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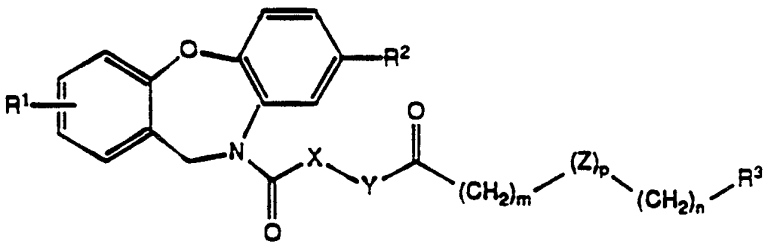
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(54) Title: SUBSTITUTED DIBENZOXAZEPINE COMPOUNDS AS ANALGESIC AGENTS



(I)

(57) Abstract

The present invention provides substituted dibenzoxazepine compounds of formula (I) which are useful as analgesic agents for the treatment of pain, pharmaceutical compositions comprising a therapeutically-effective amount of a compound of formula (I) in combination with a pharmaceutically-acceptable carrier, and a method for eliminating or ameliorating pain in an animal comprising administering a therapeutically-effective amount of a compound of formula (I) to the animal.

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SUBSTITUTED DIBENZOXAZEPINE COMPOUNDS AS ANALGESIC AGENTS

BACKGROUND OF THE INVENTION

(1) Field of the Invention

The present invention generally relates to compounds having pharmacological activity which are useful as pharmacological agents and, more particularly, as analgesic agents for the treatment of pain, to pharmaceutical compositions containing one or more of these compounds, and to methods of treatment employing these compounds. More particularly, the present invention concerns substituted dibenzoxazepine compounds, pharmaceutical compositions containing one or more of these compounds in combination with a pharmaceutically-acceptable carrier, and methods of treating pain employing these compounds.

Analgesic compounds are agents which alleviate pain without causing a loss of consciousness and, thus, which are useful for treating pain and, often, for reducing inflammation.

The major classes of analgesic compounds include narcotic analgesics, or opiates, compounds which alleviate pain and induce sleep, and analgesic-antipyretic compounds, compounds which alleviate pain and reduce fever, such as salicylates.

Although the efficacy of opiates in relieving pain is well established, the associated addiction liability of opiates is a distinct disadvantage of these compounds.

While salicylate and salicylate-like agents (non-steroidal antiinflammatory agents or NSAIDS) are also efficacious in relieving pain, they often exhibit undesirable side effects, such as gastrointestinal irritation, as with aspirin, allergic response, as with aspirin, and/or liver toxicity with extended use, as with acetaminophen.

The compounds of the present invention are neither opiates nor salicylates, and represent another class of compounds which are useful as analgesic agents.

(2) Description of the Related Art

U.S. Patent Nos. 4,559,336 and 4,614,617 (a continuation-in-part of U.S. 4,559,336) disclose 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-(sulfinyl- and sulfonyl-containing acyl)hydrazides, and intermediates thereof.

U.S. Patent No. 3,534,019 discloses hydrazides of dibenzoxazepine-, dibenzothiazepine- and dibenzodiazepine- carboxylic acids.

U.S. Patent No. 3,624,104 discloses aralkanoyl derivatives of dibenzoxazepine-N-carboxylic acid hydrazide compounds.

U.S. Patent No. 3,989,719 discloses N,N'-diacyl hydrazines.

U.S. Patents Nos. 3,917,649 and 3,992,375 (a divisional of U.S. Patent No. 3,917,649) disclose dibenzoxazepine N-carboxylic acid hydrazine compounds.

U.S. Patents Nos. 4,045,442, 4,125,532 (a divisional of U.S. Patent No. 4,045,442) and 4,170,593 (a divisional of U.S. Patent No. 4,125,532) disclose 1-(substituted amino)alkanoyl-2-(dibenzoxazepine-10-carbonyl)hydrazine compounds.

U.S. Patent No. 4,559,337 discloses 8-chlorodibenz-[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-(alkoxy-containing acyl)hydrazide compounds.

GB 1 522 003 discloses 1-acyl-2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-carbonyl)hydrazine compounds.

GB 1 331 892 discloses derivatives of dibenzoxazepine N-carboxylic acid hydrazides.

European Patent Application Publication No. 0 193 822 discloses 8-chlorodibenz[b,f][1,4]-

oxazepine-10(11H)-carboxylic acid, 2-(thio-, sulfinyl- and sulfonyl-containing acyl)hydrazide compounds.

European Patent Application Publication No. 0 218 077 discloses 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-[(substituted phenylsulfinyl)alkanoyl]hydrazide compounds and 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[(substituted phenylsulfonyl)alkanoyl]hydrazide compounds, and intermediates used in the preparation of these compounds.

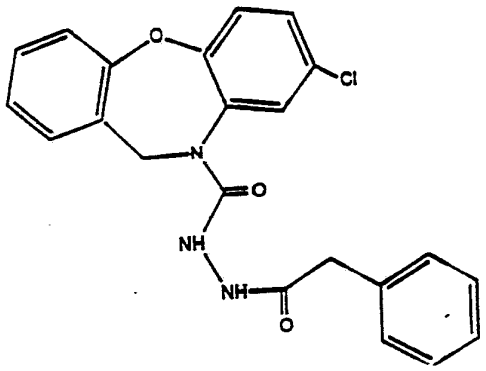
European Patent Application Publication No. 0 012 385 discloses dibenz[b,f][1,4]oxazepine derivatives.

German Patent Application Publication No. 1,170,322 discloses 10-substituted dibenz[b,f][1,4]oxazepin-11(10H)-ones.

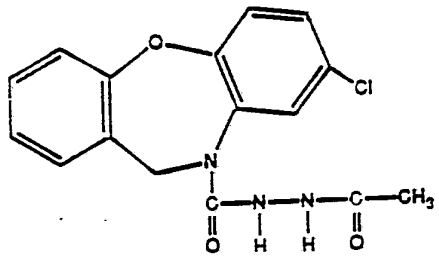
Netherlands Patent No. 67,00603 discloses substituted dibenz[b,f][1,4]oxazepine-11(10H)-one compounds.

Drower et al., "The Antiociceptive Effects of Prostaglandin Antagonists in the Rat," *European Journal of Pharmacology*, *133*, 249-256 (**1987**), disclose the study of the antinociceptive properties of two competitive antagonists of prostaglandins of the E series, 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-acetylhydrazide and 8-chlorodibenz[b,f][1,4]-oxazepine-10(11H)-carboxylic acid, 2-(5-chloro-1-oxopentyl)hydrazide.

J. H. Sanner, "Dibenzoxazepine Hydrazides as Prostaglandin Antagonists," *Intra-Science Chem. Rept.*, *6*(1), 1-9 (**1972**), describes experiments performed with two dibenzoxazepine derivatives designated SC-18637 and SC-19220, and shown below, and found that SC-18637 and SC-19220 inhibit the stimulant actions of prostaglandins on isolated smooth muscle preparations.



SC-18637



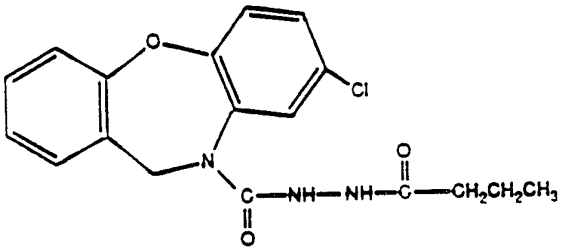
SC-19220

K. Nagarajan et al., "Synthesis of 10,11-Dihydrodibenz[b,f][1,4]oxazepine Derivatives as Potential Anticonvulsants & Psychotropic Agents," *Indian Journal of Chemistry*, *24B*, 840-844 (**1985**), disclose the synthesis of acyl, carbamoyl and thiocarbamoyl derivatives of 10,11-dihydrodibenz-[b,f][1,4]oxazepine, most of which have either a nitro or an amino group at position-2, as analogues of carbamazepine, and the evaluation of these derivatives as anticonvulsants associated with neuroleptic activity.

Other art which relates to the present invention includes that which is discussed below.

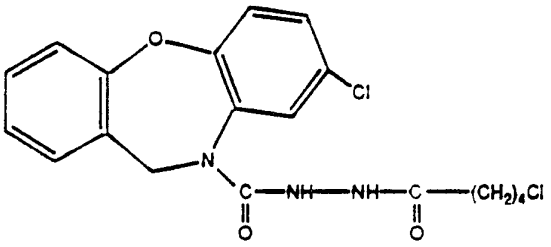
D.E. MacIntyre et al., "Antagonism of Human Platelet Responses to Stimulatory and Inhibitory Prostaglandins," *Prog. Lipid. Res.*, *20*(1-4), 453-9 (**1981**), disclose on Page 454, Lines 11-12, Page 458, Lines 43-44, and in Table 1, two dibenzoxazepine

compounds designated SC-19220 and SC-25191, and shown above and below, respectively, which were employed in an investigation of the effects of prostaglandin antagonists on platelet responses to stimulatory and inhibitory prostaglandins.



SC-25191

R. Gimet et al., "Quantitative Determination of Polymorphic Forms in a Formulation Matrix Using the Near Infra-Red Reflectance Analysis Technique," *J. Pharmaceutical & Biomedical Analysis*, 5(3), 205-211 (**1987**), disclose an analytical method for the determination of the polymorphic transformation of an active ingredient in a solid dosage form matrix, and discuss a compound designated SC-25469, and shown below, at Page 206, Lines 16-23.



SC-25469

J.H. Sanner et al., "Structure-Activity Relationships of some Dibenzoxazepine Derivatives as Prostaglandin Antagonists," *Advances in the Biosciences*, *9*, 139-148 (**1972**), disclose tests for prostaglandin antagonism on isolated guinea-pig ileum

and rat stomach fundus strips with the n-butanoyl, i-butanoyl and n-hexanoyl analogs of SC-19220 (see structure above) and, on Page 140, Lines 11-18, show the chemical structures of the compounds used in the study.

A. Rakovska et al., "Antagonistic Effect of SC-19220 on the Responses of Guinea-Pig Gastric Muscles to Prostaglandins E_1, E_2 and F_2," *Arch. int. Pharmacodyn, 268*, 59-69 (**1984**), disclose a study of the contractile responses of guinea-pig gastric muscles to SC-19220 (see structure above), and the prostaglandin-blocking activity and specificity of SC-19220 on these muscles.

W. E. Coyne et al., "Anticonvulsant Semicarbazides," *J. Med. Chem., 11*(6), 1158-1160 (**1968**), disclose the investigation of the structure-activity relationship of the anticonvulsant activity of a series of semicarbazides which was synthesized from various tricyclic amines (see Table I, Page 1160).

K. Gyires et al., "The Use of the Writhing Test in Mice for Screening Different Types of Analgesics," *Arch. int. Pharmacodyn, 267*, 131-140 (**1984**), describe a comparison of the analgesic potency of some prostaglandin synthesis inhibitors, including SC-19220 (see structure above), and morphine using the writhing test. SC-19220 is discussed on Page 133, Lines 10 and 14-16, in Table II (Page 134), and on Page 135, Lines 16-25, and Page 137, Lines 34-38.

A. Bennett et al., "Antagonism of Prostanoid-Induced Contractions of Rat Gastric Fundus Muscle by SC-19220, Sodium Meclofenamate, Indomethacin or Trimethoquinol," *Br. J. Pharmac, 71*, 169-175 (**1980**), disclose the study of the effects of several compounds, including SC-19220 (see structure above), on contractions of the rat stomach longitudinal muscle to several prostanoids. SC-19220 is discussed on Page 175, Paragraph 1, Page 170, Paragraph 4, in

Table 1 and Figure 2, on Page 172, Paragraph 2, and on Page 174, Paragraphs 1 and 2.

C. A. Maggi et al., "The Effect of SC-19220, a Prostaglandin Antagonist, on the Micturition Reflex in Rats," *European Journal of Pharmacology, 152*, 273-279 (**1988**), disclose a study in which SC-19220 (see structure above) is said to have increased the bladder capacity and reduced the voiding efficiency of micturition of urethane-anesthetized rats.

George et al., "Antagonism of Alcohol Hypnosis by Blockade of Prostaglandin Synthesis and Activity: Genotype and Time Course Effects," *Pharmacology Biochemistry & Behavior, 19*, 131-136 (**1983**), disclose a study of genetic and time-course factors of the effect of the antagonism of alcohol-induced behaviors of mice which have been pretreated with prostaglandin synthetase inhibitors and the effect of SC-19220 (see structure above) on ethanol sleep time.

S. Nakajyo et al., "Inhibitory Effect of Bassianolide, A Cyclodepsipeptide, on Drug-Induced Contractions of Isolates Smooth Muscle Preparations," *Japan. J. Pharmacol., 32*, 55-64 (**1982**), disclose a study of the effect of bassianolide on the contractile responses induced by various types of neurotransmitters and autacoids. SC-19220 (see structure above) was employed in this study, and is discussed on Page 57, Paragraph 1, in Figures 2 and 3, in Table 1, and on Page 60, Paragraph 1, Page 62, Paragraph 3, and Page 63, Paragraph 2.

A. Gomes et al., "Pharmacodynamics of Venom of the Centipede Scolopendra subspinipes dehaani," *Indian Journal of Experimental Biology, 20*, 615-618 (**1982**), disclose an investigation of the pharmacodynamic actions of the venom of the tropical centipede S. subspinipes. SC-19220 (see structure above) was employed in this study and is discussed on Page 615

(abstract), Page 616, Line 30, Page 617, Lines 13-18, in Figures 4 and 5, and on Page 618, Lines 23-26.

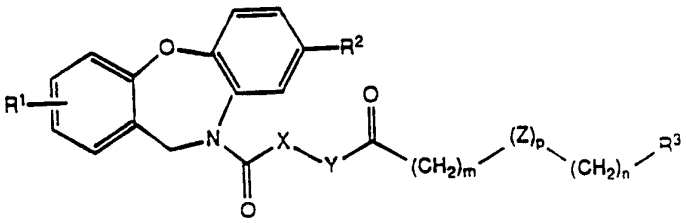
Each of the documents described hereinabove discloses compounds which are structurally different from the compounds of the present invention. Thus, the compounds of the present invention are structurally distinct from that which has been described in the art.

Compounds of the present invention have been found to exhibit activity as prostaglandin E_2 antagonists. Some of these compounds were surprisingly and unexpectedly found to be more than ten to one hundred times more effective as prostaglandin E_2 antagonists than prostaglandin antagonists reported in the literature.

Moreover, compounds within the present invention were found to be water soluble. Thus, these compounds may be much more easily formulated into compositions which are suitable for oral, parenteral and other modes of administration than similar compounds which are not water soluble.

