

ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES

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.

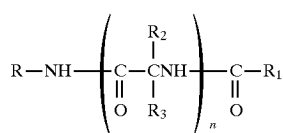
BACKGROUND OF THE INVENTION

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 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 oxazolinediones, such as trimethadione and paramethadione, are used in the treatment of non-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 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. 4,372,974 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.

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 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.

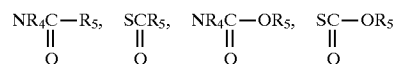
R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

R₂ and R₃ 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 R₂ and R₃ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, S(O)_n, NR₄, PR₄ 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 NR₄NR₅R₇, NR₄OR₅, ONR₄R₇, OPR₄R₅, PR₄OR₅, SNR₄R₇, NR₄SR₇, SPR₄R₅, PR₄SR₇, NR₄PR₅R₆, PR₄NR₅R₇,



R₄, R₅ and R₆ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R₄, R₅ and R₆ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group,

R₇ is R₆, COOR₈ or COR₈,

R₈ 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 effects. Toxicities may appear upon repeated dosing that are 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 ED₅₀); (2) has minimal neurological toxicity, (as expressed by the median toxic dose (TD₅₀)), relative to its potency; (3) has a maximum protective index (sometimes known as

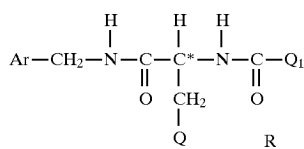
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selectivity or margin of safety), which measures the relationship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50}); and (4) is relatively safe as measured by the median lethal dose (LD_{50}) 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 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 anti-convulsant, 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 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 anti-convulsant is required for repeated dosing in a long term treatment regime, a physician may prescribe an anti-convulsant 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 N-benzyl-2-acetamido propionamide derivatives in the R configuration having the formula:



wherein

Ar is aryl which is unsubstituted or substituted with halo; Q is lower alkoxy; and Q₁ is CH₃.

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.

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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-3-methoxypropionamide,

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

(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.

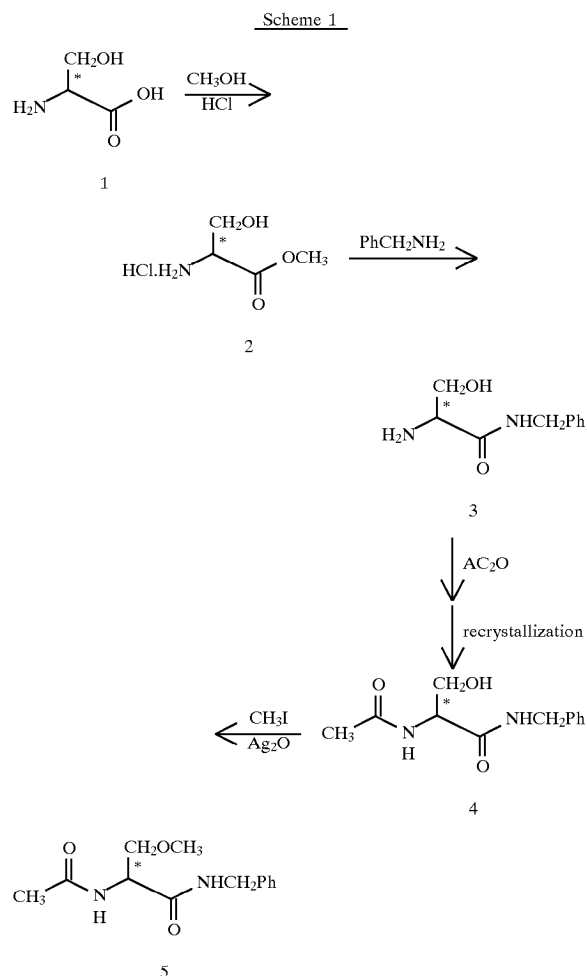
It is preferred that the compound of the present invention be substantially pure, i.e., substantially free from impurities. It is most preferred that the compounds of the present invention be at least 75% pure (w/w) and more preferably greater than about 90% pure (w/w) and most preferably greater than 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 prepared by art recognized techniques from commercially available starting materials.

An exemplary procedure is outlined in Scheme 1 hereinbelow.

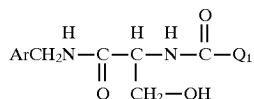
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A D serine molecule (1) is esterified under acylation conditions with an alcohol, such as acidic methanol, to provide the corresponding ester (2). 2 is reacted with ArCH_2NH_2 , such as benzylamine, under acylation conditions to form the corresponding 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 acetic anhydride provides the hydroxymethyl derivative, i.e.,

