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(12) # EUROPEAN PATENT SPECIFICATION

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(22) Date of filing: **30.06.86**

(54) **7-[(Substituted)amino]-6-[(substituted)carbonyl)-methylamino]-1-oxaspiro[4.5]decanes as analgesic agents.**

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Description

The search for strong analgesics which also possess minimal potential for dependency has been among the highest priority efforts in pharmaceutical research. These research efforts have, to a great extent, involved chemical modifications of the opiate structure and the discovery of novel compounds which possess morphine-like activity.

The discovery of endogenous polypeptide opioids has led workers in the field to consider that these peptides, possessing less rigid structures, might interact with opioid receptors other than those to which the classical rigid structure opiates, such as morphine, bind.

The concept of multiple opioid receptors has been supported by studies with nalorphine and a series of benzomorphans which display unusual pharmacological properties dissimilar from morphine, yet blocked by selective opioid antagonists. [See for example, W. R. Martin, J. Pharmacol. Exp. Ther., 197 : 517-532 (1976)].

The existence of multiple types of opioid receptors is of importance because of the possibility of separating desirable analgesic and psychotherapeutic effects of a drug compound from the undesirable abuse potential or habituating effects.

United States Patent 4,145,435 describes certain 2-amino-cycloaliphatic amide compounds as analgesics. In particular, trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide has been reported to possess selective kappa opioid receptor agonist activity, and therefore to possess analgesic activity without attendant dependence liability. [See P. V. Vanvoigtlander et al., J. Pharmacol. Exp. Ther., 224 : 7-12 (1983)].

United States Patent 4,098,904 discloses certain cis- and trans-N-(2-aminocycloaliphatic)benzamide compounds, for example, N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-3,4-dichlorobenzeneacetamide, which have potent analgesic activity, making them useful for relieving pain in warm-blooded animals.

United States Patent 4,212,878 discloses certain N-[[1-amino-4-(substituted)cyclohexyl]methyl] benzeneacetamide compounds, for example, 2-(3,4-dichlorophenyl)-N-[[8-(1-pyrrolidinyl)-1,4-dioxaspiro[4.5]dec-8-yl]methyl]acetamide, which also possess analgesic activity with diminished dependence liability.

United States Patent 4,360,531 discloses certain N-(2-aminocycloaliphatic)phenylacetamides and benzamides, for example trans-3,4-dichloro-N-methyl-[7-(1-pyrrolidinyl)-1,4-dioxaspiro[4.5]dec-8-yl]-benzamide as analgesic compounds.

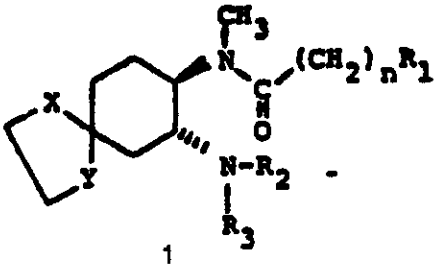
United States Patent 4,359,476 discloses certain N-(2-aminocycloaliphatic)phenylacetamides and benzamides, for example cis- and trans-4-bromo-N-[3-methoxy-2-(1-pyrrolidinyl)cyclohexyl]-N-methyl-benzamide as analgesic compounds.

United States Patent 4,438,130 discloses certain oxaspirocyclohexylbenzeneacetamide and -benzamide compounds, for example 3,4-dichloro-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzeneacetamide, possessing analgesic activity.

EP-A-0146297 and ES-A-8600259 both disclose substituted trans-1,2-diaminocyclohexyl amide compounds.

The present invention provides certain oxaspiro-2-aminocyclohexylacetamides having analgesic activity and useful in the treatment of pain in warm-blooded animals.

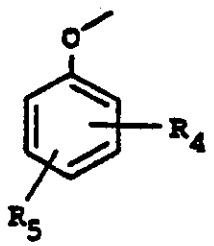
In its broadest aspect, the present invention provides compounds of structural formula 1



1

wherein n is an integer of from one to six ; either of X or Y is oxygen and the other is —CH_2— ; R_1 is selected from

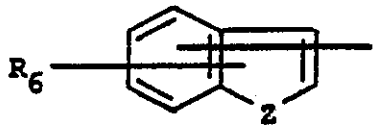
a)



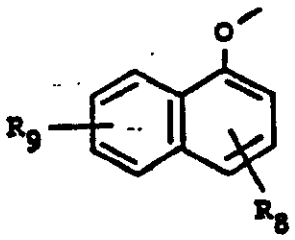
where R_4 and R_5 are independently hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of

from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl ;

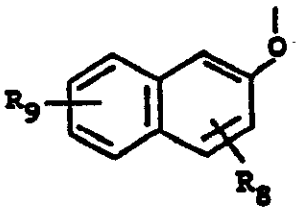
b) 3,4,5-trimethylphenoxy ;

c) 

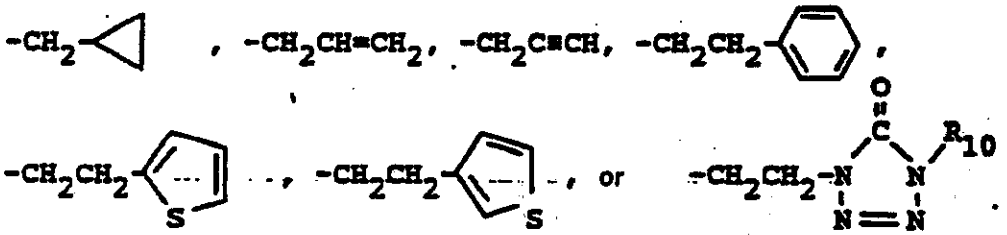
where R_6 is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl ; Z is —CH_2—, —O—, —S—, or —NR_7— where R_7 is hydrogen, alkanoyl of from one to six carbon atoms, or alkyl of from one to six carbon atoms ;

d) 

where R_8 and R_9 are independently hydrogen, fluorine, bromine, alkyl of from one to six carbon atoms, or alkoxy of from one to four carbon atoms ; or

e) 

where R_8 and R_9 are as defined above ; where R_2 is methyl and R_3 is hydrogen, alkyl of from one to six carbon atoms,

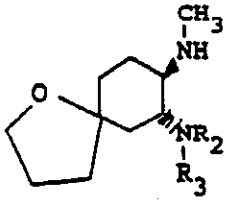


where R_{10} is alkyl of from one to four carbon atoms ; or where R_2 and R_3 when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, or hexahydro-1H-azepinyl ring ; and the pharmaceutically acceptable acid addition salts thereof.

In another aspect, the present invention provides pharmaceutical composition useful for the treatment of pain in a warm-blooded animal, the compositions containing an analgesically effective amount of a compound is structural formula 1 as defined above, in combination with a pharmaceutically acceptable carrier.

In accordance with yet another aspect of the present invention, there is provided a compound of formula 1 for use in the manufacture of a medicament for the treatment of relieving pain in a warm-blooded animal which treatment comprises administering to an animal in need of such treatment an analgesically effective amount of the medicament.

In accordance with a further aspect of the present invention, there is provided a process for preparing compounds of structural formula 1 which process comprises first reacting an oxaspirodiamine of structural formula 2



2

where R_2 and R_3 are as defined above, with a carboxylic acid having the structure

$$R_1(CH_2)_nCOOH$$

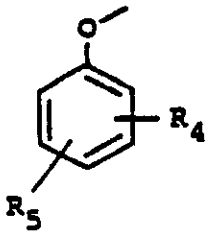
where n, and R_1 are as defined above, in the presence of a coupling reagent selected from dicyclohexylcarbodiimide or carbonyldiimidazole or with the corresponding acid chloride or acyl imidazole ; and thereafter converting the product of said reaction, if desired, to a pharmaceutically acceptable acid addition salt.

The compounds of the present invention constitute a class of derivatives of certain substituted oxaspirodiaminocyclohexane compounds of structure 1 above in which one nitrogen atom is an amine nitrogen substituted with methyl and a second substituent selected from the group R_3 as defined above, or when taken together with the nitrogen atom to which they are attached, R_2 and R_3 form a pyrrolidinyl, piperidinyl, or hexahydro-1H-azepinyl ring, and the other nitrogen atom is a N-methyl amide nitrogen further substituted with the group R_1 as defined above.

Compounds of the present invention contain one or more asymmetric carbon atoms and therefore exist in various stereoisomeric forms. Additionally, the compounds of this invention are capable of existing in different geometric isomeric forms. For example, the oxygen atom of the 5-membered spiro-ring may be positioned on the same side of the average plane of the cyclohexane ring as the amide nitrogen, or on the side opposite. The present invention contemplates all geometric and stereoisomeric forms of the compounds of structural formula 1 above.

The individual stereoisomers are obtained, if desired, from mixture of the different forms by known methods of resolution such as the formation of diastereomers, followed by recrystallization.

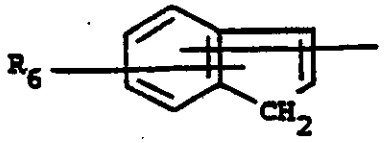
In one preferred embodiment, compounds of the present invention possess structural formula 1 above where R_1 is



where R_4 and R_5 are independently hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of from one to six carbons atoms, alkoxy of from one to six carbon atoms, or aryl.

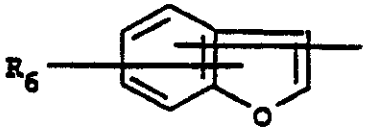
By the term « aryl » is meant phenyl ; phenyl substituted with fluorine, chlorine, alkoxy of from one to four carbon atoms, nitro, or trifluoromethyl ; 2- or 3-thienyl ; and 2- or 3-thienyl substituted with alkyl of from one to four carbon atoms or alkoxy of from one to four carbon atoms.

In another preferred embodiment, compounds of the present invention possess structural formula 1 above where R_1 is



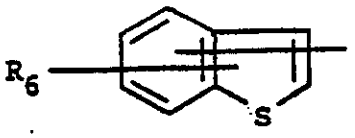
where R_6 is as defined above. In this embodiment, the most preferred compounds are subetituted inden-1-yl compounds of formula 1 above.

In another preferred embodiment, compounds of the present invention possess structural formula 1 above where R_1 is



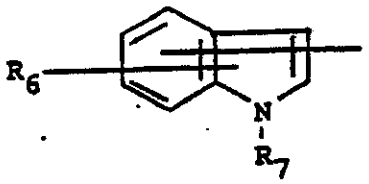
where R_6 is as defined above. In this embodiment, the most preferred compounds are substituted benzofuran-3-yl compounds of structural formula 1 above.

In yet another preferred embodiment, compounds of the present invention possess structural formula 1 above where R_1 is



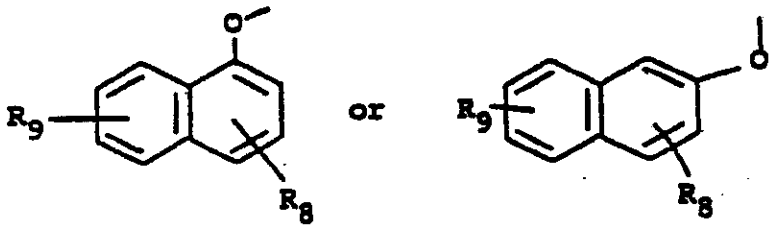
where R_6 is as defined above. In this embodiment, the most preferred compounds are substituted benzo[b] thio-phen-4-yl compounds of formula 1 above.

In another preferred embodiment, compounds of the present invention possess structural formula 1 above where R_1 is



where R_6 and R_7 are as defined above. In this embodiment, the most preferred compounds are indol-3-yl compounds of structural formula 1 above.

In another preferred embodiment, compounds of the present invention possess structural formula 1 above where R_1 is



where R_8 and R_9 are independently hydrogen, fluorine, chlorine, bromine, alkyl of from one to four carbon atoms or alkoxy of from one to four carbon atoms.

Preferred substituents for R_2 and R_3 are those where R_2 is methyl and R_3 is lower alkyl, most preferably methyl, or where R_2 and R_3 taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring.

Compounds of the present invention are exemplified by the following :

[5R-(5α,7α,8β)]-N-Methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]phenoxyacetamide.
[5S-(5α,7α,8β)]-N-Methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]phenoxyacetamide.
[5R-(5α,7β,8α)]-N-Methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]phenoxyacetamide.
[5S-(5α,7β,8α)]-N-Methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]phenoxyacetamide.
[5R-(5α,7α,8β)]-2-(4-Fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-2-(4-Fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-2-(4-Fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-2-(4-Fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-2-(4-Fluorophenoxy)-N-[7-[methyl-(2-phenylethyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-2-(4-Fluorophenoxy)-N-[7-[methyl-(2-phenylethyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-2-(4-Fluorophenoxy)-N-[7-[methyl-(2-phenylethyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-2-(4-Fluorophenoxy)-N-[7-[methyl-(2-phenylethyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide.

