

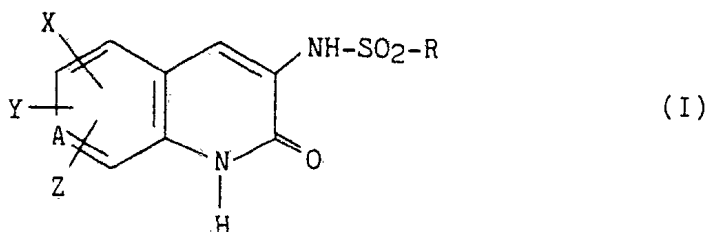


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NEW 3-SULFONYLAMINO-2(1H)-QUINOLONE COMPOUNDS, PROCESS FOR PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
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- (57) Claim

1. A compound of formula (I):



in which

X,Y,Z:

- which may be identical or different, represent a hydrogen atom, a halogen atom or a nitro, cyano, azido, trihalomethyl, linear or branched (C₁-C₆) alkyl, linear or branched (C₁-C₆) alkoxy or amino (unsubstituted or substituted with a linear or branched (C₁-C₆) acyl group) group,
- or alternatively, when they are located on two adjacent carbon atoms, form, with the carbon atoms to which they are attached, a phenyl ring or a 5- or 6-membered heterocycle containing from 1 to 3 hetero atoms, preferably a 1,2,5-oxadiazole ring,

R represents a linear or branched (C₁-C₆) alkyl, trihalomethyl, phenyl (unsubstituted or substituted with one or more halogen atoms or linear or branched (C₁-C₆) alkyl, trihalomethyl or linear or branched (C₁-C₆) alkoxy groups), 2-thienyl (unsubstituted or substituted with a halogen atom), naphthyl or styryl group,

A represents a CH radical or a nitrogen atom, its enantiomers, diastereoisomers and epimers, as well as its addition salts with a pharmaceutically acceptable base.

9. The pharmaceutical composition as claimed in claim 8, containing at least one active principle as claimed in one of claims 1 to 6, which is useful as an inhibitor of the pathological phenomena associated with hyperactivation of the excitatory amino acid-dependent pathways of neurotransmission.

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65 1 25 5

**ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT**

Application Number:

Lodged:

Invention Title:

NEW 3-SULFONYLAMINO-2(1H)-QUINOLONE COMPOUNDS,
PROCESS FOR PREPARING THEM AND PHARMACEUTICAL
COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the
best method of performing it known to :-US

The present invention relates to new 3-sulfonylamino-2(1H)-quinolone compounds, to a process for preparing them and to pharmaceutical compositions containing them.

A few 2(1H)-quinolone compounds have been described in the literature. This applies, for example, to the compounds described by C. ALABASTER et al. (J. Med. Chem., 31, 2048-2056, 1988) which are cardiac stimulators, or to those described by F. BAHR et al. (Pharmazie, 36, H.10, 1981).

The compounds described in the present invention, apart from the fact that they are new, display especially advantageous pharmacological properties: they are potent inhibitors of the phenomena linked to the hyperactivation of excitatory amino acids.

L-Glutamic acid and L-aspartic acid have the capacity to activate the neurons of the central nervous system, and many studies have demonstrated that these excitatory amino acids (EAA) satisfy the criteria that define a neurotransmitter. For this reason, the modulation of neuronal events associated with these EAA appears to be an advantageous target for the treatment of neurological diseases.

In effect, it has been demonstrated that excessive release of EAA and hyperstimulation of their receptors is probably one of the causes of the neuronal degeneration observed in epilepsy, senile dementia or strokes. However, at the present time, there is an ever-increasing number of neurodegenerative diseases in which EAA are closely implicated (Huntington's chorea, schizophrenia, amyotrophic lateral sclerosis) (McGEER E.G. et al., Nature 263, 517-519, 1976; SIMON R. et al., Science 226, 850-852, 1984).

Furthermore, while it is certain that hyperactivation of EAA-dependent neurotransmission exerts neurotoxic effects, the normal activation of this neurotransmission facilitates mnemonic and cognitive performance (LYNCH G. & BAUDRY M., Science, 224, 1057-1063, 1984; ROTHMAN S.M. & OLNEY J.W., Trends in Neuro Sci., 10, 299-302, 1987). From a pharmacological and therapeutic standpoint, it is hence appropriate to counteract only

pathological stimulations while not impairing the physiological level of activation.

5 The EAA receptors localized post- and presynaptically have been classified in 4 groups in accordance with the affinity and the electrophysiological and/or neurochemical effects of specific ligands:

10 NMDA (N-methyl-D-aspartate) receptor associated with an ion channel permeable to mono- and divalent cations including calcium but which is blocked by magnesium. Accumulation of calcium in the cell is considered to be one of the causes of neuronal death. Opening of the NMDA channel is regulated by several sites associated with the receptor and, in particular, is promoted by glycine, the effect of which is strychnine-insensitive. This glycine site constitutes one of the important targets for modulating the activation of the NMDA receptor.

15 AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor associated with an ion channel permeable to monovalent cations including sodium. Activation of this channel is considered to bring about a membrane predepolarization.

20 kainate receptor, the ionic characteristics of which are akin to those of the AMPA receptor but which differs therefrom by the level of conductance and desensitization. However, a large number of studies are tending to demonstrate that the AMPA receptor and the kainate receptor have close structural and functional analogies and constitute a single receptor family (KEINANEN K. et al., Science, 249, 556- 560, 1990).

25 ACPD (aminocyclopentanedicarboxylic acid) receptor, referred to as a metabotropic receptor since it is not coupled to an ion channel.

30

Activation of the ionotropic receptors by EAA opens the ion channels and, in particular, permits the entry of sodium, which depolarizes the cell. This first phase, which involves the AMPA receptor, then leads to hyperactivation of the NMDA receptor and to the massive accumulation of calcium (BLAKE J.F. et al., Neurosci. Letters, 89, 182-186, 1988; BASHIR Z.I. et al., Nature 349, 156-158, 1991).

The compounds of the present invention are hence directed, in a novel manner, towards counteracting the excitatory and toxic effects of EAA by a dual mechanism:

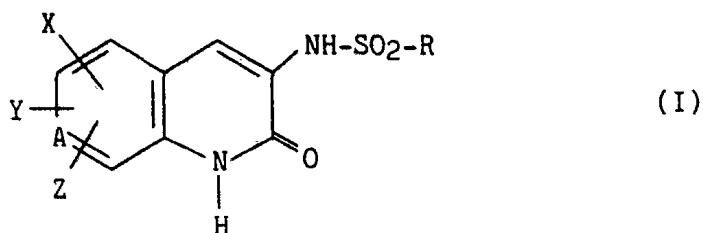
- by blocking the initial activation of the AMPA/kainate receptor,
- by modulating the hyperactivation of the NMDA receptor by blocking the glycine site.

This dual mechanism is seen to be potentially different from those described hitherto for agents that counteract the effects of EAA, since these agents have only a single mechanism of action, specific for the AMPA receptor or for the NMDA receptor or for the glycine site.

The compounds of the present invention are hence useful as inhibitors of the pathological, in particular neurotoxic, phenomena associated with hyperactivation of the excitatory amino acid-dependent pathways of neurotransmission.

They are hence potential therapeutic agents for the treatment of neurological and mental diseases involving these amino acids: acute or chronic degenerative diseases, such as stroke, spinal trauma, amyotrophic lateral sclerosis, Alzheimer's disease or schizophrenia.

More specifically, the present invention relates to the compounds of formula (I):



in which

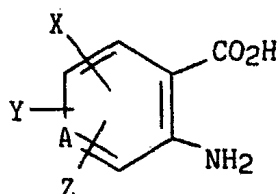
X, Y, Z:

- which may be identical or different, represent a hydrogen atom, a halogen atom or a nitro, cyano, azido, trihalomethyl, linear or branched (C₁-C₆) alkyl, linear or branched (C₁-C₆) alkoxy or amino (unsubstituted or substituted with a linear or branched (C₁-C₆) acyl group) group,
- or alternatively, when they are located on two adjacent carbon atoms, form, with the carbon atoms to which they are attached, a phenyl ring or a 5- or 6-membered heterocycle containing from 1 to 3 hetero atoms, preferably a 1,2,5-oxadiazole ring,

R represents a linear or branched (C₁-C₆) alkyl, trihalomethyl, phenyl (unsubstituted or substituted with one or more halogen atoms or linear or branched (C₁-C₆) alkyl, trihalomethyl or linear or branched (C₁-C₆) alkoxy groups), 2-thienyl (unsubstituted or substituted with a halogen atom), naphthyl or styryl group,

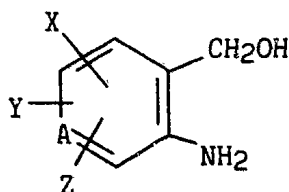
A represents a CH radical or a nitrogen atom, their enantiomers, diastereoisomers and epimers, as well as their addition salts with a pharmaceutically acceptable base.

