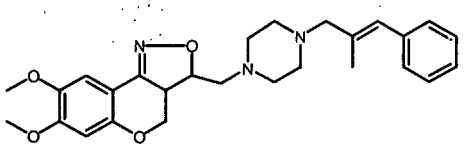
Preparation of compound 24

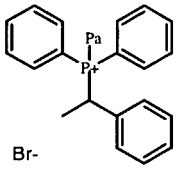


Reaction under N2 atmosphere. n-BuLi, 2.5M/hexanes (0.0062 mol) was added dropwise to a stirred solution of (p-Flurorobenzyl)triphenylphosphonium chloride (0.0062 mol) in THF (20 ml). The mixture was stirred for 15 min. A solution of intermediate 11 (prepared according A1.k) (0.00514 mol) in THF (20 ml) was added dropwise. The reaction mixture was stirred for 16 hours at 50 °C. Water was added and this mixture was extracted with Et_2O. The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3), then by HPLC (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1) to separate the (E)/(Z) isomers. Two product fraction groups were collected and their solvent was evaporated. Yield: 0.651 g of compound 24 (26%, (E)).

Example B13

Preparation of compound 25

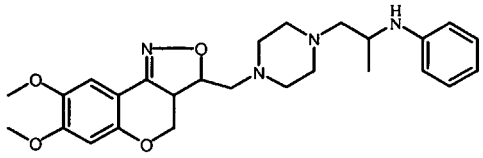


Resin 

(0.0016 mol; 1.5 mmole/g) was suspended in THF. 1.6 M BuLi (0.0015 mol) was added and the mixture was stirred for 15 min. The mixture was filtered and the filter residue (resin) was washed with anhydrous THF (3 x). The resin was suspended in THF (5 ml). Intermediate 19 (prepared according to A1.s) (0.0004 mol) was added and the reaction mixture was stirred overnight at 100 °C. The mixture was cooled, filtered and the filtrate was evaporated in vacuo. The residue was purified by preparatory HPLC (eluent: $CH_2Cl_2/(CH_3OH/NH3)$ 97/3). The product fractions were collected and the solvent was evaporated. Yield: 0.168 g of compound 25 .

Example B14

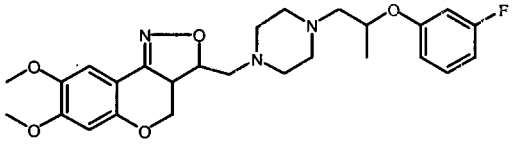
Preparation of compound 26

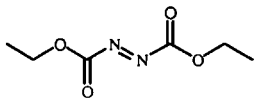


A mixture of intermediate 16 (prepared according to A1.p) (0.0025 mol), benzenamine (0.0028 mol) and $NaBH_4$ (0.0028 mol) in HOAc (50 ml) was stirred for 2 hours at room temperature. An aqueous NH_4OH solution was added. This mixture was extracted with CH_2Cl_2. The separated organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by short open column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1), then by flash column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 98/2). The product fractions were collected and the solvent was evaporated. Yield: 0.181 g of compound 26 (15%).

Example B15

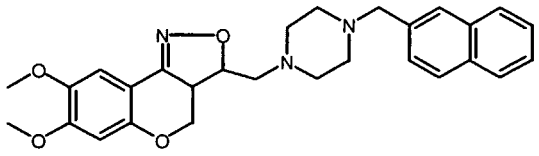
Preparation of compound 27



 (0.0018 mol) was added dropwise to a solution of intermediate 17 (prepared according to A1.q) (0.0012 mol), 3-fluorophenol (0.0018 mol) and PPh_3, pol. (0.0024 mol) in THF, dry (10 ml), under N_2 atmosphere. The reaction mixture was stirred overnight at room temperature. The mixture was filtered, washed with CH_2Cl_2 and CH_3OH, and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/EtOAc 2/1 and CH_2Cl_2/CH_3OH 96/4), then by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 97/3). The product fractions were collected and the solvent was evaporated. Yield: 0.29 g of compound 27 (50%).

Example B16

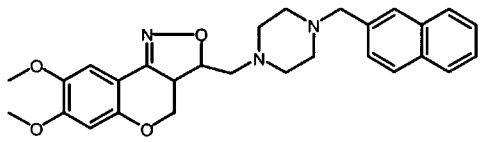
Preparation of compound 28



NaClO (4%) (0.005 mol) was added to a solution of intermediate 35 (prepared according A4.d) (0.002 mol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 4 hours at room temperature. Et_3N (0.004 mol) was added and the reaction mixture was stirred for 24 hours at room temperature. The organic layer was separated, washed with Na_2SO_3 (10%), dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: EtOAc and CH_2Cl_2/CH_3OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was taken up into diethyl ether, then filtered through dicalite and the filtrate was evaporated. The residue was dissolved in diethyl ether and converted into the hydrochloric acid salt (1:2). The precipitate was filtered off, washed with 2-propanone and diethyl ether, and dried. Yield: 0.15 g of compound 28 (15%).

Example B17

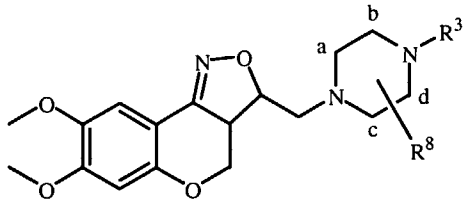
Preparation of compound 29

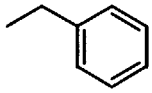
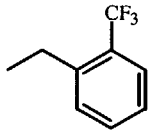
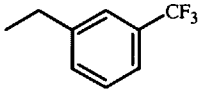
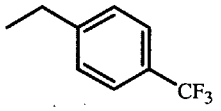
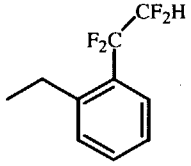
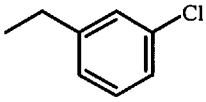
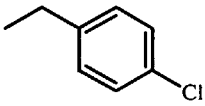
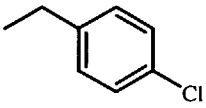
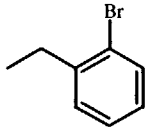
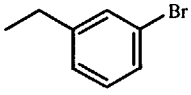
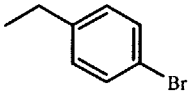
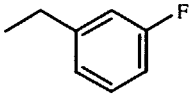


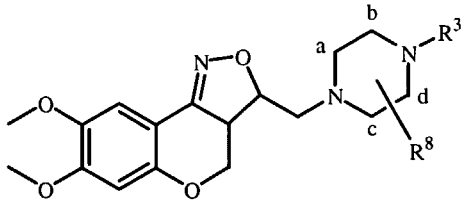
A mixture of intermediate 37 (prepared according to A5.g) (0.006 mol) and 2-(bromomethyl)naphthalene (0.003 mol) in dioxane (40 ml) was stirred at 100 °C for 6 hours, then overnight at room temperature. The reaction mixture was treated with a 10% aqueous K_2CO_3 solution, then extracted with CH_2Cl_2. The separated organic layer was evaporated. The residue was purified by short open column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5 and 90/10 and $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The product fractions were collected and the solvent was evaporated. The residue (1.49 g) was treated with diethyl ether, then dried. Yield: 0.8 g of compound 29 (53%).

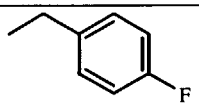
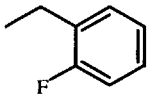
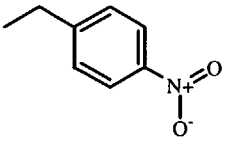
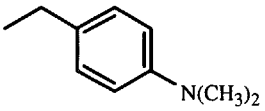
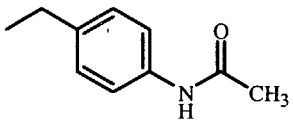
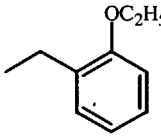
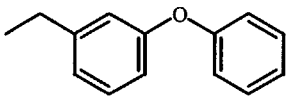
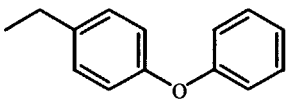
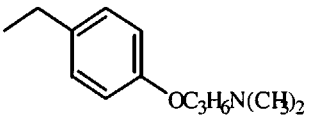
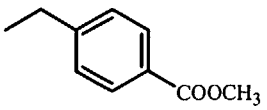
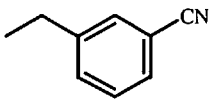
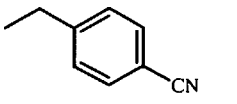
In the following tables (Tables 1-5) a number of compounds are given which have been prepared according to any one of the Examples above. All compounds have also been tested for their pharmacological activity.

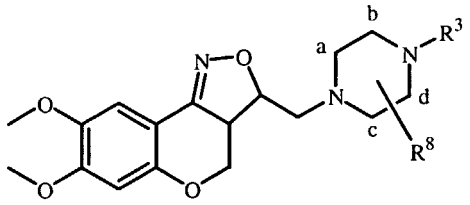
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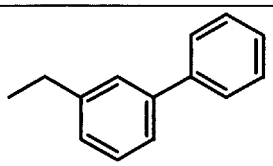
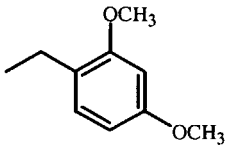
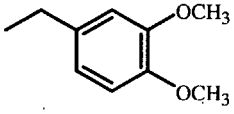
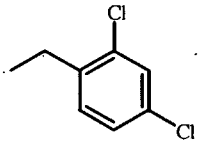
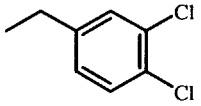
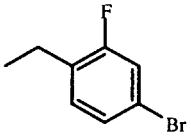
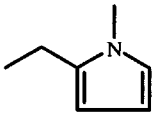
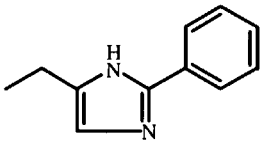
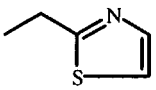
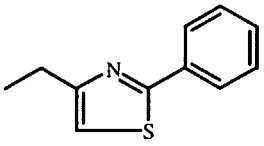
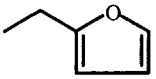


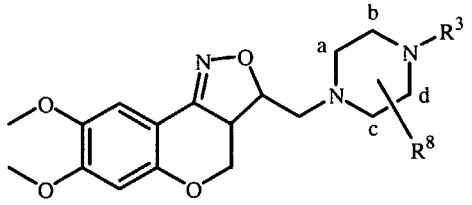
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85	B4	H	H	H	H		
89	B4	H	H	H	H		
80	B4	H	H	H	H		
14	B4	H	H	H	H		
86	B7	H	H	H	H		cis
19	B7	H	H	H	H		(B-cis)
84	B4	H	H	H	H		
90	B4	H	H	H	H		
91	B4	H	H	H	H		
285	B4	H	H	H	H		B-cis

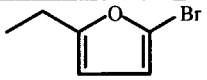
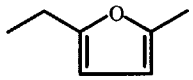
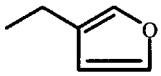
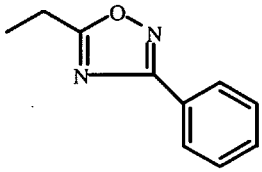
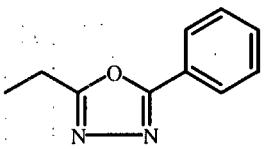
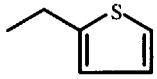
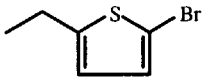
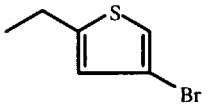
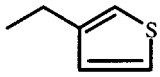
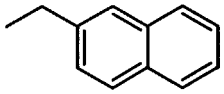
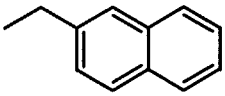
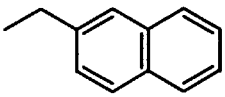
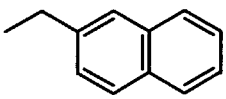
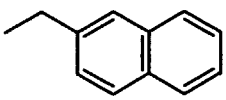