SUMMARY OF THE INVENTION

The present invention provides compounds having a structure of Formula I:



Formula I

or a pharmaceutically-acceptable salt thereof, wherein:

X: is -NH- or $-CH_2-$;

Y is: (1) $-CH_2-$ when X is -NH-, and
(2) -NH- when X is $-CH_2-$;

R^1 is: hydrogen, halogen or $-OR^4$;

R^4 is: hydrogen, alkyl or $-\overset{O}{\overset{\|}{C}}-R^8$;

Z is: oxygen, sulfur, -SO-, $-SO_2-$ or $-NR^5-$;

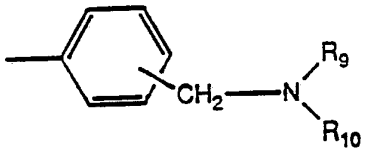
R^5 is: hydrogen or t-butyloxycarbonyl;

R^2 is: hydrogen, halogen or trifluoromethyl;

R^3 is: hydrogen, halogen, aryl, heteroaryl or $-NR^6R^7$;

R^6 and R^7 are: each independently hydrogen or

alkyl;

R^8 is: alkyl, aryl or  ;

R^9 and R^{10} are: each independently hydrogen or alkyl, or can combine together to form N-morpholino or 4-methyl-N-piperazinyl;

m and n are: each independently integers of from 0 to 3; and

P is: 0 or 1, provided that p is not 1 when m is 0.

The present invention also provides pharmaceutical compositions which are pharmaceutically acceptable, and which comprise a therapeutically-effective amount of a compound of Formula I in combination with a pharmaceutically-acceptable carrier, and a method for eliminating or ameliorating pain in an animal comprising administering a therapeutically-effective amount of a compound of Formula I to the animal.

DETAILED DESCRIPTION OF THE INVENTION

(1) Definitions

For purposes of clarity, the terms and phrases used throughout this specification and the appended claims are defined in the manner set forth directly below.

Some of the chemical structures which are presented in this specification and the appended claims have been drawn using the convention which employs lines to represent alkyl radicals, which is known by those of skill in the art.

The abbreviation "AcOH" as used herein means acetic acid.

The term "alkyl" as used herein means a saturated hydrocarbon radical having from one to ten carbon atoms, usually from one to six carbon atoms, and more usually from one to three carbon atoms, and which can be a straight or branched chain. Representative of such radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl and the like.

The term "aryl" as used herein means unsubstituted 5- and 6-membered single-ring aromatic radicals, for example, phenyl.

The term "analgesia" as used herein means the reduction, or absence, of sensibility to pain, designating particularly the relief of pain without loss of consciousness.

The term "animal" as used herein includes humans and animals.

The term "composition" as used herein means a product which results from the combining of more than one ingredient.

The phrase "ED_{50} dose" as used herein means that dose of a compound or drug which produced a biological effect, such as producing analgesia, in 50% of the animals to which the compound or drug was administered.

The phrase "EC_{50} dose" as used herein means that dose of a compound or drug which produces a 50% inhibition in a biological effect, such as contractions in isolated segments of guinea pig ileum.

The abbreviation "Et" as used herein means ethyl (CH_3CH_2-).

The abbreviation "EtOAc" as used herein means ethyl acetate.

The term "halogen" as used herein means chlorine (Cl), bromine (Br), fluorine (F) and/or iodine (I).

The term "heteroaryl" as used herein means an aryl radical, as defined above, including from one to four heteroatoms, as defined below. Representative heteroaryls include thienyl, furanyl, pyridinyl, imidazolyl, pyrimidyl, (is)oxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrrolyl and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen.

The term "hydroxy" as used herein means the group -OH.

The abbreviation "i.g." as used herein means that a compound or drug was administered intragastrically, as defined below.

The term "intragastrically" as used herein means that a compound or drug was administered into the stomach.

The abbreviation "Me" as used herein means methyl ($-CH_3$).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular,

subarachnoid, intraspinal and intrasternal injection and infusion.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, as defined directly above, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical compound or pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Some examples of materials which can serve as pharmaceutically-acceptable carriers include:
(1) sugars, such as lactose, glucose and sucrose;
(2) starches, such as corn starch and potato starch;
(3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt;
(6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol;
(12) esters, such as ethyl oleate and ethyl laurate;
(13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid;
(16) pyrogen-free water; (17) isotonic saline;
(18) Ringer's solution; (19) ethyl alcohol;
(20) phosphate buffer solutions; and (21) other non-

toxic compatible substances employed in pharmaceutical formulations.

The phrase "pharmaceutically-acceptable salts" as used herein refers to non-toxic salts of the compounds of the present invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid, or which are prepared by reacting the free acid with a suitable base. Representative salts include the hydrochloride, hydrobromide, sulfate, bisulfate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napsylate, clavulanate and the like salts and alkali metal salts such as sodium and potassium and alkaline earth salts, such as calcium and magnesium.

The abbreviation "Ph" as used herein means phenyl.

The term "phenyl" as used herein means the group C_6H_5-, derived from benzene.

The phrase "protecting group" as used herein means substituents which protect the reactive functional group from undesirable chemical reactions. Examples of such protecting groups include esters of carboxylic acids, ethers of alcohols and acetals and ketals of aldehydes and ketones.

The phrase "N-protecting group" or "N-protected" as used herein means those groups intended to protect an amino group against undesirable reactions during synthetic procedures and includes, but is not limited to, sulfonyl, acyl, acetyl, pivaloyl, t-butyloxycarbonyl (Boc), carbonylbenzyloxy (Cbz), benzoyl and an L- or D-aminoacyl residue, which may itself be N-protected similarly.

The abbreviation "RaNi" as used herein means Raney nickel.

The abbreviation "s.c." as used herein means that a compound or drug was administered subcutaneously.

The phrase "therapeutically-effective amount" as used herein means an amount of a compound, material, or composition which is an effective dose for eliminating or ameliorating pain in an animal, or for producing some other desired therapeutic effect, at a reasonable benefit/risk ratio applicable to any medical treatment.

The phrases "title compound" and "title product" as used herein mean that compound or product whose chemical name is given, and/or whose structure is shown, in the particular example, or subpart thereof, referred to. If no particular example, or subpart thereof, is referred to, it means that compound or product whose chemical name is given, and/or whose structure is shown, in the particular example in which it appears, or in the particular subpart thereof.

The term "trifluoromethyl" as used herein means the group $-CF_3$.

The abbreviation "TsOH" as used herein means p-toluenesulfonic acid.

(2) Description of Invention

In one aspect, the present invention provides compounds comprising a structure of Formula I, as described above, and pharmaceutically-acceptable salts thereof.

The compounds of the present invention comprise a class of substituted dibenzoxazepine compounds in which the 2-, 3- and/or 8-position, and/or the side chain, is substituted. Such compounds have been shown to exhibit activity as prostaglandin E_2 antagonists.

Specific compounds within the scope of the invention include, but are not limited to, the compounds discussed in the examples presented below, as well as their pharmaceutically-acceptable salts.

Contemplated equivalents of the compounds described in Formula I include compounds which otherwise correspond thereto, and which have the same general properties thereof, wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound.

Certain compounds of this invention may exist in geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans- geometric isomers, R- and S- enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

Certain compounds of the present invention may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect,

refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, S. M. Berge et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, *66*:1-19 (1977).)

In other cases, the compounds of the invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine,

diethanolamine, piperazine and the like. (See, for example, S. M. Berge et al., "Pharmaceutical Salts," supra.)

For a detailed description of Bundgaard esters and their use, see H. Bundgaard et al., "A Novel Solution Stable Water Soluble Prodrug Type for Drugs Containing a Hydroxyl or an NH- Acidic Group," *J. Med. Chem.*, *12*, 2503-2507 (1989), which is hereby incorporated herein by reference.

In another aspect, the present invention provides pharmaceutically-acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds of Formula I, as described hereinabove, formulated together with one or more pharmaceutically-acceptable carriers. The pharmaceutical compositions of the invention may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal or vaginal administration.

In yet a further aspect, the present invention provides a method for eliminating or ameliorating pain in an animal, and methods for treating central nervous disorders, including convulsions and ischemia, and asthma, enuresis, arrhythmia, diarrhea, dysmenorrhea, osteoporosis, urinary incontinence, gastric hypermotility and irritable bowel syndrome, in an animal, comprising administering a therapeutically-effective amount of a compound of Formula I, as described hereinabove, to the animal.

The most preferred embodiment of the present invention is the compound described in Example 2 below.

(3) Utility

Compounds of the present invention exhibit activity as prostaglandin E_2 antagonists (prostaglandin antagonists of the E_2 series).

Compounds within the present invention, and the pharmaceutical compositions comprising one or more of these compounds, are useful as analgesic agents for the elimination or amelioration of pain in animals.

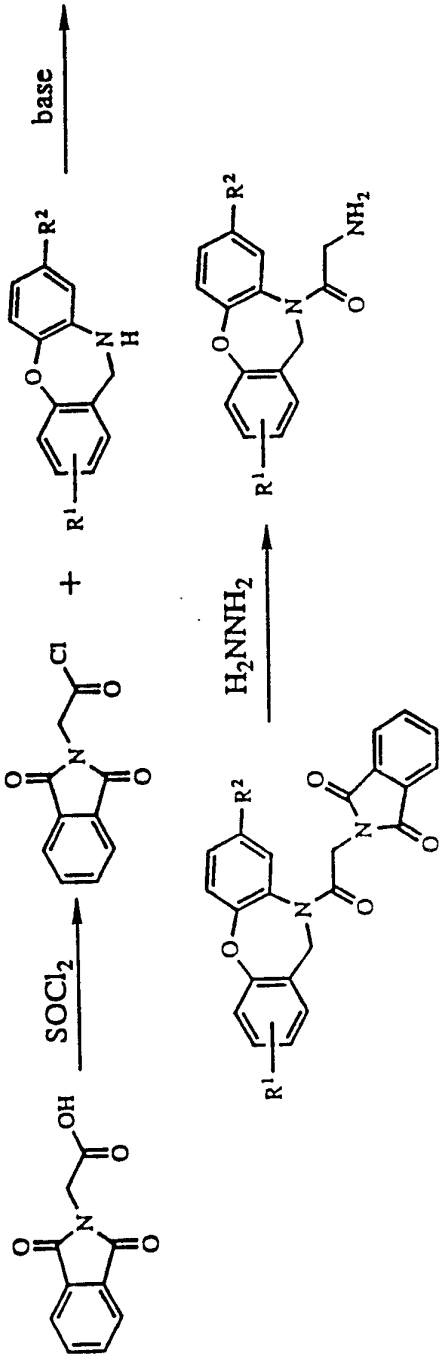
In addition to treating pain, these compounds and compositions would be useful in treating convulsions, ischemia and other central nervous system disorders, as well as osteoporosis, dysmenorrhea, asthma, enuresis, arrhythmia, diarrhea, urinary incontinence, gastric hypermotility and irritable bowel syndrome by virtue of their activity as prostaglandin E_2 antagonists.

(4) Methods of Preparation

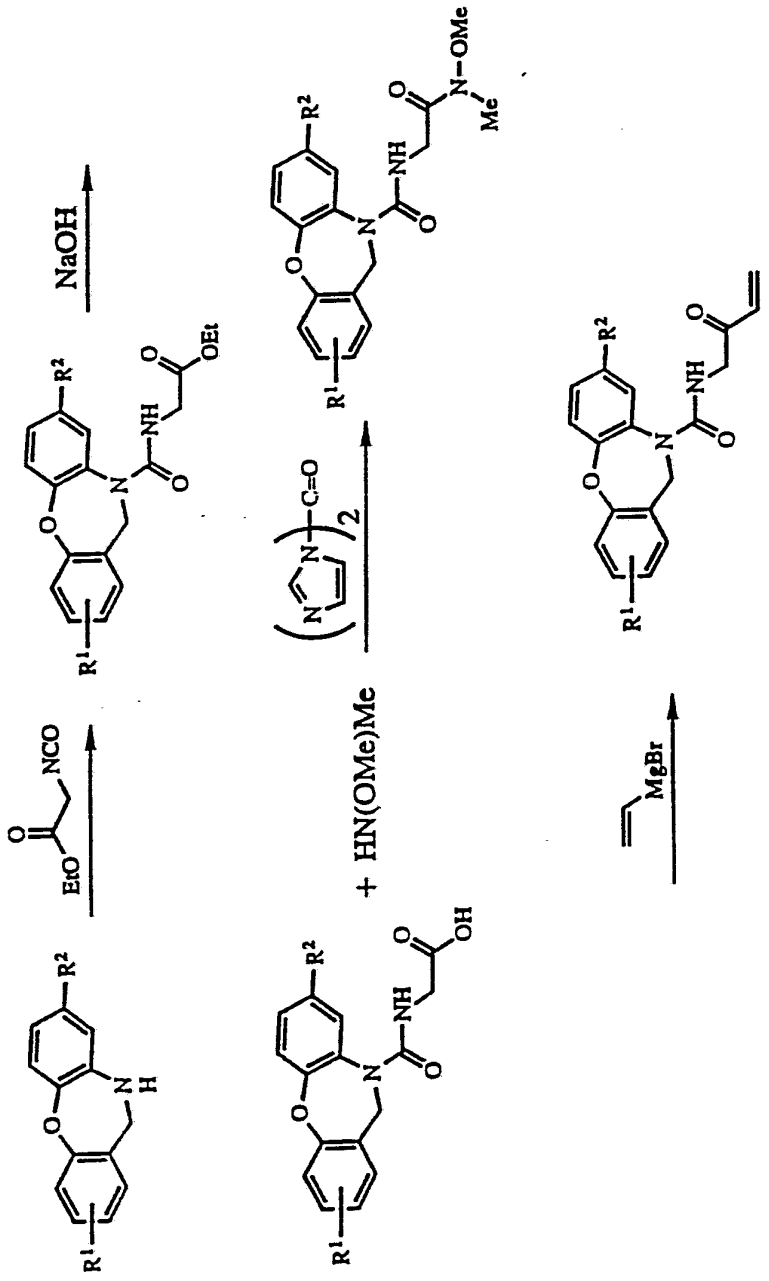
In general, the compounds of the present invention may be prepared by the methods illustrated in the following general reaction schemes, or by modifications thereof, using readily-available starting materials, reagents and conventional synthesis procedures. Unless otherwise specified, the various substituents of the compounds and materials present in the general reaction schemes are defined in the same manner as they are defined above in Formula I.