The invention also encompasses the process for preparing the compounds of formula (I), wherein a compound of formula (II):



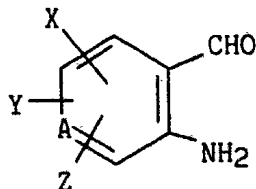
(II)

in which X, Y, Z and A have the same meaning as in formula (I),
is used as the starting material,
which starting compound is reduced, depending on the nature of
the substituents X, Y and Z,
either in an aprotic medium in the presence of lithium aluminum
hydride, aluminum hydride, diborane or borane complexes,
or in an acidic protic medium when sodium cyanoborohydride is
used,
to yield an alcohol of formula (III):



(III)

in which X, Y, Z and A have the same meaning as in the formula
(I),
which is oxidized using a metal oxide in an inert solvent, an
alkali metal halate in a protic solvent or an acid chloride in
dimethyl sulfoxide,
to yield the aldehyde of formula (IV):



(IV)

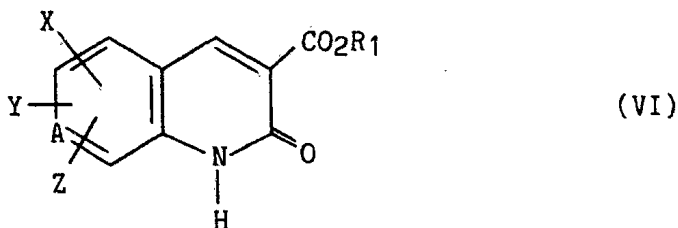
in which X, Y, Z and A have the same meaning as in the formula
(I),
which is then condensed:

1/ either:

with an alkyl malonate of formula (V), in a protic medium, in the presence of an alkali metal alcoholate, a tertiary amine or an alkali metal hydroxide:



in which R_1 represents a linear or branched (C_1 - C_6) alkyl group unsubstituted or substituted with one or more phenyl groups, to yield a 2(1H)-quinolone of formula (VI):

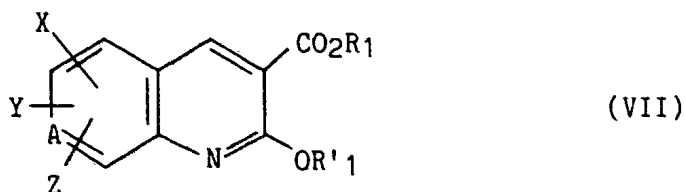


in which X, Y, Z, A and R_1 have the same meaning as above, which is protected:

- by reaction with a trialkyloxonium tetrafluoroborate in ether or dichloromethane,
- or by reaction, in an inert solvent or without a solvent, of a phosphorus oxyhalide, a phosphorus pentahalide, a thionyl halide, phosgene, thiophosgene, phosgene iminium or phosgene trimer, followed by reaction of the 2-haloquinoline thereby formed with an alkali metal alkoxide of formula $\text{R}'_1\text{OM}$ (in which R'_1 has the same meaning as R_1 and M represents an alkali metal) in an alcoholic medium,
- or by reaction with sodium hydride, butyllithium or an alkali metal alcoholate in the presence of an alkylating agent of formula $\text{R}'_1\text{V}$ (in which R'_1

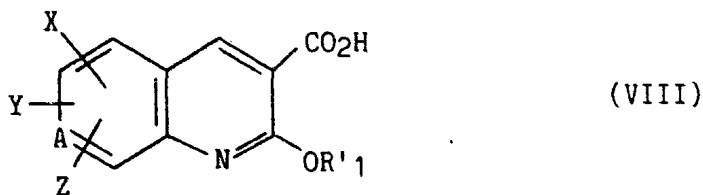
has the same meaning as above and V is a leaving group),

to yield the 2-alkoxyquinoline of formula (VII):



in which X, Y, Z, A, R₁ and R'₁ have the same meaning as above,

which is hydrolyzed in the presence of an alkali metal hydroxide in an aqueous or aqueous- alcoholic medium, to yield the acid of formula (VIII):



in which X, Y, Z, A and R'₁ have the same meaning as above,

which is:

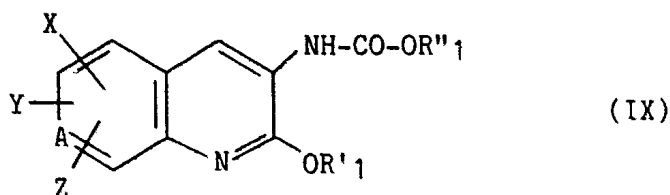
a converted to the corresponding acid azide:

- by activation of the acid function in the form of an acid anhydride or halide, followed by reaction with sodium azide in an inert solvent,
- or by reaction in an inert solvent with diphenoxyphosphoryl azide in the presence of a tertiary amine,

b rearranged by heating in an inert solvent in an anhydrous medium, adding an excess of an alcohol

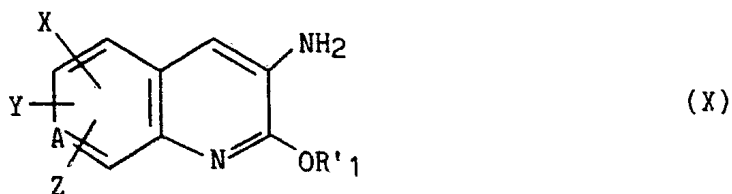
of formula R''_1OH (in which R''_1 has the same meaning as R_1) when gaseous evolution has ceased, or by direct heating in the alcohol R''_1OH ,

to yield the corresponding carbamate of formula (IX):



in which X, Y, Z, A, R'_1 and R''_1 have the same meaning as above,

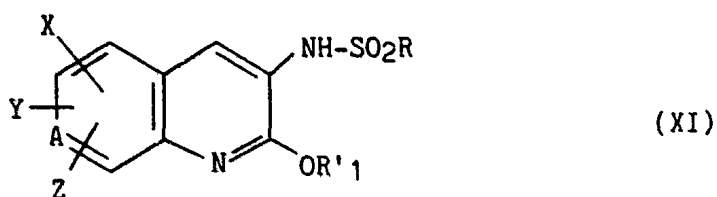
which is either hydrolyzed in an anhydrous acid medium, or hydrogenated in an anhydrous medium with hydrogen in the presence of a catalyst, to yield the amine of formula (X):



in which X, Y, Z, A and R'_1 have the same meaning as above,

which undergoes a sulfonylation by reaction with a sulfonyl halide or anhydride of respective formula RSO_2W or $(RSO_2)_2O$ (in which R has the same meaning as in the formula (I) and W represents a halogen atom), in the presence of a tertiary amine, in an aprotic medium,

to yield the sulfonamide of the formula (XI):

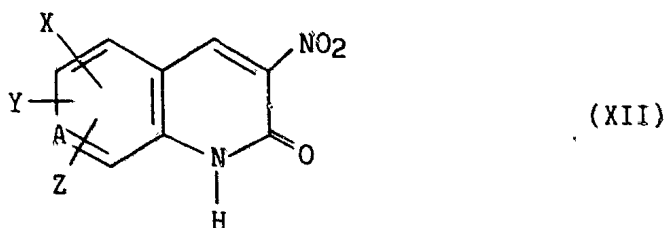


in which X, Y, Z, A, R and R'₁ have the same meaning as above,
which is deprotected, depending on the nature of the group R'₁, by heating in an acidic aqueous medium or by catalytic hydrogenation,
to yield the compound of formula (I),

2/ or:

with an alkyl nitroacetate in a protic medium, in the presence of an alkali metal alcoholate, a tertiary amine or an alkali metal hydroxide, or in an inert medium having a high boiling point, in the presence of a tertiary or secondary amine under reflux of the solvent,