[5S-(5α,7α,8β)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide.
[5R-(5α,7β,8α)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide.
[5S-(5α,7β,8α)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide.
[5R-(5α,7α,8β)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)-acetamide.
[5S-(5α,7α,8β)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)-acetamide.
[5R-(5α,7β,8α)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)-acetamide.
[5S-(5α,7β,8α)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)-acetamide.
[5R-(5α,7α,8β)]-2-(3,4-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-2-(3,4-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-2-(3,4-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-2-(3,4-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-2-(2,6-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-2-(2,6-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-2-(2,6-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-2-(2,6-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-2-(3,5-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-2-(3,5-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-2-(3,5-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-2-(3,5-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7α,8β)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7β,8α)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5S-(5α,7β,8α)]-N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
[5R-(5α,7α,8β)]-N-Methyl-N-[7-[methyl[2-(2-thienyl)ethyl]amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)acetamide.
[5S-(5α,7α,8β)]-N-Methyl-N-[7-[methyl[2-(2-thienyl)ethyl]amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)acetamide.
[5R-(5α,7β,8α)]-N-Methyl-N-[7-[methyl[2-(2-thienyl)ethyl]amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)acetamide.
[5S-(5α,7β,8α)]-N-Methyl-N-[7-[methyl[2-(2-thienyl)ethyl]amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)acetamide.
[5R-(5α,7α,8β)]-N-Methyl-N-[7-(methyl-2-propenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-indene-3-acetamide.
[5S-(5α,7α,8β)]-N-Methyl-N-[7-(methyl-2-propenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-indene-3-acetamide.
[5R-(5α,7β,8α)]-N-Methyl-N-[7-(methyl-2-propenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-indene-3-acetamide.

[5S-(5α,7β,8α)]-N-Methyl-N-[7-(methyl-2-propenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-indene-3-acetamide.

[5R-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide.

[5S-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide.

[5R-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide.

[5S-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide.

[5R-(5α,7α,8β)]-N-[7-(Dimethylamino)-1-oxaspiro[4.5]dec-8-yl]-N-methyl-1H-indole-3-acetamide.

[5S-(5α,7α,8β)]-N-[7-(Dimethylamino)-1-oxaspiro[4.5]dec-8-yl]-N-methyl-1H-indole-3-acetamide.

[5R-(5α,7β,8α)]-N-[7-(Dimethylamino)-1-oxaspiro[4.5]dec-8-yl]-N-methyl-1H-indole-3-acetamide.

[5S-(5α,7β,8α)]-N-[7-(Dimethylamino)-1-oxaspiro[4.5]dec-8-yl]-N-methyl-1H-indole-3-acetamide.

[5R-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indoleacetamide.

[5S-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indoleacetamide.

[5R-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indoleacetamide.

[5S-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indoleacetamide.

[5R-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide.

[5S-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide.

[5R-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide.

[5S-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide.

[5R-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamide.

[5S-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamide.

[5R-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamide.

[5S-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamide.

[5R-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamide.

[5S-(5α,7α,8β)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamide.

[5R-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamide.

[5S-(5α,7β,8α)]-N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamide.

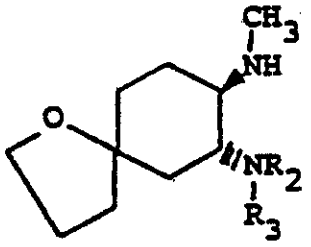
[5R-(5α,7α,8β)]-N-[7-[(Cyclopropylmethyl)methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamide.

[5S-(5α,7α,8β)]-N-[7-[(Cyclopropylmethyl)methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamide.

[5R-(5α,7β,8α)]-N-[7-[(Cyclopropylmethyl)methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamide.

[5S-(5α,7β,8α)]-N-[7-[(Cyclopropylmethyl)methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamide.

Compounds of the present invention are prepared by reactions in which an oxaspiro-diaminocyclohexane of structural formula 2



where R_2 and R_3 are as defined above is coupled with the desired carboxylic acid or reactive derivative thereof such as the corresponding acid chloride or acyl imidazole.

The appropriate carboxylic acid may be reacted directly with the diamine 2 in the presence of a coupling reagent such as dicyclohexylcarbodiimide, carbonyldiimidazole or the like. The reaction is generally carried out in a suitable solvent such as tetrahydrofuran or dioxane at ambient temperature but, depending upon the reactivity of the specific starting material employed, the reaction time, solvent employed, and reaction temperature may be varied. Reaction temperatures between —25 °C and the boiling point of the solvent may be employed.

The reaction between the acid chloride and diamine 2 is generally carried out at ambient temperature in a suitable solvent such as chloroform or dichloromethane in the presence of an acid acceptor such as tertiary amine or an alkali or alkaline earth carbonate or bicarbonate. The mixture of amine 2 and acid halide is allowed to stand until the reaction is complete as indicated by chromatographic analysis of the reaction mixture.

Alternatively, the desired starting carboxylic acid may first be converted to the corresponding acyl imidazole compound by conventional methods and the acyl imidazole then reacted with the diamine compound, 2, in the conventional manner.

In a further alternative method, the desired carboxylic acid (or reactive derivative thereof) is reacted with the oxaspiro-diaminocyclohexane 2 where R_2 is methyl and R_3 is hydrogen to form the

corresponding amide intermediate. This intermediate is then further reacted with a reactive alkyl, alkenyl, alkynyl or cycloalkyl halide such as allylchloride or bromide, propargyl chloride or bromide, or cyclopropylmethyl chloride or bromide and the like to form the compounds where R_3 is allyl, propargyl, or cyclopropylmethyl.

The desired product of any of the foregoing methods is recovered from the reaction mixture by well known techniques. For example, the crude reaction mixture may be concentrated under vacuum, if desired, to remove the solvent and other volatile components of the reaction mixture to yield the product, usually as an oil. This residual material may be further purified by dissolving it in a solvent such as diethyl ether and the resulting solution washed with water. The organic layer from this washing is separated, dried and evaporated to yield the product as an oil or crystalline solid which may then be recrystallized to obtain the pure material.

The starting carboxylic acids are known, or if novel, are prepared by reaction methods well known in the art and, for the most part, analogous to methods employed in the synthesis of known carboxylic acids of the same type.

Acid chlorides of the starting carboxylic acids are prepared by reaction of the acid compounds with, for example, thionyl chloride, phophoryl chloride, or the like.

The acyl imidazole derivatives of the carboxylic acids are prepared by reaction carbonyldiimidazole with the appropriate acid in the convention manner.

The starting oxaspiro-diaminocyclohexanes of formula 2 are prepared by the reactions shown in Reaction Sequence I. The conversion of compound 5 to compound 13 is carried out by reactions detailed in United States Patent 4,438,130 which is incorporated herein by reference.

1,4-Cyclohexanedione, (compound 4, Aldrich Chemical Co., Milwaukee, WI, U.S.A.) is converted to 8-oxo-1,4-dioxaspiro[4.5]decane, 5, by the method described by K. C. Nicolaou, J. Am. Chem. Soc., 102 (4) : 1404-1409 (1980).

(See Tables pages 9 and 10)

Compound 5 is reacted with lithium and ethyl-3-bromopropyl acetaldehyde acetal (J. Org. Chem., 37 : 1947 (1972)) in diethyl ether to produce 8-[3-(1-ethoxy)propyl]-1,4-dioxaspiro[4.5]decan-8-ol, 6.

Compound 6 is cleaved by the action of an acid resin to produce the dioxaspiro-diol intermediate 8-(2-hydroxyethyl)-1,4-dioxaspiro[4.5]decan-8-ol which is converted without further purification to trioxaspiro-[4.2.4]tetradecane, 7, by the action of triethylamine and methanesulfonyl chloride in methylene chloride.

Compound 7 is treated with perchloric acid for eighteen hours to cleave the ethylene ketal functionality and to produce 1-oxaspiro[4.5]decan-8-one, 8.

Reduction of the ketone function of compound 8 with lithium aluminum hydride in diethyl ether followed by reaction with p-toluenesulfonyl chloride produces 1-oxaspiro[4.5]decan-8-ol, 4-methylbenzenesulfonate, 9.

Compound 9 is converted to the unsaturated spiro compound 1-oxaspiro[4.5]dec-7-ene, 10, by treatment of 9 with 1,8-diazabicyclo[5.4.0]undec-5-ene.

Oxidation of the carbon-carbon double bond of compound 10 by the action of m-chloroperbenzoic acid produces a mixture of the isomers cis-(±)-(1'α,3'β,6'α)-dihydrospiro[furan-1(3H), 3'[7]-oxabicyclo[4.1.0]-heptane, 11a, and trans-(±)-(1'α,3'β,6'α)-dihydrospiro-[furan-1(3H), 3'[7]-oxabicyclo[4.1.0]-heptane, 11b.

The mixture of isomers 11a and 11b is further converted without separation to a mixture of 7-(methylamino)-1-oxaspiro[4.5]decan-8-ol, 12a, and 8-(methyl-amino)-1-oxaspiro[4.5]decan-7-ol, 12b, by heating the mixture of 11a and 11b under reflux with methylamine in the presence of a small amount of water for a period of about 10 to 24 hours.

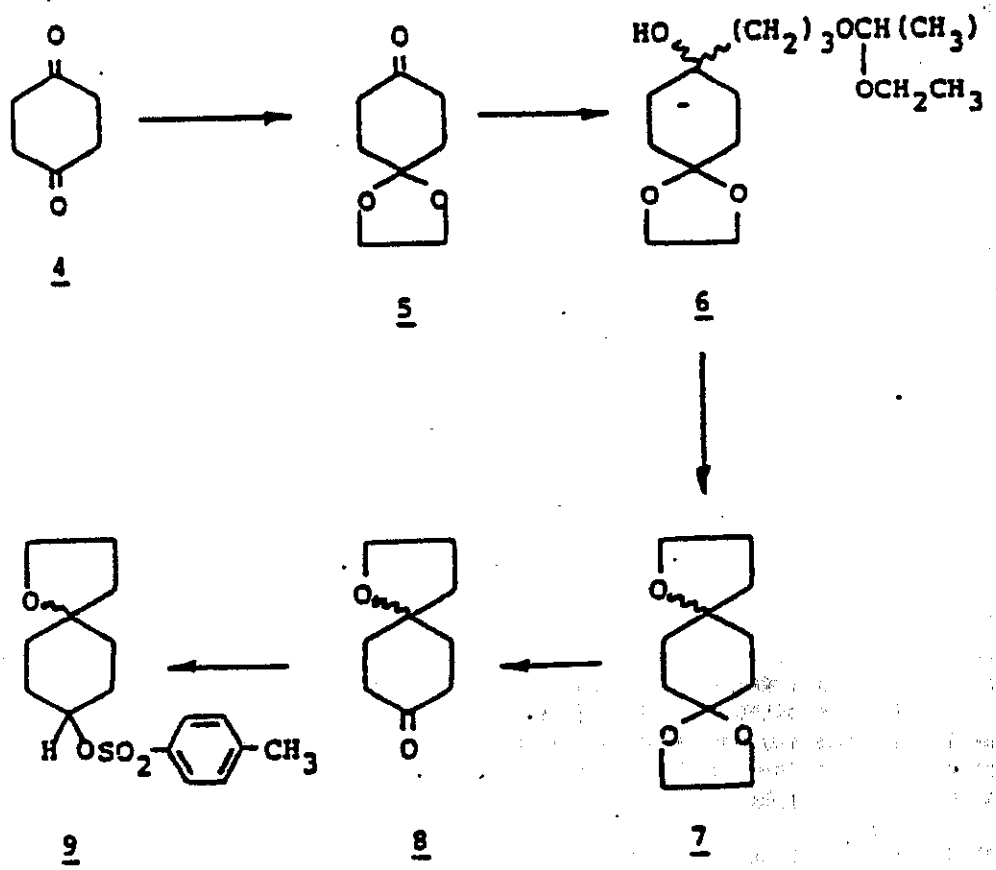
The mixture of compounds 12a and 12b is not separated, but is converted to 4',5'-dihydro-7-methylspiro[7-azabicyclo[4.1.0]heptane-3,2'(3'H)-furan], 13, by treatment with chlorosulfonic acid in diethyl ether at temperatures between about —10 °C and 5 °C.

The oxaspiro-aza-bicyclo compound, 13, is converted to the desired intermediate, 2a, (together with the unwanted isomer, 2b) by heating 13 with the appropriate amine under reflux in the presence of water and, optionally, ammonium chloride for a period of from about 10 to 24 hours, generally from about 18 to 20 hours. The mixture of isomeric oxaspiro cyclohexanediamines, 2a and 2b is separated by convention techniques, and compound 2a is employed in the preparation of the compounds of the present invention.

