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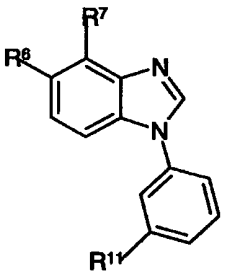

(1)

(57) Abstract

The present invention discloses compounds of general formula (1) wherein, R^{11} represents a 5– or 6–membered monocyclic heteroaryl group containing at least one nitrogen, or a 5– or 6–membered monocyclic heteroaryl group containing at least one nitrogen as the N–oxide; one of R^6 and R^7 represents hydrogen, and the other represents R'–C=O or CR'=NOR'', wherein R' and R'' each independently may be hydrogen, C_{1-8}–alkyl which may be substituted one or more times with OH, C_{2-6}–alkenyl which may be substituted one or more times with OH, C_{2-6}–alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH; provided however that when R'' represents hydrogen, C_{1-8}–alkyl, C_{2-6}–alkenyl or C_{2-6}–alkynyl then R^{11} represents a 5– or 6–membered monocyclic heteroaryl containing at least one nitrogen as the N–oxide; or a pharmaceutically acceptable salt thereof. The compounds of the invention are useful as $GABA_A$ receptor complex modulators.

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Benzimidazole compounds, pharmaceutical compositions containing the compounds and their use.

This invention relates to novel benzimidazole compounds, pharmaceutical compositions containing these compounds, methods of treating therewith, and to method of preparing such benzimidazole compounds. The novel compounds are useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the $GABA_A$ receptor complex, such as for example anxiety, sleep disorders, memory disorders, and epilepsia or other convulsive disorders.

Background of the invention

Receptors for γ-aminobutyric acid (GABA), $GABA_A$ receptors are the most abundant inhibitory receptors in mammalian brain. The $GABA_A$ receptor are structurally constituted as macromolecular heteropentameric assemblies (combinations of α, β, and γ/δ protein subunits). Several subtypes of such $GABA_A$ receptors have been described by techniques of modern molecular biology.

Each $GABA_A$ receptor complex comprises a chloride ion channel that controls chloride flux across the neuronal membrane, and multiple recognition sites for small modulatory molecules such as benzodiazepines, barbiturates, picrotoxin, and certain steroids. When GABA interacts with its receptor, the ion channel is opened, chloride influx is enhanced, the membrane is hyperpolarized and the cell becomes less responsive to excitatory stimuli. This GABA induced ion current can be regulated by diverse agents, including agents that interact with the benzodiazepine receptor or recognition site.

Agents that bind or interact with the modulatory sites on the $GABA_A$ receptor complex, such as for example the benzodiazepine receptor, can have either enhancing effect on the action of GABA, i.e. a positive modulatory effect of the receptor (agonists, partial agonists), an attenuating effect on the action of GABA, i.e. negative modulation of the receptor (inverse agonists, partial inverse agonists), or they can block the effect of both agonists and inverse agonists by competitive block (antagonists or ligands without intrinsic activity).

Agonists generally produce muscle relaxant, hypnotic, sedative, anxiolytic, and/or anticonvulsant effects, while inverse agonists produce proconvulsant, anti-inebriant, and anxiogenic effects. Partial agonists are characterized as compounds with anxiolytic effects but

without or with reduced muscle relaxant, hypnotic and sedative effects, whereas partial inverse agonists are considered to be useful as cognition enhancers.

Numerous compounds belonging to different series of compounds having affinity for the benzodiazepine receptors have been synthesized during the last three decades. However, although the benzodiazepine receptor sites are still considered as very attractive biological sites for interfering with the CNS to treat various disorders and diseases, then nearly all previously synthesized compounds acting at these receptor sites have failed during clinical development because of unacceptable side effects.

WO 96/33191 describes oxime-substituted benzimidazoles having GABA-receptor activity.

The present invention provides novel benzimidazole compounds that interact with the benzodiazepine receptor of the $GABA_A$ receptor complex. The compounds of the present invention are valuable modulators of the $GABA_A$ receptor complex with a favorable pharmacodynamic.

Object of the invention

It is an object of the present invention to provide novel benzimidazole compounds and pharmaceutically-acceptable acid addition salts thereof, which are useful in the treatment of central nervous system disorders, diseases or ailments, which are responsive to the modulation of the $GABA_A$ receptor complex, and especially the positive modulation of the $GABA_A$ receptor.