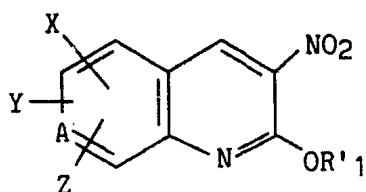
to yield the 3-nitro-2(1H)-quinolone of formula (XII):



in which X, Y, Z and A have the same meaning as in the formula (I),

which is protected according to the same techniques as those described for protection of the quinolone of formula (VI) as the 2-alkoxyquinoline of formula (VII),

to yield the 2-alkoxyquinoline of formula (XIII):



(XIII)

in which X, Y, Z, A and R'₁ have the same meaning as in the formula (I),

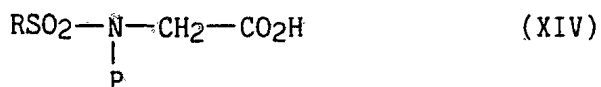
the nitro group of which is reduced in the presence of tin chloride in an alcohol or sodium hydrosulfite in water, or by catalytic hydrogenation,

to yield the amine of formula (X) defined above,

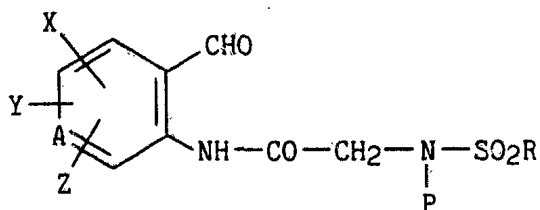
which undergoes the sulfonylation and then the deprotection which are described above, enabling a compound of formula (I) to be obtained,

3/ or:

with a protected glycine compound of formula (XIV), activated in the form of the corresponding anhydride, azide, cyanide or halide, in an inert medium, in the presence of triethylamine:



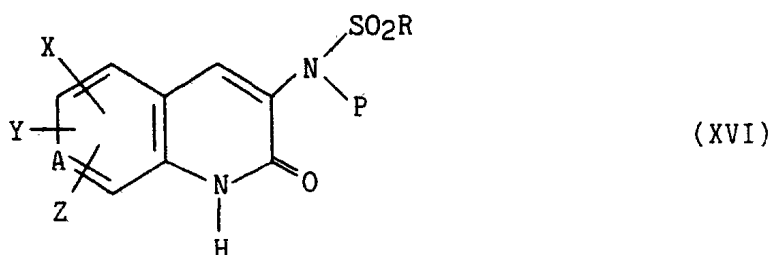
in which R has the same meaning as in the formula (I) and P represents a conventional protective group for the amine function of an amino acid, to yield the aldehyde of formula (XV):



(XV)

in which X, Y, Z, A, P and R have the same meaning as above,

which is cyclized in an alcoholic medium, in the presence of an alkali metal alcoholate, a tertiary amine or an alkali metal hydroxide, to yield quinolone of formula (XVI):



in which X, Y, Z, A, R and P have the same meaning as above,

which is deprotected in the presence of aluminium chloride in an inert solvent or by catalytic hydrogenation, to yield a compound of formula (I),

which compound of formula (I),

- when X and/or Y and/or Z represent a hydrogen atom, can undergo electrophilic substitutions according to standard techniques for substitution of aromatic ring-systems, yielding a compound of formula (I) mono-, di- or trisubstituted on the phenyl ring of the quinolone,
- when X, Y or Z represent a nitro group, can be converted to the corresponding amino or acylamino derivative, which amino derivative can itself be converted to the corresponding azido derivative according to standard techniques of organic chemistry,
- when X represents a nitro group and Y, located on an adjacent carbon, represents an azido group, can undergo a cyclization to yield the corresponding 1,2,5-oxadiazolo compound,

- can be, where appropriate, purified according to a standard purification technique,
- is separated, where appropriate, into its isomers according to a standard separation technique,
- is converted, if so desired, to its addition salts with a pharmaceutically acceptable base.

Among pharmaceutically acceptable bases, sodium hydroxide, potassium hydroxide, tert-butylamine, diethylamine, ethylenediamine, etc., may be mentioned without implied limitation.

The compounds of formula (I) possess very advantageous pharmacological properties.

It was possible to study the dual mechanism of action of the compounds of the present invention by means of membrane binding techniques and electrophysiological techniques.

1/ Membrane binding

This is carried out using a rat cortex homogenate. The membrane pellet is prepared in a conventional manner in a sucrose buffer by differential centrifugations, and then frozen until used. After thawing, 200 μ l of membrane homogenate are taken up in a Tris-HCl (30 mM), CaCl_2 (2.5 mM) buffer, pH 7.4, and incubated at 4°C for 30 minutes in the presence of 25 μ l of [^3H]-AMPA or [^3H]kainate and 25 μ l of the test product. Non-specific binding is determined in the presence of 10 μM quisqualate (AMPA binding) or 10 μM kainic acid (kainate binding). The membranes are then isolated by filtration. After drying of the filters, the radioactivity is measured by scintillation.

2/ Currents induced by EAA in *Xenopus* oocytes

Xenopus oocytes are injected with 50 ng of poly(A)⁺ mRNA isolated from rat cerebral cortex, and incubated for 2 to 3 days at 18°C to permit protein expression therein. The inward currents induced by EAA are measured in a medium of composition NaCl (82.5 mM), KCl (2.5 mM), CaCl_2 (1 mM), MgCl_2

(1 mM), NaH_2PO_4 (1 mM), HEPES (5 mM), pH 7.4, by the 2-electrode voltage-clamp method (potential = -60 mV). For measurement of the currents induced by NMDA and glycine, MgCl_2 is absent from the medium and CaCl_2 is brought to a concentration of 2 mM. The EAA agonists that induce the currents are used at the following concentrations: kainate: 100 μM ; AMPA: 30 μM ; glycine/NMDA: 3/30 μM . The test product is applied 30 seconds before and during the application of the agonist.

3/ Hippocampal excitatory postsynaptic potentials (EPSP) induced by stimulation of the glutamergic excitatory afferent pathways (Schäffer's collaterals)

Transverse sections (500 μm) of rat hippocampus are placed in a medium of composition NaCl (120 mM), KCl (5 mM), CaCl_2 (1 mM), MgSO_4 (1 mM), KH_2PO_4 (1.3 mM), NaHCO_3 (20 mM), HEPES (10 mM), glucose (10 mM), pH 7.35. The EPSP are recorded in the dendritic area of the CA1 region during stimulations of the stratum radiatum every 30 seconds (50-100 μA , 20 μs). The EPSP are evaluated at the peak of the negative wave. The test product is applied for 10 minutes.

The compounds of the present invention were studied in comparison with the most recent compounds described for their interaction with the AMPA receptor: they are 2,3-quinoxalinedione compounds, and more especially 6-cyano-7-nitro-2,3-quinoxalinedione (CNQX) and 6-nitro-7-sulfamoylbenzo[f]quinoxaline-2,3-dione (NBQX).

The binding studies showed that the compounds of the invention bind to the AMPA receptor with a very advantageous intensity, since the K_i is less than 10^{-6}M .

CNQX K_i = 0.07 μM

Example 2 K_i = 0.6 μM

They are likewise capable of inhibiting the functional activation of the currents by AMPA and kainate in *Xenopus* oocytes.

AMPA current	CNQX	Ki = 0.40 μ M
	NBQX	Ki = 0.06 μ M
	Example 2	Ki = 0.37 μ M

Kainate current	CNQX	IC ₅₀ = 0.27 μ M
	NBQX	IC ₅₀ = 0.06 μ M
	Example 2	IC ₅₀ = 0.50 μ M

The same applies to the inhibition of the hippocampal EPSP which are induced by activation of the AMPA/kainate receptors (and are hence measured in the presence of Mg⁺⁺, which blocks the NMDA receptors).

CNQX	IC ₅₀ = 2.9 μ M
NBQX	IC ₅₀ = 1 μ M
Example 2	IC ₅₀ = 10 μ M

Although the activity of the compounds of the invention with respect to the AMPA/kainate receptors is 6- to 10-fold lower than those of the quinoxalinediones, their novelty, and hence their therapeutic importance, lies in the fact that they can exert a joint inhibition of the electrophysiological phenomena induced by activation of the NMDA/glycine receptors (which is hence measured in the absence of magnesium).

Xenopus oocyte	CNQX	Ki = 2.1 μ M
	NBQX	Ki > 1000 μ M
	Example 2	Ki = 0.62 μ M

Hippocampal EPSP	CNQX	IC ₅₀ = 100 μ M
	NBQX	IC ₅₀ > 100 μ M
	Example 2	IC ₅₀ = 40 μ M

This dual mechanism of action may be assessed by calculating the ratios between the inhibitory activities with respect to the AMPA receptor and with respect to the NMDA/glycine receptor.