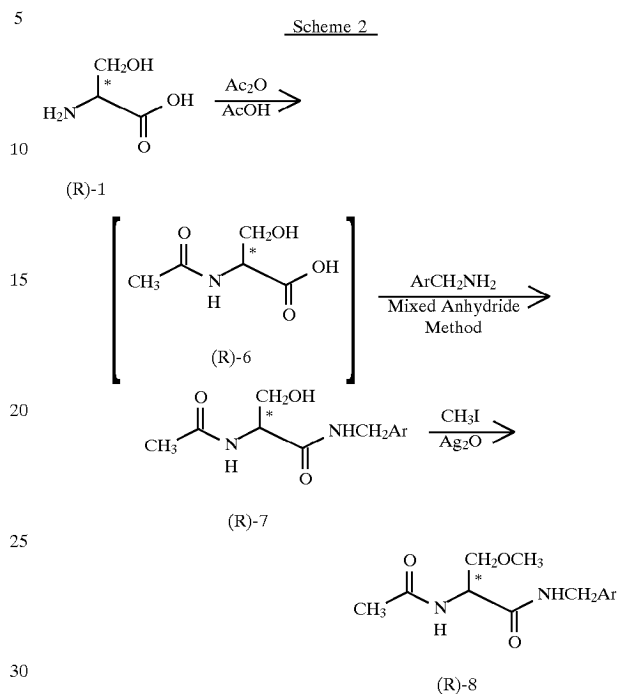


The enantiopurity of 4 was determined by techniques known in the art, including melting point, optical rotation and ^1H NMR upon addition of an organic acid in the R-configuration, such as R(-)- mandelic acid. Crystallization of 4 was repeated until the desired enantiopurity thereof was achieved. The product of 4 is converted to the ether under Williamson conditions by reacting it with QX,

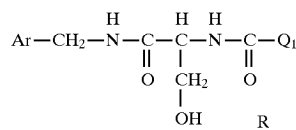
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in the presence of base (e.g., Ag_2O) to form the product (5) having Formula I.

Another variation is depicted in Scheme 2.

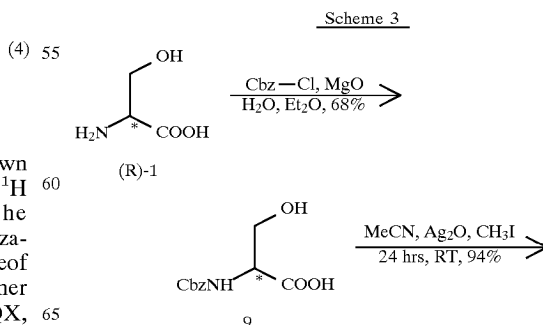


For example, beginning with D-serine (1), treatment with an acylating derivative of acetic acid such as acetic anhydride in acetic acid, gives the corresponding amide 6 which is then reacted with ArCH_2NH_2 under mixed anhydride coupling reaction conditions, as described by Anderson, et al., in *JACS*, 1967, 89, 5012-5017, the contents of which are incorporated herein by reference, to give the corresponding compound of the formula:

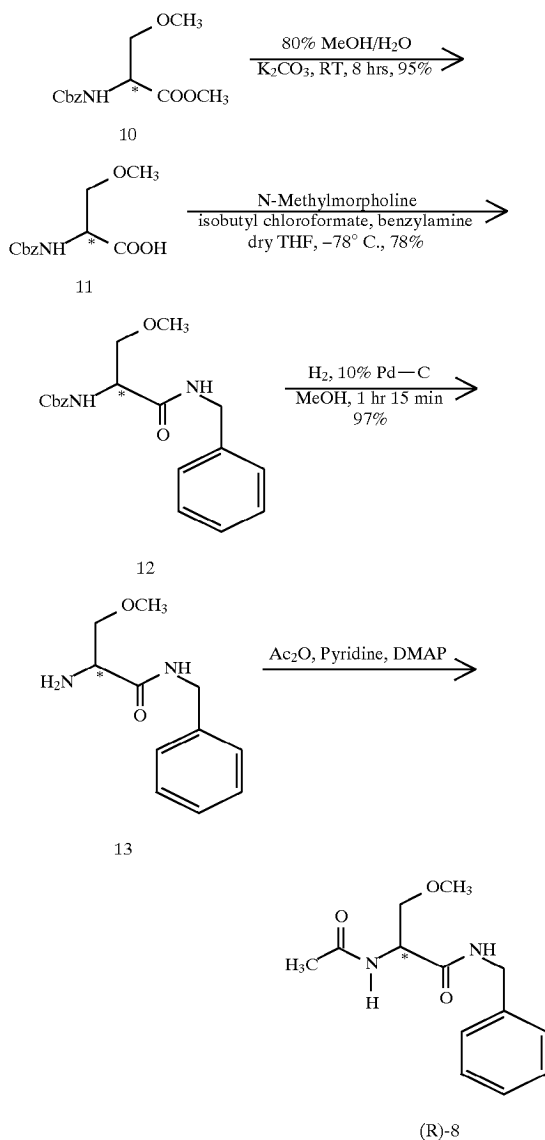


e.g., 7. Alkylation of this R-product in the presence of base under Williamson conditions, such as methyl iodide in Ag_2O , provides a product of Formula I (8).

An alternative route is depicted in Scheme 3.



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-continued
Scheme 3

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 protected serine adduct is converted to the corresponding ether under Williamson conditions by reacting it with QX wherein Q and X are defined hereinabove (e.g., CH₃I) in the presence of base (e.g., Ag₂O) 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 ArCH₂NH₂ using amide coupling methodology (e.g., mixed anhydride 1,1'-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.

If necessary, in any of the procedures described 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

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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 example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that the active compound may be administered in an convenient manner such as by the oral, intravenous (where water soluble), intramuscular or subcutaneous routes.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly into the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 1000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. For example, sustained release dosage forms are contemplated wherein the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to modify the release properties of the resin.

The active compound may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in

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