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AMINO ACID DERIVATIVE ANTICONVULSANT

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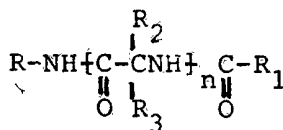
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(57) The present invention contemplates employing the compounds of Formula I in compositions of pharmaceutically acceptable dosage forms. Where the appropriate substituents are employed, the present invention also includes pharmaceutically acceptable 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.

CLAIM

1. An anticonvulsant composition comprising an anticonvulsant effective amount of a compound having the following general formula:



wherein R is aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl

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polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

R_1 is H or lower alkyl, unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

R_2 and R_3 , independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating 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;

n is 1 to 4; and

a pharmaceutically acceptable carrier.



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COMPLETE SPECIFICATION

(ORIGINAL)

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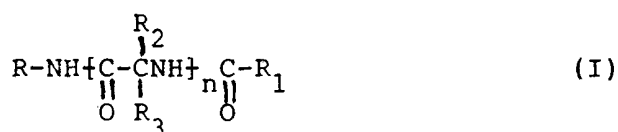
Complete Specification for the invention entitled:
AMINO ACID DERIVATIVE ANTICONVULSANT

The following statement is a full description of this invention, including the best method of performing it known to me:—

-19-

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n is i to 4.

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1 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
5 convulsions with loss of consciousness.

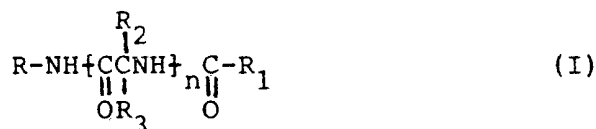
5 The mainstay of treatment for such disorders has
been the long-term and consistent administration of
anticonvulsant drugs. Most drugs in use are weak acids that,
presumably, exert their action on neurons, glial cells or
10 both of the central nervous system. The majority of these
compounds are characterized 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.

15 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
20 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
25 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.
30 relates to triazole derivatives which exhibit anticonvulsant
activity and are useful in the treatment of epilepsy and

1 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
 5 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.

10 Unfortunately, despite the many available pharma-
 cotherapeutic 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
 15 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:



20
 25 wherein R and R₁, 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;

30 R₂ and R₃, independently, are lower alkenyl, lower alkynyl,
 Heterocyclic, lower alkyl heterocyclic, polynuclear aromatic

35



1 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
5 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
10 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,
15 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,
20 amyl, hexyl, and the like.

The aryl groups of R, R₁, R₂ and R₃ are aromatic
compounds containing from 6 to 10 ring carbon atoms; and
include phenyl, α - and β -naphthyl. Moreover, the aryl
groups also include organometallic compounds wherein a metal
or metalloidal atom is sandwiched between two aromatic
25 compounds, e.g., cyclopentadienyl 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
30 the like, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenyl-
ethyl, and the like.

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

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

10 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.

15 These heterocyclic substituents include heteroaromatics and
saturated and partially unsaturated heterocyclic compounds
such as furyl, thienyl, pyranyl, pyrrolyl, imidazolyl,
pyrazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl,
indolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl,
piperidyl, pyrrolinyl, piperazinyl, quinolyl, trizaolyl,
tetrazolyl, and the like.

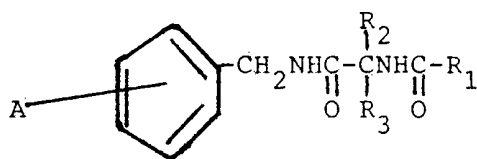
20 The polynuclear aromatic substituents contemplated
herein are polyaromatic compounds containing up to 4 fused
rings and containing up to 18 ring carbon atoms, for example,
naphthyl, anthracenyl, phenanthrenyl, azulenyl, and the like.

25 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.

30 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

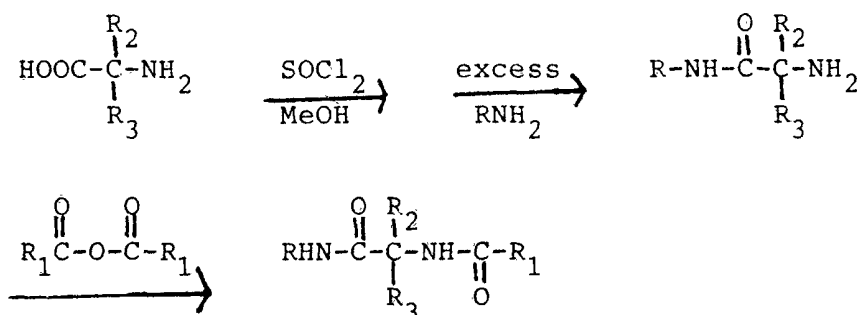
1 the alkenyl, alkynyl, aryl, heterocyclic and polynuclear
aromatic groups of R_2 and R_3 , may also be unsubstituted or
substituted with one or more substituents which can be
characterized as either electron withdrawing groups or
5 electron donating groups as defined above.

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

10 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.