	Xenopus oocyte	Hippocampal EPSP
	Ki AMPA/Ki NMDA/Gly	IC50 AMPA-Kainate/IC50 NMDA- glycine
CNQX	0.19	0.03
NBQX	<< 0.001	<< 0.001
Example 2	0.60	0.25

Thus, the dual mechanism of the compounds of the invention is 3 to 8 times as pronounced as in the case of the quinoxalinedione CNQX, which confers a much greater therapeutic potential with respect to neurotoxic phenomena associated with EAA.

The subject of the present invention is also pharmaceutical compositions containing as active principle at least one compound of formula (I), alone or in combination with one or more inert, non-toxic excipients or vehicles.

Among the pharmaceutical compositions of the invention, there may be mentioned, more especially, those which are suitable for oral, parenteral or nasal administration, simple or sugar-coated tablets, sublingual tablets, hard gelatin capsules, troches, suppositories, creams, ointments, skin gels, and the like.

The appropriate dosage varies according to the patient's age and weight, the nature and severity of the pathology and also the administration route. The latter can be oral, nasal, rectal or parenteral. Generally speaking, the single doses range between 1 and 1000 mg for a treatment administered in 1 to 3 doses per 24 hours.

The examples which follow illustrate the invention and in no way limit it.

The starting materials used are known products or products prepared according to known procedures.

EXAMPLE 1 :

3-(Trifluoromethylsulfonylamino)-2(1H)-quinolone

Stage A : 2-Methoxy-3-nitroquinoline

7.9 mmol of 3-nitro-2(1H)-quinolone (prepared from anthranilic acid according to the technique described by C.T.

ALABASTER et al., in J. Med. Chem., 31, 2048-2056, 1988), dissolved in 10 ml of phosphorus oxychloride, are brought to reflux for 2 hours. The excess phosphorus oxychloride is evaporated off under reduced pressure. The residual oil is dissolved in 50 ml of dichloromethane. This organic phase is washed with water to neutral pH, dried and evaporated under vacuum. After dissolution of the residue in 40 ml of methanol, 12 ml of a 1N solution of sodium methylate in methanol are added with stirring. The mixture is brought to reflux for 15 minutes. After cooling and evaporation of the methanol, the residue is taken up with 50 ml of dichloromethane and 50 ml of water. The organic phase is separated after settling has taken place, dried and evaporated under vacuum. The expected product is obtained after purification by chromatography on silica gel, using a hexane/ethyl acetate (9:1) mixture as elution solvent. Melting point : 105°C

Stage B : 2-Methoxy-3-aminoquinoline

7.8 mmol of the product obtained in the preceding stage are suspended in 50 ml of ethanol. 39 mmol of tin chloride dihydrate are added to this suspension and the mixture is brought to reflux for one hour. 400 ml of chloroform and 100 ml of water are added to the solution thereby obtained. The solution is alkalized by adding aqueous sodium bicarbonate solution. The suspension which forms is filtered, the organic phase is separated from the aqueous phase after settling has taken place and the latter phase is extracted again with chloroform. The combined organic phases are dried and evaporated. The expected product is obtained after purification of the residue by chromatography on silica gel, using a hexane/ethyl acetate (9:1) mixture as elution solvent. Melting point : 84°C.

Stage C : 2-Methoxy-3-(trifluoromethylsulfonyl-amino)quinoline

3.2 mmol of the product obtained in the preceding stage are dissolved in 50 ml of dichloromethane at 0°C. 3.3 mmol of triethylamine are then added to this solution, followed by 4 mmol of trifluoromethanesulfonic anhydride added dropwise. The mixture is stirred for 30 minutes at 0°C and then 30 minutes at room temperature. After washing with 10 ml of 1N hydrochloric acid, the organic phase is extracted with 1N aqueous potassium hydroxide solution and then with water. The combined organic phases are acidified with 1N hydrochloric acid and extracted with dichloromethane. The organic phase thereby obtained is then dried and evaporated. The expected product is obtained in the form of a white powder.

Melting point : 135°C

Stage D : 3-(Trifluoromethylsulfonylamino)-2(1H)-quinolone

3.4 mmol of the product obtained in the preceding stage dissolved in 20 ml of methanol and 10 ml of concentrated hydrochloric acid, are brought to reflux for 2 hours. The mixture is left overnight at room temperature. The expected product is obtained after filtering off and drying the white solid formed.

Melting point : 204°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	41.10	2.41	9.59	10.97
found	41.25	2.67	9.73	11.28

EXAMPLE 2 :

7-Nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

Stage A : 3-Nitro-6-hydroxymethylaniline

55 mmol of 5-nitroanthranilic acid are dissolved in 250 ml of anhydrous tetrahydrofuran. 110 mmol of borane/dimethyl sulfide complex are added dropwise to the above solution. The solution is then brought to reflux for 2 hours and cooled in ice, and 10 ml of water are added dropwise. When gaseous

evolution has ceased, 30 ml of concentrated hydrochloric acid are added to the above mixture and the solution is brought to reflux for 30 minutes. After cooling, it is poured onto 500 ml of ice. The aqueous phase is washed with 50 ml of dichloromethane, alkalinized with concentrated aqueous sodium hydroxide solution (30%) and extracted several times with dichloromethane. The organic phases are combined, dried and evaporated under vacuum, and yield the expected product.

Melting point : 130°C

Stage B : 3-Nitro-6-formylaniline

75 mmol of manganese dioxide are added in a single portion to a solution containing 37.6 mmol of the product obtained in the preceding stage in dichloromethane, and the suspension thereby obtained is stirred for 2 hours at room temperature. After filtration, the filtrate is evaporated and the expected product is obtained after purification of the residue by chromatography on silica gel, using a hexane/ethyl acetate (75:25) mixture as elution solvent.

Melting point : 123°C

Stage C : 7-Nitro-2(1H)-quinolone-3-carboxylic acid methyl ester

36 mmol of dimethyl malonate and 24 ml of a 1N solution of sodium methylate in methanol are added to a suspension containing 12 mmol of the product obtained in Stage B in 25 ml of methanol. The suspension is stirred for 2 days at room temperature. The green precipitate formed is then filtered off, washed with methanol and thereafter with ether and dried, and yields the expected product, which is used in Stage D without further treatment.

Stage D : 7-Nitro-2-methoxyquinoline-3-carboxylic acid methyl ester

The expected product is obtained according to the same procedure as described in Stage A of Example 1, but the product

obtained in Stage C, dissolved in 10 ml of phosphorus oxychloride, is brought to reflux for 6 hours.

Melting point : 174°C

Stage E : 2-Methoxy-7-nitroquinoline-3-carboxylic acid

5 75 mmol of the product obtained in the preceding stage are hydrolyzed in the presence of 20 ml of 1N potassium hydroxide solution and 80 ml of methanol for 1 hour 30 minutes under reflux. After evaporation of the methanol, the suspension is diluted with water. The aqueous phase, washed with
10 dichloromethane, is acidified with 1N hydrochloric acid, and the white solid which forms is extracted with dichloromethane. The organic phase, dried and evaporated, yields the expected product in the form of a white solid.

Melting point : 203°C

Stage F : 3-tert-Butoxycarbonylamino-7-nitro-2-methoxyquinoline

6 mmol of the product obtained in the preceding stage, 6.5 mmol of triethylamine and 6.5 mmol of di-
phenoxyphosphoryl azide are mixed in 100 ml of toluene. This
solution is heated to 75°C under a nitrogen atmosphere until
gaseous evolution has ceased. 100 ml of anhydrous tert-butanol
are added and the mixture is brought to reflux for one hour.
After cooling of the solution, the yellow solid is filtered off
and washed with dichloromethane. The solvents are then combined
and evaporated. The residue is taken up with 100 ml of water and
100 ml of dichloromethane. The organic phase is dried and
evaporated. The expected product is obtained after purification
of the residue by chromatography on silica gel, using a
hexane/ethyl acetate (9:1) mixture as elution solvent.

Melting point : 167°

Stage G : 3-Amino-2-methoxy-7-nitroquinoline

A suspension containing 1.5 mmol of the product obtained in the preceding stage in 25 ml of anhydrous ethyl

acetate is cooled to 0°C and saturated with dry hydrogen chloride gas. After 3 hours' stirring, the solvent is evaporated off under vacuum at room temperature in an anhydrous environment. 25 ml of 1N sodium hydroxide solution are then added and the aqueous phase is extracted with ethyl acetate. The organic phase is dried and evaporated. The expected product is obtained, after purification of the yellow solid thereby obtained by dissolution in dichloromethane, filtration and evaporation.