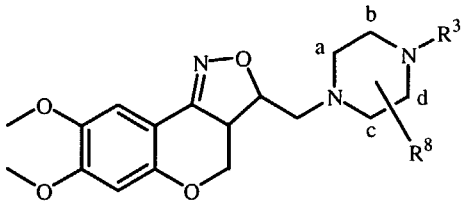
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
286	B4	H	H	H	H		B-cis HCl (1:2) Hydrate (1:1)
287	B4	H	H	H	H		B-cis
81	B4	H	H	H	H		
83	B4	H	H	H	H		
94	B4	H	H	H	H		
87	B4	H	H	H	H		
88	B4	H	H	H	H		
82	B4	H	H	H	H		
99	B4	H	H	H	H		
93	B4	H	H	H	H		
97	B4	H	H	H	H		
98	B4	H	H	H	H		

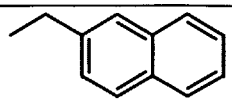
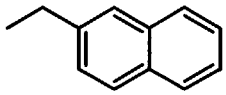
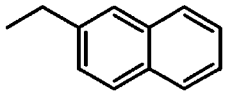
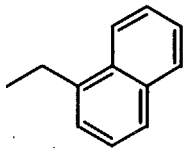
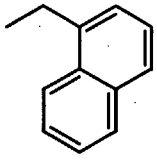
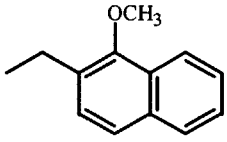
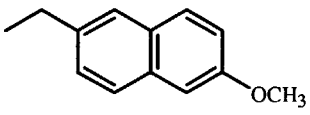
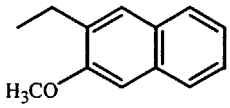
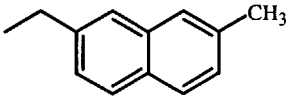
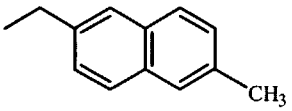
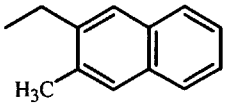


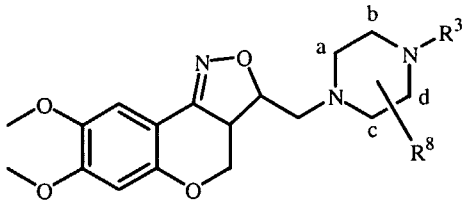
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
57	B1a/B1b	H	H	H	H		cis
95	B4	H	H	H	H		
96	B4	H	H	H	H		
288	B4	H	H	H	H		cis
289	B4	H	H	H	H		cis
290	B4	H	H	H	H		cis
291	B5b	H	H	H	H		cis
128	B5b	H	H	H	H		cis
292	B5b	H	H	H	H		cis
149	B5b	H	H	H	H		cis
293	B5b	H	H	H	H		cis

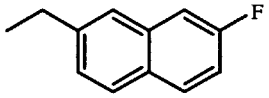
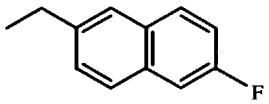
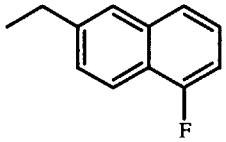
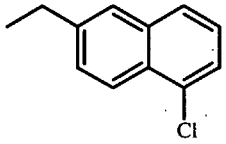
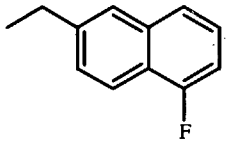
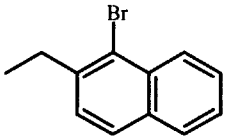
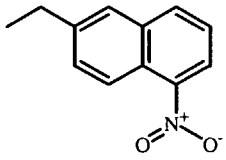
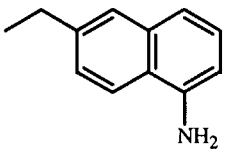
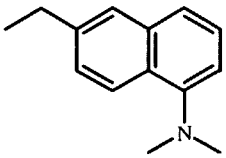
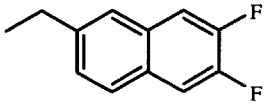


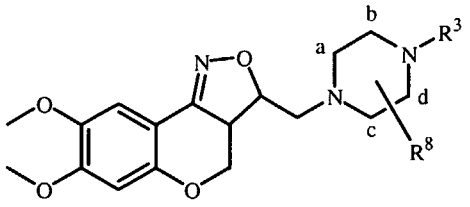
Comp. nr.	Ex. nr.	R^8				R^3	Phys.data and stereochemistry
		a	b	c	d		
294	B5b	H	H	H	H		cis
295	B5b	H	H	H	H		cis
296	B5b	H	H	H	H		cis
141	B5b	H	H	H	H		cis
138	B5b	H	H	H	H		cis
297	B5b	H	H	H	H		cis
298	B5b	H	H	H	H		cis
299	B5b	H	H	H	H		cis
300	B5b	H	H	H	H		cis
15	B5b	H	H	H	H		cis
34	B5b	H	H	H	H		[3α(R),3a α];. $HCl(1:2).H_2O(1:2)$
36	B1a/B1b	H	H	H	H		cis;.HCl(1:2)
16	B5b	H	H	H	H		[A-[3α,3a α]];. HCl(1:2)
17	B5b	H	H	H	H		[B-[3α,3a α]];. HCl(1:2)

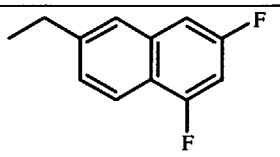
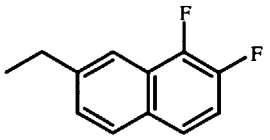
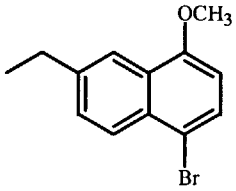
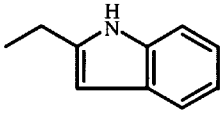
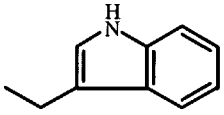
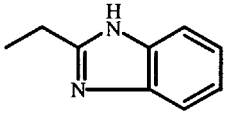
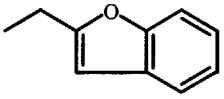
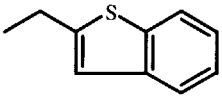
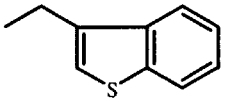
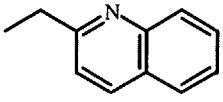
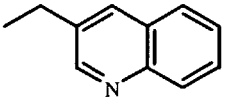


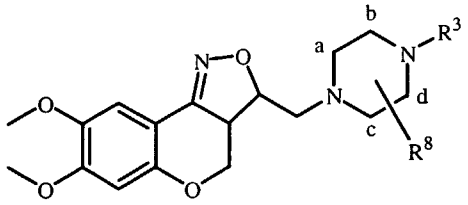
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
131	B5b	H	CH_3	H	CH_3		[3α(R*,S*),3a α]
132	B5b	CH_3	H	H	CH_3		[3α(R*,S*),3a α]; H_2O(1:1)
133	B5b	H	CH_3	H	H		[3α,3a α]
92	B4	H	H	H	H		
52	B1a/B1b	H	H	H	H		cis;.HCl(1:2)
75	B5a	H	H	H	H		cis
62	B5b	H	H	H	H		cis
71	B5b	H	H	H	H		cis
117	B5b	H	H	H	H		cis
72	B5b	H	H	H	H		cis
74	B1a/B1b	H	H	H	H		cis

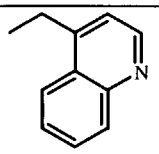
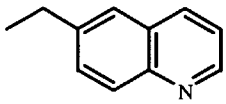
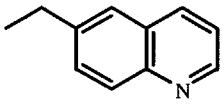
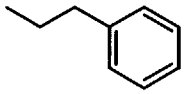
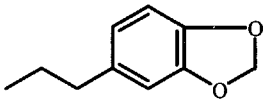
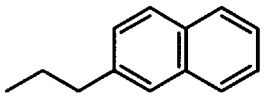
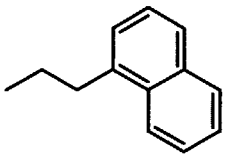
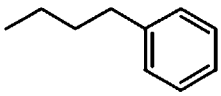
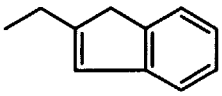
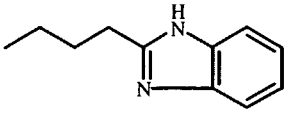
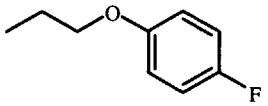
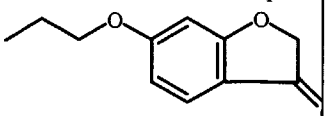


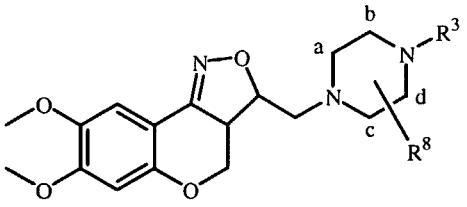
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
135	B5b	H	H	H	H		cis
76	B5b	H	H	H	H		cis
136	B5b	H	H	H	H		cis
301	B5b	H	H	H	H		cis
302	B5b	H	H	H	H		A-cis
77	B5a	H	H	H	H		cis
303	B5b	H	H	H	H		B-cis
304	B5b	H	H	H	H		B-cis
305	B5b	H	H	H	H		B-cis
140	B5b	H	H	H	H		cis

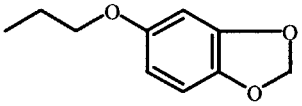
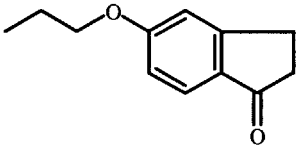
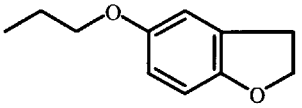
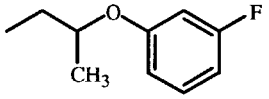
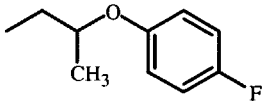
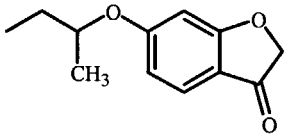
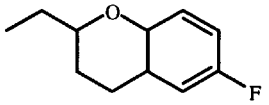
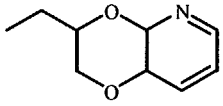
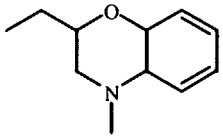
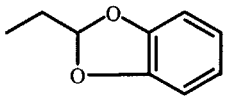


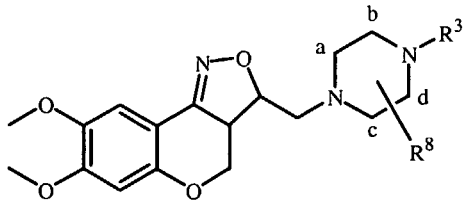
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
193	B5b	H	H	H	H		cis
206	B5b	H	H	H	H		cis
123	B5b	H	H	H	H		cis
51	B1a/B1b	H	H	H	H		cis
306	B5b	H	H	H	H		cis
37	B5b	H	H	H	H		cis;.HCl(1:2) .H_2O(1:3)
54	B5b	H	H	H	H		cis;.HCl(1:2)
49	B1a/B1b	H	H	H	H		cis;.HCl(1:2)
204	B5b	H	H	H	H		cis
45	B1a/B1b	H	H	H	H		
61	B1a/B1b	H	H	H	H		cis

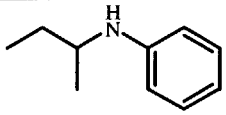
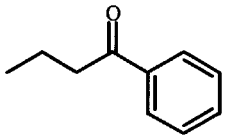
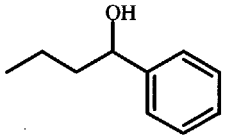
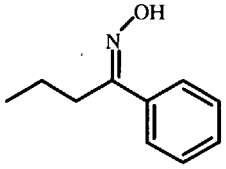
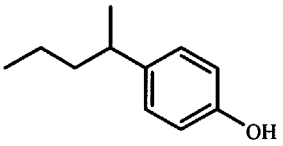
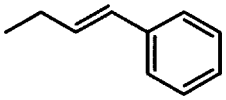
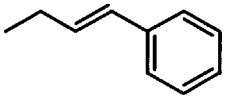
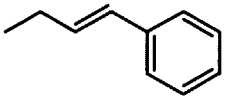
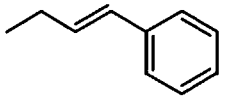
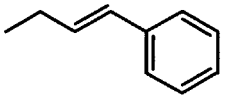
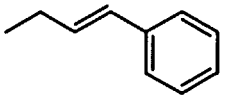