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

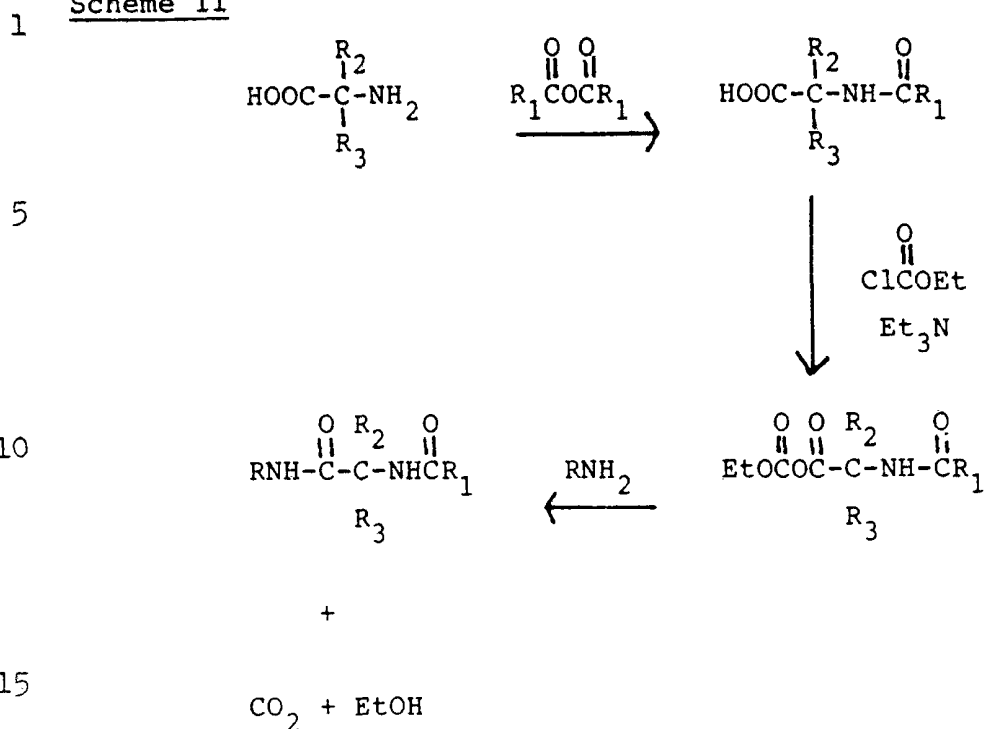
20 Scheme I



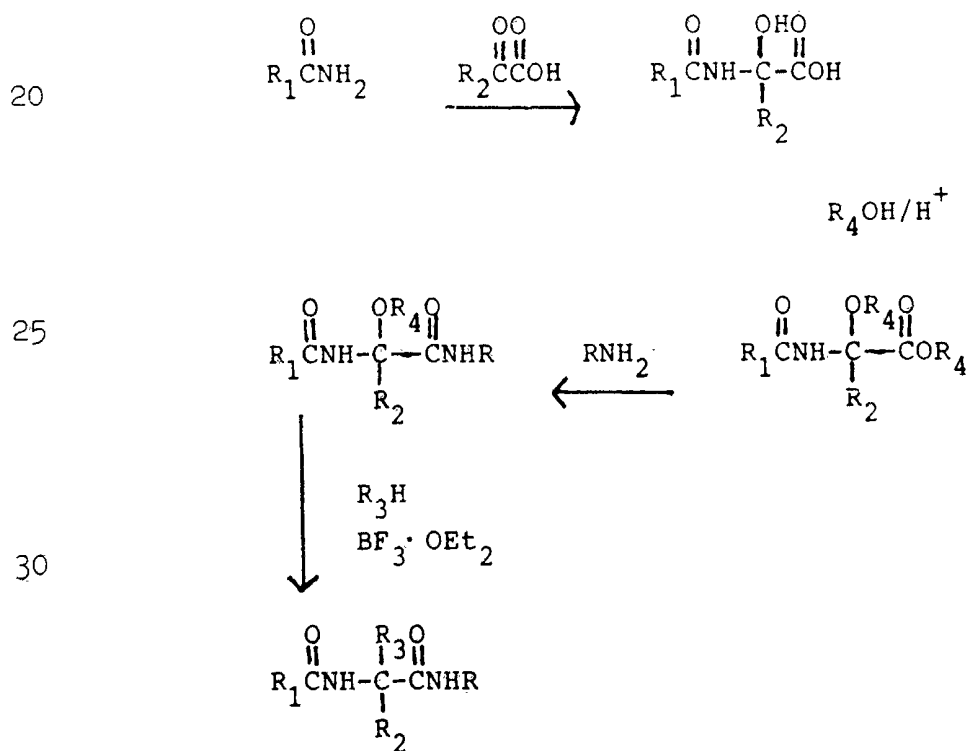
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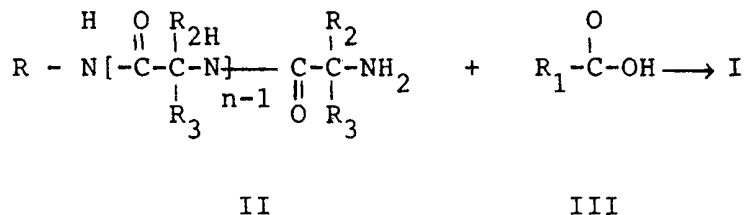
Scheme II



Scheme III

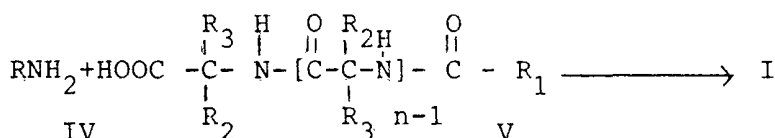


More specifically, these compounds can be prepared by art-recognized procedures from known compounds or readily preparable intermediates. For instance, compounds of Formula I can be prepared by reacting amines of Formula II with an acylating derivative of a carboxylic acid of Formula III under amide forming conditions:



wherein R, R₁, R₂, R₃ are as defined hereinabove.