Another object of the present invention is to provide pharmaceutical compositions comprising the novel benzimidazole compounds being useful for the above purposes. Still another object of the present invention is to provide a novel method of treating with the novel benzimidazole compounds.

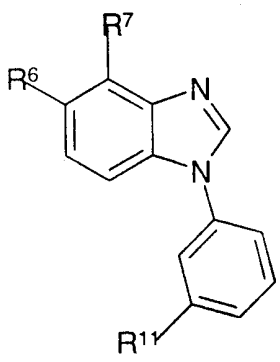
A further object of the present invention is to provide a method of preparing the novel pharmaceutical compositions.

Additional objects will be obvious from the following description, and others will be obvious to one skilled in the art.

Summary of the Invention

The invention then, inter alia, comprises the following, alone or in combination:

A compound represented by the general formula



wherein,

R^{11} represents a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen, or a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen as the N-oxide;

one of R^6 and R^7represents hydrogen, and the other represents R'-C=O or CR'=NOR", wherein R' and R" each independently may be hydrogen, C_{1-8}-alkyl which may be substituted one or more times with OH, C_{2-6}-alkenyl which may be substituted one or more times with OH, C_{2-6}-alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH;

provided however that when R" represents hydrogen, C_{1-8}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl then R^{11} represents a 5- or 6-membered monocyclic heteroaryl containing at least one nitrogen as the N-oxide;

or a pharmaceutically acceptable salt thereof.

A compound as above, wherein R" represents C_{1-6}-alkyl substituted with one hydroxy-group.

A compound as above, wherein R^7 represents hydrogen.

A compound as above, wherein R^{11} represents pyridyl-N-oxide.

A compound as above which is

5-Acetyl-1-(3-(3-pyridyl)phenyl)benzimidazole O-(2-hydroxyethyl) oxime;

5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole oxime, hydrochloride;

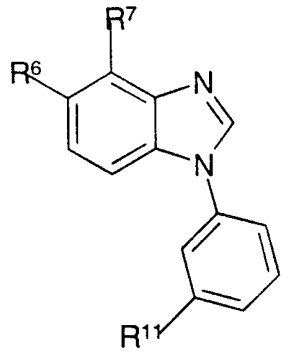
5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole O-ethyl oxime, or

5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole;

or a pharmaceutically acceptable addition salt thereof.

A method of preparing a compound as above, by which method,

(a) a compound represented by the general formula



wherein,

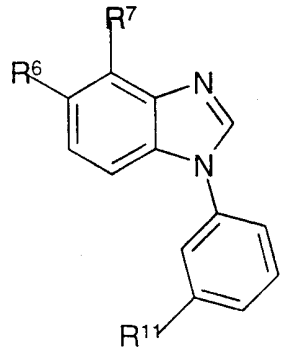
R^{11} represents a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen, or a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen as the N-oxide;

one of R^6 and R^7 represents hydrogen, and the other represents CR'=O, wherein R' represents hydrogen, C_{1-8}-alkyl which may be substituted one or more times with OH, C_{2-6}-alkenyl which may be substituted one or more times with OH, C_{2-6}-alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH;

is reacted with a compound of the formula R"-ONH_2, or an acid-addition salt thereof, wherein R" represents hydrogen, C_{1-8}-alkyl which may be substituted one or more times with OH, C_{2-6}-alkenyl which may be substituted one or more times with OH, C_{2-6}-alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH;

or

(b) a compound represented by the general formula



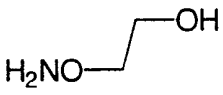
wherein,

R^{11} represents a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen;

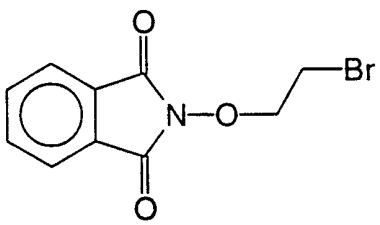
one of R^6 and R^7 is hydrogen, and the other represents R'-C=O or CR'=NOR", wherein the meaning of R' and R" is set forth above;

is subjected to oxidation with m-chloro-peroxobenzoic acid.