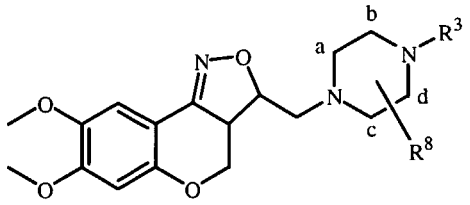
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
59	B1a/B1b	H	H	H	H		cis;.HCl(1:2) .H_2O(1:2)
58	B1a/B1b	H	H	H	H		cis
4	B1d/B1e	H	H	H	H		(B-cis)
33	B5b	H	H	H	H		cis
47	B1a/B1b	H	H	H	H		cis;.HCl(1:2)
50	B5b	H	H	H	H		cis;.HCl(1:2)
53	B5b	H	H	H	H		cis;.HCl(1:2)
32	B1a/B1b	H	H	H	H		cis
191	B5b	H	H	H	H		cis
56	B1a/B1b	H	H	H	H		cis
48	B1a/B1b	H	H	H	H		cis;.HCl(1:2)
67	B5b	H	H	H	H		cis

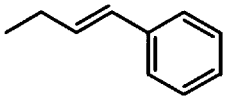
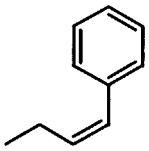
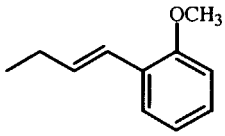
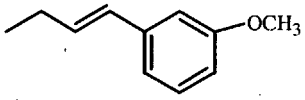
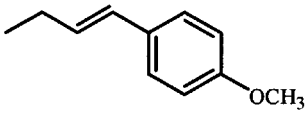
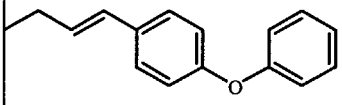
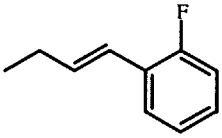
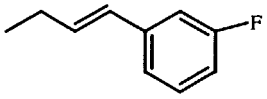
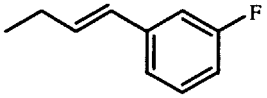
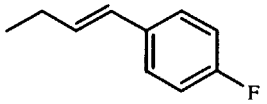
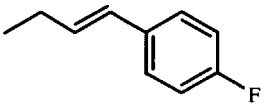


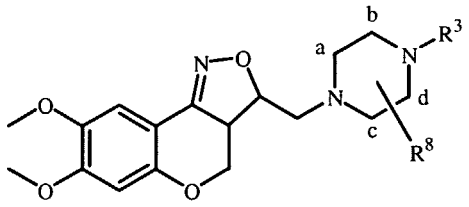
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
73	B5b	H	H	H	H		cis
78	B5b	H	H	H	H		cis
68	B5b	H	H	H	H		cis
27	B15	H	H	H	H		
147	B15	H	H	H	H		cis
142	B	H	H	H	H		cis
35	B5b	H	H	H	H		[3α(S),3a α]
307	B5b	H	H	H	H		cis
308	B5b	H	H	H	H		cis
66	B5a	H	H	H	H		cis

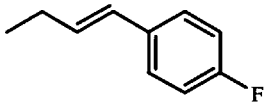
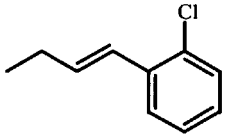
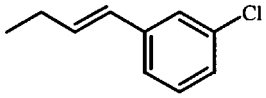
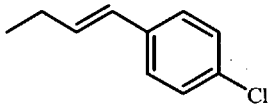
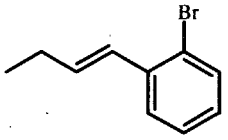
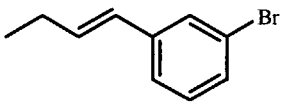
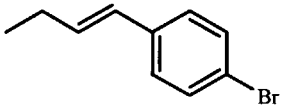
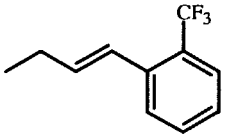
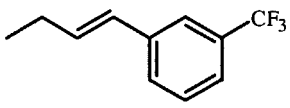
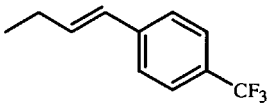
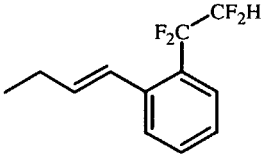


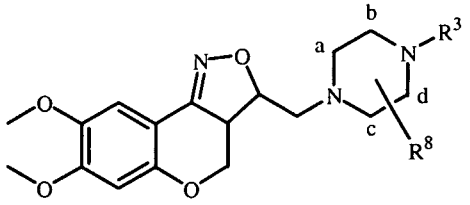
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
26	B14	H	H	H	H		[3α,3a α]
309	B14	H	H	H	H		B-cis
310	B14	H	H	H	H		B-cis
311	B14	H	H	H	H		B-cis
312	B1a/B1b	H	H	H	H		[B-[3α(E),3a α]]
2	B1a/B1b	H	H	H	H		[3α(E),3a α]
7	B1g	H	H	H	H		[A-[3α(E),3a α]]
8	B1g	H	H	H	H		[B-[3α(E),3a α]]
1	B1a/B1b	H	H	H	H		[B-[3α(E),3a α]];. HCl(1:2) .H_2O(1:1)
30	B1a/B1b	H	H	H	H		[3α(E),3a β]
46	B1a/B1b	H	H	H	H		[A-[3α(E),3a α]];. HCl(1:2)

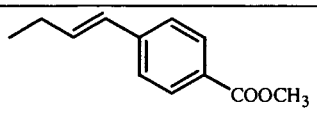
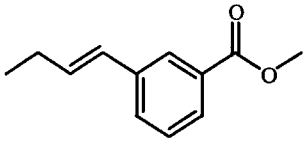
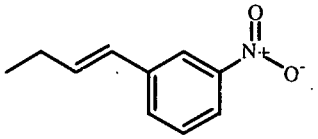
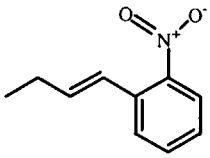
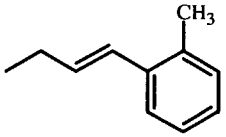
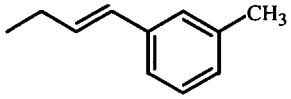
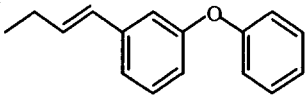
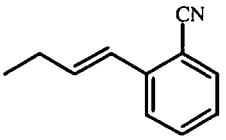
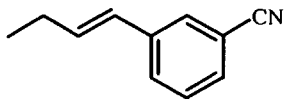
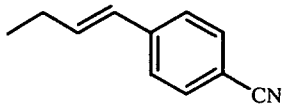


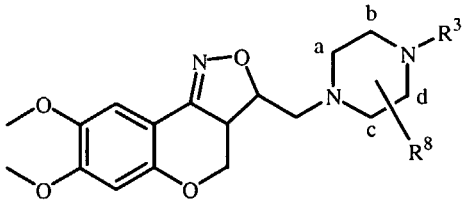
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
116	B8	H	H	H	H		cis
64	B10	H	H	H	H		[3α(Z),3a α]
41	B1a/B1b	H	H	H	H		[3α(E),3a α];. HCl(1:2)
38	B1a/B1b	H	H	H	H		[3α(E),3a α] ;. HCl(1:2)
39	B1a/B1b	H	H	H	H		[3α(E),3a α] ; .HCl(1:2)
102	B8	H	H	H	H		cis
44	B1a/B1b	H	H	H	H		[3α(E),3a α]
42	B1a/B1b	H	H	H	H		[3α(E),3a α]
189	B13B	H	H	H	H		cis
43	B1a/B1b	H	H	H	H		[3α(E),3a α] ;. HCl(1:2)
313	B1a/B1b	H	H	H	H		[A-[3α(E),3a α]]

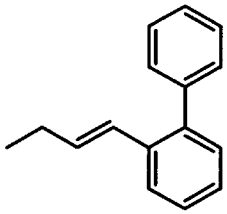
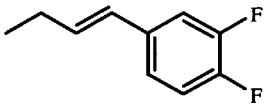
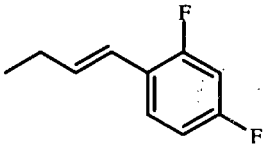
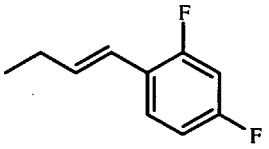
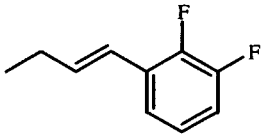
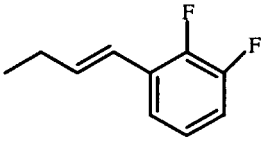
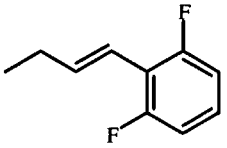
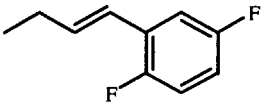
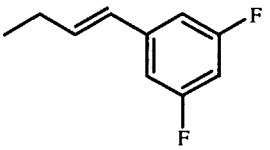


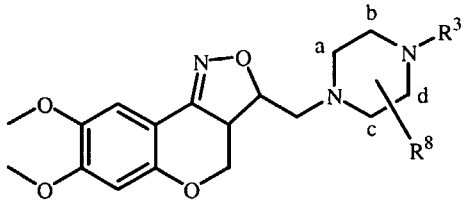
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
5	B1d/B1e	H	H	H	H		[B-[3α(E),3a α]]
100	B8	H	H	H	H		cis
108	B8	H	H	H	H		cis
113	B8	H	H	H	H		cis
105	B8	H	H	H	H		cis
106	B8	H	H	H	H		cis
107	B8	H	H	H	H		cis
111	B8	H	H	H	H		cis
101	B8	H	H	H	H		cis
103	B8	H	H	H	H		cis
112	B8	H	H	H	H		cis

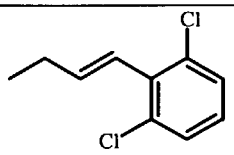
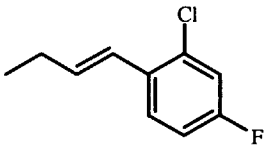
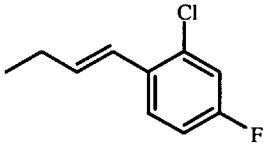
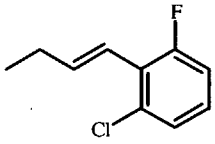
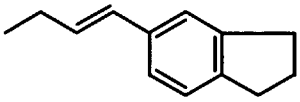
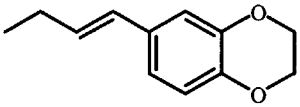
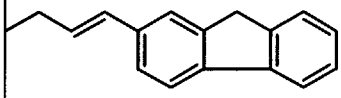
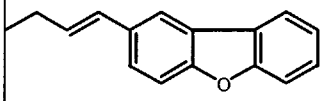
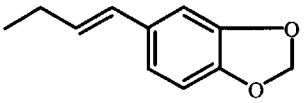
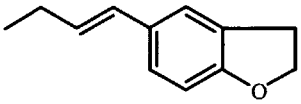


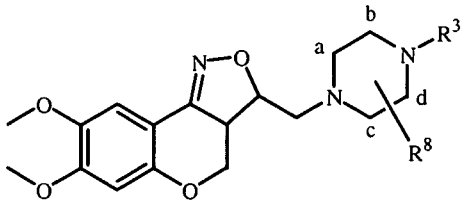
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
104	B8	H	H	H	H		cis
182	B13	H	H	H	H		cis
109	B8	H	H	H	H		cis
180	B13	H	H	H	H		cis
20	B8	H	H	H	H		cis
110	B8	H	H	H	H		cis
114	B8	H	H	H	H		cis
175	B13	H	H	H	H		cis
176	B13	H	H	H	H		cis
115	B8	H	H	H	H		cis