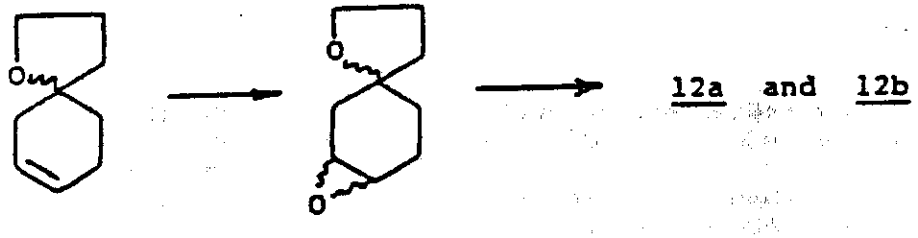
Compound 2a is reacted with the desired carboxylic acid in the presence of a coupling reagent such as carbonyldiimidazole or dicyclohexylcarbodiimide as described above or, alternatively, with the desired acid chloride or acyl imidazole to produce the compounds of the present invention, 1.

The free base form of the compounds of this invention are converted, if desired, by known methods to the corresponding acid addition salts. Suitable acids useful for this purposes include hydrochloric,

Reaction sequence 1



4 5 6 7 8 9

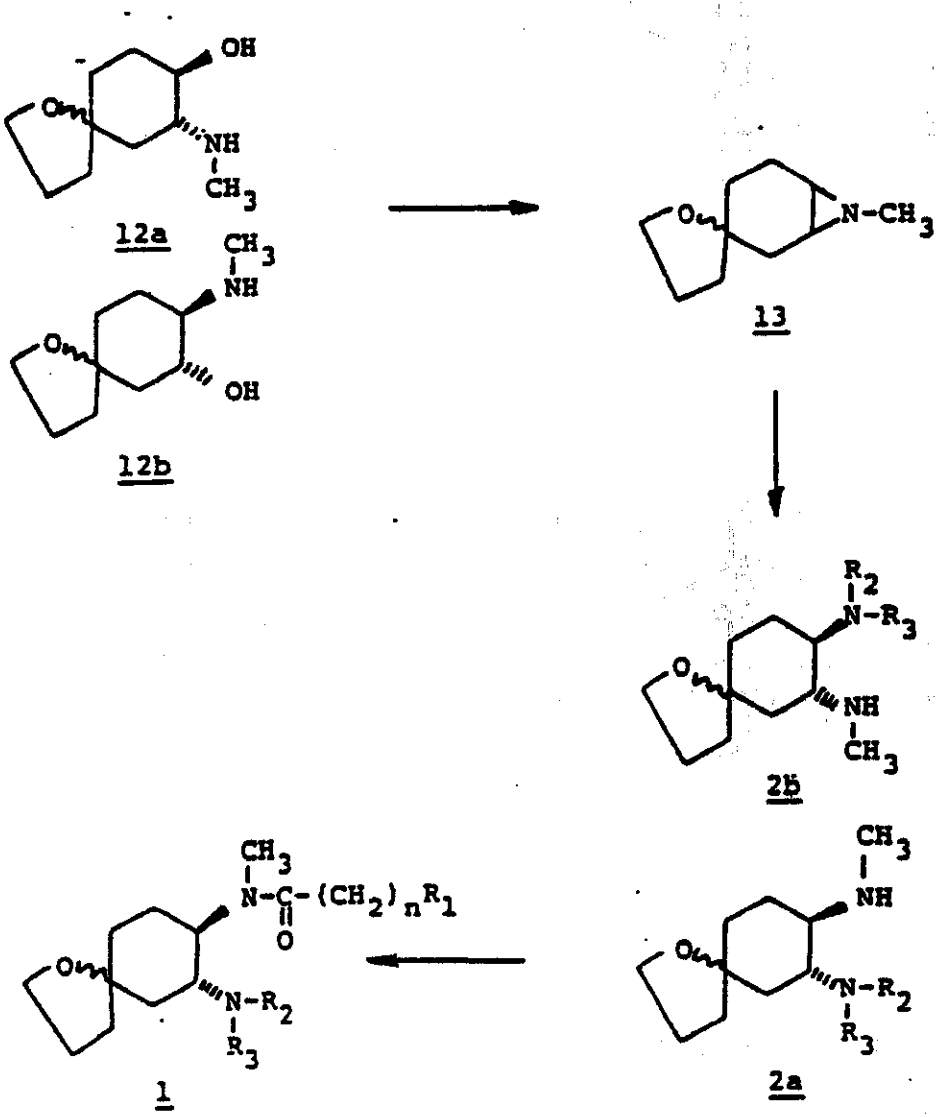


10

11a cis-
11b trans-

12a and 12b

Reaction sequence I (concluded)



hydrobromic, hydriodic, sulfuric, nitric, phosphoric, acetic, benzoic, citric, maleic, tartaric, succinic, gluconic, ascorbic, sulfamic, oxalic, pamoic, methane-sulfonic, benzenesulfonic, or mixtures thereof.

The salts are produced by contacting the free base form of the compounds of this invention with an equivalent amount of the desired acid in a suitable solvent such as water, an alcohol, or aqueous alcohol. The solvent is removed to yield the salt which may be used as such or further purified by recrystallization. In the particular cases where the compounds of this invention are made by reacting an oxaspirocyclohexanediamine with an acid chloride, the product of the reaction is the hydrochlorides salt of the desired compound which may be employed as the analgesic agent, or may be converted, if desired, to other salts by first converting to the free base.

The free base form of compounds of the present invention may be regenerated from the salts, if disered, by contacting the salt with an aqueous solution of a base such as sodium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The free base form of compounds of this invention and their corresponding acid addition salts differ in such physical characteristics as melting point and solubility in polar solvents such as water, but are otherwise considered equivalent for the purposes of this invention.

The compounds of the present invention possess significant analgesic activity with the potential for minimum dependence liability due to their selective kappa opioid receptor binding properties. In addition to acting as analgesics, selective kappa opioid agonists also cause opioid receptor-mediated sedation, diuresis, and corticosteroid elevations. Accordingly, the compounds of the present invention may also be useful diuretics and psychotherapeutic agents as well as analgesics.

Representative examples of the compounds of this invention have shown activity in standard laboratory analgesic tests such as the rat paw pressure test as shown by the data appearing in Table 1.

Moreover, representative examples of compounds of the present invention when tested in vitro to determine the extent of opioid receptor binding were found to be selectively bound to the kappa opioid receptors with much lower binding to the mu opioid receptor sites. The benefits of this selectivity in binding to opioid receptor binding sites has been discussed above and is also described in M. B. Tyers, Br. J. Pharmacol., (1980) 69 : 503-512.

Measurement of the kappa opioid receptor binding activity of compounds of the present invention was made by the following method. Guinea pig brain homogenates were prepared fresh daily utilizing the method of Gillan et al. Br. J. Pharmacol., (1980) 70 : 481-490.

The binding of tritiated etorphine to brain homogenates was measured in the presence unlabeled competitor compounds of the present invention with 200 nanomolar D-alanine-D-leucine-enkephalin (acronym DADLE) and 200 nanomolar D-ala-MePheGly-ol-enkephalin (acronym DAGO) added to saturate the delta and mu opioid receptors, respectively. The reaction was terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

Measurement of the mu and delta opioid receptor binding activity of the compounds of this invention was made by the following method. Guinea pig brain homogenates were freshly prepared daily by the method of Gillan et., cited above.

Homogenates were incubated for 150 minutes at 0 °C with either tritiated DAGO to measure mu receptor binding activity, or with tritiated DADLE in the presence of a ten-fold excess of unlabeled DAGO to measure delta opioid receptor binding. Nonspecific binding was determined in the presence of 10^{-6} molar DAGO and 10^{-6} molar DADLE.

Reactions were terminated by rapid filtration and the radioactivity bound to the filters counted by liquid scintillation spectrophotometry.

The data were analyzed by the methods of Scatchard, Ann. N. Y. Acad. Sci., 51 : 660-672 (1949) and Hill, J. Physiol., 40 : IV-VIII (1910). The inhibition of the binding of tritiated etorphine, DAGO and DADLE by cold ligands was determined from the regression of log percentage inhibition of specific binding or log concentration of cold ligand. The inhibition constant, K_i, was calculated from the equation :

$$K_i = \frac{IC_{50}}{1 + [L]/K_D}$$

where [L] is the concentration of the labeled ligand and K_D is the equilibrium dissociation constant.

The results of these tests are presented in Table I.

(See Table I page 12)

Table I

Compound	Receptor Binding (K_i moles/liter) Kappa	Mu	Rat Paw Pressure (MPE_{50} I.V.) Mg/kg
N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]-dec-8-yl]-2-benzo[b]thiophene-acetamide	1.75×10^{-9}	8.62×10^{-8} (Ratio of kappa/mu binding = 49)	0.03
N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]-dec-8-yl]-4-benzo[b]thiophene-acetamide	2.97×10^{-9}	4.84×10^{-7} (Ratio of kappa/mu binding = 163)	0.02

The compounds of the present invention and/or their non-toxic, pharmaceutically acceptable acid adition salts may be administered to mammals in pharmaceutical compositions which comprise one or more compounds of this invention and/or salts thereof in combination with a pharmaceutically acceptable non-toxic carrier.

As parenteral compositions, the compounds of this invention may be administered with conventional injectable liquid carriers such as sterile, pyrogen- free water, sterile peroxide-free ethyl oleate, dehydrated alcohols, polypropylene glycol, and mixtures thereof.

Suitable pharmaceutical adjuvants for the injectable solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of these adjuvants include ethanol, ethylenediamine tetraacetic acid (EDTA), tartrate buffers, citrate buffers, and high molecular weight polyethylene oxide viscosity regulators. These pharmaceutical formulations may be injected intramuscularly, intraperitoneally, or intravenously.

As solid or liquid pharmaceutical compositions, the compounds of the present invention may be administered to mammals orally in combination with conventional compatible carriers in solid or liquid form. These orally administered pharmaceutical compositions may contain conventional ingredients such as binding agents such as syrups, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone, and mixtures thereof.

The compositions may further include fillers such as lactose, mannitol, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof.

These oral compositions may also contain lubricants such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid, silica, or agents to facilitate disintegration of the solid formulation such as starch, and wetting agents such as sodium lauryl sulfate.

The oral pharmaceutical compositions may take any convenient form such as tablets, capsules, lozenges, aqueous or oily suspensions, emulsions, or even dry powders which may be reconstituted with water or other suitable liquids prior to use.

The solid or liquid forms may contain flavorants, sweeteners, and/or preservatives such as alkyl p-hydroxybenzoates. The liquid forms may further contain suspending agents such as sorbitol, glucose, or other sugar syrups, methyl-, hydroxymethyl-, or carboxymethylcellulose, and gelatin, emulsifying agents such as lecithin or sorbitol monooleate, and conventional thickening agents. The liquid compositions may be encapsulated in, for example, gelatin capsules.

As topically administered pharmaceutical compositions, the compounds of the present invention may be administered in the form of ointments or creams containing from about 0.1 % to about 10 % by weight of the active component in a pharmaceutical ointment or cream base.

Compounds of the present invention may be rectally administered in the form of suppositories. For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active ingredient is dispersed homogenously in the melt. The mixture is then poured into convenient sized molds and allowed to cool and solidify.

Preferably the pharmaceutical compositions of this invention are in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate amounts of the active component. The unit dosage can be a packaged preparation with the package containing discrete quantities of the preparation. For example, the package may take the form of packaged tablets, capsules, and powders in envelopes, vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or can be the appropriate number of any of these packaged forms.

The quantity of active compound in the unit dosage form may be varied or adjusted from about 0.5 mg to about 350 mg according to the particular application and the potency of the active ingredient.

When employed systematically in therapeutic use as analgesic agents in the pharmaceutical method of this invention, the compounds are administered at doses of from about 0.05 mg to about 2.0 mg of active compound per kilogram of body weight of the recipient.

The following specific preparative examples are provided to enable one skilled in the art to practice the present invention. These examples are not to be read as limiting the scope of the invention as defined by the appended claims, but merely as illustrative thereof.

Example 1

Preparation of 2-(3,4-Dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide hydrochloride

Step A - Preparation of 4',5'-Dihydro-7-methyl-spiro[7-azabicyclo[4.1.0]- heptane-3,2 (3H)-furan].

A mixture of cis-(±)-(1'α,3'β,6'α)-dihydrospirofuran-2(3H),3'-[7]-oxabicyclo[4.1.0]heptane and trans-(±)-(1'α,3'β,6'α)-dihydrospirofuran-2(3H),3'-[7]-oxabicyclo[4.1.0]heptane, prepared according to the method disclosed in United States Patent 4,438,130, is slowly added with stirring to an ice-cold 25 %-30 % aqueous solution of methylamine (Aldrich Chemical Co. Milwaukee, WI, USA). The mixture is allowed to warm to room temperature and is stirred at ambient temperature overnight and then heated under reflux for three hours.