Melting point : 166°C

Stage H : 7-Nitro-3-(trifluoromethylsulfonylamino)-
2(1H)-quinolone

2 mmol of trifluoromethanesulfonic anhydride are added dropwise to a solution, at 0°C, containing 1.7 mmol of the compound obtained in the preceding stage and 2 mmol of triethylamine in 50 ml of dichloromethane. After return to room temperature, the solution is stirred overnight, washed with water, dried and evaporated. The residue is taken up with 2 ml of methanol and 2 ml of concentrated hydrochloric acid. This solution is brought to reflux for 2 hours, cooled and extracted with ethyl acetate. The organic phase is then dried and evaporated. The expected product is then obtained after purification of the residue on silica gel, using a dichloromethane/ ethanol/acetic acid (95:4.5:0.5) mixture as elution solvent. It is then crystallized in a toluene/ethyl acetate (9:1) mixture and dried.

Melting point : 240°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	35.62	1.79	12.46	9.50
found	35.76	2.00	12.39	9.56

EXAMPLE 2 a :

7-Nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

Stages A and B of this process are identical to those described in Example 2. On the other hand, Stages C to H of Example 2 can be replaced by the following Stages C to E and can yield the same compound.

5 Stage C : N-[2-(N-benzyl-N-trifluoromethyl-sulfonylamino)acetyl]-3-nitro-6-formylaniline

8.5 mmol of 2-(N-benzyl-N-trifluoromethyl-sulfonylamino)acetyl chloride are added dropwise to a solution, at 0°C, containing 16.5 mmol of the compound described in the preceding stage in 100 ml of acetone. The solution is kept stirring for 18 hours at room temperature, the solvent is evaporated off and the residue is taken up with 100 ml of ethyl acetate. The organic phase is washed with 1N hydrochloric acid, then with 1N sodium hydroxide solution and lastly with water, then dried and evaporated. The expected product is obtained after purification of the residue by chromatography on silica gel, using a hexane/ethyl acetate (8:2) mixture as elution solvent.

Melting point : 157°C

20 Stage D : 3-(N-Benzyl-N-trifluoromethylsulfonylamino)-7-nitro-2(1H)-quinolone

A solution containing 1.8 mmol of the compound obtained in the preceding stage in 20 ml of methanol and 2 ml of a 1N solution of sodium methylate in methanol is stirred for 2 hours at room temperature. This solution is poured onto 100 ml of ice and extracted several times with ethyl acetate. The combined organic phases are dried and evaporated. The expected product is obtained after purification of the residue by chromatography on silica gel, using a hexane/ethyl acetate (75:25) mixture as elution solvent.

Melting point : 224°C

Stage E : 7-Nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

6 mmol of aluminum chloride are added to a solution containing 1.2 mmol of the product obtained in the preceding stage in 20 ml of dichloromethane at room temperature. The mixture is stirred for 2 hours and then poured onto 50 ml of ice with the addition of 20 ml of 1N hydrochloric acid. After extraction of the aqueous phase with ethyl acetate, the organic phase is dried and evaporated. The expected product is obtained after purification by chromatography on silica gel, using a dichloromethane/ethanol/acetic acid (95:4.5:0.5) mixture as elution solvent. It is crystallized in a toluene/ethyl acetate (9:1) mixture and dried under vacuum at 75°C.

Melting point : 240°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	35.62	1.79	12.46	9.50
found	35.21	1.95	12.24	9.55

Examples 3 to 5 and 8 to 10 were obtained by carrying out one of the processes described in Examples 1, 2 or 2a, using the corresponding starting materials:

EXAMPLE 3 : 3-Methylsulfonylamino-2(1H)-quinolone

This compound was obtained according to the process described in Example 1.

Melting point : 252°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	50.41	4.23	11.76	13.46
found	50.38	4.35	11.60	13.34

EXAMPLE 4 : 3-(Benzenesulfonylamino)-2(1H)-quinolone

This compound was obtained according to the process described in Example 1.

Melting point : 235°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	59.99	4.03	9.33	10.68
found	59.78	4.08	9.30	10.19

5 EXAMPLE 5 : 3-(2-Thienylsulfonylamino)-2(1H)-quinolone

This compound was obtained according to the process described in Example 1.

Melting point : 240°C

Elemental microanalysis:

10

	C %	H %	N %	S %
calculated	50.97	3.29	9.14	20.93
found	51.06	3.25	9.03	20.55

15 EXAMPLE 6 :

8-Nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

and

EXAMPLE 7 :

6-Nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

20 These two compounds were obtained by electrophilic nitration of the compound described in Example 1.

25 A solution containing 2 ml of concentrated nitric acid and 1 ml of concentrated sulfuric acid is prepared at 0°C. 330 µl of this solution are added dropwise at 0°C to a solution containing 3.4 mmol of the compound described in Example 1 in 2 ml of concentrated sulfuric acid. The mixture is then stirred for 10 minutes at 0°C and thereafter for 1 hour 30 minutes at room temperature. After cooling of the reaction medium to 0°C, 8 ml of water are added dropwise and with stirring. The yellow precipitate formed is filtered off, rinsed with water and dried. The two isomers are separated by chromatography on silica gel, using a dichloromethane/ethanol/acetic acid (90:9:1) mixture as elution solvent.

30

EXAMPLE 6 :

The 8-nitro isomer is eluted first, and is recrystallized in an ethyl acetate/hexane mixture.

Melting point : 205°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	35.62	1.79	12.46	9.51
found	35.82	2.10	12.44	9.72

EXAMPLE 7 :

The 6-nitro isomer is then eluted, and is recrystallized in isopropanol.

Melting point : > 260°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	35.62	1.79	12.46	9.51
found	35.88	2.10	12.45	9.81

EXAMPLE 8 :

6,7-Methylenedioxy-3-(trifluoromethylsulfonylamino)- 2(1H)-quinolone

This compound was obtained according to the process described in Example 1.

Melting point : > 250°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	39.29	2.10	8.33	9.54
found	39.44	2.22	8.32	9.84

EXAMPLE 9 :

6,8-Dichloro-3-(trifluoromethylsulfonylamino)-2(1H)- quinolone

This compound was obtained according to the process described in Example 2a. The intermediate obtained in Stage C is not isolated, but cyclizes spontaneously under the conditions of the reaction to yield the intermediate obtained in Stage D.

Melting point : 215°C

Elemental microanalysis:

	C %	H %	N %	Cl %	S %
calculated	33.26	1.40	7.76	19.63	8.88
found	33.47	1.70	7.74	19.65	9.05

5 EXAMPLE 10 :

7-Chloro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

This compound was obtained according to the process described in Example 2a.

Melting point : 250°C

10 Elemental microanalysis:

	C %	H %	N %	S %	Cl %
calculated	36.77	1.85	8.58	9.82	10.85
found	36.82	2.10	8.53	9.80	11.02

15 EXAMPLE 11 :

7-Chloro-3-(methylsulfonylamino)-2(1H)-quinolone

This compound was obtained according to the process described in Example 2a.

Melting point : > 260°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	44.04	3.33	10.27	11.76
found	44.07	3.45	10.03	11.61

EXAMPLE 12 :

6-Bromo-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

25 A solution of 300 µl of bromine in 10 ml of glacial acetic acid is added dropwise at room temperature to a suspension containing 3.4 mmol of the compound described in Example 1 in 10 ml of glacial acetic acid. After stirring overnight at room temperature, 10 ml of water are added. The expected product is obtained by filtering off the precipitate, and is purified by chromatography on silica gel, using a dichloromethane/ethanol/acetic acid (90:9.5:0.5) mixture as elution solvent.

30 Melting point : > 260°C

Elemental microanalysis:

	C %	H %	N %	Br	S %
calculated	32.36	1.63	7.55	21.53	8.64
found	36.52	1.93	7.60	21.81	8.28

EXAMPLE 13 :

6-Acetamido-3-(trifluoromethylsulfonylamino)-2(1H)- quinolone

A suspension containing 1.48 mmol of the compound described in Example 7 in 100 ml of ethanol is hydrogenated for one hour at atmospheric pressure in the presence of 50 mg of PtO₂. The ethanol is evaporated off under vacuum, the residue is dissolved in 100 ml of THF and the catalyst is filtered off. 1.63 mmol of triethylamine and then 1.48 mmol of acetic anhydride are added to the filtrate, and the reaction solution is stirred at room temperature for 1 h 30 min. The THF is evaporated off under vacuum and the residue is taken up in ethyl acetate. The organic phase is washed with 1N HCl solution and then extracted with 1N NaOH solution. The basic aqueous phase is reacidified with 1N HCl and extracted with ethyl acetate. After drying and purification by chromatography on silica (dichloromethane/ethanol/acetic acid, 90:9:1), the expected product is recrystallized in ethyl acetate.