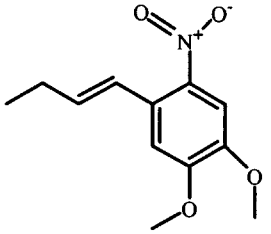
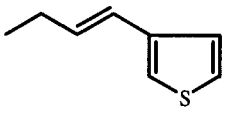
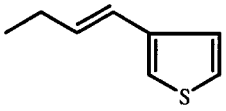
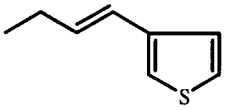
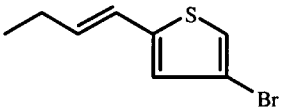
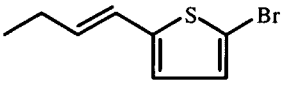
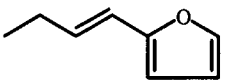
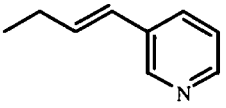
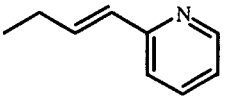
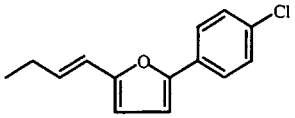
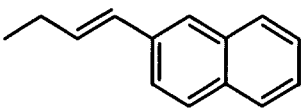


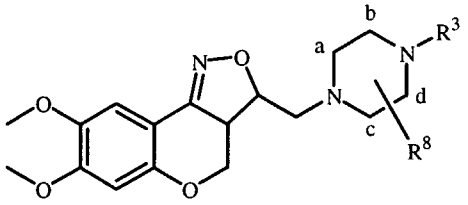
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
177	B13	H	H	H	H		cis
184	B13	H	H	H	H		(B)
172	B13	H	H	H	H		(A)
185	B13	H	H	H	H		(B)
173	B13	H	H	H	H		(A)
186	B13	H	H	H	H		(B)
167	B13	H	H	H	H		cis
170	B13	H	H	H	H		cis
171	B13	H	H	H	H		cis

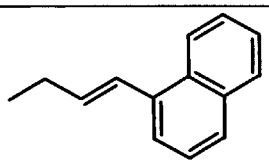
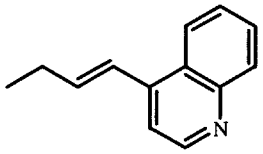
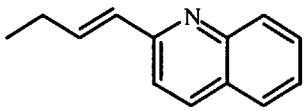
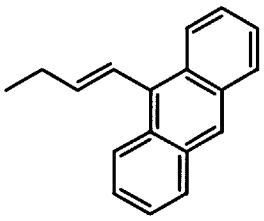
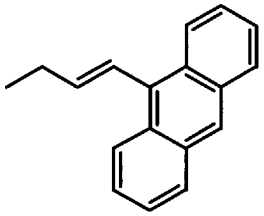
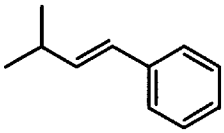
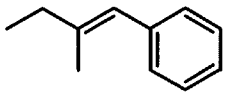
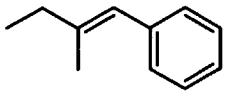
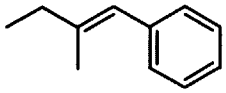


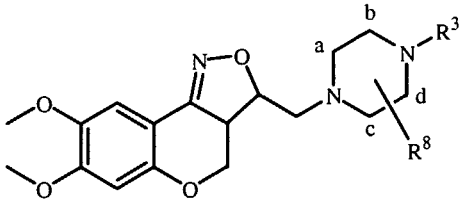
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
168	B13	H	H	H	H		cis
174	B13	H	H	H	H		(A)
187	B13	H	H	H	H		(B)
169	B13	H	H	H	H		cis
22	B10	H	H	H	H		[3α(E),3a α]
118	B7	H	H	H	H		cis
119	B7	H	H	H	H		cis
120	B6	H	H	H	H		cis
124	B6	H	H	H	H		[3α(E),3a α]
125	B6	H	H	H	H		[3α(E),3a α]

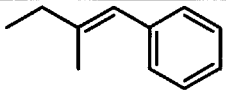
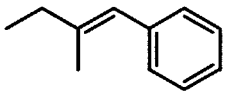
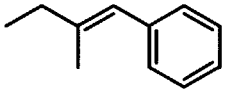
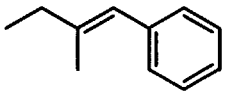
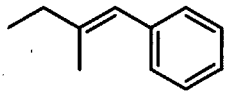
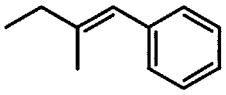
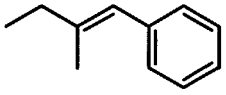
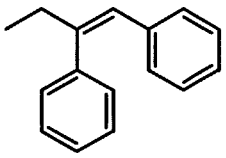
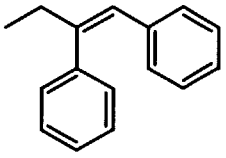
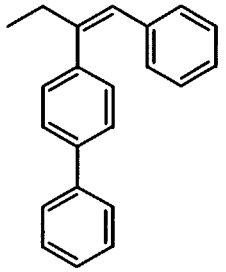


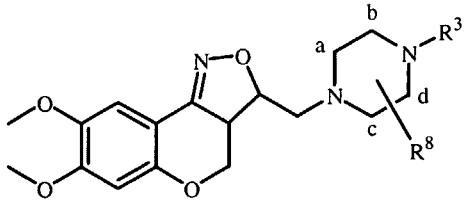
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
179	B13	H	H	H	H		cis
159	B8	H	H	H	H		cis
314	B8	H	H	H	H		[A-[3α(E),3a α]]
315	B8	H	H	H	H		[B-[3α(E),3a α]]
160	B8	H	H	H	H		cis
161	B8	H	H	H	H		cis
158	B8	H	H	H	H		cis
163	B8	H	H	H	H		cis
164	B8	H	H	H	H		cis
165	B8	H	H	H	H		cis
181	B13	H	H	H	H		cis

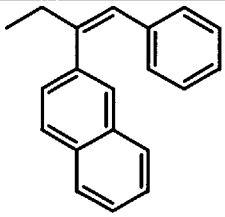
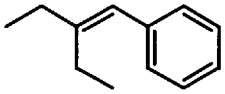
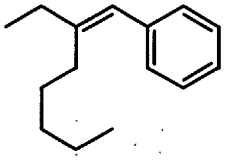
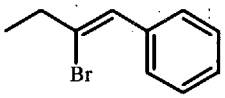
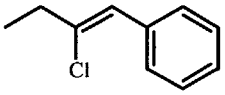
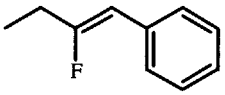
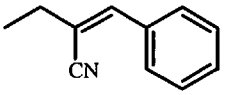
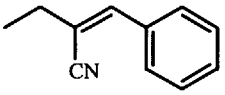
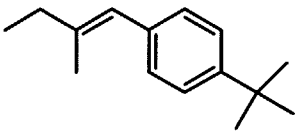
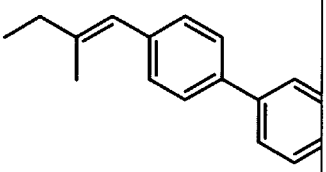


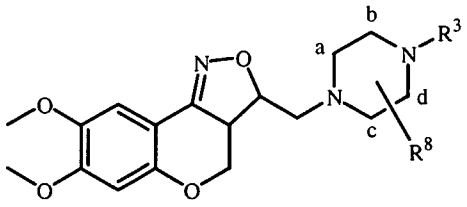
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
55	B5a	H	H	H	H		[3α(E),3a α] ;. HCl(1:2)
162	B8	H	H	H	H		cis
166	B8	H	H	H	H		cis
178	B13	H	H	H	H		(A)
188	B13	H	H	H	H		(B)
316	B13	H	H	H	H		[B-[3α(E),3a α]]
60	B5a	H	H	H	H		[3α(E),3a α]
70	B5b	H	H	H	H		[B-[3α(E),3a α]];. HCl(1:2) .H_2O(1:1)
69	B5b	H	H	H	H		[3α(E),3a α]

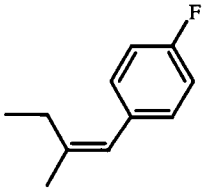
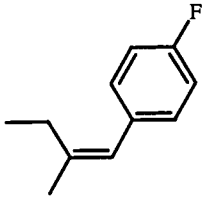
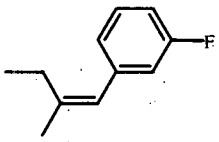
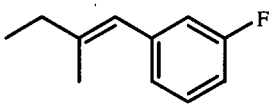
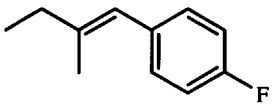
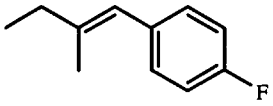
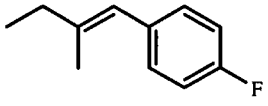
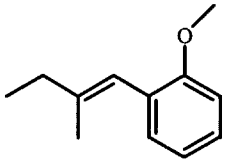
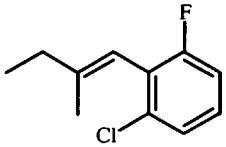
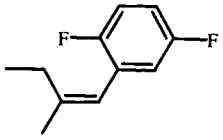


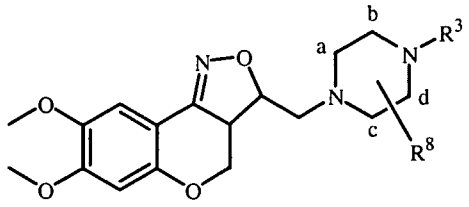
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
126	B5b	H	H	H	H		[A-[3α(E),3a α]]
129	B5b	H	H	H	H		[A-[3α(E),3a α]]; . (E)-2-Butenedioate (1:2)
134	B5a	CH_3	H	H	CH_3		[3α(R*,S*)(E),3a α]
137	B5a	H	CH_3	H	CH_3		[3α(R*,S*)(E),3a α]
139	B1a/B1b	CH_3	H	CH_3	H		[3α(R*,S*)(E),3a α]
148	B1f	H	H	H	H		[3α(Z),3a α]
190	B13	H	H	H	H		
151	B13	H	H	H	H		(A)
183	B13	H	H	H	H		(B)
152	B13	H	H	H	H		cis

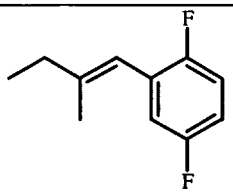
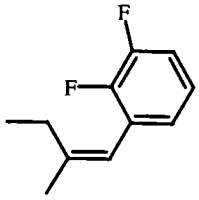
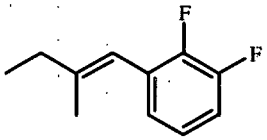
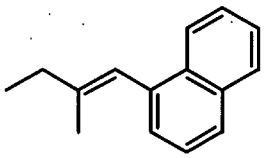
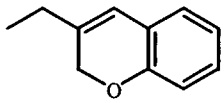
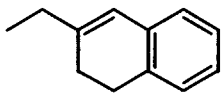
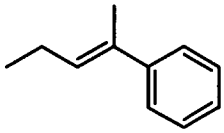
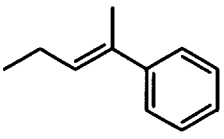
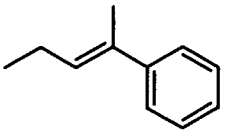


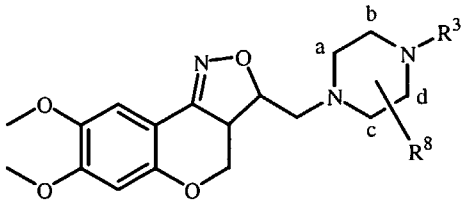
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
153	B13	H	H	H	H		cis
154	B13	H	H	H	H		cis
192	B5a	H	H	H	H		[3α(E),3a α]
143	B5a	H	H	H	H		[3α(Z),3a α]
144	B5a	H	H	H	H		[3α(Z),3a α]
146	B5a	H	H	H	H		[3α(Z),3a α]
150	B5a	H	H	H	H		[3α(Z),3a α]
317	B5a	H	H	H	H		[B-[3α(Z),3a α]]
155	B13	H	H	H	H		cis
156	B13	H	H	H	H		cis

