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# (54) ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES

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#### Related U.S. Patent Documents

Reissue of:

(64) Patent No.: 5,773,475 Issued: Jun. 30, 1998 Appl. No.: 08/818,688

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(60) Provisional application No. 60/013,522, filed on Mar. 15, 1996.

(51) Int. Cl.<sup>7</sup> ...... A61K 31/165; C07C 233/05

(52) U.S. Cl. ...... 514/616; 564/155; 564/158

(56) References Cited

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#### FOREIGN PATENT DOCUMENTS

EP 0 194 464 9/1986

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#### (57) ABSTRACT

The present invention is directed to a compound in the R configuration about the asymmetric carbon in the following formula:

$$\begin{array}{c|cccc} Ar & --CH_2NHC & --C & --N & --C & --Q_1, \\ \parallel & \parallel & \parallel & \parallel \\ O & CH_2 & O \\ & \parallel & Q \end{array}$$

pharmaceutical compositions containing same and the use thereof in treating CNS disorders in animals.

13 Claims, No Drawings



# ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

#### RELATED APPLICATION

This application claims priority from U.S. provisional application No. 60/013,522 filed on Mar. 15, 1996.

#### GOVERNMENT SUPPORT

This invention was made with Government support under 15 Grant/Contract No. NIH MS 15604 awarded by the National Institute of Health. The Government has certain rights in the invention.

#### FIELD OF THE INVENTION

The present invention relates to novel enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders.

#### BACKGROUND OF THE INVENTION

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 40 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 45 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 non- 50 convulsive 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 55 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. 60 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. 4,372,974 to Fish, et al. discloses a pharmaceutical formulation containing an aliphatic amino 65 acid compound in which the carboxylic acid and primary mine are constant by three or four unite Administration of

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these compounds in an acid pH range are useful in the treatment of convulsion disorders and also possess anxiolytic and sedative properties.

U.S. Pat. No. 5,378,729 to Kohn, et al. discloses compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders having the following general formula:

$$R - NH + \begin{bmatrix} R_2 \\ I \\ C - CNH \\ II \\ O R_3 \end{bmatrix} C - R_1$$

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl 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<sub>1</sub> 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, 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<sub>4</sub>, PR<sub>4</sub> or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, or heterocyclic lower alkyl, 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  $NR_4NR_5R_7$ ,  $NR_4OR_5$ ,  $ONR_4R_7$ ,  $OPR_4R_5$ ,  $PR_4OR_5$ ,  $SNR_4R_7$ ,  $NR_4SR_7$ ,  $SPR_4R_5$ ,  $PR_4SR_7$ ,  $NR_4PR_5R_6$ ,  $PR_4NR_5R_7$ ,

 $R_4$ ,  $R_5$  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,

 $R_7$  is  $R_6$ , COOR<sub>8</sub> or COR<sub>8</sub>,

 $R_8$  is hydrogen, 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

n is 1-4 and

a is 1–3.

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



not apparent with acute administration. Because many drugs which require chronic administration ultimately place an extra burden on the liver, including for example, liver enzyme induction or oxidative metabolism that may generate reactive species, many anticonvulsants have associated therewith liver toxicity.

