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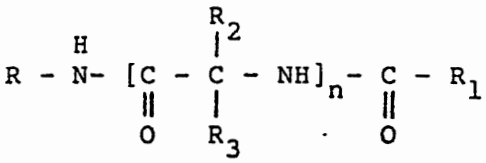
## (54) Anticonvulsant composition containing amino acid derivative and use of said amino acid derivative.

(57) The present invention relates to an anticonvulsant composition comprising a compound of the formula:



where R, $R_1$, $R_2$ and $R_3$ and n are as defined in claim 1 as effective ingredient, together with a pharmaceutically acceptable carrier, said composition being useful in the treatment of epilepsy and other CNS disorders, and the use of the above effective ingredient in the preparation of an anticonvulsant medicament.

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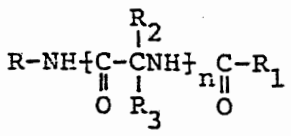
# ANTICONVULSANT COMPOSITION CONTAINING AMINO ACID DERIVATIVE AND USE OF SAID AMINO ACID DERIVATIVE

The present invention relates to compounds having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders. More specifically, the compounds of this invention can be characterized as protected amino acid derivatives having the following general formula:



(I)

wherein R and $R_1$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl. aryl lower alkyl. aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one substituent;

$R_2$ and $R_3$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one substituent, halogen or a heteroatom containing oxygen. nitrogen, sulfur or phosphorous substituted with hydrogen, lower alkyl or aryl, said lower alkyl or aryl groups being substituted or unsubstituted; and

n is 1 to 4.

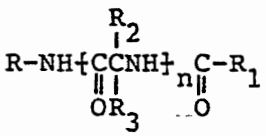
The predominant application of anticonvulsant drugs is the control and prevention of seizures associated with epilepsy or related central nervous system disorders. Epilepsy refers to many types of recurrent seizures produced by paroxysmal excessive neuronal discharges in the brain; the two main generalized seizures are petit mal, which is associated with myoclonic jerks, akinetic seizures, transient loss of consciousness, but without convulsion; and grand mal which manifests in a continuous series of seizures and convulsions with loss of consciousness.

The mainstay of treatment for such disorders has been the long-term and consistent administration of anticonvulsant drugs. Most drugs in use are weak acids that, presumably, exert their action on neurons, glial cells or both of the central nervous system. The majority of these compounds are characterized by the presence of at least one amide unit and one or more benzene rings that are present as a phenyl group or part of a cyclic system.

Much attention has been focused upon the development of anticonvulsant drugs and today many such drugs are well known. For example, the hydantoins, such as phenytoin, are useful in the control of generalized seizures and all forms of partial seizures. The oxazolidinediones, such as trimethadione and paramethadione, are used in the treatment of nonconvulsive seizures. Phenacemide, a phenyl-acetylurea, is one of the most well known anticonvulsants employed today, while much attention has recently been dedicated to the investigation of the diazepines and piperazines. For example, U.S. Patent Nos. 4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified diazepine derivatives useful in the treatment of epilepsy and other nervous disorders. U.S. Patent No. 3,887,543 to Nakanishi, et al. describes a thieno [2,3-e] [1,4] diazepine compound also having anticonvulsant activity and other depressant activity. U.S. Patent No. 4,209,516 to Heckendorn, et al. relates to triazole derivatives which exhibit anticonvulsant activity and are useful in the treatment of epilepsy and conditions of tension and agitation. U.S. Patent No. 4,372,974 to Fish, et al. discloses a pharmaceutical formulation containing an aliphatic amino acid compound in which the carboxylic acid and primary amine are separated by three or four units. Administration of these compounds in an acid pH range are useful in the treatment of convulsion disorders and also possess anxiolytic and sedative properties.

Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control and most have disturbing side-effects. Clearly, current therapy has failed to "seize control" of these debilitating diseases.

