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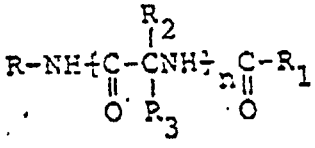
## (54) Amino acid derivative anticonvulsant.

(57) The present invention relates to compounds exhibiting central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders. The compounds of this invention have the following general formula:





and pharmaceutically acceptable salts thereof wherein
R is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;
$R_1$ is hydrogen or lower alkyl and $R_1$ is unsubstituted or is substituted with at least one electron withdrawing substituent or at least one electron donating substituent;
$R_2$ and $R_3$ are independently each hydrogen, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocycli, heterocycli lower alkyl or Z-Y, wherein $R_2$ and $R_3$ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;
Z is O, S, $NR_4$, $PR_4$ or a chemical bond;

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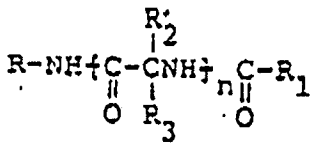
$PR_4SR_5$, $NR_4PR_5R_6$ or $PR_4NR_5R_6$,
$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, and $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and
n is 1-4.

# AMINO ACID DERIVATIVE ANTICONVULSANT

The present invention relates to compounds and pharmaceutical compositions 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 is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl and R is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group;

$R_1$ is hydrogen or lower alkyl, unsubstituted or substituted with an electron donating group or an electron withdrawing group and

$R_2$ and $R_3$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, or Z-Y wherein $R_2$ and $R_3$ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, $NR_4$, $PR_4$ or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, or halo and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is $NR_4NR_5R_6$, $NR_4OR_5$, $ONR_4R_5$, $OPR_4R_5$, $PR_4OR_5$, $SNR_4R_5$, $NR_4SR_5$, $SPR_4R_5$ or $PR_4SR_5$, $NR_4PR_5R_6$ or $PR_4NR_5R_6$,

$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl. or lower alkynyl, wherein $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

n is 1-4.

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 oxazolidinedoines, such as trimethadione and paramethadione, are used in the treatment of nonconvulsive seizures. Phenacemide, a phenylacetylurea, 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

anxiolytic and sedative properties.

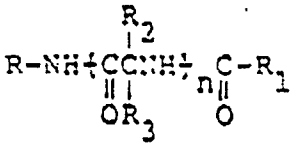
Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control and most have disturbing side-effects.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

It is therefore one object of the present invention to provide novel compounds exhibiting CNS activity, particularly anticonvulsant activity.

Another object of this invention is to provide pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders.

A further object of this invention is to provide a method of treating epilepsy and related convulsant disorders.

These and other objects are accomplished herein by providing compounds of the following general formula:



(I)

wherein R, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, Z, Y are as defined hereinabove.

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 treament of epilepsy, nervous anxiety, psychosis, insomnia and other related central nervous system disorders.

The alkyl groups when used alone or in combination with other 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 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 term aryl refers to an aromatic group which contains up to 18 ring carbon atoms and up to a total of 25 carbon atoms and includes the polynuclear aromatic substituents. These aryl groups may be monocyclic, bicyclic, tricyclic or polycyclic and are fused rings. This group includes phenyl, naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like. It also includes groups like ferrocenyl.

Lower alkenyl is a alkenyl group containing from 2 to 6 carbon atoms and at least one double bond. These groups may be straight chained or branched and may be in the Z or E form. Such groups include vinyl, propenyl, 1-butenyl, isobutenyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl, (E)-2-pentenyl, (Z)-4-methyl-2-pentenyl, (E-)-4-methyl-2-pentenyl, pentadienyl, e.g., 1,3 or 2,4-pentadienyl, and the like.

The term alkynyl include alkyne substituents containing 2 to 6 carbon atoms and may be straight chained as well as branched. It includes such groups as ethynyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynl, 2-pentynyl, 3-methyl-1-pentynl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl and the like;

The term "electron-withdrawing and electron donating" refer to the ability of a substituent to withdraw or donate electrons relative to that of hydrogen if the hydrogen atom occupied the same position in the molecule. These terms are well understood by one skilled in the art and are discussed in Advanced Organic Chemistry, by J. March, John Wiley and Sons, New York NY, pp. 16-18 (1985) and the discussion therein is incorporated herein by reference. Electron withdrawing groups include halo, including bromo, fluoro, chloro, iodo and the like; nitro, carboxy, lower alkenyl, lower alkynyl, formyl, carboxamido, aryl, quaternary ammonium and the like. Electron donating groups include such groups as hydroxy, lower alkoxy, including methoxy, ethoxy and the like; lower alkyl, such as methyl, ethyl, and the like; amino, lower alkylamino, di-(loweralkyl) amino, aryloxy such as phenoxy, mercapto, alkylthio, 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-identified groups.