Melting point : > 260°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	41.26	2.89	12.03	9.18
found	41.05	3.16	11.83	9.44

EXAMPLE 14 :

6,7-Dinitro-3-(trifluoromethylsulfonylamino)-2(1H)- quinolone

2.96 mmol of the compound described in Example 2 are dissolved in 2 ml of 96% sulfuric acid and the mixture is cooled to 0°C. A solution of 0.75 ml of 96% sulfuric acid and 1 ml of 86% nitric acid is prepared at 0°C. 275 µl of this solution are added dropwise to the reaction solution, and the mixture is stirred for 15 min at 0°C and then for 1 h while being allowed

to return to room temperature. 5 ml of ice-cold water are added and the mixture is extracted with ethyl acetate. After drying, the expected product is purified by chromatography on silica (dichloromethane/ethanol/acetic acid, 90:9:1).

5 Melting point : 236°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	31.42	1.32	14.66	8.39
found	31.38	1.51	13.95	8.12

10 EXAMPLE 15 :

7-Amino-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

1.47 mmol of the compound described in Example 2 and 6 mmol of stannous chloride dihydrate in 50 ml of ethanol are stirred for 1 h under reflux. The mixture is extracted with 3N HCl (3 x 30 ml). The aqueous phases are combined and neutralized with 3N NaOH solution to pH 5-6. The mixture is extracted with ethyl acetate (2 x 50 ml) and dried, and the product is recrystallized in an ethyl acetate/hexane mixture.

Melting point : > 260°C

20 Elemental microanalysis:

	C %	H %	N %	S %
calculated	39.09	2.62	13.68	10.44
found	39.18	3.08	13.20	10.28

EXAMPLE 16 :

7-Acetamido-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

1.1 mmol of triethylamine and 1.1 mmol of acetic anhydride are added to a solution containing 1 mmol of the compound of Example 15 in 100 ml of THF. The mixture is stirred overnight under reflux and the THF is evaporated off under vacuum. The residue is taken up in ethyl acetate. The organic phase is washed with 1N HCl solution and extracted with 1N NaOH solution. The basic aqueous phase is washed with ethyl acetate and acidified with 1N HCl solution to give a white precipitate, which is filtered off and recrystallized in ethanol.

Melting point : 315°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	41.26	2.89	12.03	9.18
found	41.31	3.30	11.82	9.23

EXAMPLE 17 :

7-Azido-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

A suspension of 1.3 mmol of the compound of Example 15 in 6 ml of 48% aqueous tetrafluoroboric acid solution is stirred for 10 min at 0°C. 10 ml of water are added, followed by a solution of 1.95 mmol of sodium nitrite in 3 ml of water added dropwise. The mixture is stirred for 30 min at 0°C and a solution of 1.95 mmol of sodium azide in 3 ml of water is added dropwise. The mixture is stirred for 10 min at 0°C and is allowed to return to room temperature while being stirred for 3 h. 20 ml of water are added and the mixture is extracted with ethyl acetate (2 x 20 ml). The organic phase is then washed with 1N HCl solution and dried over MgSO₄. The organic phase is concentrated until a precipitate has formed, and the precipitate is filtered off and recrystallized in ethyl acetate.

Melting point : 235°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	36.04	1.81	21.02	9.62
found	36.18	2.09	20.66	10.02

EXAMPLE 18 :

5,7-Dichloro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

This compound was obtained according to the process described in Example 2a.

Melting point : 254°C

Elemental microanalysis:

	C %	H %	N %	Cl %	S %
calculated	33.26	1.40	7.76	19.63	8.88
found	33.11	1.73	7.78	19.29	8.83

EXAMPLE 19 :

6,7-Dichloro-3-(trifluoromethylsulfonylamino)-2(lH)- quinolone

This compound was obtained according to the process described in Example 2a.

Melting point : 289°C

Elemental microanalysis:

	C %	H %	N %	Cl %	S %
calculated	33.26	1.40	7.76	19.63	8.88
found	33.47	1.84	7.91	19.42	9.01

EXAMPLE 20 :

7-Aza-3-(trifluoromethylsulfonylamino)-2(lH)-quinolone sodium salt

The compound was obtained from Stage A to Stage D according to the process described in Example 2a. The intermediate obtained in Stage C is not isolated, but cyclizes spontaneously under the conditions of the reaction to yield the intermediate obtained in Stage D.

Stage E : 7-Aza-3-(trifluoromethylsulfonylamino)-2(lH)-quinolone sodium salt

0.6 mmol of 7-aza-3-(N-benzyl-N-trifluoromethylsulfonylamino)-2(lH)-quinolone is hydrogenated for 24 h at atmospheric pressure in 200 ml of ethanol in the presence of 20 mg of PtO₂. The precipitate which has formed is dissolved by adding 10 ml of 2N ethanolic hydrogen chloride and heating to approximately 50°C. The catalyst is filtered off and the filtrate is evaporated to dryness. The white residue is dried under vacuum overnight. It is suspended in 20 ml of distilled water and 0.6 mmol of 1N aqueous NaOH solution is added. The solution is stirred for 15 min, the small amount of insoluble matter is filtered off and the product is lyophilized.

Elemental microanalysis:

	C %	H %	N %	S %
calculated	31.77	1.65	12.35	9.42
found	31.76	1.51	12.05	9.60

5 EXAMPLE 21 :

7-Trifluoromethylsulfonylamino)-6-hydroxy-1,2,5-oxadiazolo[3,4-g]quinolinone sodium salt

Stage A : 7-Azido-6-nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone

10 1.38 mmol of the compound of Example 17 is added in small portions to 3.5 ml of 86% nitric acid at 0°C. The mixture is stirred for 15 min at 0°C and poured onto ice. The yellow precipitate is filtered off, rinsed with water and dried under vacuum.

Stage B : 7-(Trifluoromethylsulfonylamino)-6- hydroxy-1,2,5-oxadiazolo[3,4-g]quinoline 1-oxide

15 A suspension containing 0.7 mmol of the product obtained in the preceding stage in 50 ml of toluene is stirred at 100°C for 3 h. The toluene is evaporated off under reduced pressure, the residue is taken up in ether and the precipitate is filtered off.

Stage C : 7-(Trifluoromethylsulfonylamino)-6- hydroxy-1,2,5-oxadiazolo[3,4-g]quinolinone sodium salt

20 0.7 mmol of triphenylphosphine is added to a solution containing 0.67 mmol of the product obtained in the preceding stage in 50 ml of acetone. The mixture is stirred for 15 min at room temperature and evaporated to dryness. The residue is taken up in 20 ml of ether and the mixture is extracted with 1N NaOH (2 x 10 ml). The aqueous phase is acidified with 1N HCl and extracted with ethyl acetate. After drying, the expected product is obtained by chromatography on silica (ethyl acetate/methanol, 95:5).

25

30

Melting point : 236°C

Elemental microanalysis:

	C %	H %	N %	S %
calculated	33.72	1.13	15.73	9.00
5 found	33.37	1.46	15.17	9.44

EXAMPLE 22 : Pharmaceutical composition

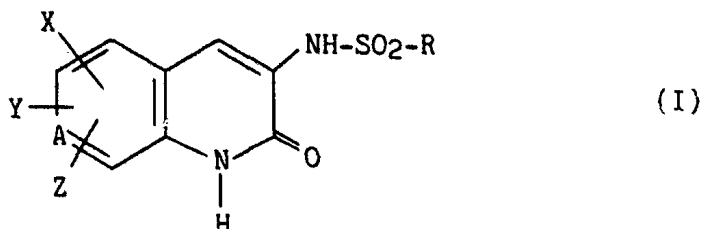
Preparation formula for 1000 tablets containing a dose of 10 mg

Compound of Example 2	10 g
Hydroxypropylcellulose.....	2 g
10 Wheat starch.....	10 g
Lactose.....	100 g
Magnesium stearate.....	3 g
Talc.....	3 g

~~CLAIMS~~

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I):



in which

X, Y, Z:

- which may be identical or different, represent a hydrogen atom, a halogen atom or a nitro, cyano, azido, trihalomethyl, linear or branched (C₁-C₆) alkyl, linear or branched (C₁-C₆) alkoxy or amino (unsubstituted or substituted with a linear or branched (C₁-C₆) acyl group) group,
- or alternatively, when they are located on two adjacent carbon atoms, form, with the carbon atoms to which they are attached, a phenyl ring or a 5- or 6-membered heterocycle containing from 1 to 3 hetero atoms, preferably a 1,2,5-oxadiazole ring,

R represents a linear or branched (C₁-C₆) alkyl, trihalomethyl, phenyl (unsubstituted or substituted with one or more halogen atoms or linear or branched (C₁-C₆) alkyl, trihalomethyl or linear or branched (C₁-C₆) alkoxy groups), 2-thienyl (unsubstituted or substituted with a halogen atom), naphthyl or styryl group,

A represents a CH radical or a nitrogen atom, its enantiomers, diastereoisomers and epimers, as well as its addition salts with a pharmaceutically acceptable base.