The present invention relates to compounds of the following general formula:



(I)

wherein R and $R_1$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one substituent;

$R_2$ and $R_3$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one substituent, halogen or a heteroatom containing oxygen, nitrogen, sulfur or phosphorous substituted with hydrogen, lower alkyl or aryl, said lower alkyl or aryl groups being substituted or unsubstituted; and

n is 1 to 4.

The present invention contemplates employing the compounds of Formula I in compositions of pharmaceutically acceptable dosage forms. Where the appropriate substituents are employed, the present invention also includes pharmaceutically acceptable addition salts. Moreover, the administration of an effective amount of the present compounds, in their pharmaceutically acceptable forms or the addition salts thereof, can provide an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia and other related central nervous system disorders.

The alkyl groups exemplary of the substituents are lower alkyl containing from 1 to 6 carbon atoms and may be straight chain or branched. These groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl, hexyl, and the like.

The aryl groups of R, $R_1$, $R_2$ and $R_3$ are aromatic compounds containing from 6 to 10 ring carbon atoms; and include phenyl, $\alpha$-and $\beta$-naphthyl. Moreover, the aryl groups also include organometallic compounds wherein a metal or metalloidal atom is sandwiched between two aromatic compounds, e.g., cyclopendienyl compounds. Ferrocene is an example of this latter class of compounds.

The aryl lower alkyl groups include, for example, benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl and the like, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenylethyl, and the like.

The lower alkenyl and lower alkynyl groups contain from 2 to 6 carbon atoms and may be straight chain or branched.

Exemplary of the unsaturated alkyl substituents, i.e., lower alkenyl and lower alkynyl are vinyl, acetylenic, allyl, propenyl, butenyl, pentenyl, hexenyl, propynyl, butynl, pentynyl, hexynyl, pentadienyl, and the like.

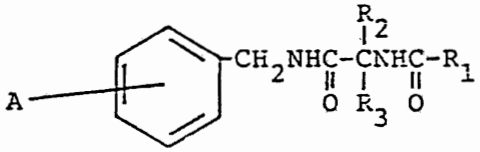
The heterocyclic substituents contemplated by the present invention are N, O or S containing rings which may be monocyclic or bicyclic or tricyclic and which may contain up to 4 heteroatoms in the rings and which may contain up to 13 ring carbon atoms and up to a total of 18 carbon atoms. These heterocyclic substituents include heteroaromatics and saturated and partially unsaturated heterocyclic compounds such as furyl, thienyl, pyranyl, pyrrolyl, imidazoyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, indolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, piperidyl, pyrrolinyl, piperazinyl, quinolyl, trizaolyl, tetrazolyl, and the like.

The polynuclear aromatic substituents contemplated herein are polyaromatic compounds containing up to 4 fused rings and containing up to 18 ring carbon atoms, for example, naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like.

The heteroatom containing substituents include, for example, methoxy, ethoxy, phenoxy, thiomethoxy, thioethoxy, thiophenoxy, methylamino, ethylamino, anilino, dimethylamino, trimethylamino, fluoro, chloro, bromo, iodo, and the like.

The aryl groups such as phenyl, ferrocenyl, and the like, the alkyl groups, the aryl lower alkyl groups, the lower alkenyl group, the lower alkynyl groups and heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, and lower alkyl polynuclear aromatic may carry one or more substituents which can be characterized as either electron withdrawing groups such as halo, including bromo, fluoro, chloro, iodo, and the like, nitro, acyl, carboxyl, carboalkoxy, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic, guanidine, quaternary ammonium, and the like; or as electron donating groups such as hydroxy, alkoxy including methoxy, ethoxy, and the like, alkyl, amino, substituted amino, phenoxy, substituted phenoxy, thiol, sulfide, disulfide, and the like. One skilled in the art will appreciate that the aforesaid substituents may have electron donating or electron withdrawing properties under different chemical conditions. Moreover, the present invention contemplates any combination of substituents selected from the above-defined groups.