If a particular enantiomer of a compound of the present invention is desired, it may be prepared by chiral synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

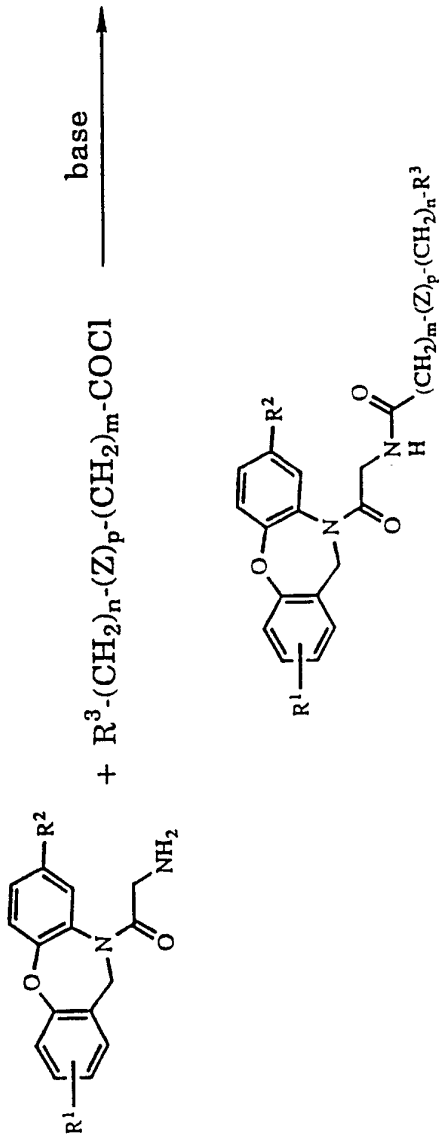
GENERAL REACTION SCHEME NO. 1



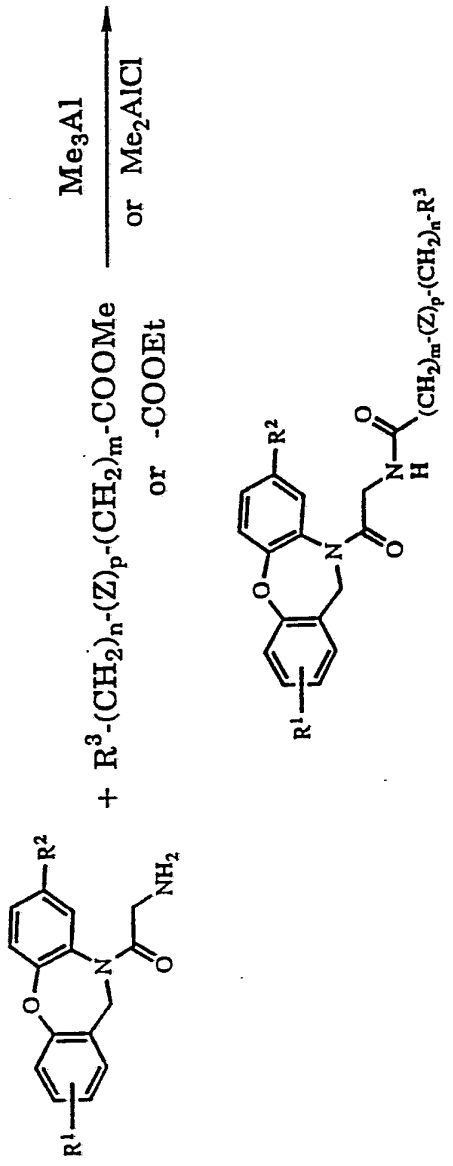
GENERAL REACTION SCHEME NO. 2



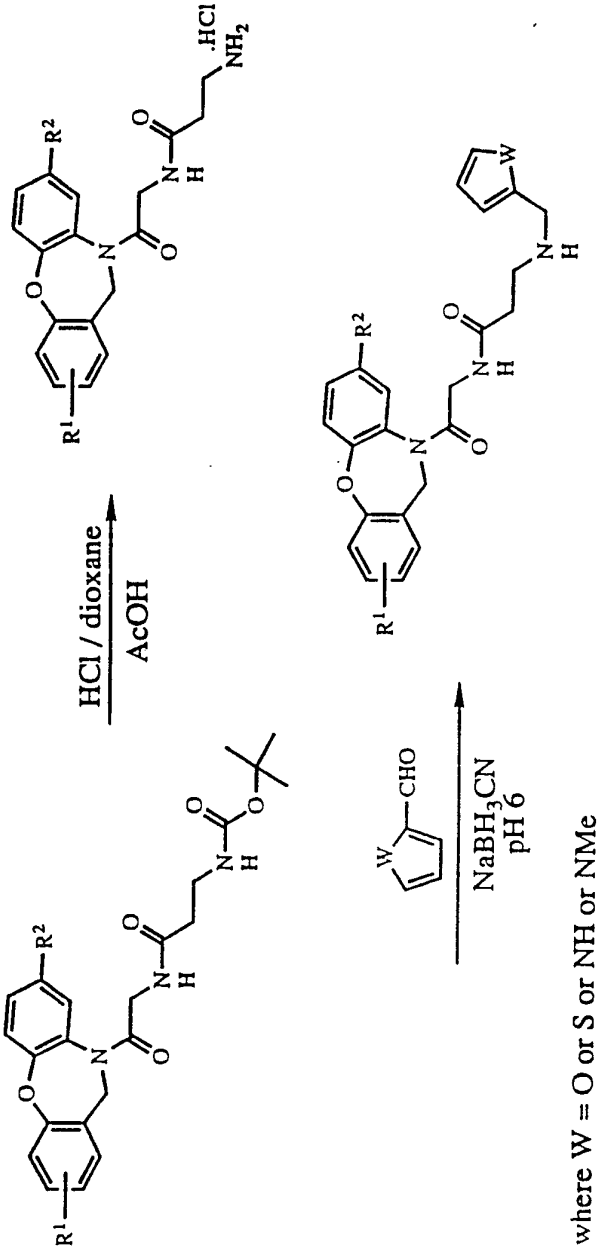
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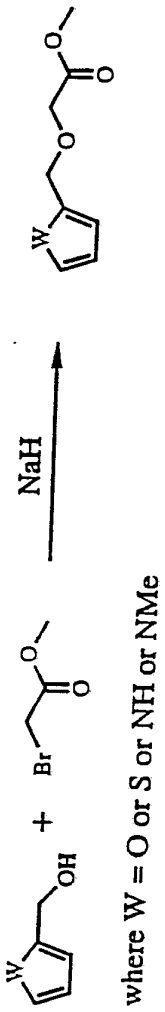
GENERAL REACTION SCHEME NO. 4



GENERAL REACTION SCHEME NO. 5

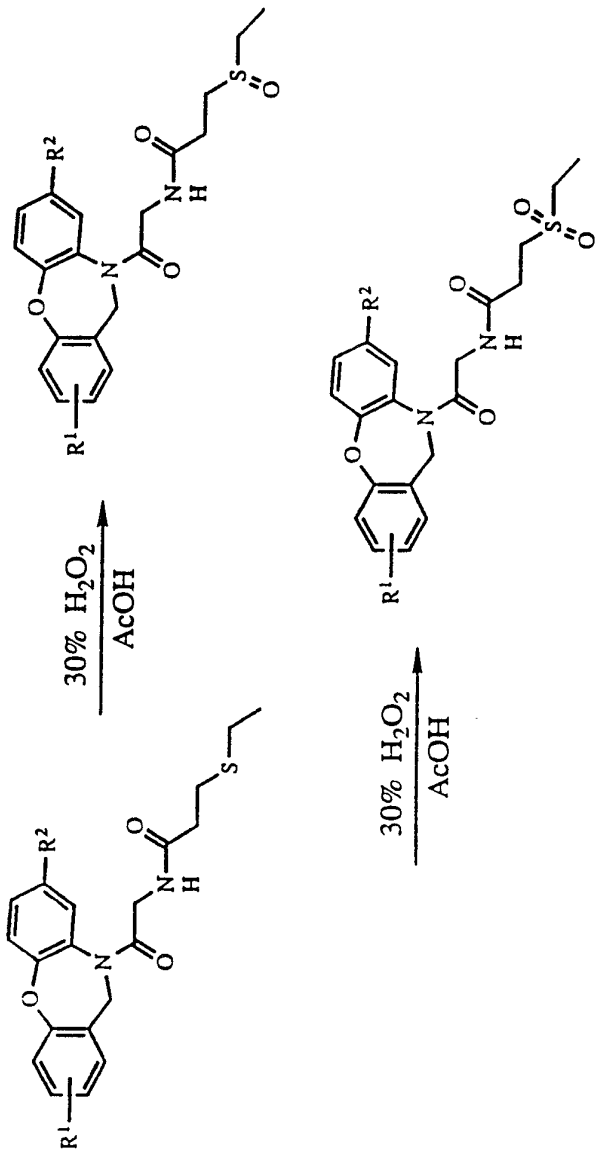


GENERAL REACTION SCHEME NO. 6

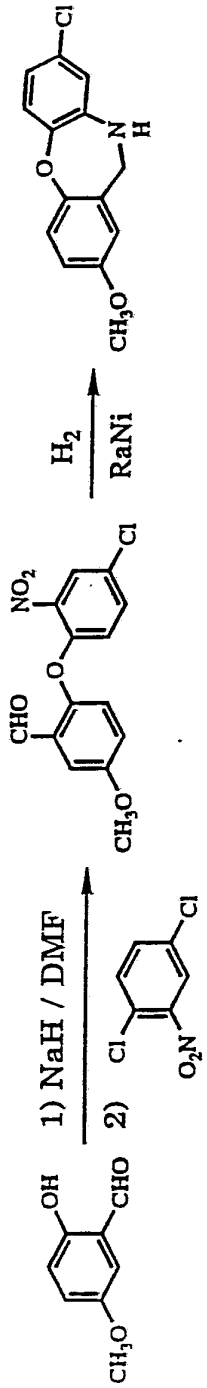


where W = O or S or NH or NMe

GENERAL REACTION SCHEME NO. 7

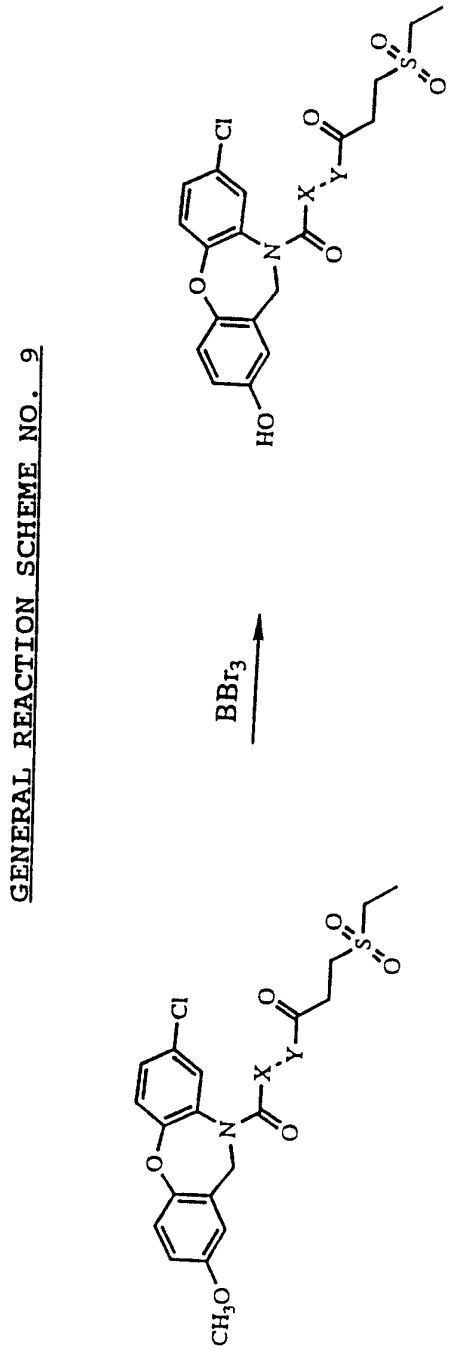


GENERAL REACTION SCHEME NO. 8

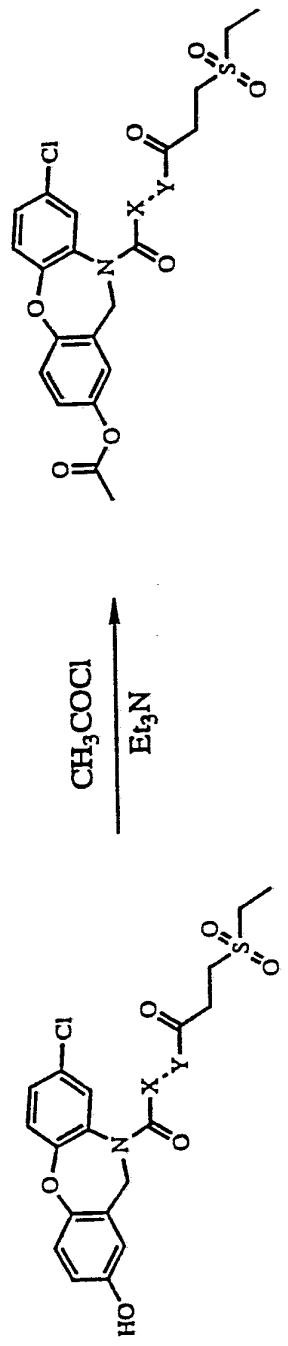


(DMF - Dimethylformamide)

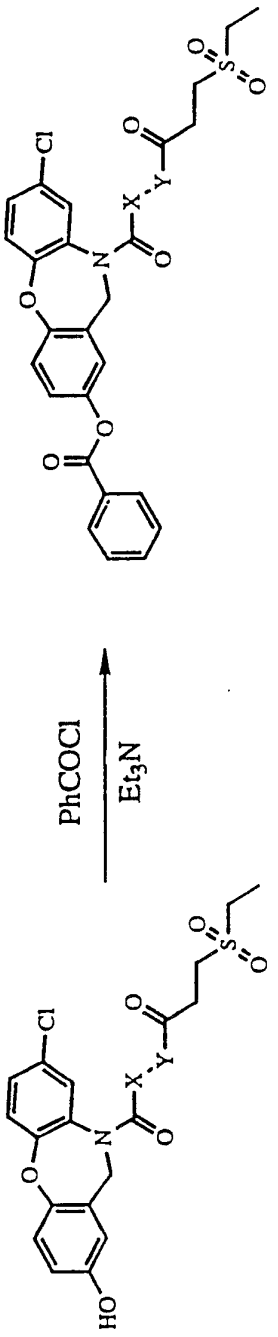
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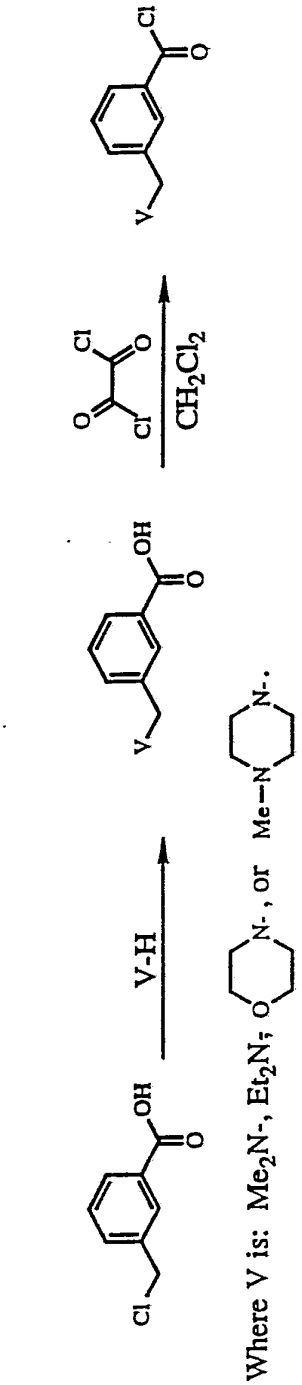
GENERAL REACTION SCHEME NO. 10