A method of preparing an intermediate compound of the formula

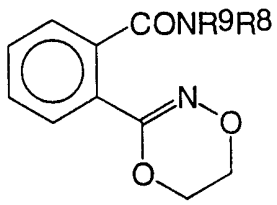


characterized by reacting a compound of the formula



with HNR^9R^8, wherein R^9 and R^8 independently may be hydrogen, C_{1-8}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-8}-alkyl, or R^9 and R^8 together form a C_{3-7} ring,

to form a compound of the formula



wherein R^9 and R^8 has the meaning set forth above,

and subsequently heating the compound in acidic environment.

a pharmaceutical composition comprising an effective amount of a compound as any above or a pharmaceutically acceptable salt thereof or an oxide thereof together with at least one pharmaceutically acceptable carrier or diluent;

the use of a compound as any above for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the modulation of the $GABA_A$ receptor complex of the central nervous system;

the use of a compound as any above for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to positive modulation of the $GABA_A$ receptor complex of the central nervous system;

the use of a compound as any above for the preparation of a medicament for the treatment of a disorder or disease selected from anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder;

a method of treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to modulation of the $GABA_A$ receptor complex of the central nervous system comprising administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound as any above;

the method as above, wherein a disorder or disease responsive to positive modulation of the $GABA_A$ receptor complex is treated;

the method as above, wherein anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder is treated; and

the method as above, wherein the active ingredient is administered in form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

Definition of substitutents

Alkyl means a straight chain or branched chain of from one to eight carbon atoms or cyclic alkyl of from three to seven carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; methyl, ethyl, propyl, isopropyl and t-butyl are preferred groups.

Alkenyl means a straight chain or branched chain of from two to six carbon atoms containing one double bond, including but not limited to ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, and 3-butenyl.

Alkynyl means a straight chain or branched chain of from two to six carbon atoms containing one triple bond, including but not limited to ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

A 5- or 6-membered monocyclic heteroaryl group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl.

Examples of pharmaceutically-acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate,

toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate for example.

Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts. Such salts are formed by procedures well known in the art.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention exist in (+) and (-) forms as well as in racemic forms. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof, with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example. The compounds of the instant invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolvation of optical isomers, known to those skilled in the art may be used, and will be apparent to the average skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Furthermore, as the compounds of the invention are oximes they can exist in two forms, Z- and E-form, depending on the arrangement of the substituents around the

-C=N- double bond. The present invention includes both the Z- and E-form of the compounds of the invention as well as mixtures thereof.

The compounds of the invention may be prepared in numerous ways.

The compounds of the invention and their pharmaceutically acceptable derivatives may thus be prepared by any method known in the art for the preparation of compounds of analogous structure and as shown in the representative examples which follows.

Starting materials for the processes described in the present patent application are known or can be prepared by known processes from commercially available chemicals.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

Biology:

4-aminobytyric acid (GABA) is the major inhibitory neurotransmitter and has been shown to act throughout both the central and peripheral nervous system. At present two types of GABA receptors are known, the $GABA_A$ and the $GABA_B$ receptors. Recent molecular biology has demonstrated that the $GABA_A$ receptors can be subdivided into numerous subreceptors consistant with the selective and or partial pharmacological effects observed with certain benzodiazepine receptor ligands as opposed to the unselective effects observed for the classical benzodiazepine receptor ligands such as for example diazepam. Activation of GABA receptors leads to alternations in membrane potential (hyperpolarization). The $GABA_A$ receptors are associated with chloride influx through its associated and integrated chloride channel, whereas $GABA_B$ receptor activation indirectly alters potassium and calcium channels as well as modifies second messenger production. The $GABA_A$ recognition sites can be activated by GABA, muscimol; and isoguvacine for example, but not by $GABA_B$ agonists such as for example baclofen. The modulatory $GABA_A$ recognition site at the benzodiazepine receptor sites can be selectively radiolabelled with ^{3}H-flunitrazepam. The affinity of various potential ligands for the benzodiazepine receptor sites can thus be evaluated by estimating the ability of test compounds to displace ^{3}H-flunitrazepam.