Preferred compounds of the present invention have the following general formula:



wherein $R_1$ is H or lower alkyl, $R_2$ and $R_3$ are as defined above and A is one to three substituents selected from the above-defined groups.

The alkyl groups of $R_1$ can be unsubstituted or substituted with one or more substituents which can be characterized as either electron withdrawing groups or electron donating groups as defined above.

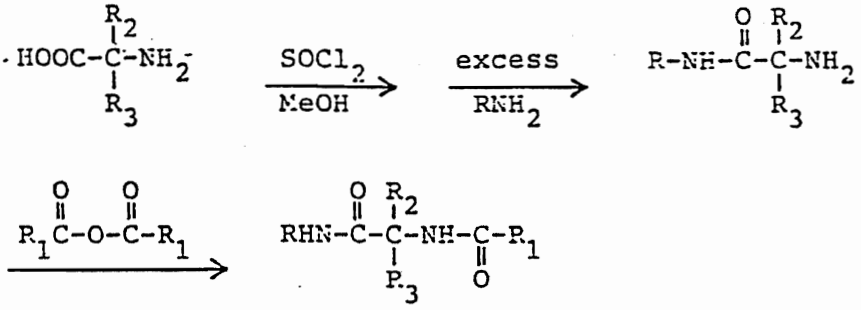
The alkyl groups of $R_2$ and $R_3$, including the alkyl portion of the aryl alkyl, or the alkyl heterocyclic and alkyl polynuclear aromatic groups, or the alkyl or aryl groups of the heteroatom containing substituents, as well as the alkenyl, alkynyl, aryl, heterocyclic and polynuclear aromatic groups of $R_2$ and $R_3$, may also be unsubstituted or substituted with one or more substituents which can be characterized as either electron withdrawing groups or electron donating groups as defined above.

The preferred compounds of the present invention are those where n is 1 but di, tri-and tetra-peptides are acceptable.

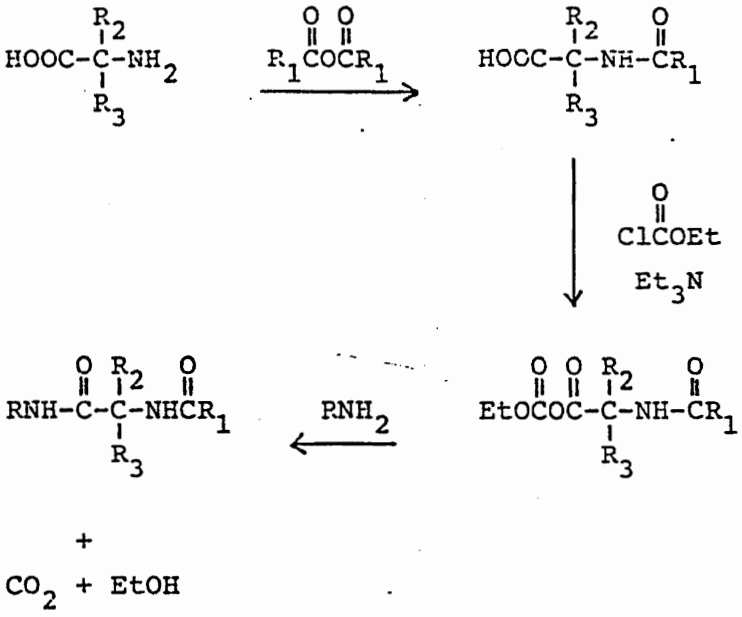
The compounds of the present invention may contain one (1) or more asymmetric carbon atoms and may exist in racemic and optically active forms. Depending upon the substituents, the present compounds may form addition salts as well. All of these forms are contemplated to be within the scope of this invention including mixtures of the stereoisomeric forms.

The following three schemes of preparation are generally exemplary of the process which can be employed for the preparation of the present complex:

Scheme I



Scheme II



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