The mixture is cooled, saturated with sodium hydroxide and then extracted diethyl ether. The ether solution is dried over anhydrous magnesium sulfate, and the ether removed under vacuum to yield a crude mixture of 7-(methylamino)-1-oxaspiro[4.5]decan-8-ol and 8-(methylamino)-1-oxaspiro[4.5]decan-7-ol.

The mixture of amino-alcohols is dissolved in diethyl ether and cooled in an ice-salt bath. Chlorosulfonic acid is added dropwise with stirring over a period of one hour. The mixture is allowed to warm to room temperature, and then stand for three hours. The ether is decanted, and the residual white salt is washed with ether. The salt is cooled in an ice bath, and aqueous sodium hydroxide is slowly added.

The crude 4',5'-dihydro-7-methyl-spiro[7-azabicyclo[4.1.0]heptane-3,2'(3'H)-furan is purified by recrystallization.

Step B - Preparation of 1-[8-(methylamino)]-1-oxaspiro-[4.5]dec-7-yl]pyrrolidine

4',5'-Dihydro-7-methyl-spiro[7-azabicyclo[4.1.0]-heptane-3,2'(3'H)-furan (0.06 mol), prepared as described in Step A above, is mixed with 0.25 mol of pyrrolidine, 10 ml of water and 0.16 g of ammonium chloride. The mixture is heated under reflux for 20 hours and then cooled to room temperature. Solid sodium hydroxide is added, and the basic mixture is extracted with diethyl ether. The ether extract is dried over anhydrous magnesium sulfate, and the ether is removed under vacuum. The mixture of (5α,7α,8β)-1-[8-(methylamino)]-1-oxaspiro[4.5]dec-7-yl]pyrrolidine and (5α,7β,8α)-1-[8-(methylamino)]-1-oxaspiro[4.5]dec-7-yl]pyrrolidine is separated by chromatography to yield the desired pure (5α,7α,8β)-1-[8-(methylamino)]-1-oxaspiro[4.5]dec-7-yl]pyrrolidine.

Step C - Preparation of 2-(3,4-Dichlorophenoxy-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide

1-[8-(Methylamino)]-1-oxaspiro[4.5]dec-7-yl]-pyrrolidine, prepared as described in Step B above, is dissolved in methylene chloride. To the stirred solution is added, at room temperature, a mixture of 3,4-dichlorophenoxy acetyl chloride and triethylamine. The mixture is allowed to stand at room temperature for about 12 hours, and ether is added to crystallize the product, mp 188-196 °C.

The infrared spectrum (neat on NaCl disk) exhibited principal absorption peaks at 1651 and 1590 reciprocal centimeters.

The 300 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the compound exhibited signals at 11.5 (broad singlet, 1H) ; 7.29 (multiplet, 2H) ; 7.06 (doublet of doublets, J = 9.3 Hz, 1H) ; 5.31 (broad doublet, J = 14 Hz, 1H) ; 4.82 (doublet, J = 14 Hz, 1H) ; 4.20 (broad singlet, 1H) ; 3.94 (broad singlet, 1H) ; 3.85 (multiplet, 2H) ; 3.55 (broad singlet, 1H) ; 3.35 (broad singlet, 1H) ; 3.06 (singlet,

3H) ; 3.01 (broad singlet, 2H) ; and 2.4-1.5 (multiplet, 14H) parts per million downfield from tetramethylsilane.

Example 2

Preparation of N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide

Step A - Preparation of 1-Naphthalenyloxyacetyl Chloride

1-Naphthalenyloxyacetic acid (Shibata et al. Tech. Repts. Tohoku Imp. Univ., 12 : 119-135 (1936) is heated with thionyl chloride under reflux until no further solid remains. The mixture is cooled and the excess thionyl chloride is removed under vacuum. Any additional thionyl chloride remaining after this treatment is removed by azeotropic distillation with carbon tetrachloride.

Step B - Preparation of N-Methyl-1-(1-naphthalenyloxy-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide

The naphthalenyloxyacetyl chloride from Step A is dissolved in a 1 : 1 mixture of diethyl ether and dichloromethane and an ethereal solution of 1-[8-(methylamino)]-1-oxaspiro[4.5]dec-7-yl]pyrrolidine (prepared as described in Example 1, Step B above) is added dropwise with stirring.

The resulting mixture is stirred for one-half hour at room temperature and then cooled to 0 °C and diethyl ether is added until no further precipiate forms. This mixture is stirred for an additional 15 minutes and the precipitated N-methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide monohydrochloride salt is collected by filtration and purified by recrystallization, mp 230-232 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the product exhibited signals at about 1.75 (multiplet, 14 H) ; 2.98 (singlet, 3H) ; about 3.3 (multiplet obscured by water signal) ; 4.55 (multiplet, 1H) ; 5.16 (doublet of doublets, 2H) ; about 7.7 (multiplet, 7H), and 10.0 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 3

Preparation of N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 121-124 °C.

The infrared spectrum of the compound (neat on an NaCl disk) showed a principal absorption peak at 1642 reciprocal centimeters.

The 300 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the compound exhibited signals at 11.5 (broad singlet, 1H) ; 7.51 (doublet, J = 7 Hz, 1H) ; 7.43 (doublet, J = 7 Hz, 1H) ; 7.25 (multiplet, 2H) ; 6.34 (singlet, 1H) ; 4.75 (broad singlet, 1H) ; 3.90 (singlet, 2H) ; 3.85 (multiplet, 3H) ; 3.65 (broad singlet, 1H) ; 3.42 (multiplet, 1H) ; 3.38 (singlet, 2H) ; 3.12 (singlet, 3H), 2.97 (broad singlet, 2H), and 2.3-1.5 (multiplet, 14H) parts per million downfield from tetramethylsilane.

Example 4

Preparation of N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-indoleacetamide

Employing the general methods detailed above the title compound was prepared, mp 199-202 °C.

The infrared spectrum of a dichloromethane solution of the compound exhibited a principal absorption peak at 1625 reciprocal centimeters.

The 300 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the compound exhibited signals at 8.3 (broad singlet, 1H) ; 6.7-7.4 (multiplet, 5H) ; 3.7-4.1 (multiplet, 6H), 2.5-3.0 (multiplet, 6H) ; and 1.5-2.1 (multiplet, 12H) parts per million downfield from tetramethylsilane.

Example 5

Preparation of N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 187-190 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 2.99 (singlet, 3H) ; about 3.35 (multiplet, signal obscured by water signal) ; 4.05 (doublet of doublets, 2H) ; 4.58 (multiplet, 1H) ; about 7.55 (multiplet, 5H) ; and 10.0 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 6

Preparation of 2-(3,5-Dichlorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 122-124 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 2.91 (singlet, 3H) ; about 3.4 (multiplet, signal obscured by water signal) ; 4.55 (multiplet, 1H) ; 5.10 (doublet of doublets, 2H) ; 7.08 (triplet, 1H) ; 7.2 (doublet, 2H) ; and 10.2 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 7

Preparation of N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)-acetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 176-179 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 2.92 (singlet, 3H) ; about 3.3 (multiplet, signal obscured by water signal) ; 4.55 (multiplet, 1H) ; 5.08 (doublet of doublets, 2H) ; about 7.3 (multiplet, 4H) ; and 9.9 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 8

Preparation of 2-(4-Fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 184 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 2.89 (singlet, 3H) ; about 3.3 (multiplet, signal obscured by water signal) ; 4.55 (multiplet, 1H) ; 4.88 (doublet of doublets, 2H) ; about 7.05 (multiplet, 4H) ; and about 9.8 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 9

Preparation of N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 105-110 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 2.92 (singlet, 3H) ; about 3.3 (multiplet, signal obscured by water signal) ; 4.55 (multiplet, 1H) ; 5.11 (doublet of doublets, 2H) ; about 7.52 (multiplet, 2H) ; 7.81 (multiplet, 2H) ; and 9.9 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 10

Preparation of N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]dec-8-yl]-4-benzo[b]thiopheneacetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 231-234 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 3.02 (singlet, 3H) ; about 3.3 (multiplet, signal obscured by water signal) ; 4.18 (doublet of doublets, 2H) ; 4.55 (multiplet, 1H) ; 7.5 (multiplet, 5H) ; and about 10.1 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

Example 11

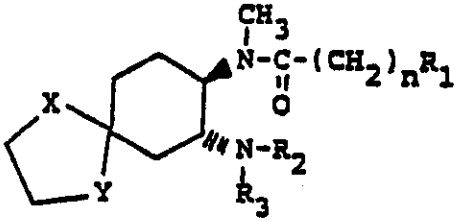
Preparation of N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]dec-8-yl]-2-(3,4,5-trimethylphenoxy)-acetamide

Employing the general methods detailed above the title compound was prepared as the monohydrochloride salt, mp 214-217 °C.

The 300 MHz proton magnetic resonance spectrum of a hexadeutero-dimethylsulfoxide solution of the compound exhibited signals at about 1.75 (multiplet, 14H) ; 2.01 (singlet, 3H) ; 2.18 (singlet, 6H) : 2.93 (singlet, 3H) ; about 3.3 (signal obscured by water signal) ; 4.55 (multiplet, 1H) ; 4.85 (doublet of doublets, 2H) ; 6.70 (singlet, 2H) ; and 10.3 (broad singlet, 1H) parts per million downfield from tetramethylsilane.

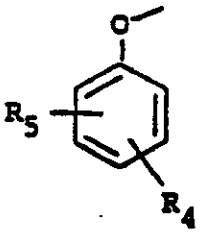
Claims (for the Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. A compound having the structure



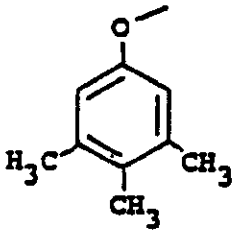
wherein n is an integer of from one to six ; either of X or Y is oxygen and the other is —CH_2— ; R^1 is selected from

a)

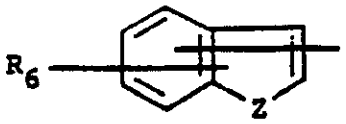


where R_4 and R_5 are independently hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl ;

b)

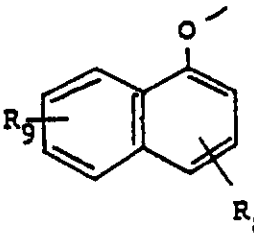


c)

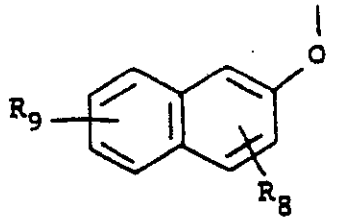


where R_6 is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl ; Z is —CH_2—, —O—, —S—, or —NR_7— where R_7 is hydrogen, alkanoyl of from two to six carbon atoms, or alkyl of from one to six carbon atoms ;

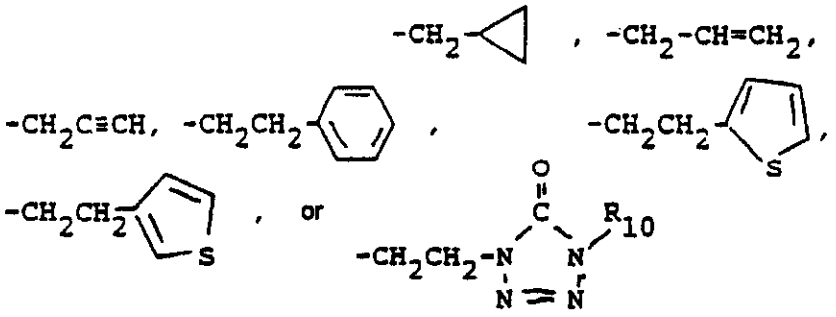
d)



where R_8 and R_9 are independently hydrogen, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, or alkoxy of from one to four carbon atoms ; or

e) 

where R_8 and R_9 are as defined above ; R_2 is methyl and R_3 is hydrogen, alkyl of from one to six carbon atoms,

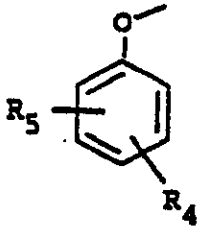


where R_{10} is alkyl of from one to four carbon atoms ; or where R_2 and R_3 when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, or hexahydro-1H-azepinyl ring ; and the pharmaceutically acceptable acid addition salts thereof.

2. A compound as defined in Claim 1, wherein n is one.

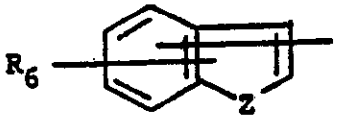
3. A compound as defined in Claim 1 or 2, wherein R_2 and R_3 taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring.