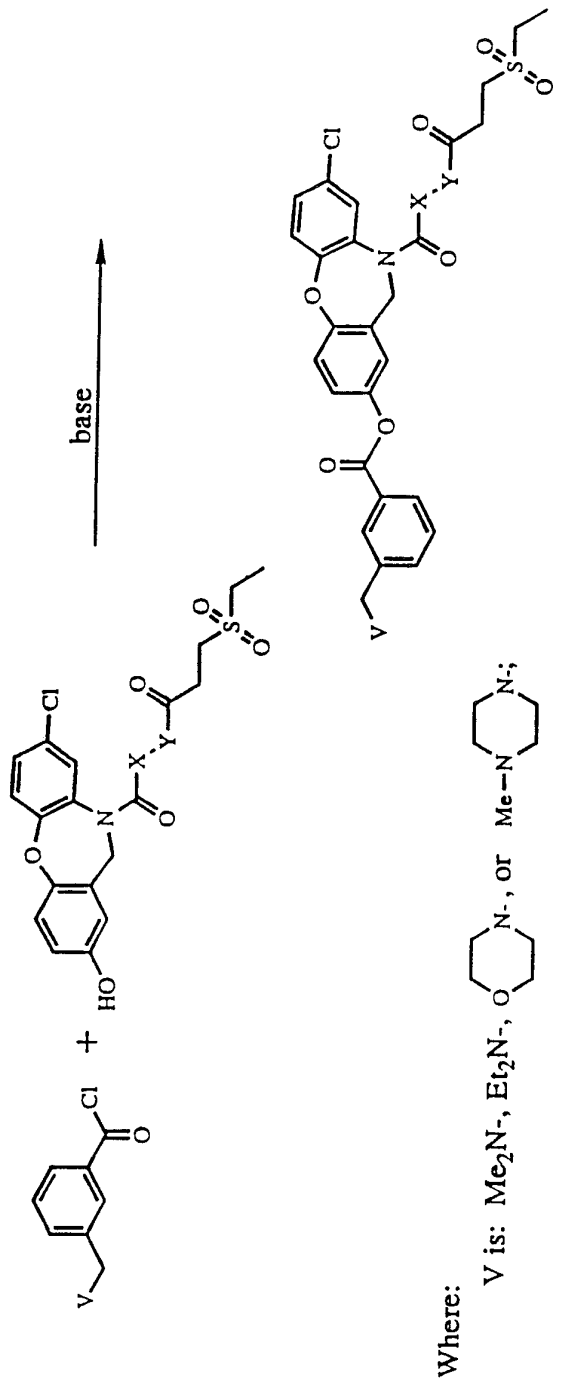
GENERAL REACTION SCHEME NO. 11



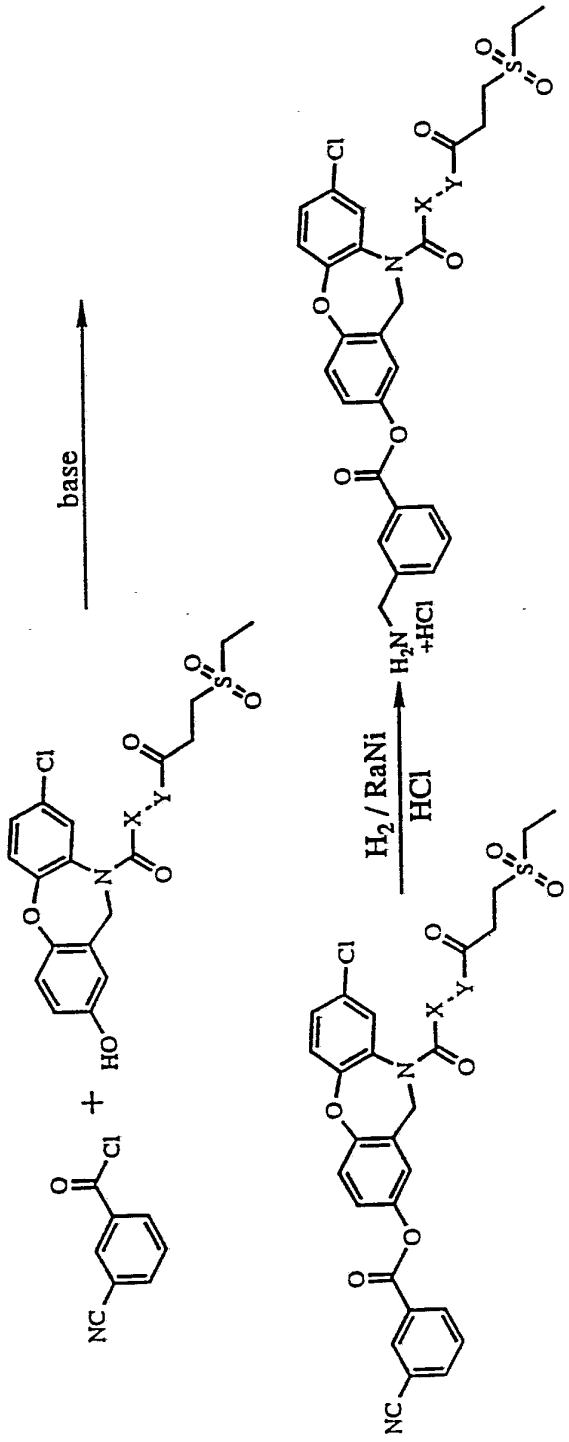
GENERAL REACTION SCHEME NO. 12



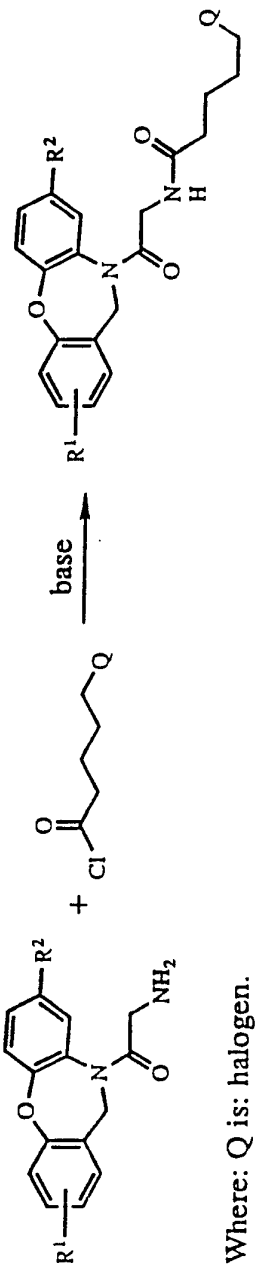
GENERAL REACTION SCHEME NO. 13



GENERAL REACTION SCHEME NO. 14

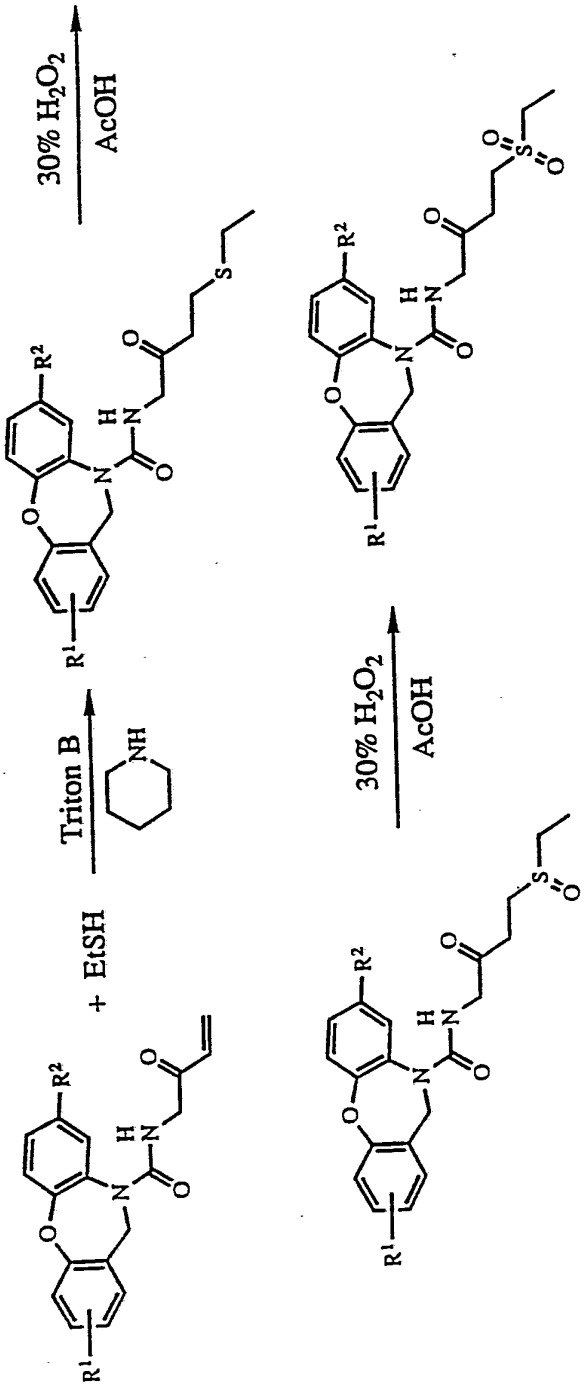


GENERAL REACTION SCHEME NO. 15

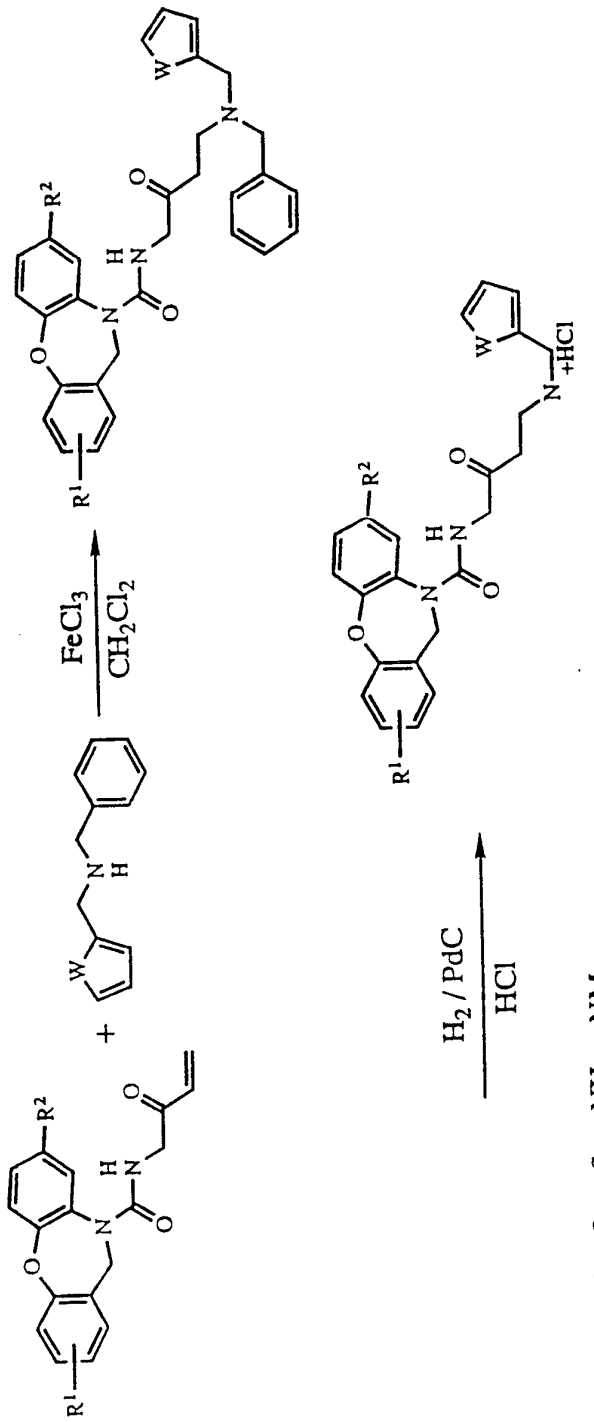


Where: Q is: halogen.

GENERAL REACTION SCHEME NO. 16

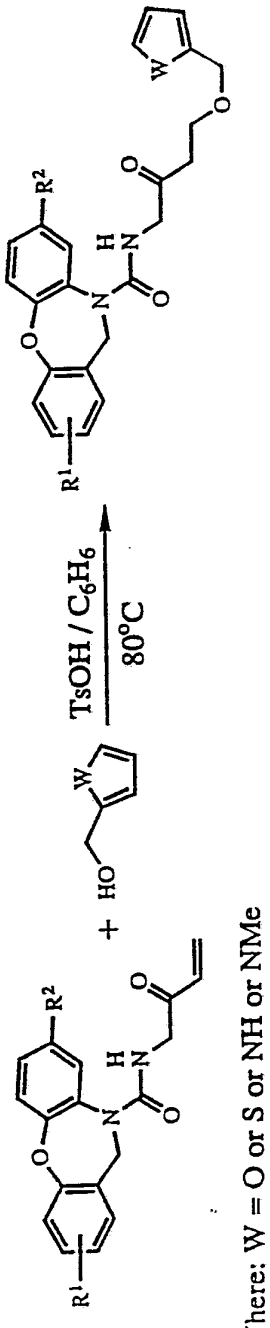


GENERAL REACTION SCHEME NO. 17



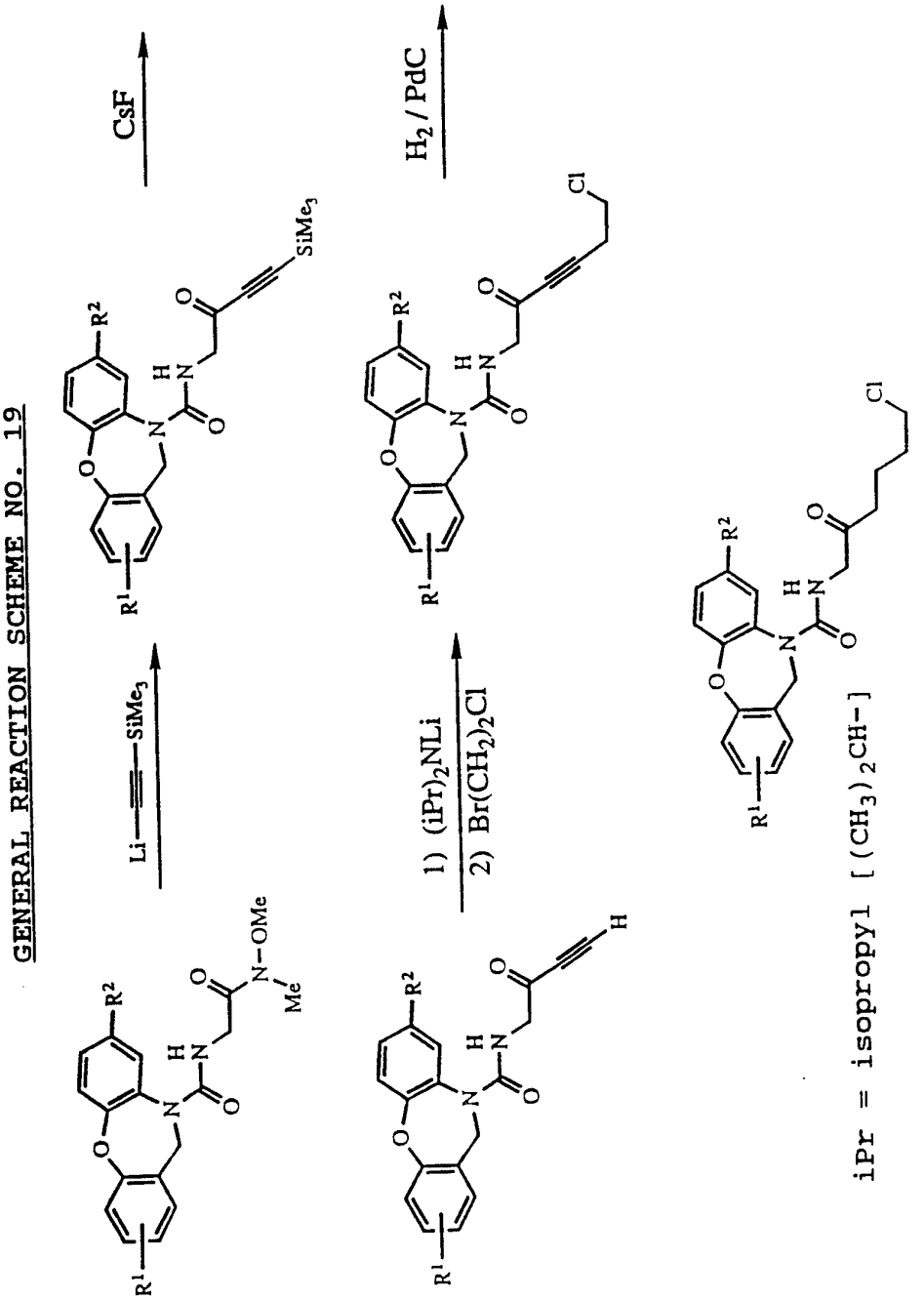
Where: W = O or S or NH or NMe

GENERAL REACTION SCHEME NO. 18



Where: W = O or S or NH or NMe

GENERAL REACTION SCHEME NO. 19



iPr = isopropyl [$(CH_3)_2CH$-]

The conditions for carrying out the individual steps in each of the general reaction schemes presented above are conventional, well-known, and capable of wide variation.

