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Kohn et al.

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[54] **AMINO ACID DERIVATIVE ANTICONVULSANT**

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[73] Assignee: **Research Corporation Technologies, Inc.**, Tucson, Ariz.

[21] Appl. No.: **3,208**

[22] Filed: **Jan. 12, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 710,610, Jun. 4, 1991, Pat. No. 5,378,729, which is a continuation-in-part of Ser. No. 354,057, May 19, 1989, abandoned, and a continuation-in-part of Ser. No. 392,870, Aug. 11, 1989, abandoned, said Ser. No. 354,057, is a continuation-in-part of Ser. No. 80,528, Jul. 31, 1987, abandoned, which is a continuation-in-part of Ser. No. 916,254, Oct. 7, 1986, abandoned, which is a continuation-in-part of Ser. No. 702,195, Feb. 15, 1985, abandoned, said Ser. No. 392,870, is a continuation of Ser. No. 80,528, Jul. 31, 1987, abandoned, which is a continuation-in-part of Ser. No. 916,254, Oct. 7, 1986, abandoned, which is a continuation-in-part of Ser. No. 702,195, Feb. 15, 1985, abandoned.

[30] **Foreign Application Priority Data**

Jun. 4, 1992 [WO] WIPO US92/04687

[51] **Int. Cl.**[6] **A61K 31/445**; A61K 31/34; C07D 211/72; C07D 261/04

[52] **U.S. Cl.** **514/231.2**; 514/315; 514/397; 514/406; 514/415; 514/424; 514/461; 514/468; 514/486; 514/616; 546/292; 548/125; 548/225; 548/250; 548/347.1; 548/245; 548/371.4; 564/152; 564/154; 564/292

[58] **Field of Search** 564/148, 155, 564/154, 152; 548/125, 245, 371.4; 514/315, 357, 461, 406, 548, 424, 415, 549, 618, 486, 231.2; 546/252, 152, 154

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(List continued on next page.)

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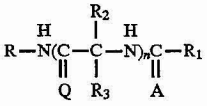
[57] **ABSTRACT**

The present invention relates to compounds of the formula



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AMINO ACID DERIVATIVE ANTICONVULSANT

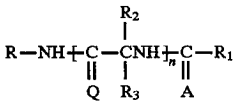
RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. patent application Ser. No. 710,610 filed on Jun. 4, 1991, now U.S. Pat. No. 5,378,729 which is a continuation-in-part of U.S. patent application Ser. No. 354,057 filed on May 19, 1989, now abandoned and U.S. patent application Ser. No. 392,870 filed on Aug. 11, 1989, now abandoned. U.S. patent application Ser. No. 354,057 is a continuation-in-part of U.S. patent application having Ser. No. 080,528, filed on Jul. 31, 1987, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 916,254, filed Oct. 7, 1986, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 702,195, filed Feb. 15, 1985, now abandoned. U.S. patent application Ser. No. 392,870 is a continuation application of U.S. patent application having Ser. No. 080,528, filed Jul. 31, 1987, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 916,254 filed Oct. 7, 1986, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 702,195 filed on Feb. 15, 1985, now abandoned.

This invention was made with Government support under NS15604 awarded by the National Institutes of Health. The Government has certain rights to this invention.

BACKGROUND OF THE INVENTION

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 of the formula:



I

or the N-oxides thereof or pharmaceutically acceptable salts thereof wherein

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, loweralkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

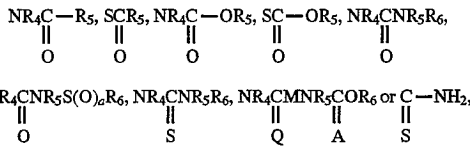
R_1 is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, SO_3^- 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, $S,S(O)_a$, NR_4, PR_4 or a chemical bond;

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

ZY taken together is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, OPR_4R_5, PR_4OR_5, SNR_4R_7, NR_4SR_7, SPR_4R_5, PR_4SR_7, $NR_4PR_5R_6$ $PR_4NR_5R_7$,



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

R_7 is R_6 or $COOR_8$ or COR_8

R_8 is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

A and Q are independently O or S, M is an alkylene chain containing up to 6 carbon atoms or a chemical bond;

n is 1–4 and

a is 1–3.