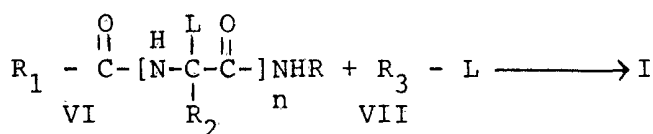
Alternatively, the compound of Formula I can be prepared by reacting an amine of Formula IV with an acylating derivative of a carboxylic acid of Formula V under amide forming conditions:



wherein R, R₁, R₂ and R₃ are as defined hereinabove.

Another useful method for preparing a compound of Formula I involves simple substitution reactions.

An exemplary procedure is as follows:



wherein R, R₁, R₂, R₄ and n have the aforesaid meanings and R₃ is defined heretofore except it is not aryl, heteroaromatic or polynuclear aromatic and L and L' are independently a good leaving group, such as halides,

1 tosylates, mesoylates, brosylates, benzyloxy and the like.
In this procedure the amine of Formula VI is reacted with a
compound of Formula VII under substitution conditions. The
reaction may take place in the presence of an acid, such as
5 inorganic acid, e.g., hydrochloric acid, sulfuric acid or
Lewis acid, such as boron trifluoride and the like or in the
presence of a base, such as triethylamine.

However, when R_3 is heteroaromatic, aryl or
polynuclear aromatic, L is hydrogen. In the procedure under
10 these circumstances, the reaction should take place in the
presence of an acid catalyst, such as an inorganic acid,
e.g., hydrochloric acid or a Lewis acid, such as
borontrifluoride.

The amide forming conditions referred to herein
involve the use of known derivatives of the described acids,
15 such as the acylhalides, (e.g., $R-C-X$,



wherein X is Cl, Br, and the like), anhydrides

20 (e.g., $R_1-\overset{\overset{O}{\parallel}}{C}-O-\overset{\overset{O}{\parallel}}{C}-R_1$), mixed anhydrides, lower alkyl esters,
carbodiimides, carbonyldiimidazoles, and the like. It is
preferred that the acylating derivative used is the

anhydride, $R_1-\overset{\overset{O}{\parallel}}{C}-O-\overset{\overset{O}{\parallel}}{C}-R_1$.

25 As in any organic reaction, solvents can be
employed such as methanol, ethanol, propanol, acetone,
tetrahydrofuran, dioxane, dimethylformamide, dichloromethane,
chloroform, and the like. The reaction is normally effected
at or near room temperature, although temperatures from 0°C
30 up to the reflux temperature of the reaction mixture can be
employed.

1 As a further convenience, the amide forming
reaction can be effected in the presence of a base, such as
tertiary organic amine, e.g., triethylamine, pyridine,
picolines and the like, particularly where hydrogen halide is
5 formed by the amide forming reaction, e.g., acyl halide and
the amine of Formula II. Of course, in those reactions where
hydrogen halide is produced, any of the commonly used
hydrogen halide acceptors can also be used.

10 The exact mineral acid or Lewis acid employed in
the reaction will vary depending on the given transformation,
the temperature required for the conversion and the
sensitivity of the reagent toward the acid in the reaction
employed.

15 The various substituents on the present new
compounds, e.g., as defined in R, R₁, R₂ and R₃ can be
present in the starting compounds, added to any one of the
intermediates or added after formation of the final products
by the known methods of substitution or conversion reactions.
For example, the nitro groups can be added to the aromatic
20 ring by nitration and the nitro group converted to other
groups, such as amino by reduction, and halo by diazotization
of the amino group and replacement of the diazo group.
Alkanoyl groups can be substituted onto the aryl groups by
Friedel-Crafts acylation. The acyl groups can be then
25 transformed to the corresponding alkyl groups by various
methods, including the Wolff-Kishner reduction and Clemmenson
reduction. Amino groups can be alkylated to form mono,
dialkylamino and trialkylamino groups; and mercapto and
hydroxy groups can be alkylated to form corresponding
30 thioethers or ethers, respectively. Primary alcohols can be
oxidized by oxidizing agents known in the art to form
carboxylic acids or aldehydes, and secondary alcohols can be

1 oxidized to form ketones. Thus, substitution or alteration
reactions can be employed to provide a variety of
substituents throughout the molecule of the starting
material, intermediates, or the final product.

5 In the above reactions, if the substituents
themselves are reactive, then the substituents can themselves
be protected according to the techniques known in the art. A
variety of protecting groups known in the art may be
employed. Examples of many of these possible groups may be
10 found in "Protective Groups in Organic Synthesis," by T.W.
Green, John Wiley & Sons, 1981.

The present compounds obviously exist in stereo-
isomeric forms and the products obtained thus can be mixtures
of the isomers, which can be resolved. Alternatively, by
15 selection of specific isomers as starting compounds or
synthetic intermediates, the preferred stereoisomer can be
produced.

The active ingredients of the therapeutic
compositions and the compounds of the present invention
20 exhibit excellent anticonvulsant activity when administered
in amounts ranging from about 10 mg to about 100 mg per
kilogram of body weight per day. A preferred dosage regimen
for optimum results would be from about 20 mg to about 50 mg
per kilogram of body weight per day, and such dosage units
25 are employed that a total of from about 1.0 gram to about 3.0
grams of the active compound for a subject of about 70 kg of
body weight are administered in a 24-hour period. This
dosage regimen may be adjusted to provide the optimum
therapeutic response and is preferably administered one to
30 three times a day in dosages of about 600 mg per
administration. For example, several divided doses may be
administered daily or the dose may be proportionally reduced

1 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,
intraveneous (where water soluble), intramuscular or
subcutaneous routes.

5 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
capsule, or it may be compressed into tablets, or it may be
10 incorporated directly with 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
15 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
20 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.