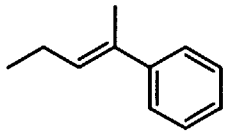
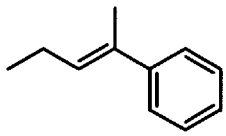
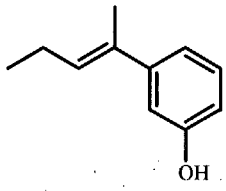
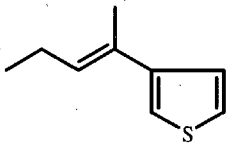
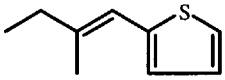
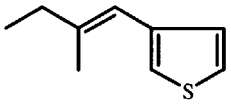
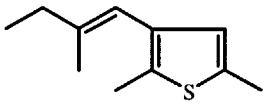
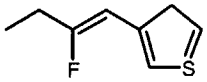
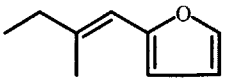
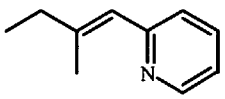
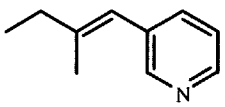
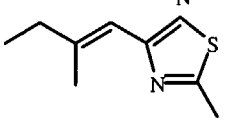


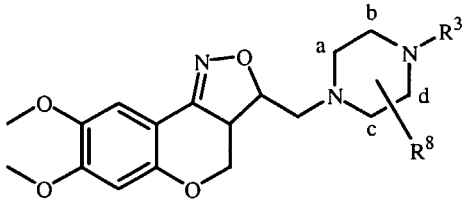
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
200	B12	H	H	H	H		[3α(Z),3a α]
207	B12	H	H	H	H		[B-[3α(Z),3a α]]
194	B12	H	H	H	H		[3α(Z),3a α]
195	B12	H	H	H	H		[3α(E),3a α]
196	B12	H	H	H	H		[3α(E),3a α]
318	B12	H	H	H	H		[A-[3α(E),3a α]]
24	B5a	H	H	H	H		[B-[3α(E),3a α]]
201	B12	H	H	H	H		[3α(E),3a α]
197	B12	H	H	H	H		[3α(E),3a α]
198	B12	H	H	H	H		[3α(Z),3a α]



Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
199	B12	H	H	H	H		[3α(E),3a α]
202	B12	H	H	H	H		[3α(Z),3a α]
203	B12	H	H	H	H		[3α(E),3a α]
157	B13	H	H	H	H		cis
65	B9	H	H	H	H		cis
21	B9	H	H	H	H		cis
25	B13	H	H	H	H		cis
205	B5b	H	H	H	H		[3α(E),3a α]
319	B5b	H	H	H	H		[A-[3α(E),3a α]]



Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
320	B5b	H	H	H	H		[B-[3α(E),3a α]]
321	B5b	H	H	H	H		[B-[3α(E),3a α]]
322	B5b	H	H	H	H		[B-[3α(E),3a α]]
323	B6	H	H	H	H		[B-[3α(E),3a α]]
130	B6	H	H	H	H		[3α(E),3a α]
18	B6	H	H	H	H		[3α(E),3a α]
324	B6	H	H	H	H		[B-[3α(E),3a α]]
325	B6	H	H	H	H		[3α(Z),3a α]
121	B6	H	H	H	H		[3α(E),3a α]
23	B11	H	H	H	H		[3α(Z),3a α]
208	B7	H	H	H	H		[B-[3α(E),3a α]]
326	B6	H	H	H	H		[B-[3α(E),3a α]]



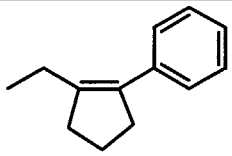
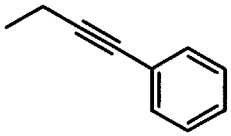
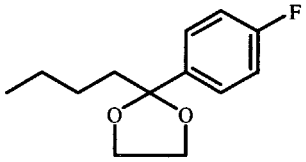
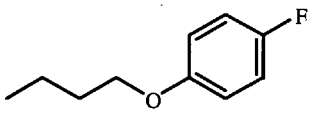
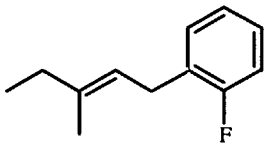
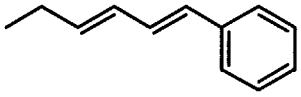
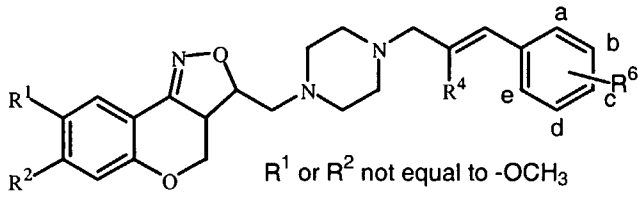
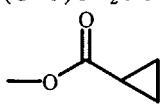
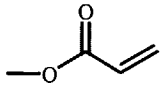
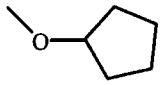
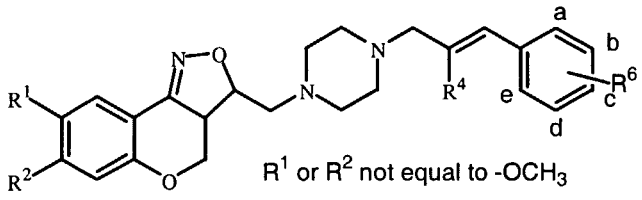
Comp. nr.	Ex. nr.	R^8 a	b	c	d	R^3	Phys.data and stereochemistry
145	B6	H	H	H	H		cis
122	B6	H	H	H	H		cis
63	B5a	H	H	H	H		cis
40	B5a	H	H	H	H		cis
327	B6	H	H	H	H		[B-[3α(E),3a α]]
127	B9	H	H	H	H		[A-[3α(E),3a α]]

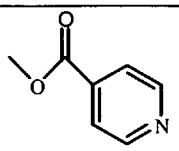
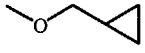
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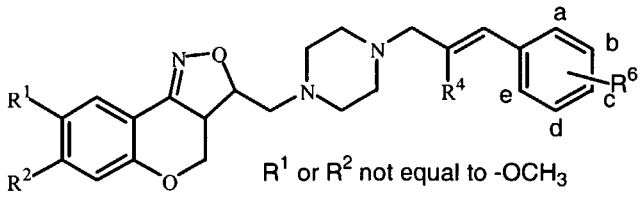


Comp. nr.	Ex. nr.	R^1	R^2	R^4	R^6	Phys.data
209	B1a/B1b	H	H	H		cis, E
263	B1a/B1b	H	H	H	c-COOMe	[3α(E),3a α]
254	B1a/B1b	H	F	CH_3		[3α(E),3a α]
232	B1f	H	OH	H		[3α(E),3a α]
237	B1f	H	OH	CH_3		[3α(E),3a α]
217	B1a/B1b	H	OCH_3	H		[3α(E),3a α]
229	B1g	H	OCH_3	H		[A-[3α(E),3a α]]; .HCl(1:2)
230	B1g	H	OCH_3	H		[B-[3α(E),3a α]]; .HCl(1:2)
328	B1g	H	OCH_3	CH_3		[3α(E),3a α]
239	B1f	H	$OC_2H_4OCH_3$	CH_3		[3α(E),3a α]
231	B1a/B1b	H	$OCH_2OC_2H_4OCH_3$	H		[3α(E),3a α]
236	B1a/B1b	H	$OCH_2OC_2H_4OCH_3$	CH_3		[3α(E),3a α]
247	B1f	H	$OC_2H_4OC_2H_4OC_2H_4$	CH_3		[3α(E),3a α];. HCl(1:2)
238	B1f	H	$O(C=O)NHC_2H_5$	CH_3		[3α(E),3a α]
233	B1f	H	$O(C=O)CH_3$	H		[3α(E),3a α]
240	B1f	H	$O(C=O)CH_3$	CH_3		[3α(E),3a α]
248	B1f	H	$O(C=O)C_2H_5$	CH_3		[3α(E),3a α]
249	B1f	H	$O(C=O)CH_2OCH_3$	CH_3		[3α(E),3a α]
250	B1f	H		CH_3		[3α(E),3a α]
329	B1f	H	$OC(=O)C(CH_3)_3$	CH_3		[3α(E),3a α]
251	B1f	H		CH_3		[3α(E),3a α]
243	B1f	H		CH_3		[3α(E),3a α]



R^1 or R^2 not equal to $-OCH_3$

Comp. nr.	Ex. nr.	R^1	R^2	R^4	R^6	Phys.data
330	B1f	H		CH_3		[3α(E),3a α]
242	B1f	H	$OC_2H_4N(CH_3)_2$	CH_3		[3α(E),3a α]
260	B1f	H	OSO_2H	CH_3		[3α(E),3a α]
211	B1a/B1b	Cl	H	H		[3α(E),3a α]
246	B1a/B1b	Cl	OCH_3	CH_3		[3α(E),3a α]
212	B1a/B1b	Br	H	H		[3α(E),3a α]
214	B1g	Br	H	H		[A-[3α(E),3a α]]
215	B1g	Br	H	H		[B-[3α(E),3a α]]
235	B1a/B1b	F	F	CH_3		[3α(E),3a α]
241	B1f	F	OCH_3	CH_3		[3α(E),3a α]
216	B1f	phenyl	H	H		[3α(E),3a α]
219	B1a/B1b	CH_3	H	H		[3α(E),3a α]
244	B1f	F	SCH_3	CH_3		[3α(E),3a α]
331	B1f	OH	OH	CH_3		[B-[3α(E),3a α]] HCl(1:2)
255	B1c	OH	OCH_3	CH_3		[3α(E),3a α]
257	B1f	$O(C=O)CH_3$	OCH_3	CH_3		[3α(E),3a α]
332	B1f	$OC_2H_4OC(=O)-CH_3$	OCH_3	CH_3		[3α(E),3a α]
333	B1f	$O(C=O)CH_3$	OCH_3	CH_3		[B-[3α(E),3a α]]
213	B1a/B1b	OCH_3	H	H		[3α(E),3a α]
3	B1c	OCH_3	OH	CH_3		[3α(E),3a α]
6	B1f	OCH_3	$O(C=O)CH_3$	CH_3		[3α(E),3a α]
334	B1f	OCH_3	$O(C=O)CH_3$	CH_3	b-F	[B-[3α(E),3a α]]
335	B1f	OCH_3	$O(C=O)CH_3$	CH_3	c-F	[B-[3α(E),3a α]]
336	B1f	OCH_3	$O(C=O)CH_3$	H	c-F	[B-[3α(E),3a α]]
337	B1f	OCH_3		CH_3	c-F	[B-[3α(E),3a α]]



R^1 or R^2 not equal to $-OCH_3$

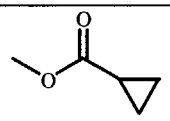
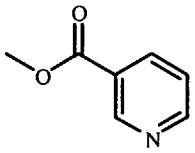
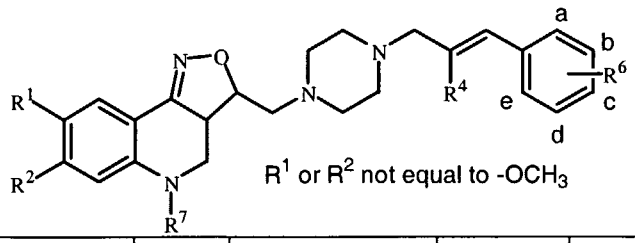
Comp. nr.	Ex. nr.	R^1	R^2	R^4	R^6	Phys.data
338	B1f	OCH_3		CH_3		[B-[3α(E),3a α]]
339	B1f	OCH_3		CH_3		[B-[3α(E),3a α]]
340	B1f	OCH_3	$OC(=O)NHC_2H_5$	CH_3		[B-[3α(E),3a α]]
341	B1f	OCH_3	$OC_2H_5N(CH_3)_2$	CH_3		[B-[3α(E),3a α]]
342	B1f	OCH_3	$OCH_2OC_2H_4OCH_3$	CH_3		[B-[3α(E),3a α]]
343	B1f	OCH_3	$OC(=O)OCH_3$	CH_3		[B-[3α(E),3a α]]
344	B1f	OCH_3	$OCH_2CH=CH_2$	CH_3		[B-[3α(E),3a α]]
345	B1f	OCH_3	OCH_2CH_2OH	CH_3		[B-[3α(E),3a α]] HCl(1:2)
346	B1f	OCH_3	OSO_2-CH_3	CH_3		[B-[3α(E),3a α]]
348	B1f	OCH_3	H	CH_3		[3α(E),3a α]]
349	B1f	OCH_3	phenyl	CH_3		[3α(E),3a α]]
350	B1f	OCH_3	SCH_3	CH_3		[3α(E),3a α]] Trifluoroacetate (1:1)