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 hydantions, 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 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. Pat. 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. Pat. 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. Pat. 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. Pat. No. 4,322,974 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.

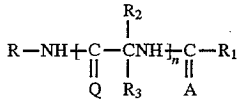
Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control and most have disturbing side-effects.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

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:



wherein R, R_1, R_2, R_3, R_4, R_5, R_6, n, Z, Y, A and Q 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 treatment of epilepsy, nervous anxiety, psychosis, insomnia and other related central nervous disorders.

The alkyl groups when used alone or in combination with other groups, 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, when used along or in combination, refers to an aromatic group which contains from 6 up to 18 ring carbon atoms and up to a total of 25 carbon atoms and includes the polynuclear aromatics. These aryl groups may be monocyclic, bicyclic, tricyclic or polycyclic and are fused rings. Polynuclear aromatic compound is meant to encompass bicyclic, tricyclic fused aromatic ring system containing from 10–18 ring carbon atoms and up to a total of 25 carbon atoms. The aryl group includes phenyl, and the polynuclear aromatics e.g., naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like. The aryl group also includes groups like ferrocenyl.

Lower alkenyl is an 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 alkyene 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-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl and the like.

The term cycloalkyl when used alone or in combination is a cycloalkyl group containing from 3 to 18 ring carbon atoms and up to a total of 25 carbon atoms. The cycloalkyl groups may be monocyclic, bicyclic, tricyclic, or polycyclic and the rings are fused. The cycloalkyl may be completely saturated or partially saturated. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclohexenyl, cyclopentenyl, cyclooctenyl, cycloheptenyl, decalinyl, hydroindanyl, indanyl, fenchyl, pinenyl, adamantyl, and the like. Cycloalkyl includes the cis or trans forms. Furthermore, the substituents may either be in endo or exo positions in the bridged bicyclic systems.

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 N.Y., 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, carboxyamido, aryl, quaternary ammonium, trifluoromethyl, aryl lower alkanoyl, carbalkoxy 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, lower alkylthio, lower alkylmercapto, disulfide (lower alkyldithio) 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.

The term acyl includes lower alkanoyl.

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. They 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, isothiazolyl, 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, pyridazinyl, 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, pyrroly, benzofuryl, benzothienyl, indolyl, methylpyrrolyl, merpholinyl, pyridyl,

pyrazinyl, imidazolyl, pyrimidinyl, pyrazolyl or pyridazinyl. The preferred heterocyclic is a 5 or 6-membered heterocyclic compound. The especially preferred heterocyclic is furyl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl, epoxy, pyrimidinyl, or pyridazinyl. The most preferred heterocyclics are furyl, pyrazolyl, pyrrolyl and pyridyl.

The preferred compounds are those wherein n is 1, but di, tri and tetrapeptides are also contemplated to be within the scope of the claims.

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 withdrawing substituent 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(loweralkyl)amino, amine lower alkyl mercapto, mercaptoalkyl, alkylthio; and alkyldithio. The term "sulfide" encompasses mercapto, mercapto alkyl and alkylthio, while the term disulfide encompasses alkyldithio. These preferred substituents may be substituted on any one of R_1, R_2, R_3, R_4, R_5 or R_6, R_7 or R_8 as defined herein.

The ZY groups representative of R_2 and R_3 include hydroxy, alkoxy, such as methoxy, ethoxy, aryloxy, such as phenoxy; thioalkoxy, such as thiomethoxy, thioethoxy; thioaryloxy such as thiophenoxy; amino; alkylamino, such as methylamino, ethylamino; arylamino, such as anilino; lower dialkylamino, such as, dimethylamino; trialkyl ammonium salt, hydrazino, alkylhydrazino and arylhydrazino, such as N-methylhydrazino, N-phenylhydrazino, carbalkoxy hydrazino, aralkoxycarbonyl hydrazino, aryloxycarbonyl hydrazino, hydroxylamino, such as N-hydroxylamino (—NH—OH), lower alkoxy amino [($NHOR_{18}$) wherein R_{18} is lower alkyl], N-lower alkylhydroxyl amino [(NCR_{18})OH wherein R_{18} is lower alkyl], N-lower alkyl-O-lower alkyl hydroxyamino, i.e., [$N(R_{18})OR_{19}$ wherein R_{18} and R_{19} are independently lower alkyl] and o-hydroxylamino (—O—NH_2); alkylamido such as acetamido, trifluoroacetamido, lower alkoxyamino, (e.g. $NH(OCH_3)$; and heterocyclicamino, such as pyrazoylamino.