Method

Tissue Preparation: Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortex from male Wistar rats (150-200 g) is homogenized for 5-10 sec in 20 ml Tris-HCl (30 mM, pH 7.4) using an Ultra-Turrax homogenizer. The suspension is centrifuged at 27,000 x g for 15 min and the pellet is washed three times with buffer (centrifuged at 27,000 x g for 10 min). The washed pellet is homogenized in 20 ml of buffer and incubated on a water bath (37°C) for 30 min to remove endogenous GABA and then centrifuged for 10 min at 27,000 x g. The pellet is then homogenized in buffer and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 30 ml buffer and the preparation is frozen and stored at -20°C.

Assay: The membrane preparation is thawed and centrifuged at 2°C for 10 min at 27,000 x g. The pellet is washed twice with 20 ml 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogenizer and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 50 mM Tris-citrate, pH 7.1 (500 ml buffer per g of original tissue), and then used for binding assays. Aliquots of 0.5 ml tissue are added to 25 µl of test solution and 25 µl of ^{3}H-FNM (1 nM, final concentration), mixed and incubated for 40 min at 2°C. Non-specific binding is determined using clonazepam (1 µM, final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fibre filters under suction and immediately washed with 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

The test value is calculated as the IC_{50} (the concentration (nM) of the test substance which inhibits the specific binding of ^{3}H-FNM by 50%).

Test results obtained by testing selected compounds of the present invention appear from the following table:

Table

Test compound:	IC_{50} (nM)
5-acetyl-1-(3-(3-pyridyl)-phenyl)-benzimidazole O-(2-hydroxyethyl)oxime	4.2
5-acetyl-1-(3-(3-pyridyl-N-oxide)-phenyl)-benzimidazole oxime	14.0
5-acetyl-1-(3-(3-pyridyl-N-oxide)-phenyl)-benzimidazole O-ethyl oxime	10.0
5-acetyl-1-(3-(3-pyridyl-N-oxide)-phenyl)-benzimidazole	12.0

Pharmaceutical Compositions

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, then it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing one (1) milligram of active ingredient or, more broadly, 0.01 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers,
lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from one to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting vax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting vax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated in solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasel cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g. gelatin or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active

component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Method of Treating

The compounds of this invention are extremely useful in the treatment of disorders or diseases of a living animal body due to their affinity for the benzodiazepine binding site of the $GABA_A$ receptor. These properties make the compounds of this invention extremely useful in the treatment of convulsions, anxiety, sleep disorders, memory disorders as well as other disorders sensitive to modulation of the $GABA_A$ receptor. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of a disorder or disease associated with the $GABA_A$ receptors. This includes especially convulsions, anxiety, sleep disorders and memory disorders.

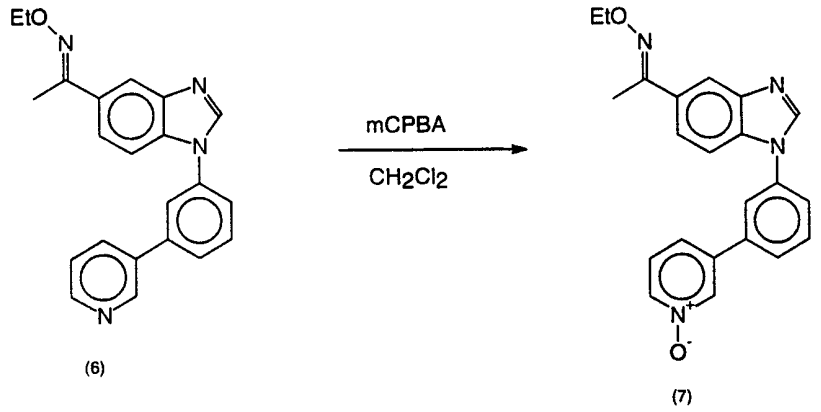
Suitable dosage range are 0.01-100 milligrams daily, 0.1-50 milligrams daily, and especially 0.1-30 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication towards which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Example 1

The following example will illustrate the invention further; however they are not to be construed as limiting.