2. A compound of formula (I) as claimed in claim 1 such that R represents a trihalomethyl group.

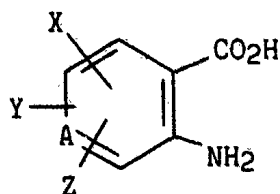
3. A compound of formula (I) as claimed in claim 1, such that at least one of the groups X, Y and Z represents a nitro group.

4. A compound of formula (I) as claimed in claim 1, such that at least one of the groups X, Y and Z represents a chloro group.

5. A compound of formula (I) as claimed in claim 1, such that X, Y or Z, when they are located on two adjacent carbons, form, with the carbon atoms to which they are attached, a 1,2,5-oxadiazole ring.

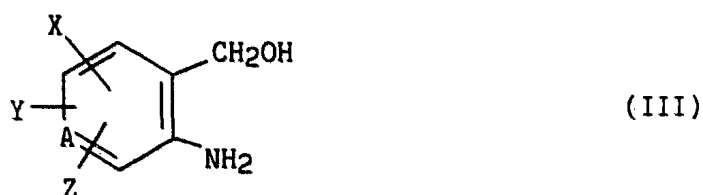
6. A compound of formula (I) as claimed in claim 1, which is 7-nitro-3-(trifluoromethylsulfonylamino)-2(1H)-quinolone.

7. A process for preparing a compound of formula (I), wherein



(II)

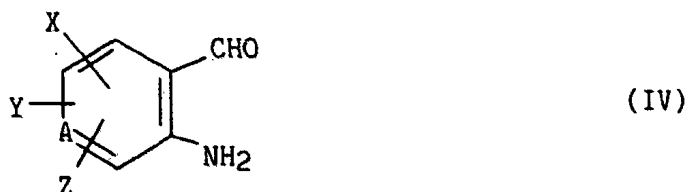
in which X, Y, Z and A have the same meaning as in formula (I), is used as the starting material, which starting compound is reduced, depending on the nature of the substituents X, Y and Z, either in an aprotic medium in the presence of lithium aluminum hydride, aluminum hydride, diborane or borane complexes, or in an acidic protic medium when sodium cyanoborohydride is used, to yield an alcohol of formula (III):



in which X, Y, Z and A have the same meaning as in the formula (I),

which is oxidized using a metal oxide in an inert solvent, an alkali metal halate in a protic solvent or an acid chloride in dimethyl sulfoxide,

to yield the aldehyde of formula (IV):



in which X, Y, Z and A have the same meaning as in the formula (I),

which is then condensed:

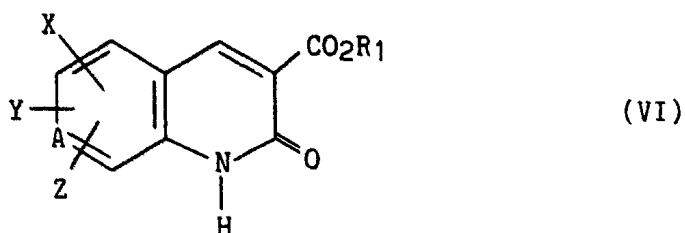
1/ either:

with an alkyl malonate of formula (V), in a protic medium, in the presence of an alkali metal alcoholate, a tertiary amine or an alkali metal hydroxide:



in which R₁ represents a linear or branched (C₁-C₆) alkyl group unsubstituted or substituted with one or more phenyl groups,

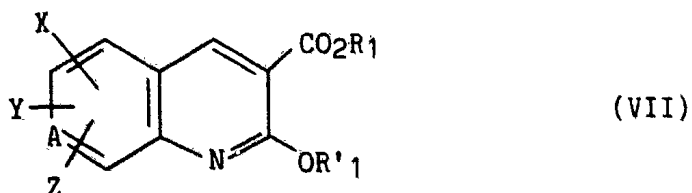
to yield a 2(1H)-quinolone of formula (VI):



in which X, Y, Z, A and R₁ have the same meaning as above, which is protected:

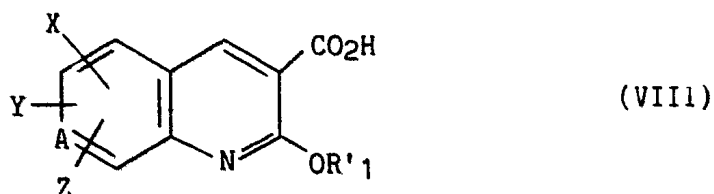
- by reaction with a trialkyloxonium tetrafluoroborate in ether or dichloromethane,
- or by reaction, in an inert solvent or without a solvent, of a phosphorus oxyhalide, a phosphorus pentahalide, a thionyl halide, phosgene, thiophosgene, phosgene iminium or phosgene trimer, followed by reaction of the 2-haloquinoline thereby formed with an alkali metal alkoxide of formula R'₁OM (in which R'₁ has the same meaning as R₁ and M represents an alkali metal) in an alcoholic medium,
- or by reaction with sodium hydride, butyllithium or an alkali metal alcoholate in the presence of an alkylating agent of formula R'₁V (in which R'₁ has the same meaning as above and V is a leaving group),

to yield the 2-alkoxyquinoline of formula (VII):



in which X, Y, Z, A, R₁ and R'₁ have the same meaning as above,

which is hydrolyzed in the presence of an alkali metal hydroxide in an aqueous or aqueous- alcoholic medium, to yield the acid of formula (VIII):



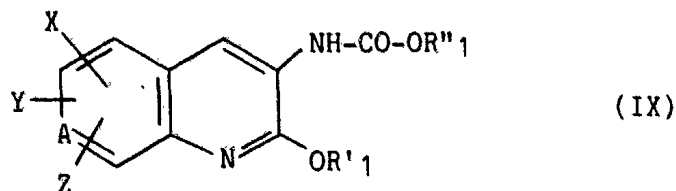
in which X, Y, Z, A and R'₁ have the same meaning as above,
which is:

a converted to the corresponding acid azide:

- by activation of the acid function in the form of an acid anhydride or halide, followed by reaction with sodium azide in an inert solvent,
- or by reaction in an inert solvent with diphenoxyphosphoryl azide in the presence of a tertiary amine,

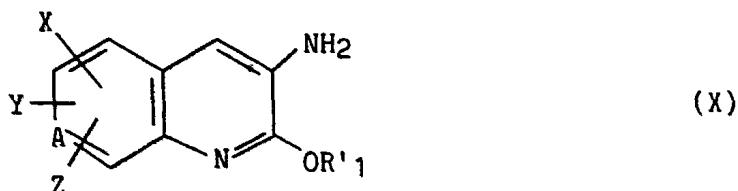
b rearranged by heating in an inert solvent in an anhydrous medium, adding an excess of an alcohol of formula R''₁OH (in which R''₁ has the same meaning as R₁) when gaseous evolution has ceased, or by direct heating in the alcohol R''₁OH,

to yield the corresponding carbamate of formula (IX):



in which X, Y, Z, A, R'₁ and R''₁ have the same meaning as above,

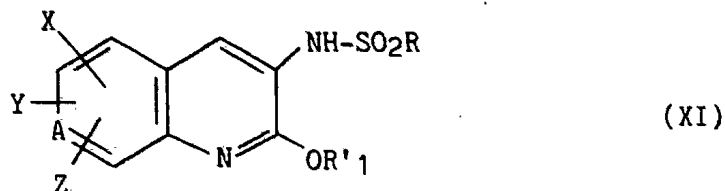
which is either hydrolyzed in an anhydrous acid medium, or hydrogenated in an anhydrous medium with hydrogen in the presence of a catalyst, to yield the amine of formula (X):



in which X, Y, Z, A and R'₁ have the same meaning as above,

which undergoes a sulfonylation by reaction with a sulfonyl halide or anhydride of respective formula RSO₂W or (RSO₂)₂O (in which R has the same meaning as in the formula (I) and W represents a halogen atom), in the presence of a tertiary amine, in an aprotic medium,

to yield the sulfonamide of the formula (XI):



in which X, Y, Z, A, R and R'₁ have the same meaning as above,

which is deprotected, depending on the nature of the group R'₁, by heating in an acidic aqueous medium or by catalytic hydrogenation,