25 The tablets, troches, pills, capsules and the like
may also contain the following: A binder such as gum traga-
canth, 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
30 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

1 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
5 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
10 pure and substantially non-toxic in the amounts employed. In
addition, the active compound may be incorporated into
sustained-release preparations and formulations.

The active compound may also be administered
parenterally or intraperitoneally. Dispersions can also be
15 prepared in glycerol, liquid polyethylene glycols, and
mixtures thereof and in oils. Under ordinary conditions of
storage and use, these preparations contain a preservative to
prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable
20 use include sterile aqueous solutions (where water soluble)
or dispersions and sterile powders for the extemporaneous
preparation of sterile injectable solutions or dispersions.
In all cases the form must be sterile and must be fluid to
the extent that easy syringability exists. It must be stable
25 under the conditions of manufacture and storage and must be
preserved against the contaminating action of microorganisms
such as bacteria and fungi. The carrier can be a solvent or
dispersion medium containing, for example, water, ethanol,
polyol (for example, glycerol, propylene glycol, and liquid
30 polyethylene glycol, and the like), suitable mixtures
thereof, and vegetable oils. The proper fluidity can be
maintained, for example, by the use of a coating such as

1 lecithin, by the maintenance of the required particle size in
the case of dispersion and by the use of surfactants. The
prevention of the action of microorganisms can be brought
about by various antibacterial and antifungal agents, for
5 example, parabens, chlorobutanol, phenol, sorbic acid,
thimerosal, and the like. In many cases, it will be
preferable to include isotonic agents, for example, sugars or
sodium chloride. Prolonged absorption of the injectable
compositions can be brought about by the use in the
10 compositions of agents delaying absorption, for example,
aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by
incorporating the active compound in the required amount in
the appropriate solvent with various of the other ingredients
enumerated above, as required, followed by filtered
15 sterilization. Generally, dispersions are prepared by
incorporating the various sterilized active ingredient into a
sterile vehicle which contains the basic dispersion medium
and the required other ingredients from those enumerated
above. In the case of sterile powders for the preparation of
sterile injectable solutions, the preferred methods of
preparation are vacuum drying and the freeze-drying technique
which yield a powder of the active ingredient plus any
additional desired ingredient from previously sterile-
20 filtered solution thereof.

As used herein, "pharmaceutically acceptable
carrier" includes any and all solvents, dispersion media,
coatings, antibacterial and antifungal agents, isotonic and
absorption delaying agents, and the like. The use of such
media and agents for pharmaceutical active substances is well
30 known in the art. Except insofar as any conventional media
or agent is incompatible with the active ingredient, its use
in the therapeutic compositions is contemplated.

1 Supplementary active ingredients can also be incorporated
into the compositions.

It is especially advantageous to formulate
parenteral compositions in dosage unit form for ease of
administration and uniformity of dosage. Dosage unit form as
5 used herein refers to physically discrete units suited as
unitary dosages for the mammalian subjects to be treated;
each unit containing a predetermined quantity of active
material calculated to produce the desired therapeutic effect
in association with the required pharmaceutical carrier. The
10 specification for the novel dosage unit forms of the
invention are dictated by and directly dependent on (a) the
unique characteristics of the active material and the
particular therapeutic effect to be achieved, and (b) the
15 limitations inherent in the art of compounding such an active
material for the treatment of disease in living subjects
having a diseased condition in which bodily health is
impaired as herein disclosed in detail.

The principal active ingredient is compounded for
convenient and effective administration in effective amounts
with a suitable pharmaceutically acceptable carrier in dosage
unit form as hereinbefore disclosed. A unit dosage form can,
for example, contain the principal active compound in amounts
ranging from about 5 to about 1000 mg, with from about 250 to
about 750 mg being preferred. Expressed in proportions, the
25 active compound is generally present in from about 10 to
about 750 mg/ml of carrier. In the case of compositions
containing supplementary active ingredients, the dosages are
determined by reference to the usual dose and manner of
administration of the said ingredients.

30 For a better understanding of the present invention
together with other and further objects, reference is made to
the following description and example.

35

EXAMPLE I

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General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Beckman IR-4250 and Perkin-Elmer 1330 spectrophotometer and calibrated against the 1601-cm^{-1} band of polystyrene. Absorption values are expressed in wave numbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Associates Models T-60 and FT-80A, and Nicolet NT-300 NMR spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were run on a Varian Associates Models FT-80A and Nicolet NT-300 instrument. Chemical shifts are in parts per million (δ values) relative to Me_4Si , and coupling constants (J values) are in hertz. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hewlett-Packard 5930 gas chromatograph-mass spectrometer and a Bell-Howell 21-491 spectrometer. High-resolution (EI mode) mass spectra were performed by Drs. James Hudson and John Chinn at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, MI.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. All anhydrous reactions were run under nitrogen, and all glassware was dried before use. In particular, acetonitrile and triethylamine were distilled from CaH_2 , while dichloromethane was distilled from P_2O_5 . Acetic anhydride, benzaldehyde and ethyl chloroformate were fractionally distilled.

1 Preparation of N-Acetyl-D,L-alanine-N'-benzylamide.

Acetic anhydride (2.20 g, 0.022 mol) was slowly added to a methylene chloride solution (30 mL) of D,L-alanine-N-benzylamide (3.80 g, 0.021 mol) and allowed to stir at room temperature (3 h). The mixture was then successively washed with H₂O (15 mL), 1% aqueous NaOH (15 mL) and H₂O (15 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was recrystallized from CH₂Cl₂.

Yield: 2.50 g (54%).

mp 139-141°C.