Other methods known in the art can also be used to synthesize the compounds of the present invention.

(5) Dosage and Mode of Administration

The compounds of the present invention, and the pharmaceutical compositions comprising one or more of these compounds in combination with a pharmaceutically-acceptable carrier, are useful in treating pain in animals. A physician or veterinarian of ordinary skill in the art can readily determine whether or not a particular patient is in pain.

The pharmaceutical compositions of the present invention, which will typically comprise one or more of the compounds of Formula I as an active ingredient in admixture with one or more pharmaceutically-acceptable carriers and, optionally, with one or more other compounds, drugs or materials, are employed therapeutically and, thus, would generally be used under the guidance of a physician. The appropriate dosage and form of administration of these compositions will be suitably selected by methods which are consistent with conventional pharmaceutical practices.

The pharmaceutical compositions of the present invention may be specially formulated for oral administration in solid or liquid form, for parenteral injection, and/or for rectal or vaginal administration. They may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually. While the preferred routes of administration are orally and parenterally, the most preferred mode of administration is orally.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage

forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the severity of the pain, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required to alleviate or ameliorate a particular patient's pain. For example, the physician or veterinarian could start doses of the compound of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the present invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, dosage levels in the range of from about

.001 mg to about 10 g, more preferably from about 1 mg to about 1000 mg, of active compound (a compound of Formula I) per kilogram of body weight per day are administered to a mammalian patient. However, the total daily usage of the compounds of Formula I, or the pharmaceutical compositions comprising such compounds, will be determined by an attending physician or veterinarian within the scope of sound medical judgement.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

The pharmaceutical compositions of the present invention comprise a compound of the present invention together with one or more pharmaceutically-acceptable carriers thereof and, optionally, with other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl

palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient (compound of Formula I) which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration and all of the other factors described above. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods for preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, with one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient (compound of Formula I) is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills,

the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile, injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed

manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient (compound of Formula I), the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is

solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the invention to the body. Such dosage forms can be made by dissolving, dispersing or otherwise incorporating a compound of the present invention in a proper medium, such as an elastomeric matrix material. Absorption

enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate-controlling membrane or dispersing the compound in a polymer matrix or gel.

Opthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include

isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

The injectable materials can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or in other sterile injectable mediums just prior to use.

The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately

prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the type described above.

The pharmaceutical compositions of the present invention may also be used in the form of veterinary formulations, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules or pellets for admixture with feed stuffs, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension or, when appropriate, by intramammary injection where a suspension or solution is introduced into the udder of the animal via its teat; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally, for example, as a pessary, cream or foam.

While the various aspects of the present invention are described herein with some particularity, those of skill in the art will recognize numerous modifications and variations which remain within the spirit of the invention. These modifications and variations are within the scope of the invention as described and claimed herein.

(6) Examples

The following examples describe and illustrate the methods for the preparation of the compounds of the present invention, as well as other aspects of the present invention, and the results achieved thereby, in further detail. Both an explanation of, and the actual procedures for, the various aspects of the present invention are described where appropriate. These examples are intended to be merely illustrative of the present invention, and not limiting thereof in either

scope or spirit. Those of skill in the art will readily understand that known variations of the conditions and processes of the preparative procedures described in these examples can be used to prepare the compounds of the present invention, and the pharmaceutical compositions comprising such compounds.

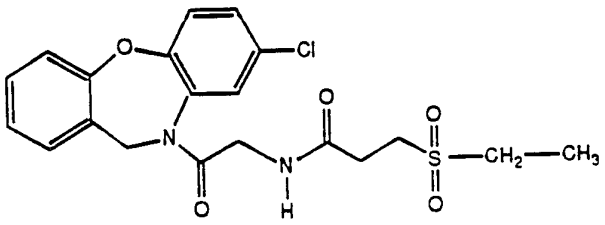
In the examples, all parts are by weight unless otherwise indicated.

All starting materials and equipment employed in the examples are commercially available. Sources for these materials include Sigma Chemical Co. (St. Louis, MO), Aldrich Chemical Co. (Milwaukee, WI), Lancaster Synthesis (Windham, NH), Fisher Scientific (Pittsburgh, PA), Boehringer Mannheim Biochemicals (Indianapolis, IN), Fluka Chemical Corp. (Ronkonkoma, NY) and Chemical Dynamics Corp. (South Plainfield, NJ). Most of the starting materials were obtained from Aldrich Chemical Co. (Milwaukee, WI).

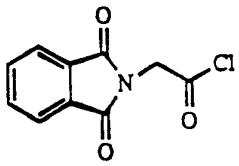
All patents and publications referred to in the examples, and throughout the specification, are hereby incorporated herein by reference, without admission that such is prior art.

Example 1

Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl) propanamide

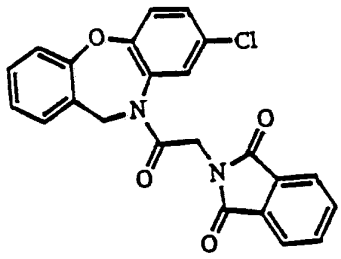


(a) Preparation of 1,3-dihydro-1,3-dioxo-2H-isoindole-2-acetyl chloride



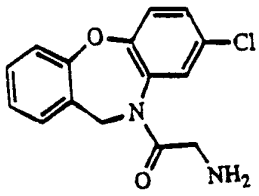
A solution of 1,3-dihydro-1,3-dioxo-2H-isoindole-2-acetic acid (7.00 g) and thionyl chloride (12 mL) was stirred at reflux under nitrogen for one hour. The thionyl chloride was distilled from the reaction, and the resulting crude product was further purified by distillation via a kugelrohr apparatus (BÜCHI, Flawil, Switzerland). [Bp: 160-180°C (oven temperature) at 10 mm Hg.] The yield of the title compound was 6.88 grams (90.2%). The structure of the title compound, and of all of the compounds synthesized in each of the subsequent examples, was confirmed by ^{1}H NMR.

(b) Preparation of 8-chloro-10,11-dihydro-10-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetyl]dibenz[b,f][1,4]oxazepine



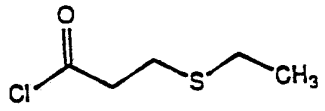
1,3-dihydro-1,3-dioxo-2H-isoindole-2-acetyl chloride (4.00 grams), 8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine (4.16 grams) and triethylamine (2.8 mL) were refluxed in toluene (100 mL) under nitrogen for 3 hours. The resulting mixture was poured into 1N HCl at 0°C, and the biphasic mixture was shaken vigorously. The insoluble product was collected by filtration, washed with toluene and ethyl ether, and dried in vacuo at 56°C. The yield of the title compound was 6.36 grams (85%). Mp: 184-185°C.

(c) Preparation of 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine



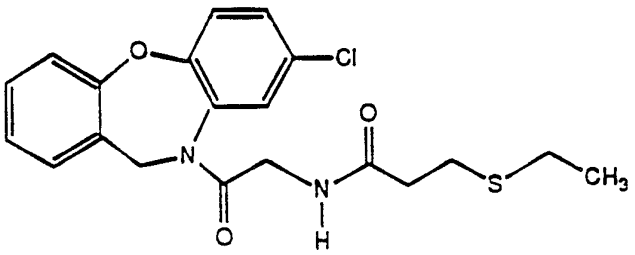
Hydrazine monohydrate (1.25 mL) and 8-chloro-10,11-dihydro-10[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetyl]-dibenz[b,f][1,4]-oxazepine (5.00 grams) were refluxed in absolute ethanol (125 mL) for 4 hours. The resulting mixture was filtered hot, and the collected solid was rinsed twice with ethanol, and then with hot methylene chloride. The filtrate and rinses were combined, evaporated in vacuo, and purified by flash chromatography through silica gel 60 (300 mL) using 95:5:0.5 chloroform:methanol:ammonium hydroxide. Trituration of the purified product with ethyl ether/hexane yielded the title compound as a white solid. Yield: 2.91 grams (84%). Mp: 108-109°C.

(d) Preparation of 3-(ethylthio)propanoyl chloride



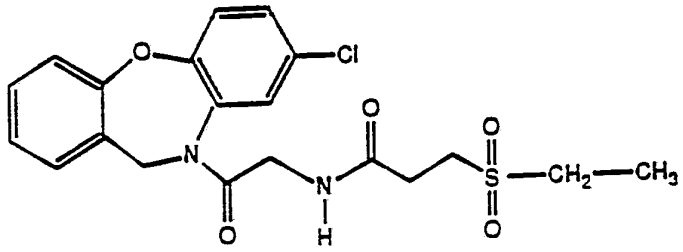
3-(ethylthio)propanoic acid (3.00 grams) was stirred at ambient temperature in thionyl chloride (2.4 mL) (exothermic reaction) until the vigorous bubbling subsided. The reaction was then refluxed on a steam bath for thirty minutes and distilled in vacuo. The yield of the title compound was 1.3 grams (38%). Bp: 80-83°C at 11 mm Hg.

(e) Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylthio)propanamide



A solution of 3-(ethylthio)propanoyl chloride (0.87 grams) in methylene chloride (10 mL) was added dropwise to a stirred solution of 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepine (1.50 grams) and triethylamine (0.84 mL) in methylene chloride (40 mL) in an ice bath at 5°C under nitrogen. The ice bath was removed, and the reaction was stirred for 3 hours. The reaction was diluted with methylene chloride (50 mL) and washed with 50 mL each of 1N HCl, saturated aqueous sodium bicarbonate, and brine. The solution was then dried over $MgSO_4$ and evaporated in vacuo. The yield of the title compound was 1.90 grams (90%). Mp: 148-151°C.

(f) Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide

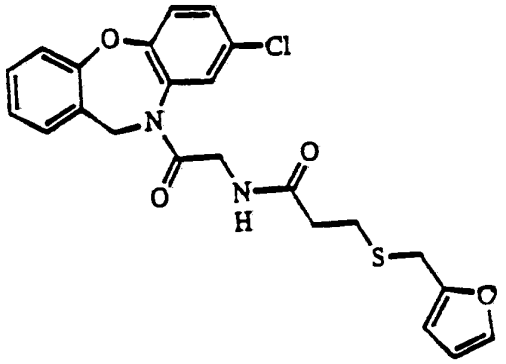


Hydrogen peroxide (30 weight per cent in water; 1.19 mL) was added dropwise to a stirred solution of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylthio)propanamide (1.50 grams) in acetic acid (11 mL) in an oil bath at 58°C under nitrogen. (The mixture had to be heated on a steam bath in order for it to form a solution.) After one hour, the temperature of the oil bath was raised to 72°C, and additional hydrogen peroxide was added (0.8 mL). After 3 hours, the reaction was evaporated in vacuo to remove most of the acetic acid. The residue was taken up in ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate. The aqueous wash was extracted once with ethyl acetate (50 mL), and the organic extracts were combined, washed with 50 mL each of saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was flash chromatographed twice: first, through silica gel 60 (400 mL) using 95:5 chloroform:methanol, and then through silica gel 60 (350 mL) using 3:1 ethyl acetate:chloroform. The chromatographed product was recrystallized from ethanol (3A). The yield of the title compound was 1.30 grams (80%) in the form of shiny white crystals. Analysis

calculated for $C_{20}H_{21}ClN_2O_5S$: C, 54.98; H, 4.84; N, 6.41, Cl, 8.11; S, 7.34. Found: C, 54.93; H, 4.89; N, 6.43; Cl, 8.30; S, 7.44. Differential Scanning Calorimetry (DSC): 167-168°C.

Example 2

Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide

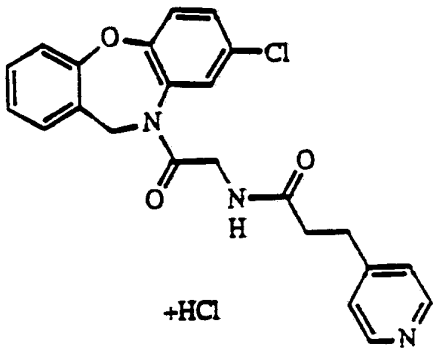


Trimethylaluminum (2.0 M in toluene; 4.6 mL) was added dropwise via syringe to a stirred solution of methyl 3-[(2-furanylmethyl)thio]propanoate (0.75 gram) and 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepine (1.00 gram) in toluene (30 mL) at room temperature under nitrogen, and the reaction was stirred for 5 hours. Methanol (14 mL) was then added, and the reaction was stirred at room temperature overnight. The reaction was evaporated in vacuo, and the resulting orange residue was partitioned between chloroform (50 mL) and 1 N NaOH (50 mL). The layers were separated and the aqueous layer was extracted with chloroform (50 mL). The combined chloroform extracts were washed with 1 N NaOH (50 mL), 1 N HCl (2 x 50 mL), and brine (50 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 3:1 chloroform:ethyl acetate followed by recrystallization from cyclohexane/ethyl acetate. The yield of the title compound was 0.63 gram (40%) in the form of a tan solid. Analysis calculated for $C_{23}H_{21}ClN_2O_4S$: C, 60.46;

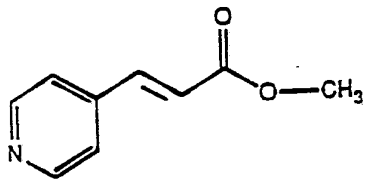
H, 4.63; N, 6.13; Cl, 7.67; S, 7.02. Found: C, 60.16; H, 4.62; N, 6.05; Cl, 8.06; S, 7.02. DSC: 90-95°C.

Example 3

Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride



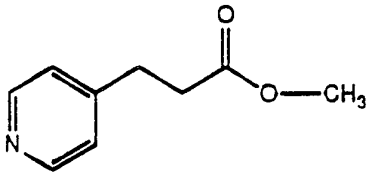
(a) Preparation of methyl 3-(4-pyridinyl)propenoate



Methyl (triphenylphosphoranylidene)acetate (3.4 grams) and 4-pyridine-carboxaldehyde (10.00 grams) were refluxed in tetrahydrofuran under nitrogen overnight. The reaction was evaporated in vacuo, and the residue was suspended in hexane (400 mL), heated to boiling on a steam bath for 5 minutes, and filtered through a filter aide. The filter cake was rinsed with hot hexane (2 x 200 mL), and the rinses and filtrate were combined and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (1500 mL) using 3:7 ethyl acetate:methylene chloride. The resulting waxy solid was suspended in a

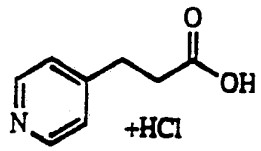
minimum amount of cyclohexane to yield the product as a white crystalline solid. Yield: 7.06 grams (46%).