The starting material of the following examples can be obtained as described in WO 96/33191

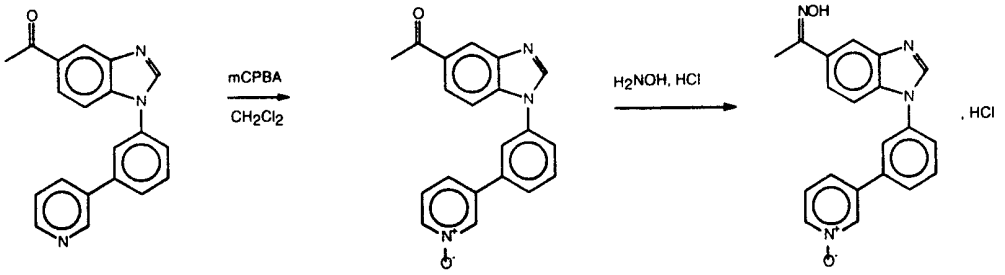
5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole O-ethyl oxime **(7)**



(6) (7)

To a stirred solution of **6** (1.7 g, 4.77 mmol) in dichloromethane (25 ml) was added m-chloroperbenzoic acid (mCPBA) (1.23 g, 7.13 mmol) in portions at ambient temperature and stirring was continued overnight. The reaction mixture was washed with aqueous sodium hydroxide (1M), dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographied on a silica gel column using a mixture of ethyl acetate and methanol (9:1 v/v) as the eluent. The crude product obtained from the eluate was recrystallized from ethanol to yield **7**(1.15 g, 65%). M.p. 189-190°C.

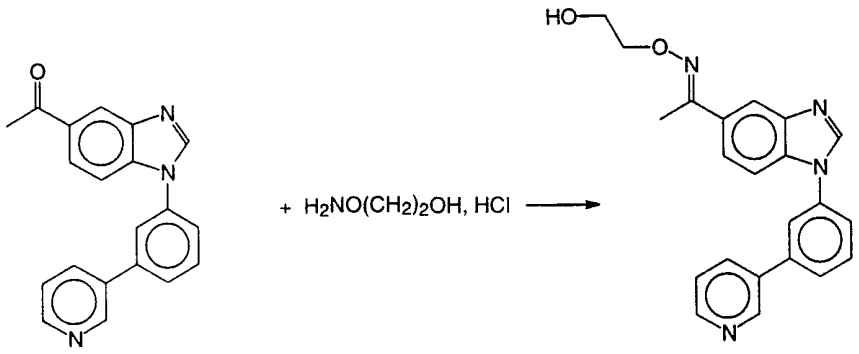
5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole oxime, hydrochloride **(9)**



(5) (8) (9)

(5) (2.0 g, 6.4 mmol) was treated with mCPBA as described above to yield **(8)**(1.0 g, 48%). This N-oxide (1 g, 3.0 mmol) was suspended in methanol (50 ml) and hydroxylamine hydrochloride (0.32 g, 4.6 mmol) was added. The mixture was refluxed overnight, and the cooled mixture was poured into water (100 ml). The precipitate was filtered off, washed with water and dried to yield **(9)**, hydrochloride (0.86 g, 82%). M.p. 298-300°C.

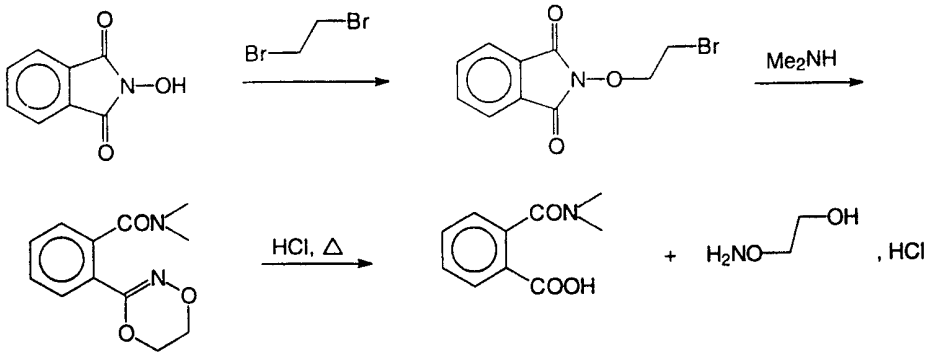
5-Acetyl-1-(3-(3-pyridyl)phenyl)benzimidazole O-(2-hydroxyethyl) oxime**(10)**



5 10

To a suspension of **(5)**(5.0 g, 16 mmol) in ethanol (50 ml) was added O-(2-hydroethyl)hydroxylamine, hydrochloride (2.7 g, 24 mmol) and triethylamine (3.3 ml, 24 mmol) and the mixture was heated to reflux overnight. The cooled mixture was poured into water (200 ml) and the resulting suspension was extracted with ethyl acetate. The organic extract was dried over sodium sulfate and concentrated under reduced pressure. The concentrate was chromatographied on a silica gel column using a mixture of ethyl acetate and methanol (9:1 v/v) as the eluent. The crude product obtained from the eluate was recrystallized from ethanol to yield **(10)** (1.95 g, 33%). M.p. 168-170°C.