The term halo includes fluoro, chloro, bromo, iodo and the like.

As employed herein, the heterocyclic substituent contains at least one sulfur, nitrogen or oxygen, but

also may include one or several of said atoms. The heterocyclic substituents contemplated by the present invention include heteroaromatics and saturated and partially saturated heterocyclic compounds. These heterocyclics may be monocyclic, bicyclic, tricyclic or polycyclic and are fused rings. The may contain up to 18 ring atoms and up to a total of 17 ring carbon atoms and a total of up to 25 carbon atoms. The heterocyclics are also intended to include the so-called benzoheterocycles. Representative heterocyclics include furyl, thienyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, is othiazolyl, isoxazolyl, piperidyl, pyrrolinyl, piperazinyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, benzofuryl, benzothienyl, morpholinyl, benzoxazolyl, tetrahydrofuryl, pyranyl, indazolyl, purinyl, indolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrrolidinyl, furazanyl, N-methylindolyl, methylfuryl, puridazinyl, pyrimidinyl, pyrazinyl, pyridyl, epoxy, aziridino, oxetanyl, azetidinyl, the N-oxides of the nitrogen containing heterocycles, such as the nitric oxides of pyridyl, pyrazinyl, and pyrimidinyl and the like. The preferred heterocyclic are thienyl, furyl, pyrrolyl, benzofuryl, benzothienyl, indolyl, methylpyrrolyl, morpholinyl. The preferred heterocyclic is a 5 or 6-membered heterocyclic compound. The especially preferred heterocyclic is furyl.

The preferred compounds are those wherein n is 1, but di, tri and tetrapeptides are acceptable.

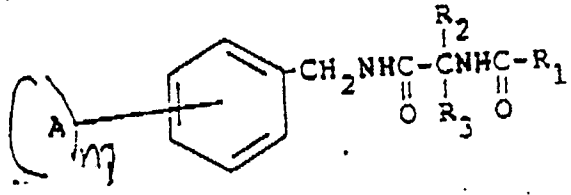
The preferred values of R is aryl lower alkyl, especially benzyl, and the preferred $R_1$ is H or lower alkyl. The most preferred $R_1$ group is methyl.

The most preferred electron donating substituent and electron donating substituent for $R_1$ e.g., are halo, nitro, alkanoyl, formyl, arylalkanoyl, aryloyl, carboxyl, carbalkoxy, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, di(loweralky)lamino, amino lower alkyl, mercapto and alkylthio.

The ZY groups representative of $R_2$ and $R_3$ include alkoxy, such as methoxy, ethoxy, aryloxy, such as phenoxy; thioalkoxy, such as thiomethoxy, thioethoxy; thioaryloxy such as thiophenoxy, alkylamino, such as methylamino, ethylamino, arylamino, such as anilino, lower dialkylamino, such as, dimethylamino, hydrazino, alkylhydrazino and aryl hydrazino, such as N-methylhydrazino and N-phenylhydrazino, and hydroxylamino, such as N-hydroxylamino (-NH-OH) and O-hydroxylamino (-O-$NH_2$).

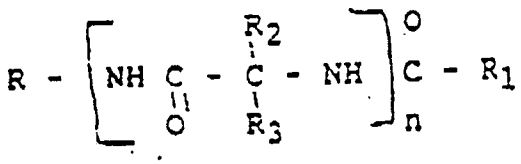
It is preferred that at least one of $R_2$ and $R_3$ is hydrogen and that the other is heterocyclic. The preferred heterocyclics include furyl, thienyl, benzothienyl, benzofuryl, morpholinyl, indolyl, pyrrolyl, methylpyrrolyl. It is also preferred that one of $R_2$ and $R_3$ is methyl, phenyl, isopropyl, 2-thiomethylethyl, ethoxy, methoxy, anilino, propenyl, ethylamino and methylamino.

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 hydrogen or an electron donating group or electron-withdrawing group and m is 0-5. It is preferred that A is hydrogen (i.e., m = 0). However, values of m, equalling 1, 2, or 3 are also preferred.

Especially preferred compounds of the Formula I have the formula



wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic alkyl which is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;

$R_1$ is hydrogen or lower alkyl which is unsubstituted or substituted with at leat one electron withdrawing group or one electron donating group,

$R_2$ and $R_3$ are independently hydrogen, lower alkenyl, lower alkynyl, Z-Y or a heterocyclic group which may be unsubstituted or substituted with at least one electron withdrawing or one electron donating group, with

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