¹H NMR (DMSO-d₆): δ 1.22 (d, J = 7.1 Hz, 3H), 1.84 (s, 3H), 4.04-4.50 (m, 3H), 7.26 (s, 5H), 8.11 (br d, J = 7.3 Hz, 1H), 8.42 (br t, J = 6 Hz, 1H).

¹³C NMR (DMSO-d₆): 18.2, 22.4, 41.9, 48.2, 126.5, 126.9, 128.1, 139.4, 168.9, 172.4 ppm.

IR (CHCl₃) 3440, 3300, 3005, 1660, 1515 cm⁻¹.

Mass spectrum (CI mode), m/e: 221 (P+1); mol wt 220.1208 (Calculated for C₁₂H₁₆N₂O₂, 220.1212).

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1 Preparation of N-Acetyl-D- and L-amino acid-N-benzylamides.

General Procedure. The D- or L-amino acid amide
(11 mmol) was dissolved in dichloromethane (15 mL) and then
acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added
dropwise. The solution was stirred at room temperature
5 (18 h) and then concentrated to dryness. The residue was
recrystallized from chloroform/hexane.

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1 N-Acetyl-D-alanine-N'-benzylamide.

Yield: 1.36 g (56%).

mp 139-141°C.

$[\alpha]_D^{23} = +36.2$ (c 2.5, MeOH).

5 ^1H NMR (80 MHz, DMSO- d_6): δ 1.25 (d, J = 7.1 Hz, 3H), 1.86 (s, 3H), 4.10-4.50 (m, 1H), 4.30 (d, J = 6.0 Hz, 2H), 7.26 (s, 5H), 8.09 (d, J = 7.3 Hz, 1H), 8.40 (t, J = 6.0 Hz, 1H).

10 ^{13}C NMR (80 MHz, DMSO- d_6): 18.3, 22.5, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.2, 172.5 ppm.

IR (KBr): 3290, 1635 (br), 1540, 1455, 700, 695 cm^{-1} .

Mass spectrum, m/e (relative intensity): 221 (30), 114 (20), 106 (40), 91 (80), 87 (100), 77 (5), 72 (20), 65 (5).

Elemental analysis

15 Calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ 65.42% C; 7.34% H; 12.72% N.
Found 65.31% C; 7.28% H; 12.63% N.

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1 N-Acetyl-L-alanine-N'-benzylamide.

Yield: 1.11 g (46%).

mp 139-142°C.

$[\alpha]_D^{23} = -35.3$ (c 2.5, MeOH).

5 ^1H NMR (80 MHz, DMSO- d_6): δ 1.23 (d, J = 7.2 Hz, 3H), 1.86 (s, 3H), 4.26-4.35 (m, 1H), 4.29 (d, J = 5.8 Hz, 2H), 7.22-7.33 (s, 5H), 8.10 (d, J = 7.4 Hz, 1H), 8.42 (t, J = 5.8 Hz, 1H).

10 ^{13}C NMR (80 MHz, DMSO- d_6): 18.3, 22.6, 42.0, 48.4, 126.7, 127.0 (2C), 128.3 (2C), 139.5, 169.2, 172.6 ppm.

IR (KBr): 3290, 1635 (br), 1545, 1450, 700, 695 cm^{-1} .

Mass spectrum, m/e (relative intensity): 221 (40), 114 (40), 106 (80), 106 (80), 91 (75), 87 (100), 77 (5), 72 (15), 65 (5).

15 Elemental analysis

Calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ 65.42% C; 7.34% H; 12.72% N.

Found 65.58% C; 7.32% H; 12.43% N.

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Preparation of N-Acetyl-D,L-phenylglycine-N'-methanamide.

Acetic anhydride (2.90 g, 28 mmol) was added dropwise to D,L-phenylglycine-N-methanamide (3.4 g, 20 mmol) and allowed to stir at room temperature (1.5 h). During this time, a copious white precipitate formed. This material was collected by filtration, dried in vacuo and recrystallized from absolute alcohol.

Yield: 2.00 g (49%).

mp 232-235°C (dec).

^1H NMR (DMSO- d_6): δ 1.89 (s, 3H), 2.58 (d, J = 4.6 Hz, 3H), 5.42 (d, J = 8.1 Hz, 1H), 7.35 (s, 5H), 8.18 (br q, J = 4.2 Hz, 1H), 8.47 (d, J = 8.1 Hz, 1H).

^{13}C NMR (DMSO- d_6): 22.4, 25.5, 56.3, 127.1, 127.3, 128.1, 139.0, 168.9, 170.3 ppm.

IR (KBr): 3310, 1645 cm^{-1} .

Mass spectrum (CI mode), m/e : 207 (P+1).

Elemental analysis

Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$	64.06% C; 6.86% H; 13.58% N.
Found	63.79% C; 6.66% H; 13.27% N.

1 Preparation of N-Acetylglycine-N'-benzylamide.

5 The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 1.84 g (81%).

mp 140-142°C.

10 ^1H NMR (DMSO- d_6): δ 1.88 (s, 3H), 3.74 (d, $J = 5.3$ Hz, 2H), 4.30 (d, $J = 5.1$ Hz, 2H), 7.27 (s, 5H), 8.37 (br s, 1H), 8.75 (br s, 1H).

15 ^{13}C NMR (DMSO- d_6): 22.5, 42.0, 42.5, 126.6, 127.1 (2C), 128.1 (2C), 139.3, 169.0, 169.6 ppm.

IR (KBr): 3060, 1655, 1640, 1560, 1545, 1450, 1300, 740, 710 cm^{-1} .

Mass spectrum, m/e (relative intensity): 206 (3), 147 (12), 106 (100), 91 (75), 73 (50).