Table 2B :

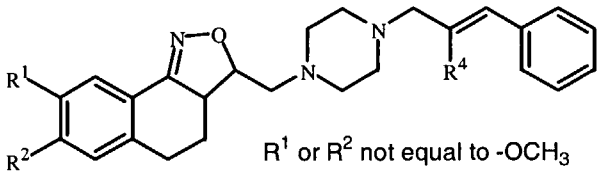


R^1 or R^2 not equal to $-OCH_3$

Comp. nr.	Ex. nr.	R^7	R^1	R^2	R^4	R^6	Phys.data
210	B2a	H	H	H	H		[3α(E),3a α]
234	B2a	H	H	H	CH_3		[3α(E),3a α]
256	B1a/B1b	H	OCH_3	OCH_3	H		[3α(E),3a α]
351	B1a/B1b	H	OCH_3	OCH_3	H	b-F	[3α(E),3a α]
352	B1a/B1b	H	OCH_3	OCH_3	H	b-F	[A-[3α(E),3a α]]
353	B1a/B1b	H	OCH_3	OCH_3	H	b-F	[B-[3α(E),3a α]]
354	B1a/B1b	H	OCH_3	OCH_3	H	c-F	[3α(E),3a α]
258	B1a/B1b	H	OCH_3	OCH_3	H		[3α(E),3a α]
12	B3b	H	OCH_3	OCH_3	CH_3		[A-[3α(E),3a α]]
253	B3b	H	OCH_3	OCH_3	CH_3		[B-[3α(E),3a α]]
11	B3a	H	OCH_3	OCH_3	CH_3		[3α(E),3a α]
223	B16	H	OCH_3	OCH_3	H		[3α(E),3a α]
261	B1f	H	H	OCH_3	CH_3		[3α(E),3a α]
228	B2b	CH_3	H	H	H		[3α(E),3a α]
252	B3a	CH_3	OCH_3	OCH_3	CH_3		[3α(E),3a α]
259	B1a/B1b	benzyl	H	OCH_3	CH_3		[3α(E),3a α]
222	B16	$C(=O)CF_3$	OCH_3	OCH_3	H		[3α(E),3a α]
224	B2b	$C(=O)CF_3$	H	H	H		[3α(E),3a α]
225	B2b	$C(=O)CH_3$	H	H	H		[3α(E),3a α]
226	B2b		H	H	H		[3α(E),3a α]
227	B2b		H	H	H		[3α(E),3a α]

5

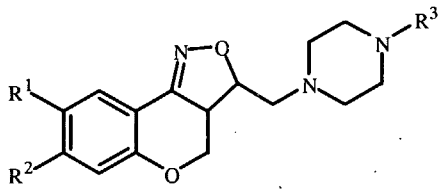
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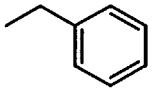
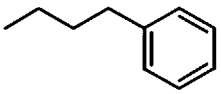
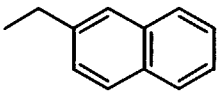
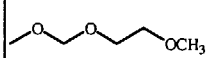
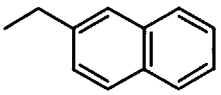
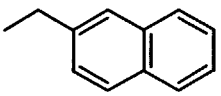
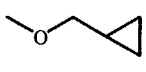
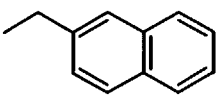
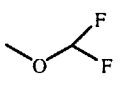
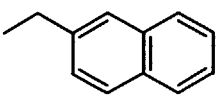


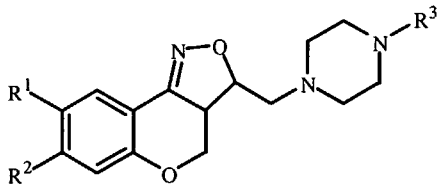
R^1 or R^2 not equal to $-OCH_3$

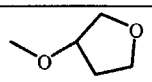
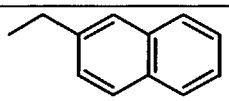
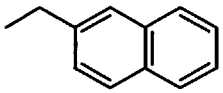
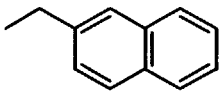
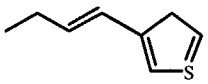
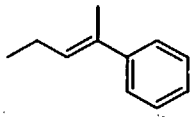
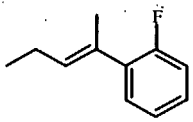
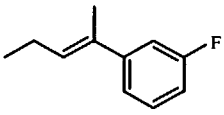
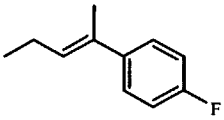
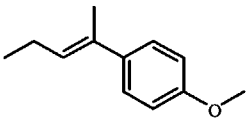
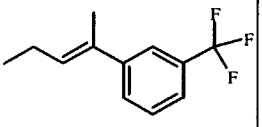
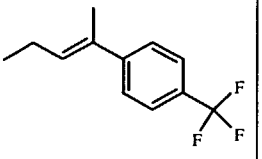
Comp. nr.	Ex. nr.	R^1	R^2	R^4	Phys.data
220	B16	H	OCH_3	H	[3α(E),3a α]; .HCl(1:2)
218	B5a	H	H	H	[3α(E),3a α]

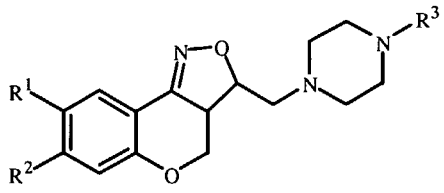
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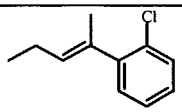
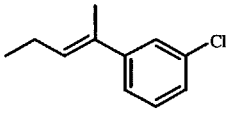
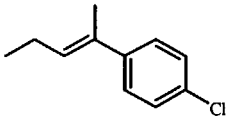
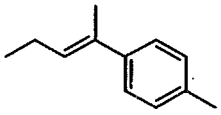
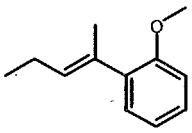
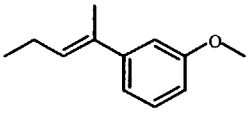
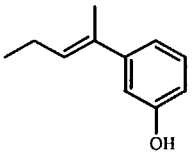
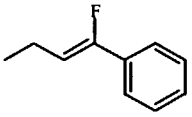
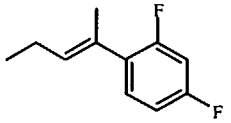
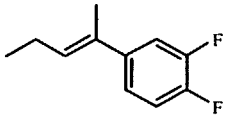
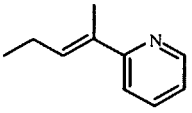


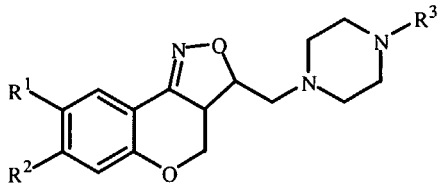
Comp nr.	Ex. nr.	R^1	R^2	R^3	Phys.data
262	B1a/B1b	H	H		cis
264	B1a/B1b	H	H		cis
265	B1a/B1b	H	OCH_3		cis; HCl(1:2)
267	B1a/B1b	H			cis
268	B1f	H	OH		cis
269	B1f	H			cis
270	B1f	H			cis



Comp nr.	Ex. nr.	R^1	R^2	R^3	Phys.data
271	B1f	H			[3α(E),3a α]
273	B1f	H	$O(C=O)CH_3$		cis
355	B1f	OCH_3	$O(C=O)CH_3$		B-cis
357	B1f	OCH_3	$O(C=O)CH_3$		[B-[3α(E),3a α]]
358	B1f	OCH_3	$O(C=O)CH_3$		[B-[3α(E),3a α]]
359	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]j
360	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
361	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
362	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
363	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
364	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]



Comp nr.	Ex. nr.	R^1	R^2	R^3	Phys.data
365	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
366	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
367	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]
368	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
369	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
370	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
371	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
372	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]] HCl (1:2)
373	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
374	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
375	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]



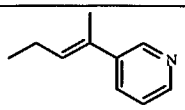
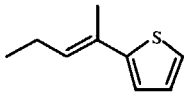
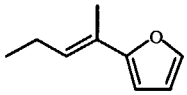
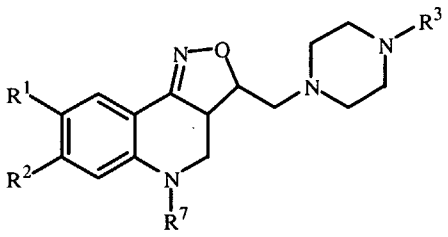
Comp nr.	Ex. nr.	R^1	R^2	R^3	Phys.data
376	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
377	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]
378	B1f	OCH_3	OCH_3		[B-[3α(E),3a α]]

Table 3B :



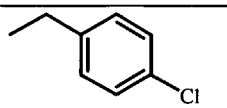
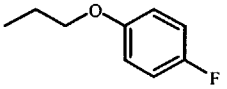
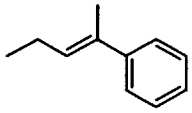
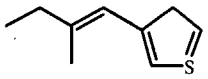
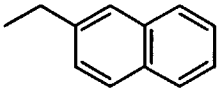
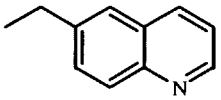
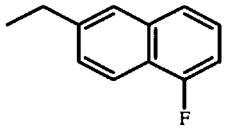
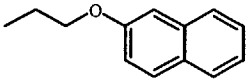
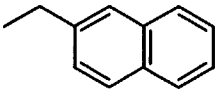
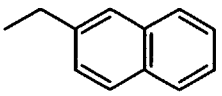
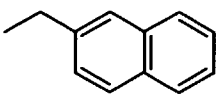
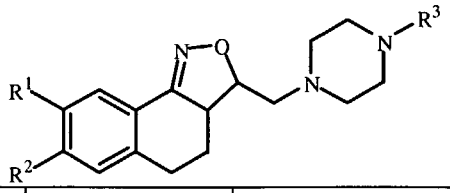
Comp nr.	Ex. nr.	R^7	R^1	R^2	R^3	Phys.data
275	B5a	H	OCH_3	OCH_3		cis
274	B5a	H	OCH_3	OCH_3		cis
379	B1f	H	OCH_3	OCH_3		[3α(E),3a α]
380	B1f	H	OCH_3	OCH_3		[3α(E),3a α]
272	B5a	H	OCH_3	OCH_3		cis
276	B5a	H	OCH_3	OCH_3		cis
381	B5a	H	OCH_3	OCH_3		cis
382	B5a	H	OCH_3	OCH_3		
9	B2a	H	H	H		cis
10	B2b	$C(=O)CH_3$	H	H		cis
266	B2b	CH_3	H	H		cis

Table 3C :



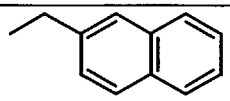
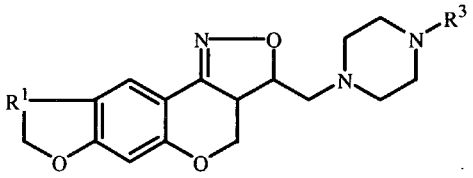
Comp nr.	Ex. nr.	R^1	R^2	R^3	Phys.data
28	B16	H	OCH_3		cis; HCl(1:2)

Table 4:



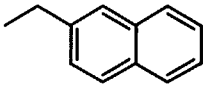
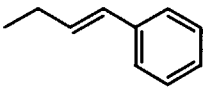
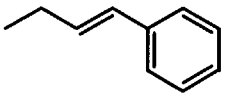
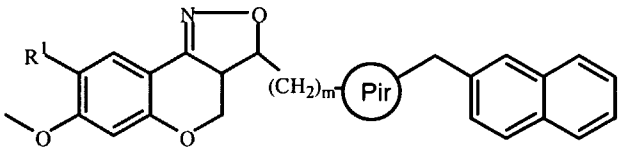
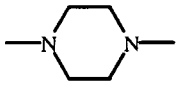
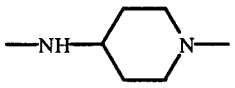
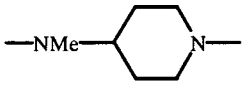
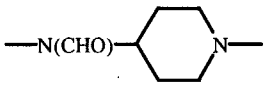
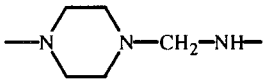
Comp. nr.	Ex. nr.	R^1	R^3	Phys.data
277	B1a/B1b	O		cis; .HCl(1:2)
278	B1a/B1b	O		[3α(E),3a α]; .HCl(1:2)
279	B1a/B1b	CH_2		[3α(E),3a α]