Research is continuing in this area to find better and more effective anticonvulsant agents, especially for long term treatment (chronic administration). Obviously, the ideal drug is one that has high pharmacological activity, minimal side effects and is relatively non-toxic and safe to the animal that is being treated. More specifically, the ideal anticonvulsant drug is one that satisfies the following four criteria: (1) has a high anticonvulsant activity, (expressed as a low ED<sub>50</sub>); (2) has minimal neurological toxicity, (as expressed by the median toxic dose ( $TD_{50}$ )), relative to its potency; (3) has a maximum protective index (sometimes known as selectivity or margin of safety), which measures the rela- 20 tionship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD<sub>50</sub>/ED<sub>50</sub>); and (4) is relatively safe as measured by the median lethal dose (LD50) relative to its potency and is non-toxic to the animal that is being treated, e.g., it exhibits minimal adverse effects on the remainder of the treated animal, its organs, blood, its bodily functions, etc. even at high concentrations, especially during long term chronic 30 administration of the drug. Thus, for example, it exhibits minimal, i.e., little or no liver toxicity. Although not as critical in short term or acute administration of an anticonvulsant, since the animal may tolerate some low levels of toxicity, the fourth criteria outlined above is extremely important for an anti-convulsant which is to be taken over a long period of time (chronic administration) or in high dosage. It may be the most important factor in determining which anti-convulsant to administer to a patient, especially 40 if chronic dosing is required. Thus, an anti-convulsant agent which has a high anti-convulsant activity, has minimal neurological toxicity and maximal P.I. (protective index) may unfortunately exhibit such toxicities which appear upon repeated high levels of administration. In such an event, acute dosing of the drug may be considered, but it would not be used in a treatment regime which requires chronic administration of the anti-convulsant. In fact, if an anticonvulsant is required for repeated dosing in a long term 50 treatment regime, a physician may prescribe an anticonvulsant that may have weaker activity relative to a second anti-convulsant, if it exhibits relatively low toxicity to the animal. An anti-convulsant agent which meets all four criteria is very rare.

However, the present inventor has found such a group of compounds that is generally potent, exhibit minimal neurological toxicity, has a high protective index and is relatively non-toxic to the body organs, including the liver upon multiple dosing.

#### SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to 65 N-benzyl-2-acetamido propionamide derivatives in the R configuration baying the formula:

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wherein

Ar is aryl which is unsubstituted or substituted with halo; Q is lower alkoxy; and

 $Q_1$  is  $CH_3$ .

The present invention contemplates employing the compound of Formula I in a pharmaceutical composition. Moreover, the administration of an effective amount of the present compounds in their pharmaceutically acceptable forms provides an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia, and other related central nervous disorders.

These drugs exhibit high anti-convulsant activity, minimal neurological toxicity, high P.I. and minimal toxicity. These anti-convulsants are utilized in a treatment regime requiring acute dosing, and especially chronic dosing thereof to the patient.

As shown hereinbelow, the compounds of the present invention exhibit minimal effects on liver, which is in contrast to other anti-convulsant compounds.

## DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "alkoxy" refers to an O-alkyl group attached to the main chain through an oxygen bridge, wherein alkyl is as defined hereinabove. The alkoxy groups are lower alkoxy groups containing one to six carbon atoms, and more preferably, one to three carbon atoms. The most preferred alkoxy groups are propoxy, isopropoxy, ethoxy and especially methoxy.

The term "aryl", when used alone or in combination, refers to a phenyl group which is unsubstituted or substituted with halo.

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

It is preferred that Q in the compound of formula I is alkoxy having 1–3 carbon atoms. The most preferred alkoxy group is propoxy, isopropoxy, ethoxy and especially methoxy.

The Ar group as defined herein, is phenyl, which may be unsubstituted or substituted as defined herein. It is most preferred that the aryl group, i.e., phenyl, is unsubstituted or substituted with only one halo group. It is more preferred that if substituted, the halo substituent is in the para or meta position. It is even more preferred that the phenyl group is unsubstituted.

Examples of the compounds of the present invention include:

(R)-N-Benzyl-2-acetamido-3-methoxy propionamide,

(R)-N-(3-Fluorobenzyl)-2-acetamido-3methoxypropionamide,

(R)-N-(4-Fluorobenzyl)-2-acetamide-3methoxypropionamide,

(R)-N-Benzyl-2-acetamido-3-ethoxy propionamide.

As indicated by the asterisk in formula I, the compounds of the present invention contain at least one asymmetric carbon. The stereochemistry of the asymmetric carbon at the



asterisk is in the R configuration. The inventor has found that the R stereoisomer at the asymmetric carbon at the asterisk is significantly more efficacious than the corresponding S enantiomer or a racemic mixture thereof.

It is preferred that the compound of the present invention 5 be substantially pure, i.e., substantially free from impurities. It is most preferred that the compounds of the present invention be at least 75% pure (w/w) and more preferably greater than about 90% pure (w/w) and most preferably greater than about 95% pure (w/w).