Elemental analysis

20 Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ 64.05% C; 6.86% H; 13.58% N.
Found 64.03% C; 6.79% H; 13.61% N.

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Preparation of N-Acetyl-D,L-valine-N¹-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.35 g (86%).

mp 192-193°C.

¹H NMR (DMSO-d₆): δ 0.83 (d, J = 6.7 Hz, 6H), 1.87 (s, 3H), 1.73-2.09 (m, 1H), 4.11 (d, J = 8.8 Hz, 1H), 4.27 (d, J = 5.8 Hz, 2H), 7.26 (s, 5H), 7.89 (d, J = 8.8 Hz, 1H), 8.84 (t, J = 5.8 Hz, 1H).

¹³C NMR (DMSO-d₆): 18.1, 19.2, 22.4, 30.2, 41.9, 57.8, 126.6, 127.1 (2C), 128.1 (2C), 139.4, 169.2, 171.1 ppm.

IR (KBr): 1625, 1540, 1535, 1450, 1380, 1290, 750, 695 cm⁻¹.

Mass spectrum, m/e (relative intensity): 142 (16), 114 (43), 106 (29), 91 (57), 72 (100).

Elemental analysis

Calculated for C₁₄H₂₀N₂O₂ 67.70% C; 8.13% H; 11.28% N.

Found 67.58% C; 8.05% H; 11.10% N.



Preparation of N-Acetyl-D,L-phenylglycine-N¹-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.05 g (66%).

mp 202-203°C.

¹H NMR (DMSO-d₆): δ 1.91 (s, 3H), 4.27 (d, J = 5.6 Hz, 2H), 5.50 (d, J = 7.9 Hz, 1H), 7.21 (s, 5H), 7.36 (s, 5H), 8.38-8.86 (m, 2H).

¹³C NMR (DMSO-d₆): 22.3, 42.0, 56.3, 126.6 (2C), 127.0, 127.1 (2C), 127.4 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 169.9 ppm.

IR (KBr): 3020, 1635, 1580, 1540, 1450, 1265, 745, 690 cm⁻¹.

Mass spectrum, m/e (relative intensity): 283 (20), 264 (21), 149 (100), 131 (20), 118 (34), 106 (92), 91 (70), 79 (56), 77 (54), 65 (45), 51 (37).

Elemental analysis

Calculated for C ₁₇ H ₁₈ N ₂ O ₂	72.31% C; 6.44% H; 9.92% N.
Found	72.49% C; 6.47% H; 9.89% N.

1 Preparation of N-Acetyl-D- and L-phenylglycine-N-benzylamide.

General Procedure. The chiral Boc-protected phenylglycine-N-benzylamide was dissolved in trifluoroacetic acid (0.04 M) and was stirred at room temperature (30 min), during which time gas evolved. The solution was concentrated
5 in vacuo and the residue was redissolved in enough methanol to form a solution of 0.2 M. Methanesulfonic acid (1 equiv) was added dropwise and stirred for 5 min. After concentrating the solution in vacuo, the residue was repeatedly dissolved in methanol and the solvent was removed
10 (3 times). The residue was then dried under vacuum (18 h), leaving a yellow oil.

Without further purification, the phenylglycine-N-benzylamide methanesulfonate was dissolved in tetrahydrofuran (0.2 M) and then was cooled in an ice bath. Triethylamine
15 (2 equiv) was added dropwise, followed by acetyl chloride (1 equiv). The ice bath was removed and stirring was continued at room temperature (18 h). The solution was concentrated in vacuo and the residue was recrystallized from 1:1 95% ethanol/water.
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1 N-Acetyl-D-phenylglycine-N¹-benzylamide.

The reaction was run on an 11.9 mmol scale.

Yield: 2.97 g (88%).

mp 219-221°C.

5 $[\alpha]_D = -103.0$ (c 1%, EtOH).

^1H NMR (DMSO- d_6): δ 1.91 (s, 3H), 4.27 (d, J = 5.5 Hz, 2H),
5.50 (d, J = 7.8 Hz, 1H), 7.14-7.44 (m, 10H), 8.56 (d, J =
7.8 Hz, 1H), 8.79 (t, J = 5.5 Hz, 1H).

10 ^{13}C NMR (DMSO- d_6): 22.4, 42.0, 56.4, 126.7, 127.0 (2C),
127.2 (2C), 127.4, 127.9 (2C), 128.1 (2C), 138.9, 139.0,
168.9, 170.0 ppm.

IR (KBr): 3260, 1620, 1525, 1450, 1370, 720, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity): 203 (2), 149 (94),
106 (100), 91 (32), 86 (43), 77 (14).

15 Elemental analysis

Calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ 72.32% C; 6.43% H; 9.92% N.

Found 72.04% C; 6.22% H; 9.78% N.

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1 N-Acetyl-L-phenylglycine-N'-benzylamide.

Beginning with 16.1 mmol N-t-Boc-L-phenylglycine-N-benzylamide.

Yield: 2.99 g (66%).

mp 221-222°C.

5 $[\alpha]_D = +105.1$ (c 1%, EtOH).

^1H NMR (DMSO- d_6): δ 1.99 (s, 3H), 4.36 (d, J = 5.6 Hz, 2H),
5.60 (d, J = 8.0 Hz, 1H), 7.23-7.53 (m, 10H), 8.60 (d, J =
8.0 Hz, 1H), 8.83 (t, J = 5.6 Hz, 1H).

10 ^{13}C NMR (DMSO- d_6): 22.4, 42.1, 56.5, 126.8, 127.1 (2C),
127.3 (2C), 127.5, 128.2 (4C), 139.0, 139.1, 169.1,
170.1 ppm.