<u>O-(2-hydroxyethyl)hydroxylamine, hydrochloride:</u>



<u>N-(2-bromoethoxy)phtalimide:</u>

To a solution of N-hydroxyphtalimide (5.0 g, 30.7 mmol) in DMF (50 ml) was added triethylamine (4.27 ml, 30.7 mmol) and 1,2-dibromoethane (10.6 ml, 0.12 mmol) and the mixture was stirred in a nitrogen atmosphere at ambient temperature overnight. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was trituated with water to leave the crystalline product (6.56 g, 89%).

N,N-Dimethyl-2-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzamide:

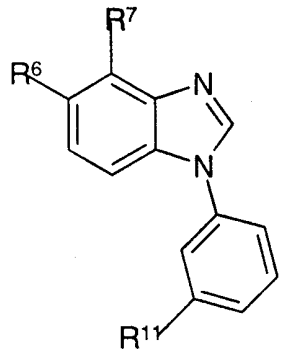
N-(2-Bromoethoxy)phtalimide (6.56 g, 27.3 mmol) was suspended in THF (30 ml). Gaseous dimethylamine was gently bubbled through this suspension until a clear orange-red solution had formed. This resulting solution was stirred at ambient temperature overnight. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using a mixture of ethyl acetate and methanol (9:1 v/v) as the eluent. Yield: 4.53 g (71%).

O-(2-Hydroxyethyl)hydroxylamine:

A solution of N,N-dimethyl-2-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzamide (4.53 g, 19.4 mmol) in hydrochloric acid (50 ml, 6M) was heated to reflux overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. Toluene was added to the residue and the resulting mixture was evaporated to dryness to yield the desired product (3.3 g, contaminated with dimethylammonium chloride) which was used without further purification.

Claims

1. A compound represented by the general formula



wherein,

R^{11} represents a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen, or a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen as the N-oxide;

one of R^6 and R^7represents hydrogen, and the other represents R'-C=O or CR'=NOR", wherein R' and R" each independently may be hydrogen, C_{1-8}-alkyl which may be substituted one or more times with OH, C_{2-6}-alkenyl which may be substituted one or more times with OH, C_{2-6}-alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH;

provided however that when R" represents hydrogen, C_{1-8}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl then R^{11} represents a 5- or 6-membered monocyclic heteroaryl containing at least one nitrogen as the N-oxide;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R" represents C_{1-6}-alkyl substituted with one hydroxy-group.

3. The compound of claim 1, wherein R^7 represents hydrogen.

4. The compound of claim 1, wherein R^{11} represents pyridyl-N-oxide.

5. The compound of claim 1, which is
5-Acetyl-1-(3-(3-pyridyl)phenyl)benzimidazole O-(2-hydroxyethyl) oxime;
5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole oxime, hydrochloride;
5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole O-ethyl oxime, or
5-Acetyl-1-(3-(3-pyridyl-N-oxide)phenyl)benzimidazole;
or a pharmaceutically acceptable addition salt thereof.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of the claims 1-5 and a pharmaceutically acceptable carrier, excipient or diluent.

7. The use of a compound according to any of claims 1-5 for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which the disease or disorder is responsive to the modulation of the $GABA_A$-receptor complex of the central nervous system.

8. The use of a compound according to any of claims 1-5 for the preparation of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which the disease or disorder is responsive to positive modulation of the $GABA_A$-receptor complex of the central nervous system.

9. The use of a compound according to any of claims 1-5 for the preparation of a medicament for the treatment of a disorder or disease selected from anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder.

10. The use of a compound according to any of claims 1-5 for the preparation of a medicament for the treatment of a disorder or disease selected from anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder.

11. A method of treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to modulation of the $GABA_A$ receptor complex of the central nervous system comprising administering to such a living animal body, including a human, in need thereof a therapeutically-effective amount of a compound according to any of claims 1-5.