It is also preferred that the compounds of the present invention be substantially enantiomerically pure, i.e., substantially free from the corresponding S isomer. It is more preferred that the compounds of the present invention contain at least 90% (w/w) R stereoisomer, and most preferably greater than about 95% (w/w) in the R stereoisomer. Thus, the present invention contemplates compounds having at most about 10% S isomer (w/w), and even more preferably less than about 5% S isomer (w/w).

The compounds of the present invention in the R form are 20 prepared by art recognized techniques from commercially available starting materials.

An exemplary procedure is outlined in Scheme 1 hereinbelow:

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The enantiopurity of 4 was determined by techniques known in the art, including melting point, optical rotation and  $^1H$  NMR upon addition of an organic acid in the R-configuration, such as R(–)- mandelic acid. Crystallization of 4 was repeated until the desired enantiopurity thereof was achieved. The product of 4 is converted to the ether under Williamson conditions by reacting it with QX, wherein Q is as defined herein above and X is good leaving groups, such as OTs, OMs, or halide (e.g.,  $\mathrm{CH_3I}$ ) and the like in the presence of base (e.g.,  $\mathrm{Ag_2O}$ ) to form the product (5) having Formula I.

A D serine molecule (1) is esterified under acylation conditions with an alcohol, such as acidic methanol, to 50 provide the corresponding ester (2). 2 is reacted with ArCH<sub>2</sub>NH<sub>2</sub>, such as benzylamine, under acylation conditions to form the corresponding amide (3). Acylation of the free amino group, with an acylating derivative of

such as acetic acid, or lower alkyl ester of acetic acid, or  $_{65}$  acetic anhydride provides the hydroxymethyl derivative,

Another variation is depicted in Scheme 2.

Scheme 2



(R)-8

For example, beginning with D-serine (1), treatment with an acylating derivative of acetic acid such as acetic anhydride in acetic acid, gives the corresponding amide 6 which is then reacted with ArCH<sub>2</sub>NH<sub>2</sub> under mixed anhydride coupling reaction conditions, as described by Anderson, et al., in JACS, 1967, 89, 5012–5017, the contents of which are incorporated herein by reference, to give the corresponding 25 compound of the formula:

e.g., 7. Alkylation of this R-product in the presence of base under Williamson conditions, such as methyl iodide in Ag<sub>2</sub>O, provides a product of Formula I (8).

An alternative route is depicted in Scheme 3.

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-continued
OCH<sub>3</sub>

H<sub>2</sub>, 10% Pd—C

MeOH, 1 hr 15 min
97%

Ac<sub>2</sub>O, Pyridine, DMAP

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OCH<sub>3</sub>

Ac<sub>2</sub>O, Pyridine, DMAP

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D Serine (1) is protected with a N-protecting group known in the art, by standard techniques. Thus, for example, it is reacted with carbobenzoxy chloride (CBZ-cl, benzyl chloroformate) generating the N-protected CBZ-D-serine adduct 9. The product serine adduct is converted to the corresponding ether under Williamson conditions by reacting it with QX wherein Q and X are defined hereinabove 40 (e.g., CH<sub>3</sub>I) in the presence of base (e.g., Ag<sub>2</sub>0) to form an ether 10. Under these conditions, the acid is also esterified. Subsequent hydrolysis of the ester group in 10 permits amide coupling with ArCH<sub>2</sub> NH<sub>2</sub> using amide coupling methodology (e.g., mixed anhydride 1,1' 45 Carbonyldiimidazole) to give the amide 12. Deprotection of the N-protecting group provide the free amine 13 which is then reacted with an acylating agent such as acetic anhydride in base, (e.g., pyridine) to provide the product (R)-8.

(R)-8

If necessary, in any of the procedures described 50 hereinabove, the optical purity of the product may be enhanced by further separation of the S enantiomer from the R enantiomer, by standard techniques known in the art, such as chiral chromatography using a standard chiral support known in the art.

Alternatively, in any of the procedures provided hereinabove, a racemic D serine may be utilized as the starting material. Following the procedures in any of the schemes outlined hereinabove would provide the racemic mixture, which can be resolved into the R isomer by standard techniques known in the art such as chiral chromatography.

The active ingredients of the therapeutic compositions and the compounds of the present invention exhibit excellent anticonvulsant activity when administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For

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