(b) Preparation of methyl 4-pyridinepropanoate



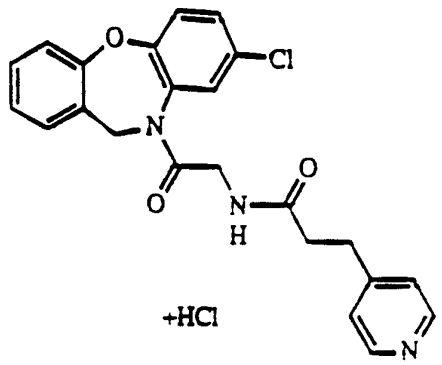
Methyl 3-(4-pyridinyl)propenoate (7.00 grams) and 10% palladium on carbon (1.00 gram) were vigorously stirred in methanol (70 mL) at room temperature under a hydrogen atmosphere for 5 hours. The catalyst was removed by filtration through a filter aide, and the filtrate was evaporated in vacuo. The crude product was purified by distillation in a kugelrohr apparatus. Yield: 5.14 grams (73%). Bp: 125°C (oven temperature) at 0.6 mm Hg.

(c) Preparation of 4-pyridinepropanoic acid, monohydrochloride



Methyl 4-pyridinepropanoate (1.00 gram) and sodium hydroxide (50 weight per cent; 0.83 gram) were stirred in methanol (5 mL) and water (3 mL) for three hours at room temperature. The reaction was evaporated in vacuo to a volume of approximately 1 mL, and a solution of 50:50 water:concentrated HCl was added. The resulting solution was evaporated in vacuo, and the moist residue was treated with absolute ethanol (10 mL) and heated to boiling on a steam bath. The resulting mixture was filtered, and the collected solid was rinsed with hot ethanol (1.5 mL). The rinse and filtrate were combined and evaporated in vacuo to a volume of approximately 1 mL. The resulting mixture was treated with ethyl ether (15 mL), and the solid product was collected by filtration, washed with ethyl ether, and dried in vacuo at 80°C. Yield: 0.52 gram (46%). Mp: 204-207°C.

(d) Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride

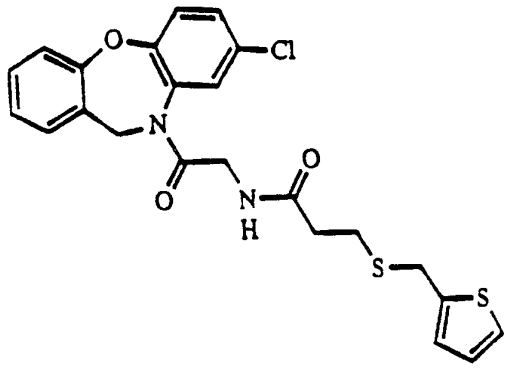


Triethylamine (0.8 mL) was added to a stirred mixture of 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepine (0.77 gram) and 4-pyridinepropanoic acid, monohydrochloride (0.50 gram) in dimethylformamide (10 mL) at room temperature under a nitrogen atmosphere. After 5 minutes, the mixture was cooled to 5°C in an ice bath, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (0.56 gram) was added. The reaction was stirred at room temperature under a nitrogen atmosphere for 60 hours, partitioned between saturated aqueous sodium bicarbonate (100 mL) and ethyl acetate (75 mL), and filtered. The layers of the filtrate were separated, and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The ethyl acetate extracts were combined, washed with aqueous saturated sodium bicarbonate (2 x 100 mL), water (100 mL), and brine (100 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 9:1 ethyl acetate:ethanol. The purified product was taken up in ethyl acetate and treated with

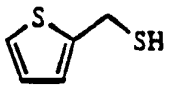
9.5 M HCl in ethanol to pH 1. The precipitated product was collected by filtration and dried in vacuo at 80°C. Yield: 0.233 gram (19%). Analysis calculated for $C_{23}H_{20}ClN_3O_3$ x 1 HCl: C, 60.27; H, 4.62; N, 9.17; Cl, 15.47. Found: C, 59.88; H, 4.66; N, 8.99; Cl, 15.58.

Example 4

Preparation of N-[2-(8-chlorodibenz-10-11-dihydrobenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide

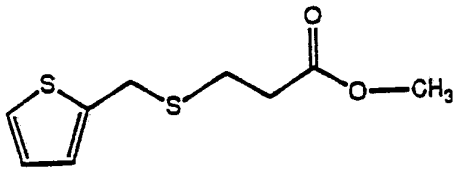


(a) Preparation of 2-thiophenemethanethiol



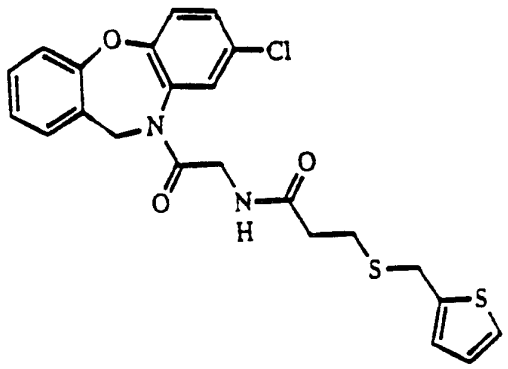
To a stirring solution of thiourea in concentrated hydrochloric acid (40 mL) and water (50 mL) at 30°C was added 2-thiophenemethanol (47 grams). The solution was stirred at room temperature for 16 hours. The reaction mixture was then heated to 60°C, and allowed to cool to room temperature and stirred for 6 hours. To the resulting solution was added 50% aqueous NaOH (50 mL), and then the solution was stirred overnight. The aqueous solution was extracted with ether (2 x 500 mL), dried over $MgSO_4$, and evaporated in vacuo. The yield of the title compound was 12.2 grams (23%).

(b) Preparation of methyl 3-[(2-thienylmethyl)thio]propanoate



A solution of 2-thiophenemethanethiol (12 grams), methylacrylate (7.94 grams), piperidine (3 mL) and N-benzyltrimethylammonium hydroxide (3 mL) was stirred for 16 hours at room temperature. The reaction mixture was distilled in vacuo to yield the desired title compound. Yield: 16.5 grams (83%). Bp: 140°C at 1 mmHg.

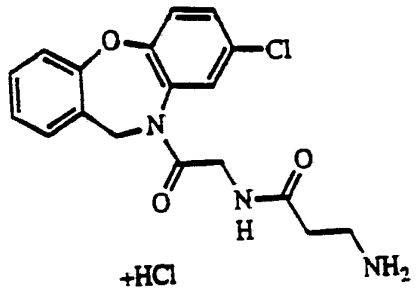
(c) Preparation of N-[2-(8-chlorodibenz-10-11-dihydrobenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide



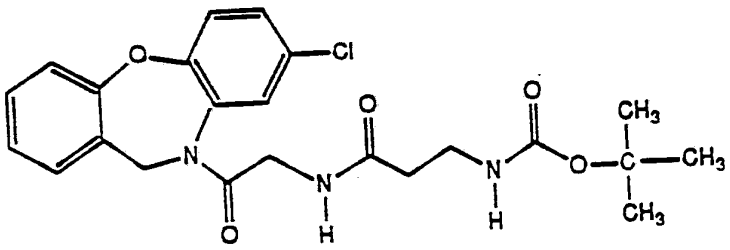
To a room temperature solution of 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepine (1.0 gram) and methyl 3-[(2-thienylmethyl)-thio]propanoate (0.75 gram) in toluene (30 mL) under a nitrogen atmosphere was added trimethylaluminum (2.0 M in toluene; 4.0 mL). The resulting solution was stirred at room temperature for 6 hours. Methanol (14 mL) was added to the reaction mixture, and the resulting mixture was allowed to stir overnight. The reaction mixture was then partitioned between $CHCl_3$ and 1 M NaOH. The NaOH was extracted with $CHCl_3$. The combined extracts were washed with 1 M HCl and brine, dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by medium pressure liquid chromatography through silica gel 60 using 1:1 hexane:ethyl acetate to yield 820 mg of a gummy foam. The material was crystallized from ethyl acetate/hexane to afford white crystals. The yield of the title compound was 0.808 gram (49%). Analysis calculated for $C_{23}H_{21}ClN_2O_3S_2$: C, 58.40; H, 4.48; N, 5.92; Cl, 7.50; S, 13.56. Found: C, 58.31; H, 4.56; N, 5.98; Cl, 7.33; S, 13.74. DSC: 97°C.

Example 5

Preparation of 3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride



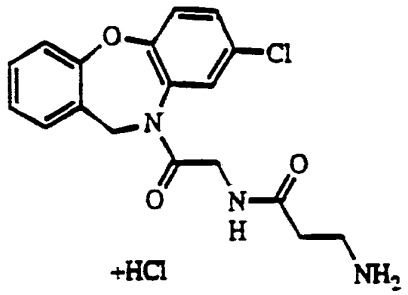
(a) Preparation of 1,1-dimethylethyl [3-[[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepin-10-yl)-2-oxoethyl]amino]-3-oxopropyl]carbamoate



To a stirred solution of N-[(1,1-dimethylethoxy)carbonyl]-β-alanine (0.72 gram) in anhydrous tetrahydrofuran (20 mL) at 5°C under a nitrogen atmosphere was added, in portions, 1,1'-carbonyldiimidazole (0.67 gram). The reaction was stirred at 5°C for 30 minutes, and then at room temperature for 90 minutes. To the reaction was then

added 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepine (1.00 gram), and the reaction was stirred at room temperature under a nitrogen atmosphere overnight. The reaction was partitioned between saturated aqueous sodium bicarbonate (50 mL) and chloroform (50 mL). The layers were separated, and the aqueous layer was extracted with chloroform (50 mL), and the chloroform extracts were combined, washed with 25 mL each of saturated aqueous sodium bicarbonate, water, and brine, dried over $MgSO_4$, and evaporated <u>in vacuo</u>. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 3:1 ethyl acetate:hexane. The yield of the title compound was 1.23 grams (77%).

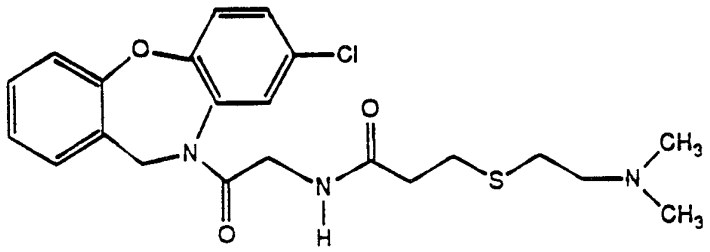
(b) Preparation of 3-amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]propanamide, monohydrochloride



A solution of 1,1-dimethylethyl [3-[[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepin-10-yl)-2-oxoethyl]amino]-3-oxopropyl]carbamate (8.1 grams), glacial acetic acid (50 mL), and 6.95 M HCl in dioxane (27 mL) was stirred at room temperature for 20 minutes. The reaction was evaporated in vacuo, and the residue was co-evaporated in vacuo twice with ethanol (3A; 170 mL each time). The resulting foam was crystallized from ethyl acetate/ethanol and dried in vacuo at 56°C. The yield of the title compound was 5.79 grams (85%). Analysis calculated for $C_{18}H_{26}ClN_3O_3S$ x HCl: C, 54.56; H, 4.83; N, 10.60; Cl, 17.89. Found: C, 54.30; H, 4.79; N, 10.49; Cl, 16.77. DSC: 216-217°C.

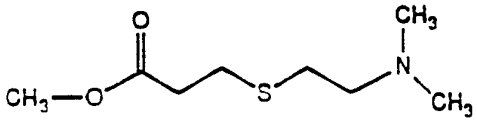
Example 6

Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride



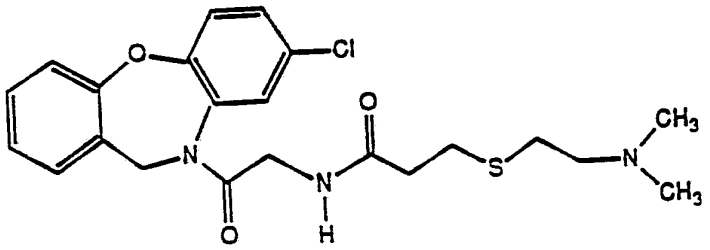
+HCl

(a) Preparation of methyl 3-[[2-(dimethylamino)ethyl]thio]propanoate



A solution of N,N-dimethylethanethiol (25 grams), methyl acrylate (25 grams), piperidine (6 grams), and N-benzyltrimethylammonium hydroxide (90 mL) was stirred at room temperature for 16 hours. The reaction mixture was then purified by distillation in vacuo (Bp: 80-100°C at 1 mm Hg), followed by flash chromatography through silica gel 60 using 95:5:0.5 chloroform: methanol:ammonium hydroxide. The yield of the title compound was 11.8 grams (26%).

(b) Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]-thio]propanamide, monohydrochloride

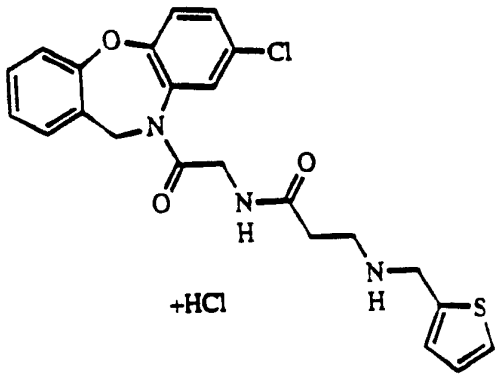


+HCl

A solution of 10-(aminoacetyl)-8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepine (2.83 grams), methyl 3-[[2-(dimethylamino)ethyl]thio]propanoate (2.0 grams), and dimethylaluminum chloride (1 M in toluene; 26.2 mL) in toluene (100 mL) was stirred under a nitrogen atmosphere at room temperature for 16 hours. Methanol was added to the reaction solution, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between chloroform and 1 N NaOH, and the layers were separated. The aqueous layer was extracted once more with chloroform, and the combined chloroform extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by medium pressure liquid chromatography through silica gel 60 using 95:5:1 chloroform:methanol:ammonium hydroxide to yield 0.754 grams (17%) of the free base of the desired product as a gummy foam. The foam was dissolved in 0.5 M HCl (25 mL) and lyophilized to yield the hydrochloride salt as a white powder. Analysis calculated for $C_{22}H_{26}ClN_3O_3S$ x 1 HCl X 0.33 H_2O: C, 53.77; H, 5.88; N, 8.55. Found: C, 53.93; H, 5.68; N, 8.36.