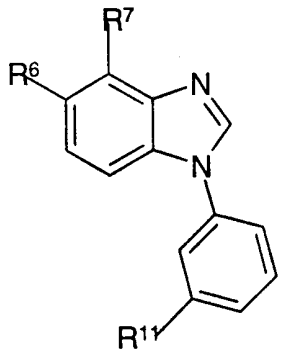
12. The method according to claim 11, wherein a disorder or disease responsive to positive modulation of the $GABA_A$ receptor complex is treated.

13. The method according to claim 11, wherein anxiety, sleep disorders, memory disorders, epilepsy or any other convulsive disorder is treated.

14. The method according to claim 11, wherein the active ingredient is administered in form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically-acceptable carrier or diluent.

15. A method of preparing a compound according to any of the claims 1-5, by which method,

(a) a compound represented by the general formula



wherein,

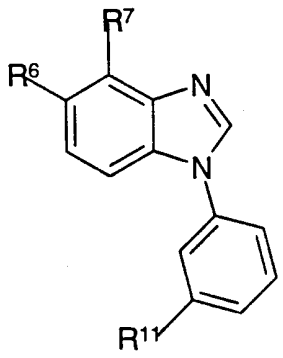
R^{11} represents a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen, or a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen as the N-oxide;

one of R^6 and R^7 represents hydrogen, and the other represents CR'=O, wherein R' represents hydrogen, C_{1-8}-alkyl which may be substituted one or more times with OH, C_{2-6}-alkenyl which may be substituted one or more times with OH, C_{2-6}-alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH;

is reacted with a compound of the formula R"-ONH_2, or an acid-addition salt thereof, wherein R" represents hydrogen, C_{1-8}-alkyl which may be substituted one or more times with OH, C_{2-6}-alkenyl which may be substituted one or more times with OH, C_{2-6}-alkynyl which may be substituted one or more times with OH, or phenyl which may be substituted one or more times with OH:

or

(b) a compound represented by the general formula



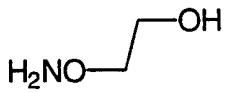
wherein,

R^{11} represents a 5- or 6-membered monocyclic heteroaryl group containing at least one nitrogen;

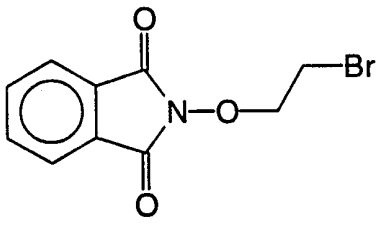
one of R^6 and R^7 is hydrogen, and the other represents R'-C=O or CR'=NOR", wherein the meaning of R' and R" is set forth above;

is subjected to oxidation with m-chloro-peroxobenzoic acid.

16. A method of preparing an intermediate compound of the formula

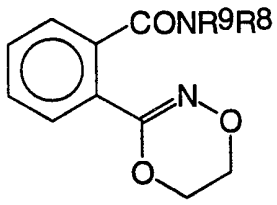


characterized by reacting a compound of the formula



with HNR^9R^8, wherein R^9 and R^8 independently may be hydrogen, C_{1-8}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkyl-C_{1-8}-alkyl, or R^9 and R^8 together form a C_{3-7} ring,

to form a compound of the formula



wherein R^9 and R^8 has the meaning set forth above,

and subsequently heating the compound in acidic environment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 98/00432

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/10 A61K31/44 C07C239/20

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 33191 A (NEUROSEARCH AS) 24 October 1996 cited in the application see claims	1-15
X	EP 0 616 807 A (NEUROSEARCH AS ;MEIJI SEIKA KAISHA (JP)) 28 September 1994 see page 20,table1,compounds 50a,52a,59a see page 6 - page 7; claims	1-15
A	DASHYANT DHANAK ET AL: "A synthesis of pyrrole derivatives from O-(2-hydroxyethyl)-ketoximes" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS.,1986, pages 903-904, XP002089698 LETCHWORTH GB see page 903,footnote and compound 4	16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 1999	25/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 98/00432

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DASHYANT DHANAK ET AL: "Synthesis of '6!(2,4)pyridinophanes" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1.,1987, pages 2829-2832, XP002089699 LETCHWORTH GB see pages 2829 and 2831,compound 7 -----	16

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00432

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 98/00432

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 5554630 A	10-09-1996
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