Table 5:



Comp. nr.	Ex. nr.	R^1	m	Pir	Phys.data
280	B1a/B1b	H	2		trans
29	B17	OCH_3	1		cis
281	B17	OCH_3	1		cis
282	B17	OCH_3	1		cis
283	B17	OCH_3	1		cis

C. Pharmacological examples

Example C1 : Binding experiment for α_2-adrenergic receptor subtypes and for 5-HT transporter

General

The interaction of the compounds of Formula (I) with hα_2-receptors and h5-HT-transporters was assessed in *in vitro* radioligand binding experiments. In general, a low concentration of a radioligand with a high binding affinity for a particular receptor or transporter is incubated with a sample of a tissue preparation enriched in a particular receptor or transporter or with a preparation of cells expressing cloned human receptors in a buffered medium. During the incubation, the radioligand binds to the receptor or transporter. When equilibrium of binding is reached, the receptor bound radioactivity is separated from the non-bound radioactivity, and the receptor- or transporter-bound activity is counted. The interaction of the test compounds with the receptor is assessed

in competition binding experiments. Various concentrations of the test compound are added to the incubation mixture containing the receptor- or transporter preparation and the radioligand. The test compound in proportion to its binding affinity and its concentration inhibits binding of the radioligand. The radioligand used for $h\alpha_{2A}$, $h\alpha_{2B}$ and $h\alpha_{2C}$ receptor binding was [^{3}H]-raulwolscine and for the h5-HT transporter was [^{3}H]paroxetine.

Cell culture and membrane preparation.

CHO cells, stabile transfected with human adrenergic-α_{2A}-, -α_{2B} or α_{2C} receptor cDNA, were cultured in Dulbecco's Modified Eagle's Medium (DMEM)/Nutrient mixture Ham's F12 (ratio 1:1)(Gibco, Gent-Belgium) supplemented with 10 % heat inactivated fetal calf serum (Life Technologies, Merelbeke-Belgium) and antibiotics (100 IU/ml penicillin G, 100 μg/ml streptomycin sulphate, 110 μg/ml pyruvic acid and 100 μg/ml L-glutamine). One day before collection, cells were induced with 5 mM sodiumbutyrate. Upon 80-90 % of confluence, cells were scraped in phosphate buffered saline without Ca^{2+} and Mg^{2+} and collected by centrifugation at 1500 x g for 10 min. The cells were homogenised in Tris-HCl 50 mM using an Ultraturrax homogenizer and centrifuged for 10 min at 23,500 x g. The pellet was washed once by resuspension and rehomogenization and the final pellet was resuspended in Tris-HCl , divided in 1 ml aliquots and stored at –70°C.

Binding experiment for α_2-adrenergic receptor subtypes

Membranes were thawed and re-homogenized in incubation buffer (glycylglycine 25 mM, pH 8.0). In a total volume of 500 μl, 2-10 μg protein was incubated with [^{3}H]raulwolscine (NET-722) (New England Nuclear, USA) (1 nM final concentration) with or without competitor for 60 min at 25°C followed by rapid filtration over GF/B filter using a Filtermate196 harvester (Packard, Meriden, CT). Filters were rinsed extensively with ice-cold rinsing buffer (Tris-HCl 50 mM pH 7.4). Filter-bound radioactivity was determined by scintillation counting in a Topcount (Packard, Meriden, CT) and results were expressed as counts per minute (cpm). Non-specific binding was determined in the presence of 1 μM oxymetazoline for $h\alpha_{2A}$- and $h\alpha_{2B}$ receptors and 1 μM spiroxatrine for $h\alpha_{2C}$ receptors.

Binding experiment for 5–HT transporter

Human platelet membranes (Oceanix Biosciences Corporation, Hanover, MD, USA) were thawed, diluted in buffer (Tris-HCl 50 mM, 120 mM NaCl and 5 mM KCl) and quickly (max 3 s) homogenised with an Ultraturrax homogenizer. In a total volume of 250 μL, 50-100 μg protein was incubated with [^{3}H]paroxetine (NET-869) (New England Nuclear, USA) (0.5 nM final concentration) with or without competitor for 60 min at 25 °C . Incubation was stopped by rapid filtration of the incubation mixture over GF/B filters, pre-wetted with 0.1 % polyethyleneamine, using a Filtermate196 harvester (Packard, Meriden, CT). Filters were rinsed extensively with ice-cold buffer and radioactivity on the filters was counted in a Topcount liquid scintillation counter (Packard, Meriden, CT). Data were expressed as cpm. Imipramine (at 1 μM final concentration) was used to determine the non-specific binding.

Data analysis and results

Data from assays in the presence of compound were calculated as a percentage of total binding measured in the absence of test compound. Inhibition curves, plotting percent of total binding versus the log value of the concentration of the test compound, were automatically generated, and sigmoidal inhibition curves were fitted using non-linear regression. The pIC_{50} values of test compounds were derived from individual curves.

All compounds according to formula (I) produced an inhibition at least at the hα_{2A} site (but often also at the hα_{2B} and hα_{2C} sites) and simultaneously at the 5-HT transporter site of more than 50 % (pIC_{50}) at a test concentration ranging between 10^{-6} M and 10^{-9} M in a concentration-dependent manner. For a selected number of compounds, covering most of the various embodiments of Formula (I), the results of the *in vitro* studies are given in Table 6.

Table 6 : Some results of the *in vitro* experiments (pIC_{50}-values). n.d. : not determined.

Comp nr.	$h\alpha_{2A}$	$h\alpha_{2B}$	$h\alpha_{2C}$	5HTT
1	8.20	8.49	8.96	8.29
3	8.63	8.59	8.73	7.79
8	8.34	8.14	7.92	7.75
9	7.99	8.33	6.97	8.80
14	6.37	6.19	6.58	6.44
15	7.90	7.84	7.94	7.77
16	8.27	8.21	8.17	8.43
21	8.79	7.73	8.98	8.92
24	7.86	8.41	8.54	8.26
26	6.28	6.99	6.61	6.17
27	8.39	8.22	8.81	7.74
28	8.11	7.74	7.15	8.36
29	6.33	6.66	6.72	8.26
31	6.10	6.20	6.00	6.30
32	7.90	7.84	7.94	7.77
41	7.80	8.30	7.90	8.50
43	6.99	7.19	6.86	7.80
45	7.24	7.15	7.36	7.16
47	6.18	6.35	6.07	7.30
48	7.88	8.24	8.36	6.90
54	7.72	7.42	7.44	7.38
65	7.88	7.74	8.29	8.29
72	7.33	6.75	7.18	8.16
76	7.14	7.05	7.60	8.80
79	6.00	6.00	6.00	6.00
81	6.00	6.00	6.00	6.84
90	6.71	6.00	7.04	6.52

97	6.00	6.00	6.00	6.45
110	7.16	6.95	7.46	7.52
125	7.25	6.85	7.46	7.87
127	6.85	6.91	7.59	7.20
129	7.91	8.01	8.17	8.55
143	7.11	7.60	7.63	7.62
154	7.27	7.39	7.06	7.05
157	7.87	7.28	7.13	7.48
181	6.55	6.11	6.49	7.63
185	6.84	7.11	7.53	7.90
195	8.34	8.80	8.68	8.70
196	7.84	8.44	8.09	8.41
199	8.92	9.00	8.78	7.89
201	8.36	8.49	8.34	8.12
217	8.78	8.21	7.85	7.27
218	6.74	6.88	5.90	6.34
220	8.12	7.85	7.36	7.18
224	6.96	7.66	7.13	7.31
226	6.85	7.09	6.96	8.08
233	8.33	8.20	7.94	7.36
234	8.57	8.88	8.41	7.71
237	9.11	8.90	8.93	7.94
238	8.56	8.62	8.59	8.07
239	9.31	8.62	9.54	7.85
241	7.78	8.13	8.20	7.01
242	9.49	9.44	8.97	7.95
243	8.27	7.77	8.29	6.75
244	8.42	8.13	8.87	6.90
246	7.55	7.90	7.86	7.50
250	8.40	8.17	8.48	7.09
251	8.43	8.31	8.26	6.89

253	8.24	7.94	7.98	6.60
257	7.52	8.37	8.65	7.46
260	8.61	8.21	8.59	7.22
265	8.46	7.68	7.56	7.83
266	7.84	7.80	7.45	8.88
267	8.49	7.90	8.55	8.30
268	9.00	8.26	8.05	8.24
271	8.41	7.86	7.37	8.53
272	6.50	7.57	6.87	8.32
273	8.11	7.68	7.51	7.88
277	8.61	8.10	7.77	6.97
278	8.49	8.14	8.16	6.61
279	8.45	8.03	8.24	7.45
280	7.04	6.35	6.42	8.09
281	7.05	7.19	7.31	7.25
282	7.66	7.26	7.64	8.06
283	7.00	7.33	7.13	8.89
285	6.22	6.24	6.44	6.59
291	6.07	6.00	6.00	6.00
296	6.12	6.39	6.14	6.06
300	6.46	6.03	6.20	6.14
304	7.71	7.23	7.19	7.41
309	7.30	n.d.	7.23	6.41
310	6.67	n.d.	7.19	6.06
312	8.08	n.d.	8.20	7.62
314	7.95	8.16	8.19	8.06
316	7.98	6.76	6.92	6.39
320	8.23	7.70	8.17	7.49
323	8.21	n.d.	8.02	7.82
329	7.70	7.56	7.74	7.48
332	8.35	n.d.	9.22	7.23
333	8.32	8.42	8.33	7.52

334	8.57	n.d.	8.64	7.58
337	7.68	n.d.	7.88	7.88
340	9.00	n.d.	8.42	7.64
341	8.44	n.d.	8.91	8.66
342	8.07	n.d.	9.79	7.76
343	8.63	n.d.	8.91	7.43
344	8.45	n.d.	8.68	8.00
346	8.65	n.d.	8.91	8.37
348	8.92	n.d.	8.88	7.75
350	8.39	n.d.	8.68	7.69
351	7.95	8.16	8.19	8.06
355	8.29	n.d.	8.15	7.87
358	8.83	n.d.	8.49	7.43
359	8.10	n.d.	8.46	7.35
361	7.90	n.d.	8.51	8.38
366	7.89	n.d.	8.48	7.94
379	7.56	7.71	7.39	7.46
380	7.78	8.35	7.99	7.63

Example C2 : *In vivo* experiment for α_2-adrenoceptor antagonism and for serotonine (5-HT) reuptake inhibition activity.

A. Medetomidine-test

The onset and end of medetomidine (0.10 mg/kg, i.v.)-induced loss of righting was recorded in overnight-starved Wiga male rats (200-250 g). The intensity of the loss of righting was scored: 0 = normal behaviour, 1 = slight ataxia, 2 = pronounced ataxia, 3 = loss of righting for a period < 5 min, 4 = loss of righting for a period > 5 min. Under standard conditions, test compound or solvent was administered (s.c. or p.o.) 1 h before medetomidine. Criterion for drug-induced antagonism: (1) antagonism of loss of righting: duration = 0 min (1.4% false positive controls; n = 74) (2) reversal of

ataxia: score < 2 (0% false positives). Criterion for drug-induced potentiation: loss of righting reflex over a period longer than 120 min (0% false positives). Centrally acting α_2-adrenoceptor antagonists or behavioural stimulants antagonise the loss of righting ; sedative compounds may result in prolongation.

The following observations were made : onset of loss of righting (min), end of loss of righting (min) and intensity of loss of righting (score 0-4). The observations were performed at 1 h following s.c. (solutions) or p.o. (suspensions) administration, respectively. Starting dose was 10 mg/kg (References : Berger, U.V., Grzanna, R., Molliver, M.E., Exp. Neurol. 103, 111-115 (1989), Fuller, R.W., Perry, K.W., Molloy, B.B., Eur. J. Pharmacol. 33, 119-124 (1975) and Lassen, B.J., Psychopharmacol. 57, 151-153 (1978)).