Furthermore, in still another embodiment Z may be O, S, NR_4 or PR_4 and Y may be hydrogen, lower alkyl or aryl and R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, n and a are as defined hereinabove.

In a still further embodiment, ZY may be

$$NR_4CR_5,\ SCR_5\ \text{or}\ NR_4C(=O)OR_5,\ SC(=O)OR_5$$

and R, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, n and a are as defined hereinabove.

When R_2 or R_3 is heterocyclic, the preferred heterocyclics are furyl, tetrahydrofuryl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl or epoxy. The most preferred heterocyclic is furyl, pyridyl, pyrazoyl and pyrrolyl.

The preferred heterocyclic groups representative of R_2 and R_3 have the formula

XI

or those corresponding partially or fully saturated form thereof wherein n is 0 or 1

A, Z, L and J are independently CH, or a heteroatom selected from the group consisting of N, O, S, and

G is CH, or a heteroatom selected from the group consisting of N, O and S,

but when n is O, G is CH, or a heterocyclic selected from the group consisting of NH, O and S with the proviso that at most two of A, E, L, J and G are heteroatoms.

If the ring depicted hereinabove contains a nitrogen ring atom, then the N-oxide forms are also contemplated to be within the scope of the invention.

When R_2 or R_3 is a heterocyclic of the above formula, it may be bonded to the main chain by a ring carbon atom. When n is O, R_2 or R_3 may additionally be bonded to the main chain by a nitrogen ring atom.

R_2 or R_3 may independently also be SO_3^-, or SO_2^-.

Furthermore, ZY may also be

$$NR_4CNR_5R_6,\ NR_4CNR_5S(O)aR_6,\ NR_4C(=O)NR_5R_6,\ C(=O)NH_2\ \text{or or}$$

$$R_4CMNR_5COR_6.$$
(Q, A)

When R_2 is alkenyl the alkenyl group is a lower alkenyl group having 1–6 carbon atoms. The alkenyl group may be substituted with an electron donating group and more preferably with an electron withdrawing group, such as COOH.

As indicated hereinabove, Q and A may be O or S; in other words, the main chain may contain only C=O, only —C=S or combinations thereof. All such permutations are contemplated herein. It is preferred that the compounds of the present invention contain no more than 2 C=S moieties, it is even more preferred that the compounds of the present invention contain no more than 1 C=S moiety. The most preferred embodiment are when A and Q are both oxygen.

An embodiment of the present application is one in which the compounds are of Formula I wherein R is lower cycloalkyl or lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group and R_1, R_2, R_3, Z, Y or ZY taken together, R_4, R_5, R_6, R_7, R_8, n and a are as defined herein.

Another embodiment of the present invention include compounds of Formula I wherein R_1 is lower cycloalkyl or lower cycloalkyl lower alkyl and R_1 may be unsubstituted or substituted with an electron donating group or electron withdrawing group and R_1, R_2, R_3, Z, Y, or ZY taken together, R_4, R_5, R_6, R_7, R_8 n and a are as defined hereinabove.

Another embodiment of the present invention includes compounds of Formula I wherein R_2 is lower cycloalkyl or lower cycloalkyl lower alkyl and R_2 may be unsubstituted or substituted with an electron donating group or electron withdrawing group, and R, R_1, R_3, R_4, R_5, R_6, R_7, R_8 and a are as defined hereinabove.

Still another embodiment of the present invention include compounds of Formula I wherein R_3 is lower cycloalkyl or lower cycloalkyl lower alkyl and R_3 may be unsubstituted or substituted with an electron donating or electron withdraw-

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