4. A compound as defined in Claim 1, 2 or 3 wherein R_1 is



where R_4 and R_5 are as defined therein.

5. A compound as defined by Claim 1, 2 or 3, wherein R_1 is



where R_6 and Z are as defined therein.

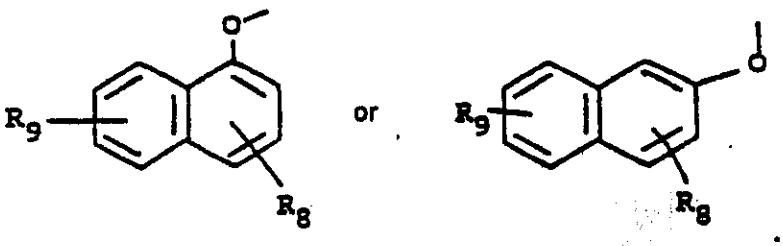
6. A compound as defined in Claim 5, wherein Z is —CH_2—.

7. A compound as defined in Claim 5, wherein Z is oxygen.

8. A compound as defined in Claim 5, wherein Z is sulfur.

9. A compound as defined in Claim 5, wherein Z is —NR_7— where R_7 is as defined therein.

10. A compound as defined in Claim 1, 2 or 3 wherein R_1 is



where R_8 and R_9 are as defined therein.

11. A compound as defined by Claim 4 selected from the group consisting of:
N-methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]phenoxyacetamide.
2-(4-fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
2-(4-fluorophenoxy)-N-[7-[methyl-(2-phenylethyl)-amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide.
N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)acetamide.
2-(3,4-dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
2-(2,6-dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
2-(3,5-dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.

12. A compound as defined by Claim 9 selected from the group consisting of:
N-methyl-N-(methyl-2-propenylamino)-1-oxaspiro-[4.5]dec-8-yl]-1H-indene-3-acetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide.

13. A compound as defined by Claim 7 selected from the group consisting of:
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamide.
N-[7-[(cyclopropylmethyl)methylamino]-1-oxaspiro-[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamide.

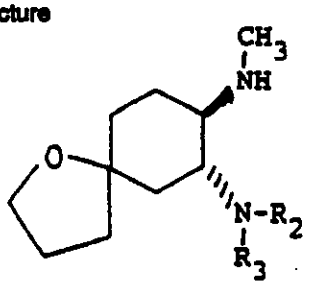
14. A compound as defined by Claim 9 selected from the group consisting of:
N-[7-(dimethylamino)-1-oxaspiro-[4.5]dec-8-yl]-N-methyl-1H-indole-3-acetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indoleacetamide.

15. A compound as defined by Claim 10 selected from the group consisting of:
N-methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
N-methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
N-methyl-N-[7-[methyl[2-(2-thienyl)ethyl]amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)-acetamide.

16. A pharmaceutical composition comprising a compound as claimed in any preceding claim together with a pharmaceutically acceptable carrier or diluent.

17. A compound as claimed in any one of Claims 1 to 15 or pharmaceutical composition as claimed in Claim 16, for use in the manufacture of a medicament for the treatment of pain alleviation in a warm-blooded animal.

18. A process for preparing a compound of the structural formula 1, as defined in claim 1, and the pharmaceutically acceptable acid addition salts thereof; which process comprises the steps of first reacting an oxaspirodiamine of the structure



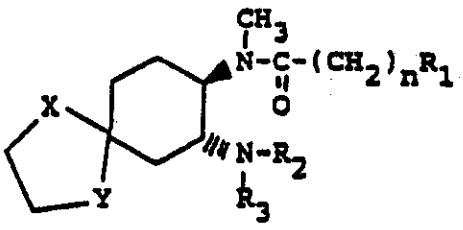
where R_2 and R_3 are as defined above, with a carboxylic acid having the structure

$$R_1(CH_2)_nCOOH$$

where n and R_1 are as defined above, in the presence of a coupling reagent selected from dicyclohexylcarbodiimide or carbonyldiimidazole or with the corresponding acid chloride or acyl imidazole; and thereafter converting the product of said reaction, if desired, to a pharmaceutically acceptable acid addition salt.

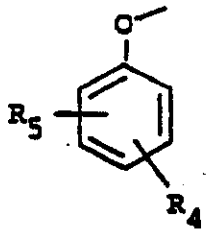
Claims (for the Contracting State AT)

1. A process for preparing a compound of the structural formula



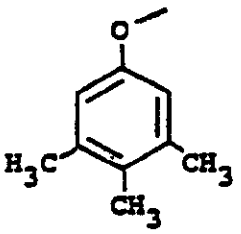
wherein n is an integer of from one to six ; either of X or Y is oxygen and the other is —CH_2— ; R_1 is selected from

a)

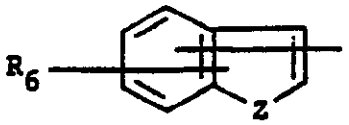


where R_4 and R_5 are independently hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or aryl ;

b)

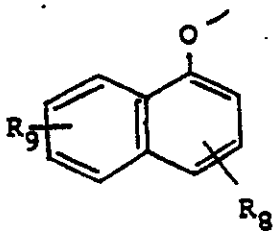


c)



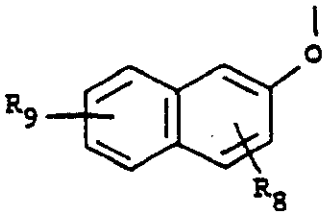
where R_6 is hydrogen, fluorine, chlorine, alkyl of from one to six carbon atoms, or aryl ; Z is —CH_2—, —O—, —S— , or —NR_7— where R_7 is hydrogen, alkanoyl of from two to six carbon atoms, or alkyl of from one to six carbon atoms ;

d)

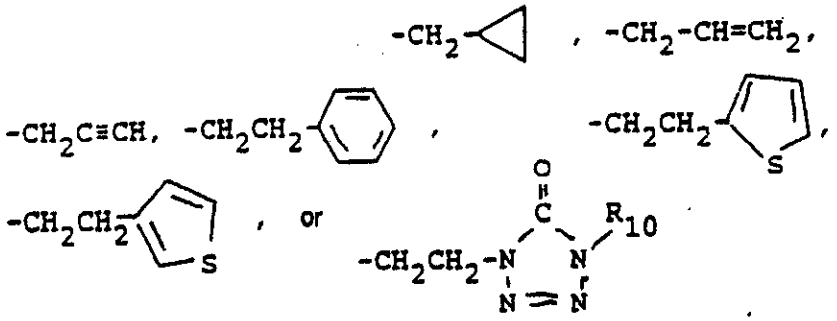


where R_8 and R_9 are independently hydrogen, fluorine, chlorine, bromine, alkyl of from one to six carbon atoms, or alkoxy of from one to four carbon atoms ; or

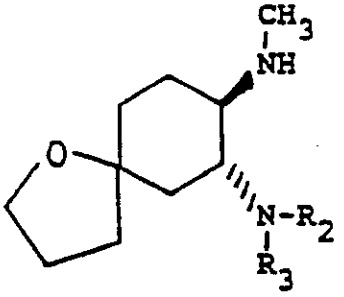
e)



where R_8 and R_9 are as defined above ; R_2 is methyl and R_3 is hydrogen ; alkyl of from one to six carbon atoms ;



where R_{10} is alkyl of from one to four carbon atoms ; or where R_2 and R_3 when taken together with the nitrogen atom to which they are attached, form a pyrrolidinyl, piperidinyl, or hexahydro-1H-azepinyl ring ; and the pharmaceutically acceptable acid addition salts thereof ; which method comprises the steps of first reacting an oxaspirodiamine of the structure



where R_2 and R_3 are as defined above ; with a carboxylic acid having the structure

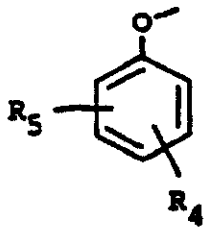
$$R_1(CH_2)_nCOOH$$

where n and R_1 are as defined above, in the presence of a coupling reagent selected from dicyclohexylcarbodiimide or carbonyldiimidazole or with the corresponding acid chloride or acyl imidazole ; and thereafter converting the product of said reaction, if desired, to a pharmaceutically acceptable acid addition salt.

2. A process according to Claim 1, wherein n is one.

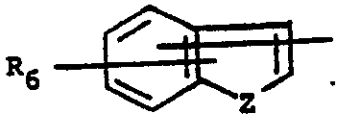
3. A process according to Claim 1 or 2, wherein R_2 and R_3 taken together with the nitrogen atom to which they are attached form a pyrrolidinyl ring.

4. A process according to Claim 1, 2 or 3, wherein R_1 is



where R_4 and R_5 are as defined therein.

5. A process according to Claim 1, 2 or 3, wherein R_1 is



where R_6 and Z are as defined therein.

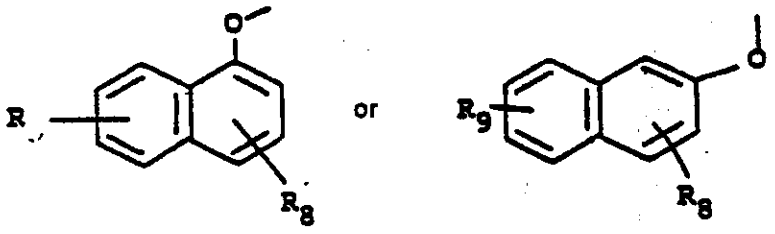
6. A process according to Claim 5, wherein Z is —CH_2—.

7. A process according to Claim 5, wherein Z is oxygen.

8. A process according to Claim 5, wherein Z is sulfur.

9. A process according to Claim 5, wherein Z is —NR_7— where R_7 is as defined therein.

10. A process according to Claim 1, 2 or 3, wherein R_1 is



where R_8 and R_9 are as defined therein.

11. A process according to Claim 4 in which one of the following compounds is prepared :

N-methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]phenoxyacetamide.
2-(4-fluorophenoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
2-(4-fluorophenoxy)-N-[7-[methyl-(2-phenylethyl)-amino]-1-oxaspiro[4.5]dec-8-yl]acetamide.
N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)acetamide.
N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluoromethylphenoxy)acetamide.
2-(3,4-dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
2-(2,6-dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
2-(3,5-dichlorophenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.

12. A process according to Claim 9 in which one of the following compounds is prepared :
N-methyl-N-[7-(methyl-2-propenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-indene-3-acetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indeneacetamide.

13. A process according to Claim 7 in which one of the following compounds is prepared :
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamide.
N-[7-[(cyclopropylmethyl)methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamide.

14. A process according to Claim 9 in which one of the following compounds is prepared :
N-[7-(dimethylamino)-1-oxaspiro-[4.5]dec-8-yl]-N-methyl-1H-indole-3-acetamide.
N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indoleacetamide.

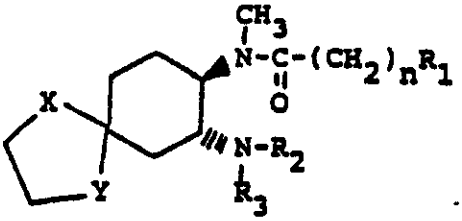
15. A process according to Claim 10 in which one of the following compounds is prepared :
N-methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
N-methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide.
N-methyl-N-[7-[methyl[2-(2-thienyl)ethyl]amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)-acetamide.

16. A process for preparing a pharmaceutical composition, which process comprises combining a compound prepared by a process as claimed in any preceding claim together with a pharmaceutically acceptable carrier or diluent.

17. A process to prepare a composition or a compound as claimed in any of the preceeding claims, for use in the manufacture of a medicament for the treatment of pain alleviation in a warm blooded animal.