IR (KBr): 3295, 1630, 1530, 1450, 1395, 720, 695 cm^{-1} .

Mass spectrum, m/e (relative intensity): 223 (1), 203 (2),
149 (98), 106 (100), 91 (32), 86 (43), 77 (11).

15 Elemental analysis

Calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	72.32% C; 6.43% H; 9.92% N.
Found	72.53% C; 6.49% H; 9.67% N.

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1 Preparation of N-Acetyl-D,L-alanine-N¹-(3-methoxy)benzylamide.

5 The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 0.47 g (17%).

mp 112-115°C.

10 ¹H NMR (DMSO-d₆): δ 1.23 (d, J = 7.1 Hz, 3H), 1.85 (s, 3H), 3.73 (s, 3H), 3.99-4.48 (m, 1H), 4.25 (d, J = 6.1 Hz, 2H), 6.58-7.35 (m, 4H), 8.05 (d, J = 7.4 Hz, 1H), 8.35 (t, J = 6.0 Hz, 1H).

15 ¹³C NMR (DMSO-d₆): 18.1, 22.5, 41.8, 48.3, 54.9, 112.2, 112.3, 119.0, 129.2, 141.0, 159.3, 169.0, 172.4 ppm.

IR (KBr): 3270, 3065, 1625, 1580, 1450, 1260, 1150, 1095, 900, 775, 700, 690 cm⁻¹.

Elemental analysis

Calculated for C₁₃H₁₈N₂O₃ 62.37% C; 7.26% H; 11.19% N.

20 Found 62.29% C; 7.13% H; 11.08% N.

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Preparation of N-Trimethylacetyl-D,L-alanine-N'-benzylamide.

D,L-Alanine-N-benzylamide (3.56 g, 20 mmol) was dissolved in dichloromethane (25 mL) and trimethylacetic anhydride (4.10 g, 4.46 mL, 22 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The solid residue was recrystallized from benzene/petroleum ether (30-60°C). Yield: 2.07 g (40%).

mp 123-124°C.

^1H NMR (DMSO- d_6): δ 1.12 (s, 9H), 1.27 (d, J = 7.1 Hz, 3H), 4.23-4.42 (m, 1H), 4.31 (d, J = 5.4 Hz, 2H), 7.23-7.30 (m, 5H), 7.38 (d, J = 7.4 Hz, 1H), 8.26 (t, J = 5.4 Hz, 1H).

^{13}C NMR (DMSO- d_6): 18.1, 27.2 (3C), 37.9, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 172.5, 177.1 ppm.

IR (KBr): 3300, 1630, 1535 (br), 1455, 745, 695 cm^{-1} .

Mass spectrum, m/e (relative intensity): 262 (2), 203 (19), 156 (18), 128 (51), 106 (31), 91 (100), 77 (15), 65 (28).

Elemental analysis

Calculated for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$ 68.66% C; 8.47% H; 10.68% N.

Found 68.91% C; 8.14% H; 10.61% N.



1 Preparation of N-Acetyl-D,L-methionine-N¹-benzylamide.

5 N-Acetyl-D,L-methionine (4.78 g, 25 mmol) was combined with acetonitrile (75 mL) and the mixture was placed into an ice/salt water bath (-5°C). Triethylamine (2.53 g, 3.48 mL, 25 mmol) was added dropwise, followed by ethyl
10 chloroformate (2.71 g, 2.39 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C (20 min). Benzylamine (3.00 g, 3.06 mL, 28 mmol) in acetonitrile (5 mL) was added dropwise and the mixture was stirred at -5°C (1 h) and then room temperature (18 h).

15 The mixture was filtered and a white precipitate was collected and dried in vacuo and identified as the desired product (¹H NMR and ¹³C NMR analyses). The filtrate was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride.

20 The latter filtrate containing tetrahydrofuran was concentrated in vacuo and the resulting residue was purified by flash column chromatography (ethyl acetate). A white solid ($R_f = 0.50$, ethyl acetate) was isolated and was identified as the desired product (¹H NMR and ¹³C NMR analyses). The two solids identified as N-acetyl-D,L-methionine-N-benzylamide were combined and recrystallized from benzene/petroleum ether (30-60°C).

25 Yield: 2.98 g (43%).

mp 134-135°C.

30 ¹H NMR (DMSO-d₆): δ 1.69-1.94 (m, 2H), 1.87 (s, 3H), 2.02 (s, 3H), 2.29-2.59 (m, 2H), 4.10-4.53 (m, 1H), 4.29 (d, J = 6.0 Hz, 2H), 7.26 (s, 5H), 8.12 (d, J = 8.5 Hz, 1H), 8.47 (t, J = 6.0 Hz, 1H).

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1 ^{13}C NMR (DMSO- d_6): 14.6, 22.5, 29.7, 31.8, 42.0, 52.0,
126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.5, 171.4 ppm.
IR (KBr): 3280, 1630, 1545, 1460, 750, 700 cm^{-1} .
Mass spectrum, m/e (relative intensity): 280 (3), 206 (100),
5 164 (29), 146 (20), 106 (54), 91 (76), 77 (14), 65 (24).
Elemental analysis
Calculated for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ 59.96% C; 7.20% H; 9.99% N.
Found 60.02% C; 7.14% H; 9.91% N.

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Preparation of N-Acetylalanine-N'-(3-fluoro)benzylamide.