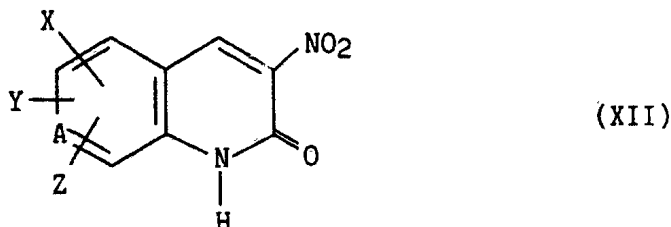
to yield the compound of formula (I),

2/ or:

with an alkyl nitroacetate in a protic medium, in the presence of an alkali metal alcoholate, a tertiary amine or an alkali metal hydroxide, or in an inert medium having a high boiling point, in the presence of

a tertiary or secondary amine under reflux of the solvent,

to yield the 3-nitro-2(1H)-quinolone of formula (XII):

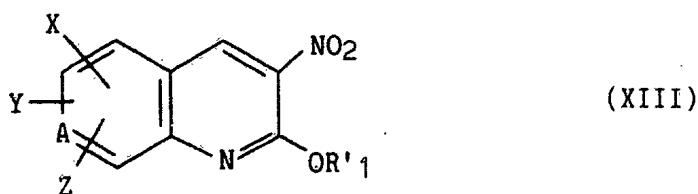


5

in which X, Y, Z and A have the same meaning as in the formula (I),

which is protected according to the same techniques as those described for protection of the quinolone of formula (VI) as the 2-alkoxyquinoline of formula (VII),

to yield the 2-alkoxyquinoline of formula (XIII):



in which X, Y, Z, A and R'1 have the same meaning as in the formula (I),

the nitro group of which is reduced in the presence of tin chloride in an alcohol or sodium hydrosulfite in water, or by catalytic hydrogenation,

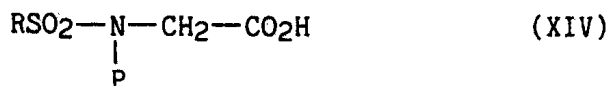
to yield the amine of formula (X) defined above,

which undergoes the sulfonylation and then the deprotection which are described above, enabling a compound of formula (I) to be obtained,

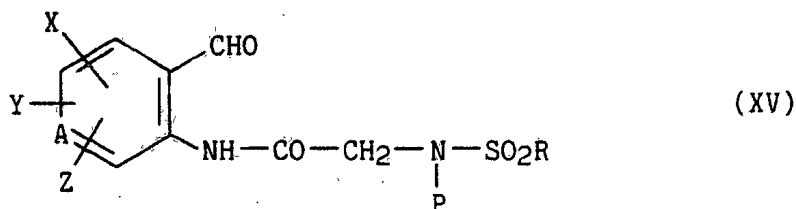
3/ or:

with a protected glycine compound of formula (XIV), activated in the form of the corresponding anhydride,

azide, cyanide or halide, in an inert medium, in the presence of triethylamine:

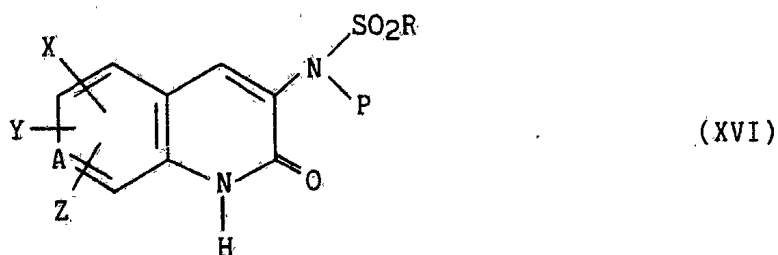


in which R has the same meaning as in the formula (I) and P represents a conventional protective group for the amine function of an amino acid, to yield the aldehyde of formula (XV):



in which X, Y, Z, A, P and R have the same meaning as above,

which is cyclized in an alcoholic medium, in the presence of an alkali metal alcoholate, a tertiary amine or an alkali metal hydroxide, to yield quinolone of formula (XVI):



in which X, Y, Z, A, R and P have the same meaning as above,

which is deprotected in the presence of aluminum chloride in an inert solvent or by catalytic hydrogenation,

to yield a compound of formula (I),

which compound of formula (I),

- when X and/or Y and/or Z represent a hydrogen atom, can undergo electrophilic substitutions according to standard techniques for substitution of aromatic ring-systems, yielding a compound of formula (I) mono-, di- or trisubstituted on the phenyl ring of the quinolone,
- when X, Y or Z represent a nitro group, can be converted to the corresponding amino or acylamino derivative, which amino derivative can itself be converted to the corresponding azido derivative according to standard techniques of organic chemistry,
- when X represents a nitro group and Y, located on an adjacent carbon, represents an azido group, can undergo a cyclization to yield the corresponding 1,2,5-oxadiazolo compound,
- can be, where appropriate, purified according to a standard purification technique,
- is separated, where appropriate, into its isomers according to a standard separation technique,
- is converted, if so desired, to its addition salts with a pharmaceutically acceptable base.

8. A pharmaceutical composition containing as active principle at least one compound as claimed in any one of claims 1 to 6, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic vehicles.

9. The pharmaceutical composition as claimed in claim 8, containing at least one active principle as claimed in one of claims 1 to 6, which is useful as an inhibitor of the pathological phenomena associated with hyperactivation of the excitatory amino acid-dependent pathways of neurotransmission.

DATED this 12th day of November 1992.

ADIR ET COMPAGNIE

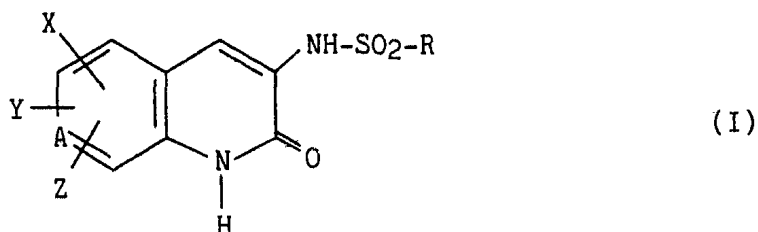
WATERMARK PATENT & TRADEMARK ATTORNEYS
"THE ATRIUM"
290 BURWOOD ROAD
HAWTHORN. VIC. 3122.

ABSTRACT

NEW 3-SULFONYLAMINO-2(1H)-QUINOLONE COMPOUNDS,
PROCESS FOR PREPARING THEM
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

ADIR ET COMPAGNIE
1 RUE CARLE HEBERT
F-92415 COURBEVOIE CEDEX

Compounds of formula (I):



in which
X, Y, Z:

- which may be identical or different, represent a hydrogen atom, a halogen atom or a nitro, cyano, azido, trihalomethyl, linear or branched (C₁-C₆) alkyl, linear or branched (C₁-C₆) alkoxy or amino (unsubstituted or substituted with a linear or branched (C₁-C₆) acyl group) group,
- or alternatively, when they are located on two adjacent carbon atoms, form, with the carbon atoms to which they are attached, a phenyl ring or a 5- or 6-membered heterocycle containing from 1 to 3 hetero atoms, preferably a 1,2,5-oxadiazole ring,

R represents a linear or branched (C₁-C₆) alkyl, trihalomethyl, phenyl (unsubstituted or substituted with one or more halogen atoms or linear or branched (C₁-C₆) alkyl, trihalomethyl or linear or branched (C₁-C₆) alkoxy groups), 2-thienyl (unsubstituted or substituted with a halogen atom), naphthyl or styryl group,

A represents a CH radical or a nitrogen atom.

Medicinal products.