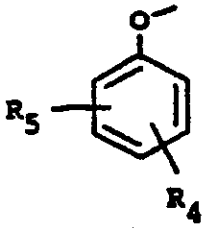
Patentansprüche (für die Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. Verbindung mit der Struktur



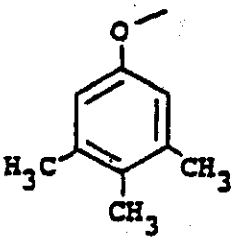
worin n eine ganze Zahl von eins bis sechs ist ; eines von X und Y Sauerstoff bedeutet und das andere für —CH_2— steht ; R_1 ausgewählt ist aus

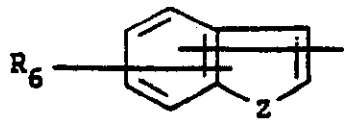
a)



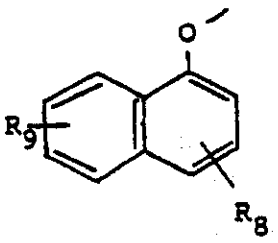
worin R_4 und R_5 unabhängig voneinander Wasserstoff, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl mit einem bis sechs Kohlenstoffatomen, Alkoxy mit einem bis sechs Kohlenstoffatomen oder Aryl bedeuten ;

b)

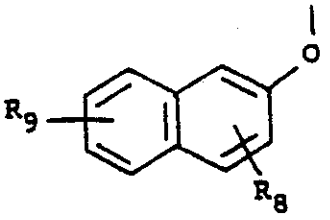


c) 

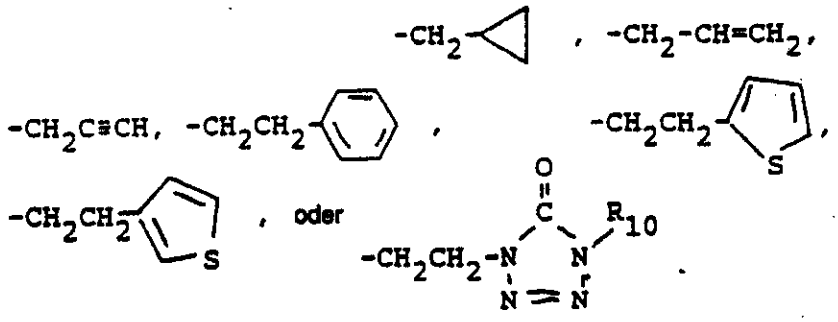
worin R_6 Wasserstoff, Fluor, Chlor, Alkyl mit einem bis sechs Kohlenstoffatomen oder Aryl bedeutet; Z für —CH_2—, —O—, —S— oder —NR_7— steht, worin R_7 Wasserstoff, Alkanoyl mit zwei bis sechs Kohlenstoffatomen oder Alkyl mit einem bis sechs Kohlenstoffatomen darstellt;

d) 

worin R_8 und R_9 unabhängig voneinander Wasserstoff, Fluor, Chlor, Brom, Alkyl mit einem bis sechs Kohlenstoffatomen oder Alkoxy mit einem bis vier Kohlenstoffatomen bedeuten; oder

e) 

worin R_8 und R_9 der obigen Definition entsprechen; R_2 Methyl ist und R_3 Wasserstoff, Alkyl mit einem bis sechs Kohlenstoffatomen,

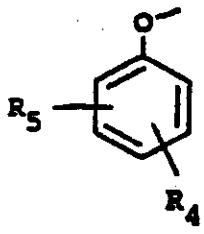


bedeutet, worin R_{10} Alkyl mit einem bis vier Kohlenstoffatomen darstellt, oder worin R_2 und R_3 zusammengenommen mit dem Stickstoffatom, an dem sie hängen, einen Pyrrolidinyl, Piperidinyl oder Hexahydro-1H-azepinylring bilden, und die pharmazeutisch akzeptablen Säureadditionssalze davon.

2. Verbindung, wie in Anspruch 1 definiert, worin n eins ist.

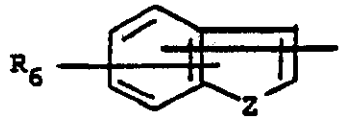
3. Verbindung, wie in Anspruch 1 oder 2 definiert, worin R_2 und R_3 zusammengenommen mit dem Stickstoffatom, an dem sie hängen, einen Pyrrolidinylring bilden.

4. Verbindung, wie in Anspruch 1, 2 oder 3 definiert, worin R_1



ist, worin R_4 und R_5 der darin angeführten Definition entsprechen.

5. Verbindung, wie in Anspruch 1, 2 oder 3 definiert, worin R_1



bedeutet, worin R_6 und Z der darin angeführten Definition entsprechen.

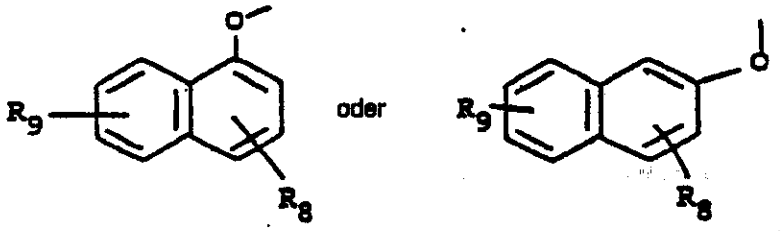
6. Verbindung, wie in Anspruch 5 definiert, worin Z für —CH_2— steht.

7. Verbindung, wie in Anspruch 5 definiert, worin Z für Sauerstoff steht.

8. Verbindung, wie in Anspruch 5 definiert, worin Z für Schwefel steht.

9. Verbindung, wie in Anspruch 5 definiert, worin Z für —NR_7— steht, worin R_7 der darin angeführten Definition entspricht.

10. Verbindung, wie in Anspruch 1, 2 oder 3 definiert, worin R_1



ist, worin R_8 und R_9 der darin angegebenen Definition entsprechen.

11. Verbindung, wie in Anspruch 4 definiert, ausgewählt aus der Gruppe bestehend aus:
N-Methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]-phenoxyacetamid.
2-(4-Fluorphenoxy)-N-[7-(1-pyrrolidinyl)-amino]-1-oxaspiro[4.5]dec-8-yl]-acetamid.
2-(4-FLuorphenoxy)-N-[7-[methyl-(2-phenyläthyl)-amino]-1-oxaspiro[4.5]dec-8-yl]-acetamid.
N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)-acetamid.
N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluormethylphenoxy)-acetamid.
2-(3,4-Dichlorphenoxy)-N-methyl-[7(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
2-(2,6-Dichlorphenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
2-(3,5-Dichlorphenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.

12. Verbindung, wie in Anspruch 9 definiert, ausgewählt aus der Gruppe bestehend aus:
N-Methyl-N-[7-(methyl-2-propylenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-inden-3-acetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indenacetamid.

13. Verbindung, wie in Anspruch 7 definiert, ausgewählt aus der Gruppe bestehend aus:
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamid.
N-[7-[(Cyclopropylmethyl)-methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamid.

14. Verbindung, wie in Anspruch 9 definiert, ausgewählt aus der Gruppe bestehend aus:
N-[7-(Dimethylamino)-1-oxaspiro[4.5]dec-8-yl]-N-methyl-1H-indol-3-acetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indolacetamid.

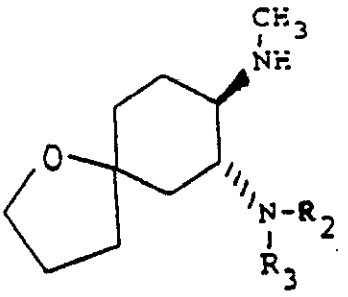
15. Verbindung, wie in Anspruch 10 definiert, ausgewählt aus der Gruppe bestehend aus:
N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
N-Methyl-N-[7-[methyl-[2-(2-thienyl)-äthyl]-amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)-acetamid.

16. Pharmazeutische Zusammensetzung umfassend eine Verbindung, wie in einem vorhergehenden Anspruch beansprucht, mit einem pharmazeutisch akzeptablen Träger- oder Verdünnungsmittel.

17. Verbindung, wie in einem der Ansprüche 1 bis 15 beansprucht, oder eine pharmazeutische Zusammensetzung, wie in Anspruch 16 beansprucht, zur Verwendung bei der Herstellung eines Medikaments zur Schmerzlinderungsbehandlung bei einem Warmblüter.

18. Verfahren zur Herstellung einer Verbindung der Strukturformel 1, wie in Anspruch 1 definiert, und der pharmazeutisch akzeptablen Säureadditionssalze davon; welches Verfahren die Schritte umfaßt, daß zuerst ein Oxaspirodiamin der Struktur

(Siehe Formel Seite 24 f.)



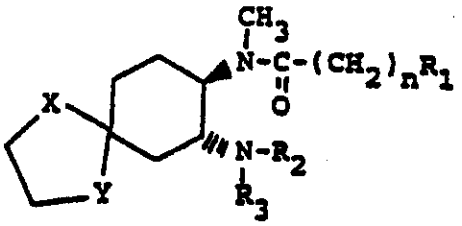
worin R_2 und R_3 der obigen Definition entsprechen, mit einer Carbonsäure mit der Struktur

$$R_1(CH_2)_nCOOH\ ,$$

worin n und R_1 der obigen Definition entsprechen, in Anwesenheit eines Kupplungsreagens ausgewählt aus Dicyclohexylcarbodiimid oder Carbonyldiimidazol oder mit dem entsprechenden Säurechlorid oder Acylimidazol umgesetzt wird; und danach das Produkt dieser Reaktion gewünschtenfalls in ein pharmazeutisch akzeptables Säureadditionssalz übergeführt wird.

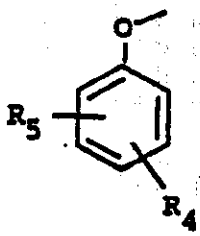
Patentansprüche (für den Vertragsstaat AT)

1. Verfahren zur Herstellung einer Verbindung mit der Strukturformel



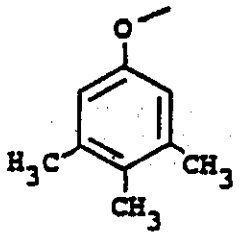
worin n eine ganze Zahl von eins bis sechs ist; eines von X und Y Sauerstoff bedeutet und das andere für —CH_2— steht; R_1 ausgewählt ist aus

a)

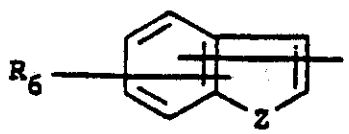


worin R_4 und R_5 unabhängig voneinander Wasserstoff, Fluor, Chlor, Brom, Nitro, Trifluormethyl, Alkyl mit einem bis sechs Kohlenstoffatomen, Alkoxy mit einem bis sechs Kohlenstoffatomen oder Aryl bedeuten;

b)

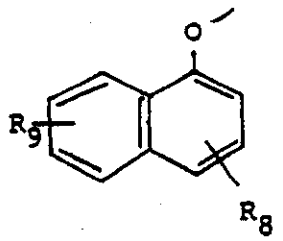


c)



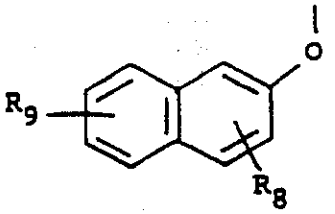
worin R_6 Wasserstoff, Fluor, Chlor, Alkyl mit einem bis sechs Kohlenstoffatomen oder Aryl bedeutet; Z für —CH_2—, —O—, —S— oder —NR_7— steht, worin R_7 Wasserstoff, Alkanoyl mit einem bis sechs Kohlenstoffatomen oder Alkyl mit einem bis sechs Kohlenstoffatomen darstellt;

d)

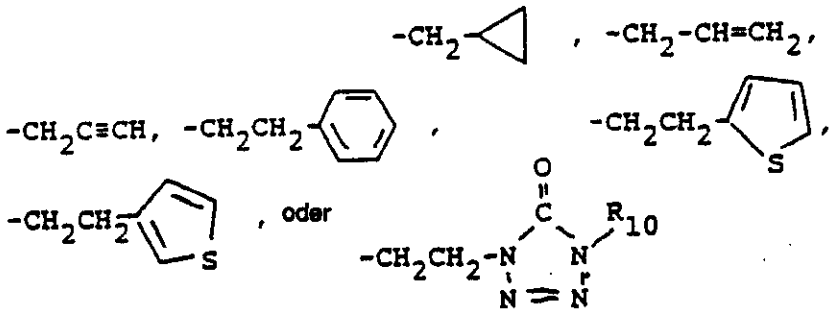


worin R_8 und R_9 unabhängig voneinander Wasserstoff, Fluor, Chlor, Brom, Alkyl mit einem bis sechs Kohlenstoffatomen oder Alkoxy mit einem bis vier Kohlenstoffatomen bedeuten; oder

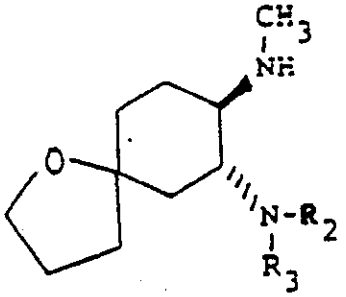
e)



worin R_8 und R_9 der obigen Definition entsprechen; R_2 Methyl ist und R_3 Wasserstoff; Alkyl mit einem bis sechs Kohlenstoffatomen;



worin R_{10} Alkyl mit einem bis vier Kohlenstoffatomen darstellt; oder worin R_2 und R_3 zusammengenommen mit dem Stickstoffatom, an dem sie hängen, einen Pyrrolidinyl-, Piperidinyl- oder Hexahydro-1H-azepinylring bilden; und der pharmazeutisch akzeptablen Säureadditionssalze davon; welches Verfahren die Schritte umfaßt, daß zuerst ein Oxaspirodiamin der Struktur



worin R_2 und R_3 der obigen Definition entsprechen, mit einer Carbonsäure mit der Struktur

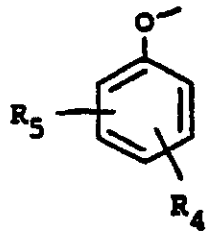
$$R_1(CH_2)_nCOOH\,,$$

worin n und R_1 der obigen Definition entsprechen, in Anwesenheit eines Kupplungsreagens ausgewählt aus Dicyclohexylcarbodiimid oder Carbonyldiimidazol oder mit dem entsprechenden Säurechlorid oder Acylimidazol umgesetzt wird; und danach das Produkt dieser Reaktion gewünschtenfalls in ein pharmazeutisch akzeptables Säureadditionssalz übergeführt wird.