Example 7

Preparation of N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride

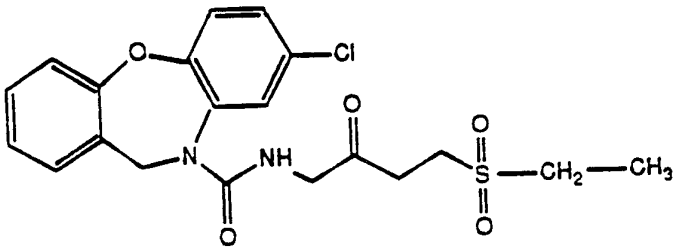


A mixture of 3-amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride (2.00 grams) in methanol (160 mL) and potassium hydroxide (0.38 gram) was stirred at room temperature until a solution formed. To this was added a solution of thiophene-2-carboxaldehyde (0.62 gram) in methanol (20 mL), and the solution was stirred at room temperature under a nitrogen atmosphere for 4 hours. To the solution was then added sodium cyanoborohydride (0.46 gram), and the pH of the reaction was adjusted to approximately 6 with acetic acid. The reaction was stirred at room temperature under a nitrogen atmosphere for 48 hours, made acidic to pH 2 with 2 N HCl, and evaporated in vacuo. The residue was suspended in water (150 mL), made basic to pH 11 with 1 N NaOH, and extracted with chloroform (150 mL, and then 2 x 100 mL). The combined chloroform extracts were washed with 1 N NaOH (2 x 100 mL), water (100 mL) and brine (150 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 95:5 chloroform:ethanol (3A). The purified product was taken up in absolute ethanol (20

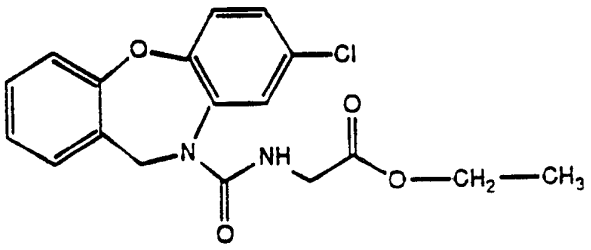
mL), cooled in an ice water bath, and acidified with 9.5 M HCl in ethanol (1.5 mL). After several minutes, the solution was evaporated in vacuo, and the resulting foam was dried in vacuo at 56°C. The yield of the title compound was 0.79 gram (32%). Analysis calculated for $C_{23}H_{22}ClN_3O_3S$ x 1 HCl: C, 56.10; H, 4.71; N, 8.53; Cl, 14.40; S, 6.51. Found: C, 55.74; H, 4.72; N, 8.47; Cl, 14.51; S, 6.49.

Example 8

Preparation of 8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide



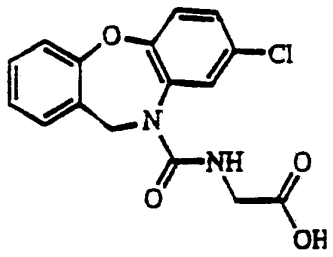
(a) Preparation of ethyl [[8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-carbonyl]amino]acetate



8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine (5.00 grams) and ethyl isocyanoacetate (3.07 grams) were stirred together in refluxing toluene (50 mL) under a nitrogen atmosphere for 4 hours. An additional 1.0 gram of ethyl isocyanoacetate was added, and refluxing was continued overnight. The reaction was evaporated in vacuo, and the residue was taken up in ethyl ether. The solution was washed with 100 mL each of 1 N NaOH, water, 1 N HCl, water, and brine, dried over $MgSO_4$, and evaporated in vacuo to a yellowish oil,

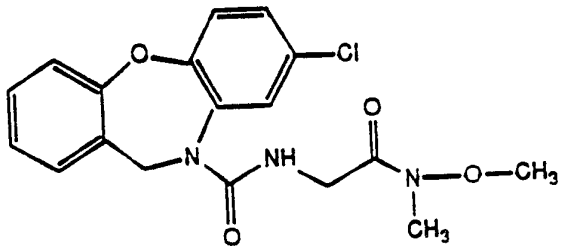
which solidified on standing. The yield of the title compound was 7.12 grams (91%).

(b) Preparation of [[8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)carbonyl]amino]acetic acid



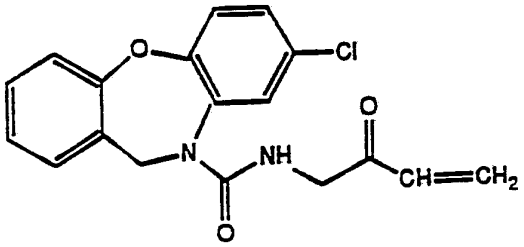
Ethyl [[8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepin-10-yl)carbonyl]amino acetate (6.77 grams) and 1 N NaOH (25 mL) were stirred in methanol (350 mL) at room temperature overnight. The reaction was evaporated in vacuo, and the residue was taken up in water (300 mL). The solution was washed with ethyl ether (2 x 300 mL), acidified with 1 N HCl (40 mL), and extracted with ethyl ether (2 x 350 mL). The combined ethereal extracts were washed with brine (300 mL), dried over $MgSO_4$, and evaporated in vacuo. The quantitative yield of the title compound was 6.29 grams.

(c) Preparation of 2-[[(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)carbonyl]amino]-N-methoxy-N-methylacetamide



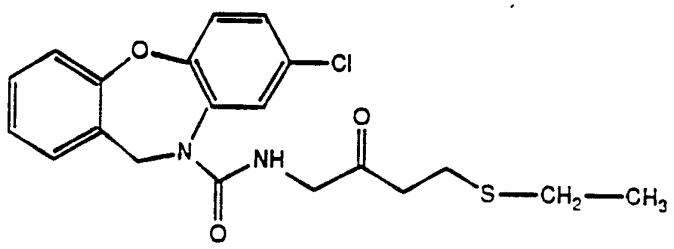
To a 5°C, stirred solution of 1,1'-carbonyldiimidazole (2.12 grams) in anhydrous tetrahydrofuran (60 mL) under a nitrogen atmosphere was added dropwise, a solution of [[8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-carbonyl]-amino]acetic acid (4.00 grams) in tetrahydrofuran (20 mL). The reaction was stirred under nitrogen for one hour at 5°C, and then at room temperature for 4 hours. To the reaction was then added triethylamine (1.9 mL) and N,O-dimethyl-hydroxylamine hydrochloride (1.30 grams), and the reaction was stirred at room temperature under a nitrogen atmosphere for 48 hours. The reaction was evaporated in vacuo, and the residue was partitioned between 1 N HCl (200 mL) and ethyl acetate (200 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (200 mL). The ethyl acetate extracts were combined, washed with 200 mL each of 1 N HCl, water, saturated aqueous potassium carbonate, water, and brine, dried over $MgSO_4$, and evaporated in vacuo. The yield of the title compound was 3.20 grams (71%).

(d) Preparation of 8-chloro-N-(2-oxo-3-butenyl)-dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide



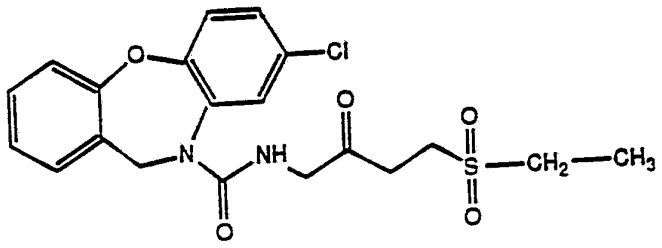
To a stirred solution of 2-[[(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-carbonyl]amino]-N-methoxy-N-methylacetamide (3.2 grams) in anhydrous tetrahydrofuran (35 mL) at -70°C (dry ice/acetone bath) under a nitrogen atmosphere was added dropwise a solution of vinylmagnesium bromide (1.0 M in tetrahydrofuran; 28 mL) in tetrahydrofuran (15 mL). The ice bath was removed, and the reaction was stirred to room temperature for one hour. The reaction was poured into 1 M NaH_2PO_4 (250 mL) and extracted with ethyl acetate (3 x 200 mL). The combined ethyl acetate extracts were washed with 1 M NaH_2PO_4 (2 x 250 mL) and brine (250 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (500 mL) using 9:1 methylene chloride:ethyl acetate to yield a colorless glass. The yield of the title compound was 2.25 grams (77%).

(e) Preparation of 8-chloro-N-[4-(ethylthio)-2-oxobutyl]dibenz[b,f][1,4]oxazepine-10(11H)-carboxamide



A solution of 8-chloro-N-(2-oxo-3-butenyl)-dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide (1.00 gram), ethanethiol (0.23 mL), piperidine (0.092 mL), and N-benzyltrimethylammonium hydroxide (0.092 mL) in methylene chloride (16 mL) and methanol (4 mL) was stirred at room temperature for 5 hours. The reaction was diluted with methylene chloride (100 mL), washed with 100 mL each of 1 N HCl (two times), water, saturated aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 92:8 methylene chloride: ethyl acetate to yield a colorless oil. The yield of the title compound was 0.38 gram. (32%).

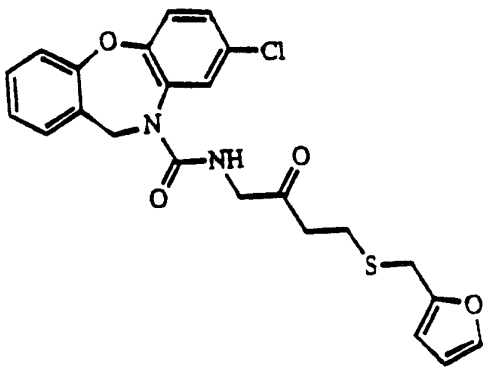
(f) Preparation of 8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide



To a stirred solution of 8-chloro-N-[4-(ethylthio)-2-oxobutyl]dibenz[b,f][1,4]-oxazepine-10(11H)-carboxamide (0.38 gram) in glacial acetic acid (3 mL) in an oil bath at 60°C under a nitrogen atmosphere was added 30 weight per cent of aqueous hydrogen peroxide (0.3 mL). After one hour, an additional 0.1 mL of hydrogen peroxide was added, and the reaction was stirred for another hour. The reaction was evaporated in vacuo to remove most of the acetic acid, and the residue was suspended in saturated aqueous sodium bicarbonate (25 mL). The suspension was extracted with ethyl acetate (2 x 25 mL), and the combined organic extracts were washed with 25 mL each of saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 3:1 ethyl acetate:hexane to yield a white solid. The yield of the title compound was 0.159 gram (39%). Analysis calculated for $C_{20}H_{21}ClN_2O_5S$: C, 54.98; H, 4.84; N, 6.41; Cl, 8.11; S, 7.34. Found: C, 55.03; H, 4.90; N, 6.32; Cl, 8.40; S, 7.37. DSC: 140-142°C.

Example 9

Preparation of 8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide



A solution of 8-chloro-N-(2-oxo-3-butenyl)dibenz-[b,f][1,4]oxazepin-10(11H)-carboxamide (0.75 gram), furfuryl mercaptan (0.23 mL), piperidine (0.069 mL), and N-benzyltrimethylammonium hydroxide (0.069 mL) in methylene chloride (12 mL) and methanol (3 mL) was stirred at room temperature for 6 hours. The reaction was diluted with methylene chloride (75 mL), washed with 75 mL each of 1 N HCl (two times), water, saturated aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography through silica gel 60 (350 mL) using 95:5 methylene chloride: ethyl acetate to yield a colorless oil. Analysis calculated for $C_{23}H_{21}ClN_2O_4S$ x 0.1 EtOAc: C, 60.34; H, 4.72; N, 6.01; Cl, 7.61; S, 6.88. Found: C, 59.94; H, 4.84; N, 5.87; Cl, 8.13; S, 6.65.

The foregoing examples are provided to enable one of ordinary skill in the art to practice the present invention. These examples are merely illustrative, however, and should not be read as limiting the scope of the invention as it is claimed in the appended claims.

(7) Description of Assays.

(a) Writhing Assay

The Writhing Assay is one of the most widely-used experimental procedures for measuring the analgesic activity of different narcotic and nonnarcotic analgesic agents, and involves the continuous, chemically-induced pain of visceral origin to an animal, such as a mouse or rat. [Gyires et al., *Arch. int. Pharmacodyn, 267*, 131-140 (**1984**); C. Vander Wende et al., *Fed. Proc., 15*, 494 (**1956**); Koster et al., *Fed. Proc., 18*, 412 (**1959**); and Witken et al., *J. Pharmacol. exp. Ther., 133*, 400-408 (**1961**).] Chemicals which may be used to induce this pain include phenylbenzoquinone (PBQ) and acetic acid. As a result of the chemical irritation to the animal, a characteristic stretching and writhing of the animal (dorsiflexion of the animal's back, extension of its hindlimbs and the strong contraction of its abdominal musculature) will generally occur. The intensity of this pain reaction is determined by the number of writhes exhibited by the animal during a given period of time. Drugs which reduce the number of writhes of the animal appear to restore the normal nociceptive threshold of the animal.

Compounds of the present invention exhibit analgesic activity in mice, as shown by the results of the Writhing Assay presented in Table I hereinbelow.

Charles River male albino mice, weighing 20 to 30 grams, were used in this assay.

Thirty minutes after subcutaneous or intragastric administration to ten mice of 30 mg per kilogram of body weight of a compound of the present invention ("test compound"), 0.1 mg per 10 g of body weight of a 0.025% w/v solution of PBQ was injected intraperitoneally into each mouse. Ten mice which were given saline in place of a test compound of the invention were used as a control group.

Five minutes later, each mouse was individually placed into a glass beaker for observation, and the number of writhes occurring during the following ten-minute period was counted.

A test compound was considered to have produced analgesia in a mouse if, in accordance with the conditions set forth above, and under the test criteria employed for this assay, after the administration of 30 mg per kilogram of body weight of a compound of the present invention to the mouse, the number of writhes elicited by a mouse injected with PBQ was equal to, or less than, one-half the median number of writhes recorded for the saline-treated control group of mice that day, as described by Taber in "Predictive Value of Analgesic Assays in Mice and Rats," *Advances in Biochemical Psychopharmacology*, *8*, 191 (**1974**).

The results for the particular compounds of the present invention analyzed in this assay, and discussed in the examples identified below which correspond thereto are presented in Table I hereinbelow.

The standard initial screening dose of a test compound employed in this assay was 30 mpk per gram of body weight for both routes of administration. If this initial screening dose of the test compound produced analgesia in seven of ten mice, then the effect of additional doses of the test compound on the writhing response was evaluated, and then the ED_{50} dose was generally calculated. (The slopes of the dose-response curves for all test compounds analyzed were compared as described by Tallarida and Murray, Manual of Pharmacologic Calculations, Page 11 (Springer Verlag, New York, 1981)).

All ED_{50} doses calculated are also presented below in parentheses in Table I under the heading "WRITHING ASSAY." As Table I shows, the rank order of potency of the more potent compounds of the present invention tested in the Writhing Assay was (referring to the

particular example which describes the preparation of the compound): Example 1 > Example 2 > Example 3 > Example 9. Thus, N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl) propanamide (Example 1) was determined to be the most potent compound of the invention tested in this assay and, thus, is an especially preferred compound of the present invention.

(b) Prostaglandin (PGE) Antagonism Assay

In order to determine the effectiveness of several of the compounds of the present invention ("test compounds") as prostaglandin E_2 antagonists, a prostaglandin antagonism assay was conducted, as described below, to determine the ability of these compounds to inhibit prostaglandin E_2-induced contractions of segments of guinea pig ileum. If a test compound inhibits prostaglandin E_2-induced contractions, it suggests that the compound functionally antagonizes prostaglandin E_2.