B. pCA-test

Male Wiga rats were used (body weight: 200 ± 20 g). One hour after administration of test compound or solvent, a solution of pCA was injected subcutaneously (5 mg/kg ; 10 ml/kg). Forty-five minutes after the pCA injection, head-twitches (HTW) are counted and the excitation (EXC) were scored over three successive 5 min intervals (starting 45, 50 and 55 minutes after pCA-administration. The scores were given by a trained observator according to the intensity scale: 0 = absent or doubtful, 1 = present, 2 = pronounced, 3 = maximal. For statistical analysis, the head-twitches counted during the 15-min observation time were cumulated. For the other phenomena, the median value of the three 5-min-intervals was used.

Standard observations were performed at 1 h following s.c.or p.o. administration. The starting dose was in general 10 mg/kg. Doses were initially given to 2 animals. When both animals show activity for at least one of the observations, the compound was considered active and testing was repeated at a 4 times lower dose. When activity was found in only one out of the two animals, an additional animal was tested. When activity was found in this additional animal, the compound was also considered to be active and testing was repeated at a 4 times lower dose. In all other cases the compound was considered inactive at the particular time-route-dose (Reference :

Janssen, P.A.J., Niemegeers, C.J.E., Awouters, F., Schellekens, K.H.L., Megens, A.A.H.P., Meert, T.FJ. Pharmacol. Exp. Therap. 244, 685-693 (1988)).

Results

A large number of compounds according to the invention showed a central activity (minimal effective dose) both in the medetomidine test and in the pCA-test of less than or equal to 10 mg/kg.

Example C3 : [^{35}S]GTPγS binding assay

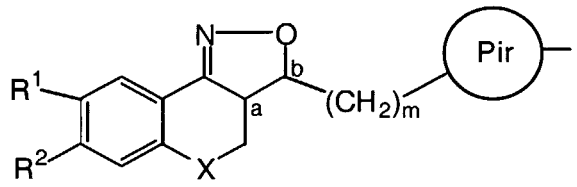
Membranes of the hα_{2A} adrenoceptor expressing CHO cell line were thawed and re-homogenised in 20 mM Hepes buffer. The incubation medium consisted of: 20 mM Hepes buffer, pH 7.5, 1 μM GDP, 3 mM $MgCl_2$, 100 mM NaCl, 0.25 nM [^{35}S]GTPγS and 10 μg protein per well of a 96-well plate. Antagonists and the reference agonist noradrenaline (3 μM) were added 20 min before the[^{35}S]GTPγS. The incubation (20 min, 37°C) was ended by rapid filtration through GF/B filters and binding quantified by liquid scintillation counting.

Results

All compounds according to the invention evaluated in the GTPγS binding assay did not show significant increases of [^{35}S]GTPγS binding to the hα_{2A} receptor up to 10 μM. All compounds evaluated in the assay were able to inhibit noradrenaline-induced increases of [^{35}S]GTPγS binding, thereby showing their antagonistic nature at this receptor.

Claims

1. A compound according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the N-oxide form thereof, wherein :

X is CH_2, N-R^7, S or O ;

R^7 is selected from the group of hydrogen, alkyl, phenyl, phenylalkyl, alkylcarbonyl, alkyloxycarbonyl and mono- and dialkylaminocarbonyl, the phenyl and alkyl groups being optionally substituted with one or more halo atoms;

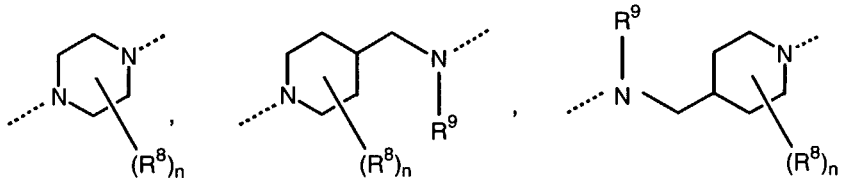
R^1 and R^2 are each, independently from each other, selected from the group of hydrogen, hydroxy, cyano, halo, OSO_2H, OSO_2CH_3, phenyl, phenylalkyl, alkyloxy, alkyloxyalkyloxy, alkyloxyalkyloxyalkyloxy, tetrahydrofuranyloxy, alkylcarbonyloxy, alkylthio, alkyloxyalkylcarbonyloxy, pyridinylcarbonyloxy, alkylcarbonyloxyalkyloxy, alkyloxycarbonyloxy, alkenyloxy, alkenyl-carbonyloxy and mono-and dialkylaminoalkyloxy, the alkyl and aryl radicals being optionally substituted with one or more hydroxy or halo atoms or amino groups ; or

R^1 and R^2 may be taken together to form a bivalent radical -R^1-R^2- selected from the group of -CH_2-CH_2-O-, -O-CH_2-CH_2-, -O-CH_2-O-, -CH_2-O-CH_2- and -O-CH_2-CH_2-O- ;

a and b are asymmetric centers ;

$(CH_2)_m$ is a straight hydrocarbon chain of m carbon atoms, m being an integer ranging from 1 to 4 ;

Pir is an optionally substituted radical according to any one of Formula (IIa), (IIB or (IIc)



(II)

(a) (b) (c)

wherein :

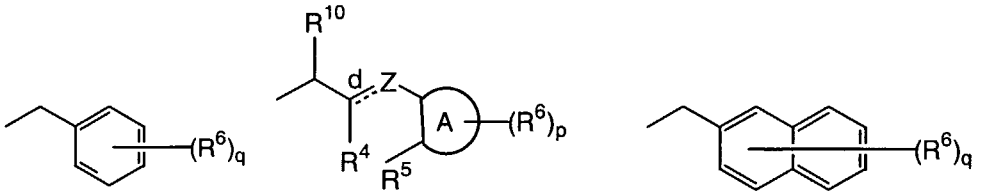
each R^8 is independently from each other, selected from the group of hydrogen, hydroxy, amino, nitro, cyano, halo and alkyl ;

n is an integer ranging from 1 to 5 ;

R^9 is selected from the group of hydrogen, alkyl and formyl ; and

R^3 represents an optionally substituted aromatic homocyclic or heterocyclic ring system together with an optionally substituted and partially or completely hydrogenated hydrocarbon chain of 1 to 6 atoms long with which said ring system is attached to the Pir radical and of which may contain one or more heteroatoms selected from the group of O, N and S.

2 A compound according to claim 1, characterized in that R^3 is a radical according to any one of Formula (III)



(III)

(a) (b) (c)

wherein :

d is a single bond while Z is a bivalent radical selected from the group of $-CH_2-$, -C(=O)-, -CH(OH)-, -C(=N-OH)-, –CH(alkyl)-, -O-, -S-, -S(=O),

-NH- and –SH-; or d is a double bond while Z is a trivalent radical of formula =CH- or =C(alkyl);

A is a 5- or 6-membered aromatic homocyclic or heterocyclic ring, selected from the group of phenyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, oxadiazolyl and isoxazolyl ;

p is an integer ranging from 0 to 4 ;

q is an integer ranging from 0 to 7 ;

R^4 is selected from the group of hydrogen, alkyl, phenyl, biphenyl, naphthyl, halo and cyano, the alkyl and aryl radicals being optionally substituted with one or more hydroxy or halo atoms or amino groups ;

R^5 is equal to R^4 ; or

R^4 and R^5 may be taken together to form a bivalent radical $-R^4-R^5-$ selected from the group of $-CH_2-$, =CH-, $-CH_2-CH_2-$, -CH=CH- , -O-, -NH-, =N-, -S-, $-CH_2N(-alkyl)-$, -CH=N-, $-CH_2O-$ and $-OCH_2-$;

each R^6 is independently from each other, selected from the group of hydrogen, hydroxy, amino, nitro, cyano, halo, carboxyl, alkyl, phenyl, alkyloxy, phenyloxy, alkylcarbonyloxy, alkyloxycarbonyl, alkylthio, mono- and dialkylamino, alkylcarbonylamino, mono- and dialkylaminocarbonyl, mono- and dialkylaminocarbonyloxy, mono- and dialkylaminoalkyloxy, the alkyl and aryl radicals being optionally substituted with one or more hydroxy or halo atoms or amino groups ; or

two vicinal radicals R^6 may be taken together to form a bivalent radical $-R^6-R^6-$ selected from the group of $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-O-CH_2-C(=O)-$, $-O-CH_2-O-$, $-CH_2-O-CH_2-$, $-O-CH_2-CH_2-O-$, -CH=CH-CH=CH-, -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH-, -N=CH-CH=CH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-C(=O)-$ and $-CH_2-CH_2-CH_2-CH_2-$; and

R^{10} is selected from the group of hydrogen, alkyl, phenylalkyl and phenyl.

3. A compound according to claim 2, characterized in that X=O or NH ; R^1 and R^2 are both alkyloxy ; m = 1 ; Pir is a radical according to Formula (IIa) wherein

R^8 is hydrogen and n = 4 ; R^3 is a radical according to Formula (IIIb) wherein Z is =CH-, d is a double bond, A is a phenyl ring, R^4 is an alkyl and R^{10} is hydrogen .

4. A compound according to any one of claims 1-3 for use as a medicine.

5. A compound which is degraded *in vivo* to yield a compound according to any one of claims 1-3.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient a therapeutically effective amount of a compound according to any one of claims 1 - 3 or a compound according to claim 5.

7. A process for making a pharmaceutical composition according to claim 6, comprising mixing a compound according to any one of claims 1-3 or a compound according to claim 5 and a pharmaceutically acceptable carrier.

8. The use of a compound according to any one of claims 1 -3 or a compound according to claim 5 for the manufacture of a medicament for treating depression, anxiety and body weight disorders.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient a therapeutically effective amount of a compound according to any one of claims 1-3 or a compound according to claim 5 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.

10. The use of a pharmaceutical composition according to claim 9 for the manufacture of a medicament to improve efficacy and/or onset of action in the treatment of depression, anxiety and body weight disorders.

11. The use of a compound according to any one of claims 1-3 or a compound according to claim 5 for the manufacture of a medicament for the treatment of

depression, anxiety and body weight disorders, said treatment comprising the simultaneous or sequential administration of a compound according to any one of claims 1-3 or a compound according to claim 5 and one or more other compounds selected from the group of antidepressants, anxiolytics and antipsychotics.

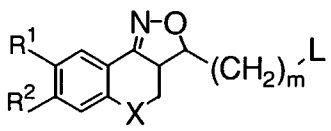
12. The use of one or more compounds selected from the group of antidepressants, anxiolytics and antipsychotics for the manufacture of a medicament for the treatment of depression, anxiety and body weight disorders, said treatment comprising the simultaneous or sequential administration of one or more compounds selected from the group of antidepressants, anxiolytics and antipsychotics and a compound according to any one of claims 1-3 or a compound according to claim 5.

13. The use of a pharmaceutical composition according to claim 9 to improve efficacy and/or onset of action in the treatment of depression, anxiety and body weight disorders.

14. A process for making a pharmaceutical composition according to claim 9, comprising mixing a compound according to any one of claims 1-3 or a compound according to claim 5 and a compound selected from the group of antidepressants, anxiolytics and antipsychotics and a pharmaceutically acceptable carrier.

15. A process for preparing a compound according to any one of claims 1 - 3, characterized in that a compound according to Formula (IV) is reacted with a compound according to Formula (V) or Formula (VII).

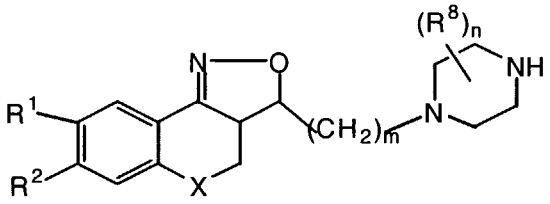
16. A compound according to the general Formula (IV)



(IV)

wherein R^1, R^2, X and m are defined as in Formula (I) and L is a leaving group, excluding 3,3a,4,5-tetrahydronaphto[1,2-c]isoxazole-3-acetic acid

17. A compound according to the general Formula (VIII)



(VIII)

wherein R^1, R^2, X, m, R^8 and n are defined as in Formula (I).

18. A compound according to claim 16, characterized in that L is selected from the group of $OSO_2C_6H_4(CH_3)$, OSO_2CH_3, Cl, Br and I.