2. Verfahren nach Anspruch 1, worin n eins ist.

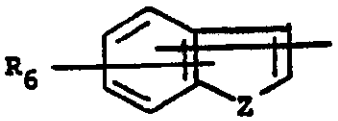
3. Verfahren nach Anspruch 1 oder 2, worin R_2 und R_3 zusammengenommen mit dem Stickstoffatom, an dem sie hängen, einen Pyrrolidinylring bilden.

4. Verfahren nach Anspruch 1, 2 oder 3, worin R_1



bedeutet, worin R_4 und R_5 der darin angeführten Definition entsprechen.

5. Verfahren nach Anspruch 1, 2 oder 3, worin R_1



bedeutet, worin R_6 und Z der darin angeführten Definition entsprechen.

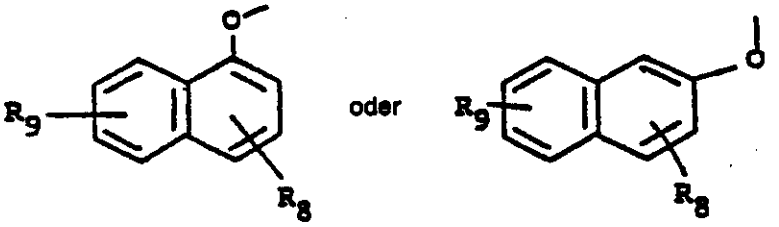
6. Verfahren nach Anspruch 5, worin Z für $—CH_2—$ steht.

7. Verfahren nach Anspruch 5, worin Z Sauerstoff ist.

8. Verfahren nach Anspruch 5, worin Z Schwefel ist.

9. Verfahren nach Anspruch 5, worin Z für $—N_7—$ steht, worin R_7 der darin angeführten Definition entspricht.

10. Verfahren nach Anspruch 1, 2 oder 3, worin R_1



ist, worin R_8 R_9 der darin angeführten Definition entsprechen.

11. Verfahren nach Anspruch 4, bei welchem eine der folgenden Verbindungen hergestellt wird:
N-Methyl-N-[7-(methyl-2-propynylamino)-1-oxaspiro[4.5]dec-8-yl]-phenoxyacetamid.
2-(4-Fluorphenoxy)-N-[7-(1-pyrrolidinyl)-amino]-1-oxaspiro[4.5]dec-8-yl]-acetamid.
2-(4-Fluorphenoxy)-N-[7-[methyl-(2-phenyläthyl)-amino]-1-oxaspiro[4.5]dec-8-yl]-acetamid.
N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-nitrophenoxy)-acetamid.
N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-(3-trifluormethylphenoxy)-acetamid.
2-(3,4-Dichlorphenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
2-(2,6-Dichlorphenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
2-(3,5-Dichlorphenoxy)-N-methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.

12. Verfahren nach Anspruch 9, bei welchem eine der folgenden Verbindungen hergestellt wird:
N-Methyl-N-[7-(methyl-2-propenylamino)-1-oxaspiro[4.5]dec-8-yl]-1H-inden-3-acetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indenacetamid.

13. Verfahren nach Anspruch 7, bei welchem eine der folgenden Verbindungen hergestellt wird:
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-2-benzo[b]furanacetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-benzo[b]furanacetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzo[b]furanacetamid.
N-[7-[(Cyclopropylmethyl)-methylamino]-1-oxaspiro[4.5]dec-8-yl]-N,2-dimethyl-3-benzo[b]furanacetamid.

14. Verfahren nach Anspruch 9, bei welchem eine der folgenden Verbindungen hergestellt wird:
N-[7-(Dimethylamino)-1-oxaspiro[4.5]dec-8-yl]-N-methyl-1H-indol-3-acetamid.
N-Methyl-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3-indolacetamid.

15. Verfahren nach Anspruch 10, bei welchem eine der folgenden Verbindungen hergestellt wird:
N-methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamid.

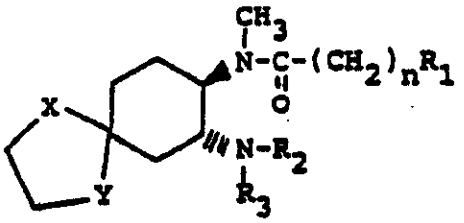
N-Methyl-2-(1-naphthalenyloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-acetamid.
N-Methyl-N-[7-[methyl-[2-(2-thienyl)-äthyl]-amino]-1-oxaspiro[4.5]dec-8-yl]-2-(1-naphthalenyloxy)-acetamid.

16. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches Verfahren die Vereinigung einer mittels eines in einem vorhergehenden Anspruch beanspruchten Verfahrens hergestellten Verbindung mit einem pharmazeutisch akzeptablen Träger- oder Verdünnungsmittel umfaßt.

17. Verfahren zur Herstellung einer Zusammensetzung oder einer Verbindung, wie in einem der vorhergehenden Ansprüche beansprucht, zur Verwendung bei der Herstellung eines Medikamentes zur Schmerzlinderungsbehandlung bei einem Warmblüter.

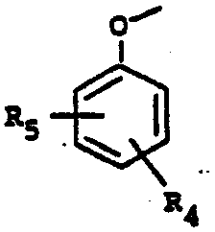
Revendications (pour les Etats contractants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. Un composé, caractérisé par la structure



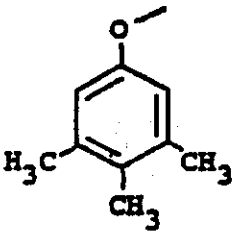
dans laquelle n est un entier de un à six, l'un des X ou Y est un atome d'oxygène et l'autre est le radical —CH_2—; R_1 est choisi parmi

a)

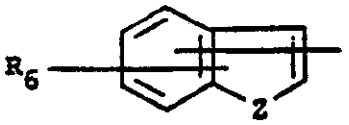


où R_4 et R_5 sont indépendamment un atome d'hydrogène, de fluor, de chlore, de brome, un radical nitro, trifluorométhyle, alkyle d'un à six atomes de carbone, alcoxy d'un à six atomes de carbone, ou aryle ;

b)

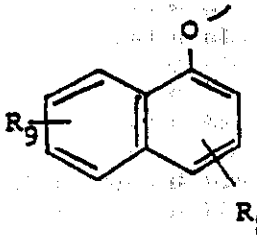


c)

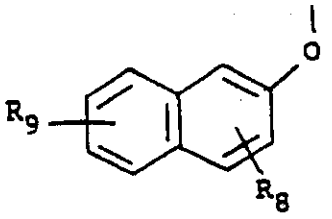


où R_6 est un atome d'hydrogène, de fluor, de chlore, un radical alkyle d'un à six atomes de carbone, aryle ; Z est —CH_2—, —O—, —S— ou —NR_7, où R_7 est un atome d'hydrogène, un groupe alkanoyle de deux à six atomes de carbone, ou aryle d'un à six atomes de carbone ;

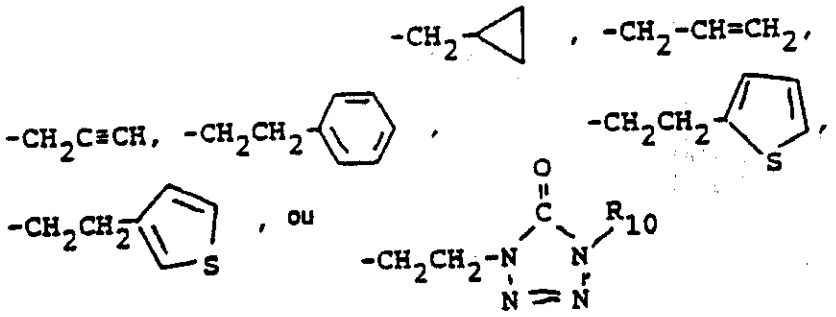
d)



dans laquelle R_8 et R_9 sont indépendamment un atome d'hydrogène, de fluor, de chlore, de brome, un radical alkyle d'un à six atomes de carbone, ou alcoxy d'un à quatre atomes de carbone ; ou

e) 

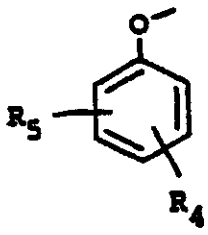
où R_8 et R_9 sont tels que définis plus haut :

R_2 est un groupe méthyle et R_3 est un atome d'hydrogène, un groupe alkyle d'un à six atomes de carbone, 

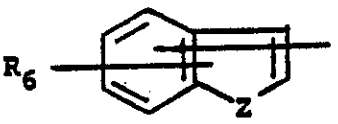
où R_{10} est un groupe alkyle d'un à quatre atomes de carbone ; ou bien R_2 et R_3 forment ensemble avec l'atome d'azote auquel ils sont attachés, un cycle pyrrolidinyle, pipéridinyle ou hexahydro-1H-azépinyle ; et ses sels d'addition acides acceptables du point de vue pharmaceutique.

2. Un composé suivant la revendication 1, caractérisé en ce que n est égal à un.

3. Un composé suivant les revendications 1 ou 2, caractérisé en ce que R_2 et R_3 forment ensemble un cycle pyrrolidinyle avec l'atome d'azote auquel ils sont fixés.

4. Un composé suivant les revendications 1, 2 ou 3 caractérisé en ce que R_1 est 

où R_4 et R_5 sont tels que définis plus haut.

5. Un composé suivant les revendications 1, 2 ou 3 caractérisé en ce que R_1 est 

où R_6 et Z sont tels que définis plus haut.

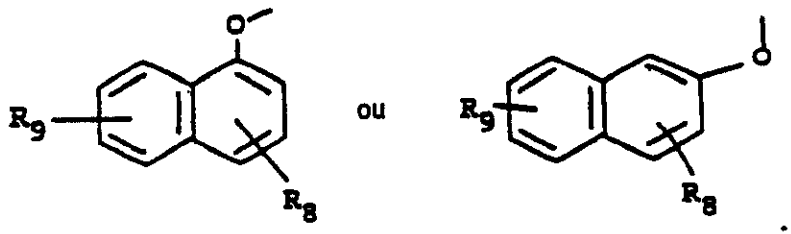
6. Un composé suivant la revendication 5, caractérisé en ce que Z est un radical —CH_2—.

7. Un composé suivant la revendication 5, caractérisé en ce que Z est un atome d'oxygène.

8. Un composé suivant la revendication 5, caractérisé en ce que Z est un atome de soufre.

9. Un composé suivant la revendication 5, caractérisé en ce que Z est un radical —NR_7—, où R_7 est tel que défini plus haut.

10. Un composé suivant les revendications 1, 2 ou 3 caractérisé en ce que R_1 est



où R_8 et R_9 sont tels que définis plus haut.

11. Un composé suivant la revendication 5, caractérisé en ce qu'il est choisi dans le groupe comprenant les composés suivants :

N-méthyl-N-[7-(méthyl-2-propynylamino)-1-oxaspiro[4.5]déc-8-yl]phénoxyacétamide.
N-méthyl-2-(4-fluorophénoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]déc-8-yl]acétamide.
N-méthyl-2-(4-fluorophénoxy)-N-[7-(méthyl-(2-phényléthyl)-amino]-1-oxaspiro[4.5]déc-8-yl]acétamide.
N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-2-(3-nitrophénoxy)acétamide.
N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-2-(3-trifluorométhylphénoxy)acétamide.
2-(3,4-dichlorophénoxy)-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.
2-(2,6-dichlorophénoxy)-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.
2-(3,5-dichlorophénoxy)-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.

12. Un composé suivant la revendication 9, caractérisé en ce qu'il est choisi dans le groupe comprenant les composés suivants :

N-méthyl-N-[7-(méthyl-2-propénylamino)-1-oxaspiro[4.5]déc-8-yl]-1H-indène-3-acétamide.
N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-3-indèneacétamide.