Male albino guinea pigs weighing 200 to 500 grams were sacrificed by cervical dislocation. The ilea were then quickly removed from the guinea pigs and placed in a modified Tyrode solution, a solution which is known to those skilled in the art, containing one-half of the usual amount of magnesium ions.

Segments of ileum about 2 cm long were then cut and mounted in a 10-mL tissue bath containing the modified Tyrode solution. The solution was maintained at 37°C and aerated with a gaseous mixture of 95% oxygen and 5% carbon dioxide. Data for a control prostaglandin E_2 dose response curve plotting concentration of prostaglandin E_2 versus the intensity of contractions, detected isotonically, was then obtained by experimentally adjusting the dose of the prostaglandin E_2 being injected into the tissue bath, in a manner known by those of skill in the art.

Solutions or suspensions containing an initial concentration (3 micromolar) of a test compound in modified Tyrode solution ("test solutions/ suspensions") were then separately substituted for the control bath solution. Each test solution/suspension was then kept in constant contact with the ileum tissue, except for brief periods to drain the bath in preparation for rinsing with fresh test solution/suspension. A second prostaglandin E_2 dose

response curve was then generated for prostaglandin E_2 in the presence of a test compound.

A dose ratio of EC_{50} doses was then calculated from the results of each test in a manner known by those of skill in the art. A test compound was determined to be "active" if the initial concentration used yielded at least a two-fold shift (dose ratio greater than or equal to 2) in the dose response curve for prostaglandin E_2. An estimated pA_2 value (a statistical constant which is a common measure of expressing the potency of a particular drug as an antagonist) was reported for "active" compounds under the assumption that the slope of the Schild plot does not deviate significantly from -1.0. If the initial concentration of test compound yielded at least a five-fold shift (dose ratio greater than or equal to 5) in the dose response curve for prostaglandin E_2, then varying concentrations of the test compound were assayed, and a pA_2 value for that compound was calculated by Schild plot calculations, as described by H. O. Schild, "pA, A New Scale for the Measurement of Drug Antagonism," Br. J. Pharmacol, 2, 189 (1947). The higher the value calculated for the pA_2, the more potent a particular compound is as a prostaglandin E_2 antagonist.

The results of this prostaglandin antagonism assay are also presented in Table I below. The compounds of the present invention which were tested in this assay, and for which results are presented in Table I, correspond to the particular examples specified in Table I.

The results in Table I show that all of the compounds of the present invention tested in this assay exhibit activity as prostaglandin E_2 antagonists. Some of these compounds, such as N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide (Example 2), were surprisingly and unexpectedly found to be 10 to 100

times more effective as prostaglandin E_2 antagonists than prostaglandin E_2 antagonists reported in the literature.

Table I

Data Generated from the Assays

Example Number	WRITHING ASSAY (ED_{50} Dose (mpk))		PGE IN GUINEA PIG ILEUM (pA_2)
	S.C.	I.G.	
1	Active (11.2)	Active (5.9)	Active (5.7*)
2	Active (14.8)	Active (13.5)	Active (8.0)
3	Active (16.9)	Active	Active (5.7*)
4	**	**	Active (7.9)
5	Active	**	Active (5.5*)
6	Active	Active	Active (5.9*)
7	**	**	Active (6.5)
8	Active	**	Active (5.6*)
9	Active	Active	Active (7.2)

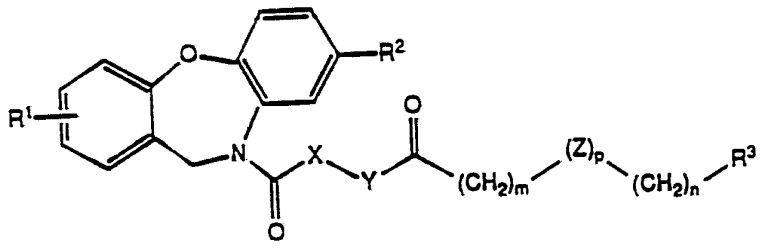
* = Estimated pA_2 value.

** = Indicates that, in accordance with the particular conditions set forth above for the Writhing Assay, and under the test criteria employed for that assay, after the administration of an initial screening dosage of 30 mg per kilogram of the compound, the number of writhes elicited by a mouse injected with PBQ was not equal to, or less than, one-half the median number of writhes recorded for the saline-treated control group of mice that day.

While the present invention has been described herein with some specificity, and with reference to certain preferred embodiments thereof, those of ordinary skill in the art will recognize numerous variations, modifications and substitutions of that which has been described which can be made, and which are within the scope and spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the animal being treated, dosage-related adverse effects, if any, and analogous considerations. Likewise, the specific pharmacological responses observed may vary according to, and depending upon, the particular active compound selected, or whether there are present certain pharmaceutical carriers, as well as the type of formulation and mode of administration employed. Such expected variations and/or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended therefore that all of these modifications and variations be within the scope of the present invention as described and claimed herein, and that the invention be limited only by the scope of the claims which follow, and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound having a structure of the formula:



or a pharmaceutically-acceptable salt thereof, wherein:

X: is -NH- or $-CH_2-$;

Y is: (1) $-CH_2-$ when X is -NH-, and
(2) -NH- when X is $-CH_2-$;

R^1 is: hydrogen, halogen or $-OR^4$;

R^4 is: hydrogen, alkyl or $-\overset{O}{\overset{\|}{C}}-R^8$;

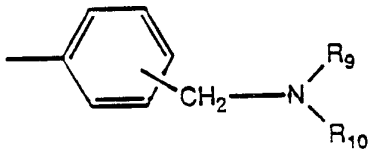
Z is: oxygen, sulfur, -SO-, $-SO_2-$ or $-NR^5-$;

R^5 is: hydrogen or t-butyloxycarbonyl;

R^2 is: hydrogen, halogen or trifluoromethyl;

R^3 is: hydrogen, halogen, aryl, heteroaryl or $-NR^6R^7$;

R^6 and R^7 are: each independently hydrogen or alkyl;

R^8 is: alkyl, aryl or  ;

R^9 and R^{10} are: each independently hydrogen or alkyl, or can combine together to form N-morpholino or 4-methyl-N-piperazinyl;

m and n are: each independently integers of from 0 to 3; and

P is: 0 or 1, provided that p is not 1 when m is 0.

2. A compound of Claim 1 wherein R^1 is hydrogen.

3. A compound of Claim 2 wherein Z is sulfur, $-SO_2-$ or $-NR^5-$.

4. A compound of Claim 3 wherein R^2 is halogen and R^5 is hydrogen.

5. A compound of Claim 4 wherein R^6 and R^7 are both hydrogen, or are both methyl.

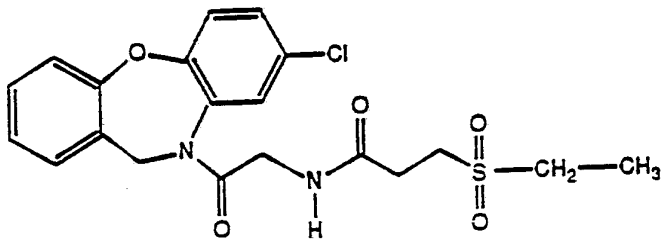
6. A compound of Claim 5 wherein m is 2.

7. A compound of Claim 6 wherein R^3 is hydrogen, aryl, heteroaryl or $-NR^6R^7$.

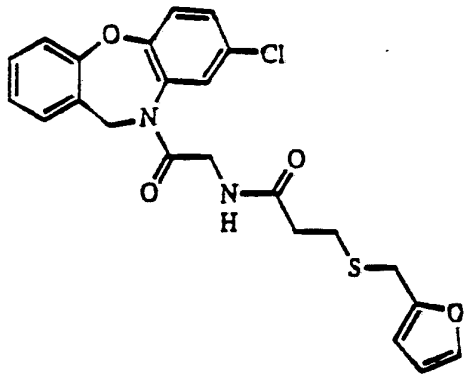
8. A compound of Claim 7 wherein R^3 is hydrogen, heteroaryl or $-NR^6R^7$.

9. A compound of Claim 8 wherein R^3 is hydrogen, furan, thiophene, pyridine or $-NR^6R^7$.

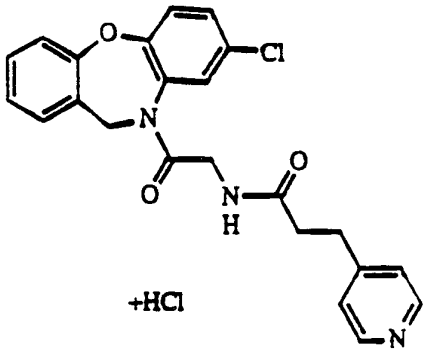
10. A compound of Claim 1, wherein the compound is:



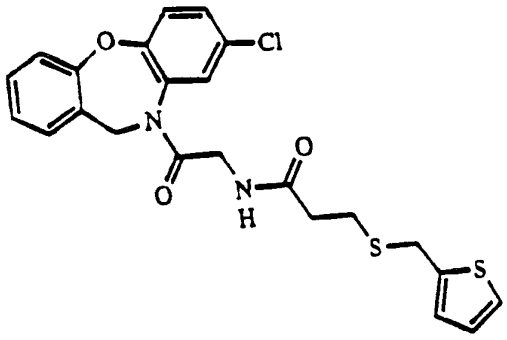
11. A compound of Claim 1, wherein the compound is:



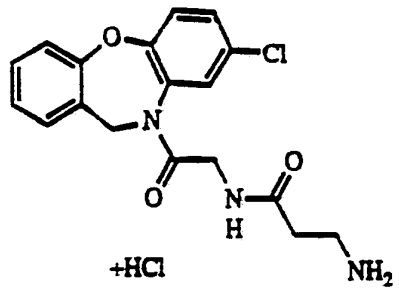
12. A compound of Claim 1, wherein the compound is:



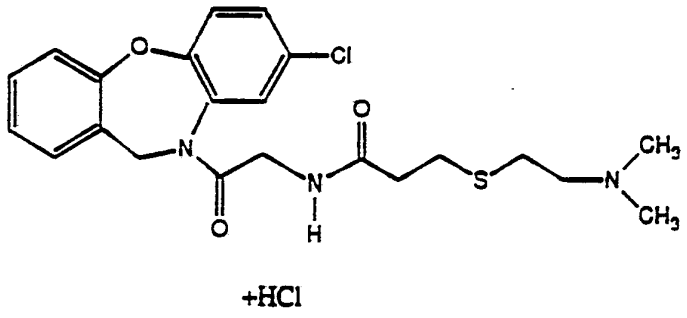
13. A compound of Claim 1, wherein the compound is:



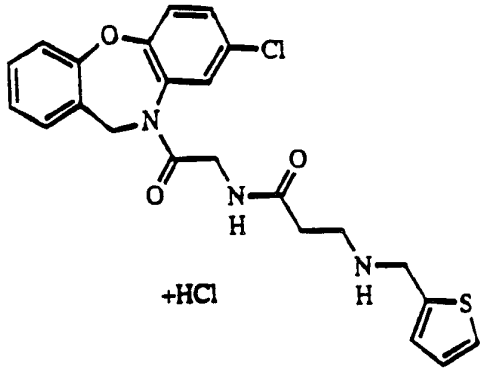
14. A compound of Claim 1, wherein the compound is:



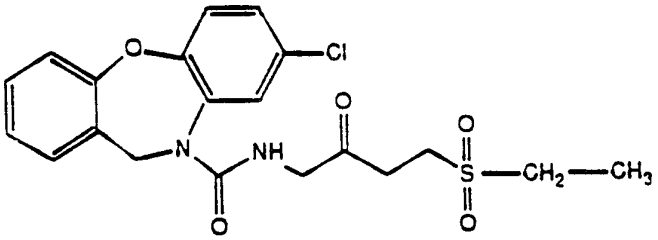
15. A compound of Claim 1, wherein the compound is:



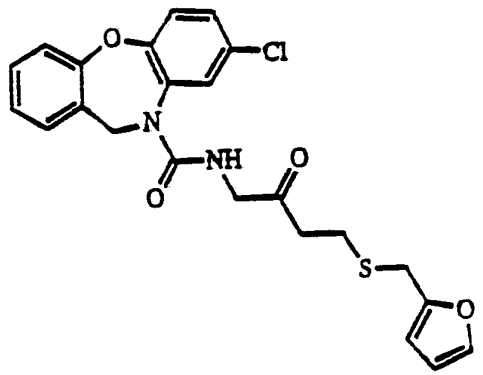
16. A compound of Claim 1, wherein the compound is:



17. A compound of Claim 1, wherein the compound is:



18. A compound of Claim 1, wherein the compound is:



19. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically-effective amount of a compound of Claim 1.

20. The pharmaceutical composition of Claim 19 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;
or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

21. A method for treating central nervous disorders in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

22. The method of Claim 21 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;

or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

23. A method for treating pain in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

24. The method of Claim 23 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide; or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

25. A method for treating enuresis in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

26. The method of Claim 25 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-

oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;
or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

27. A method for treating dysmenorrhea in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

28. The method of Claim 27 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;

or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

29. A method for treating osteoporosis in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

30. The method of Claim 29 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;
or
8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

31. A method for treating convulsions in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

32. The method of Claim 31 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;

or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

33. A method for treating ischemia in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

34. The method of Claim 33 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;

or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

35. A method for treating urinary incontinence in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

36. The method of Claim 35 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide; or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

37. A method for treating gastric hypermotility in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

38. The method of Claim 37 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-

[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide; or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

39. A method for treating irritable bowel syndrome in an animal comprising administering to said animal a therapeutically-effective amount of a compound of Claim 1.

40. The method of Claim 39 wherein the compound is:

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-

[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, monohydrochloride;

N-[2-(8-chlorodibenz-10-11-dihydrobenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)thio]propanamide;

3-Amino-N-[2-(8-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[[2-(dimethylamino)ethyl]thio]propanamide, monohydrochloride;

N-[2-(8-chloro-10,11-dihydrodibenz-[b,f][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-thienylmethyl)amino]propanamide, monohydrochloride;

8-chloro-N-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide;

or

8-chloro-N-[4-[(2-furanylmethyl)thio]-2-oxobutyl]dibenz[b,f][1,4]oxazepin-10(11H)-carboxamide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08217

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D267/20; C07D413/12; A61K31/55; //(C07D413/12, 307:00, 267:00)(C07D413/12,267:00, 213:00)(C07D413/12,333:00,267:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 193 822 (G.D. SEARLE & CO.) 10 September 1986 cited in the application see the whole document & US,A,4 614 617 cited in the application & US,A,4 559 336 cited in the application	1-40
A	EP,A,0 193 148 (G.D. SEARLE & CO.) 3 September 1986 see the whole document & US,A,4 559 337 cited in the application	1-40
A	EP,A,0 218 077 (G.D. SEARLE & CO.) 15 April 1987 cited in the application see the whole document	1-40

"Special categories of cited documents :[10]

"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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14 JANUARY 1993	28.01.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P. BOSMA

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9208217
SA 65658

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 14/01/93

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		US-A- 4614617	30-09-86
		AU-B- 576944	08-09-88
		AU-A- 5400986	28-08-86
		CA-A- 1251204	14-03-89
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		AU-A- 6182786	05-03-87
		CA-A- 1278571	02-01-91
		JP-A- 62089670	24-04-87
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