13. Un composé suivant la revendication 7, caractérisé en ce qu'il est choisi dans le groupe comprenant les composés suivants :

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-2-benzo[b]furanacétamide.
N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-3-benzo[b]furanacétamide.
N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-4-benzo[b]furanacétamide.
N-[7-[(cyclopropylméthyl)méthylamino]-1-oxaspiro-[4.5]déc-8-yl]-N-méthyl-3-benzo[b]furanacétamide.

14. Un composé suivant la revendication 9, caractérisé en ce qu'il est choisi dans le groupe comprenant les composés suivants :

N-[7-(diméthylamino)-1-oxaspiro-[4.5]déc-8-yl]-N-méthyl-1H-indole-3-acétamide.
N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-3-indoleacétamide.

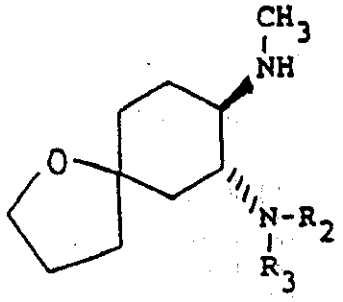
15. Un composé suivant la revendication 10, caractérisé en ce qu'il est choisi dans le groupe comprenant les composés suivants :

N-méthyl-2-(1-naphtalényloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.
N-méthyl-2-(1-naphtalényloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.
N-méthyl-N-[7-[méthyl[2-(2-thiényl)éthyl]amino]-1-oxaspiro[4.5]déc-8-yl]-2-(1-naphtalényloxy) acétamide.

16. Une composition pharmaceutique, caractérisée en ce qu'elle comprend un composé suivant l'une quelconque des revendications précédentes avec un support ou un diluant acceptable du point de vue pharmaceutique.

17. Un composé suivant l'une quelconque des revendications 1 à 15 ou une composition pharmaceutique suivant la revendication 16, utile dans la fabrication d'un médicament pour le traitement permettant de soulager la douleur chez un animal à sang chaud.

18. Un procédé de préparation d'un composé de formule structurale 1 suivant la revendication 1, et de ses sels d'addition acides acceptable du point de vue pharmaceutique, caractérisé en ce qu'il comprend d'abord la réaction d'une oxaspirodiamine de formule structurale

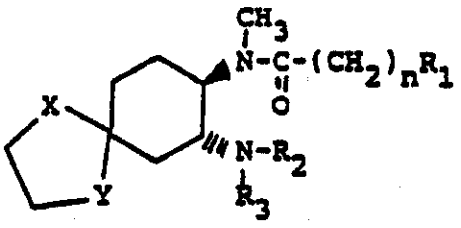


dans laquelle R_2 et R_3 sont tels que définis plus haut, avec un acide carboxylique ayant la structure $R_1(CH_2)_nCOOH$, dans laquelle n et R_1 sont tels que définis plus haut, en présence d'un réactif de

couplage choisi parmi le dicyclohexylcarbodiimide ou le carbonyldiimidazole ou bien avec le chlorure d'acide ou l'acyl imidazole correspondant ; et ensuite la conversion du produit de la réaction, si cela est désiré, en un sel d'addition acide acceptable du point de vue pharmaceutique.

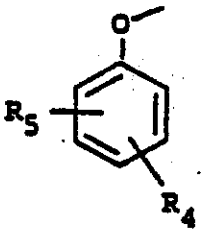
Revendications (pour l'état contractant AT)

1. Un procédé pour préparer un composé ayant la formule structurale



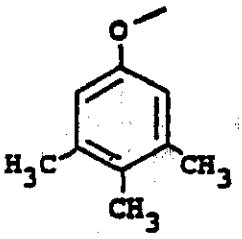
dans laquelle n est un entier de un à six, l'un des X ou Y est un atome d'oxygène et l'autre est le radical —CH_2— ; R_1 est choisi parmi

a)

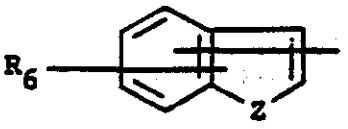


où R_4 et R_5 sont indépendamment un atome d'hydrogène, de fluor, de chlore, de brome, un radical nitro, trifluorométhyle, alkyle d'un à six atomes de carbone, alcoxy d'un à six atomes de carbone, ou aryle ;

b)

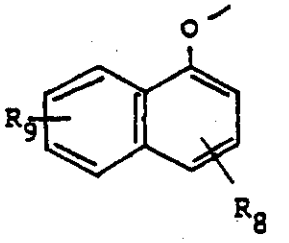


c)

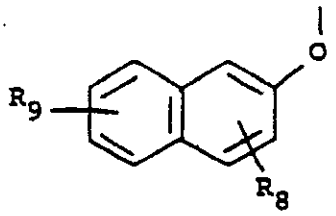


où R_6 est un atome d'hydrogène, de fluor, de chlore, un radical alkyle d'un à six atomes de carbone, aryle ; Z est —CH_2—, —O—, —S— ou —NR_7, où R_7 est un atome d'hydrogène, un groupe alkanoyle de deux à six atomes de carbone, ou aryle d'un à six atomes de carbone ;

d)

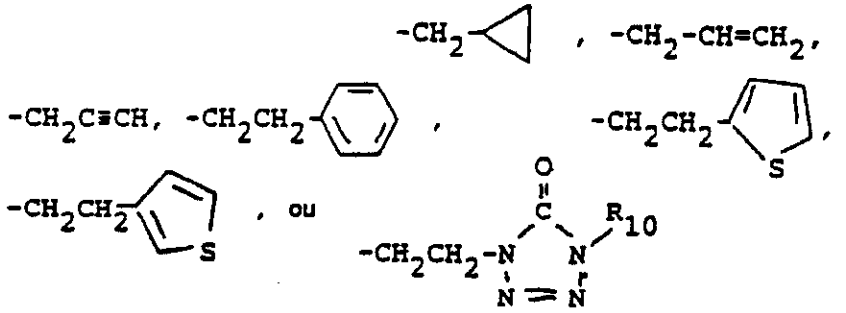


dans laquelle R_8 et R_9 sont indépendamment un atome d'hydrogène, de fluor, de chlore, de brome, un radical alkyle d'un à six atomes de carbone, ou alcoxy d'un à quatre atomes de carbone ;

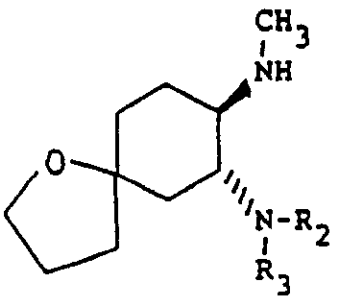


où R_8 et R_9 sont tels que définis plus haut ;

R_2 est un groupe méthyle et R_3 est un atome d'hydrogène, un groupe alkyle d'un à six atomes de carbone,



où R_{10} est un groupe alkyle d'un à quatre atomes de carbone ; ou bien R_2 et R_3 forment ensemble avec l'atome d'azote auquel ils sont attachés, un cycle pyrrolidinyle, pipéridinyle ou hexahydro-1H-azépinyle ; et ses sels d'addition acides acceptables du point de vue pharmaceutique ; caractérisé en ce que ce procédé comprend d'abord la réaction d'une oxaspirodiamine de formule structurale



dans laquelle R_2 et R_3 sont tels que définis plus haut, avec un acide carboxylique ayant la structure

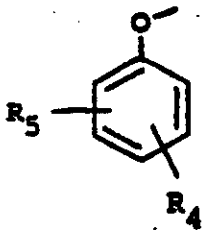
$$R_1(CH_2)_nCOOH\ ,$$

dans laquelle n et R_1 sont tels que définis plus haut, en présence d'un réactif de couplage choisi parmi le dicyclohexylcarbodiimide ou le carbonyldiimidazole ou bien avec le chlorure d'acide ou l'acyl imidazole correspondant ; et ensuite la conversion du produit de la réaction, si cela est désiré, en un sel d'addition acide acceptable du point de vue pharmaceutique.

2. Un procédé suivant la revendication 1, caractérisé en ce que n est égal à un.

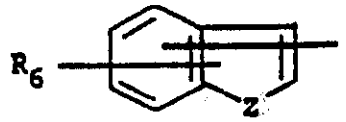
3. Un procédé suivant les revendications 1 ou 2, caractérisé en ce que R_2 et R_3 forment ensemble un cycle pyrrolidinyle avec l'atome d'azote auquel ils sont fixés.

4. Un procédé suivant les revendications 1, 2 ou 3 caractérisé en ce que R_1 est



où R_4 et R_5 sont tels que définis plus haut.

5. Un procédé suivant les revendications 1, 2 ou 3 caractérisé en ce que R_1 est



où R_6 et Z sont tels que définis plus haut.

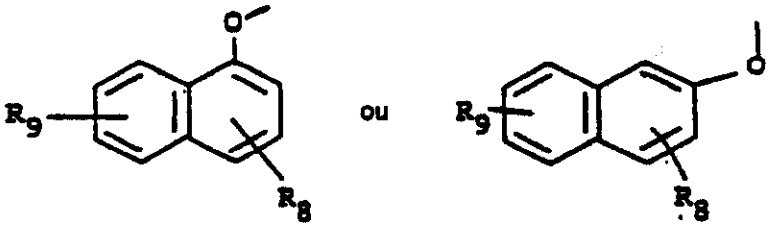
6. Un procédé suivant la revendication 5, caractérisé en ce que Z est un radical —CH_2—.

7. Un procédé suivant la revendication 5, caractérisé en ce que Z est un atome d'oxygène.

8. Un procédé suivant la revendication 5, caractérisé en ce que Z est un atome de soufre.

9. Un procédé suivant la revendication 5, caractérisé en ce que Z est un radical —NR_7—, où R_7 est tel que défini plus haut.

10. Un procédé suivant les revendications 1, 2 ou 3 caractérisé en ce que R_1 est



où R_8 et R_9 sont tels que définis plus haut.

11. Un procédé suivant la revendication 4, caractérisé en ce que l'un des composés suivants est préparé :

N-méthyl-N-[7-(méthyl-2-propynylamino)-1-oxaspiro[4.5]déc-8-yl]phénoxyacétamide.

N-méthyl-2-(4-fluorophénoxy)-N-[7-(1-pyrrolidinyl)amino]-1-oxaspiro[4.5]déc-8-yl]acétamide.

N-méthyl-2-(4-fluorophénoxy)-N-[7-(méthyl-(2-phényléthyl)-amino]-1-oxaspiro[4.5]déc-8-yl]acétamide.

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-2-(3-nitrophénoxy)acétamide.

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-2-(3-trifluorométhylphénoxy)acétamide.

2-(3,4-dichlorophénoxy)-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.

2-(2,6-dichlorophénoxy)-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.

2-(3,5-dichlorophénoxy)-N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.

12. Un procédé suivant la revendication 9, caractérisé en ce que l'un des composés suivants est préparé :

N-méthyl-N-[7-(méthyl-2-propényl-amino)-1-oxaspiro[4.5]déc-8-yl]-1H-indène-3-acétamide.

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]-3-indèneacétamide.

13. Un procédé suivant la revendication 7, caractérisé en ce que l'un des composés suivants est préparé :

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-2-benzo[b]furanacétamide.

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-3-benzo[b]furanacétamide.

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-4-benzo[b]furanacétamide.

N-[7-[(cyclopropylméthyl)méthylamino]-1-oxaspiro-[4.5]déc-8-yl]-N-méthyl-3-benzo[b]furanacétamide.

14. Un procédé suivant la revendication 9, caractérisé en ce que l'un des composés suivants est préparé :

N-[7-(diméthylamino)-1-oxaspiro-[4.5]déc-8-yl]-N-méthyl-1H-indole-3-acétamide.

N-méthyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]déc-8-yl]-3-indoleacétamide.

15. Un procédé suivant la revendication 10, caractérisé en ce que l'un des composés suivants est préparé :

N-méthyl-2-(1-naphtalényloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.

N-méthyl-2-(1-naphtalényloxy)-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]déc-8-yl]acétamide.

N-méthyl-N-[7-[méthyl[2-(2-thiényl)éthyl]amino]-1-oxaspiro[4.5]déc-8-yl]-2-(1-naphtalényloxy) acétamide.

16. Un procédé pour préparer une composition pharmaceutique, caractérisé en ce qu'il comprend la combinaison d'un composé préparé suivant l'une quelconque des revendications précédentes avec un support ou un diluant acceptable du point de vue pharmaceutique.

17. Un procédé pour préparer une composition ou un composé suivant l'une quelconque précédentes, utile dans la fabrication d'un médicament pour le traitement permettant de soulager la douleur chez un animal à sang chaud.

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Title
7-[(SUBSTITUTED)AMINO]-8-[(SUBSTITUTED)CARBONYL)-METHYLAMINO]-1-OXASPIRO[4.5]DECANES AS ANALGESIC AGENTS

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C07D A61K

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05.11.1987 EPO: Search report published on 04.11.1987
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