N-Acetylalanine (3.28 g, 25 mmol) was combined with acetonitrile (100 mL) and the mixture was placed into an ice/salt bath at -5°C . Triethylamine (2.53 g, 3.5 mL, 25 mmol) was added dropwise followed by the addition of ethyl chloroformate (2.71 g, 2.40 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C . The mixture was then stirred at -5°C for 20 minutes. 3-Fluorobenzylamine (3.58 g, 28 mmol) and acetonitrile (5 mL) was added dropwise and was stirred at -5°C for one hour and then at room temperature for 18 hours. The reaction became homogeneous during this time interval.

The solution was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (100 mL) and cooled in the freezer for 3 hours resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo and identified as triethylammonium hydrochloride (3.51 g, mp $253-257^{\circ}\text{C}$). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from chloroform/diethyl ether. Yield: 3.22 g (54%).

mp $120-121^{\circ}\text{C}$.

^1H NMR ($\text{DMSO}-d_6$): δ 1.27 (d, $J = 7.1$ Hz, 3H), 1.90 (s, 3H), 4.23-4.41 (m, 1H), 4.33 (d, $J = 6.1$ Hz, 2H), 7.05-7.37 (m, 4H), 8.19 (d, $J = 7.1$ Hz, 1H), 8.53 (t, $J = 6.1$ Hz, 1H).

^{13}C NMR ($\text{DMSO}-d_6$): 17.9, 22.4, 41.5, 48.5, 113.3 (d, $J = 20.4$ Hz), 113.5 (d, $J = 21.7$ Hz), 122.8, 130.1 (d, $J = 7.9$ Hz), 142.4 (d, $J = 7.4$ Hz), 162.3 (d, $J = 243.6$ Hz), 169.6, 172.8 ppm.

IR (KBr): 3280, 1645, 1545, 1450, 745, 680 cm^{-1} .

1 Mass spectrum, m/e (relative intensity): 238 (18), 151 (22),
124 (49), 114 (47), 109 (100), 87 (76), 72 (27).

Elemental analysis

Calculated 60.48% C; 6.36% H; 11.76% N.

5 Found 60.55% C; 6.32% H; 11.71% N.

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Preparation of D,L- α -Acetamido-N-benzyl-3-thiopheneacetamide

D,L- α -Acetamido-3-thiopheneacetic acid (2.99 g, 15 mmol) was combined with acetonitrile (60 mL) and the mixture was placed into an ice/salt water bath (-5°C). Triethylamine (1.51 g, 2.10 mL, 15 mmol) was added dropwise, followed by ethyl chloroformate (1.63 g, 1.43 mL, 15 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C (20 min). Benzylamine (1.77 g, 1.80 mL, 16.5 mmol) in acetonitrile (10 mL) was added dropwise and the mixture was stirred at -5°C (1 h) and then room temperature (18 h). The mixture was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride (¹H NMR analysis). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from 1:1 95% ethanol/water.

Yield: 1.91 g (44%).

mp 198-199°C.

¹H NMR (DMSO-d₆): δ 1.91 (s, 3H), 4.29 (d, J = 5.2 Hz, 2H), 5.61 (d, J = 7.9 Hz, 1H), 7.15-7.50 (m, 3H), 8.55 (d, J = 7.9 Hz, 1H), 8.74 (t, J = 5.2 Hz, 1H).

¹³C NMR (DMSO-d₆): 22.3, 42.0, 52.5, 122.4, 126.1, 126.7, 127.0 (3C), 128.2 (2C), 139.0, 139.2, 169.0, 169.8 ppm.

IR (KBr): 3460, 1675, 1570, 1400, 720, 695 cm⁻¹.

Mass spectrum, m/e (relative intensity): 288 (2), 245 (3), 155 (88), 112 (100), 91 (31), 85 (17), 65 (7).

Elemental analysis

Calculated for C₁₅H₁₆N₂O₂S 62.48% C; 5.59% H; 9.71% N.

Found 62.41% C; 5.47% H; 9.55% N.

Preparation of D,L- α -Acetamido-N-benzyl-2-thiopheneacetamide

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (6.26 g, 25 mmol) was combined with dry ether (175 mL) and then boron trifluoride etherate (5.68 g, 5.0 mL, 40 mmol) was added dropwise, resulting in a homogeneous solution. After stirring a short time, a small amount of a yellow oil separated from the solution. Thiophene (8.41 g, 8.0 mL, 100 mmol) was then added dropwise via syringe and the reaction was stirred at room temperature (4 d). The mixture was cooled in an ice bath and cold aqueous saturated NaHCO_3 (200 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The organic washings and the original ether layer were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography, using 94:6 chloroform/methanol as an eluant ($R_f = 0.7$ 94:6 chloroform/methanol), and then recrystallized from benzene.

Yield: 2.67 g (37%).

mp 167-169°C.

^1H NMR ($\text{DMSO}-d_6$): δ 1.91 (s, 3H), 4.31 (d, $J = 6.0$ Hz, 2H), 5.74 (d, $J = 7.9$ Hz, 1H), 6.99-7.44 (m, 8H), 8.64 (d, $J = 7.9$ Hz, 1H), 8.85 (t, $J = 6.0$ Hz, 1H).

^{13}C NMR ($\text{DMSO}-d_6$): 22.4, 42.3, 52.2, 125.6, 125.8, 126.6, 126.9, 127.3 (2C), 128.3 (2C), 139.0, 141.4, 169.2, 169.3 ppm.

Mass spectrum, m/e (relative intensity): 289 (2), 181 (6), 155 (100), 112 (100), 91 (100), 85 (34), 74 (24).

Elemental analysis

Calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ 62.48% C; 5.59% H; 9.71% N.

Found 62.64% C; 5.73% H; 9.61% N.

Preparation of D,L- α -Acetamido-N-benzyl-2-furanacetamide.

N-Acetyl-D,L-2-(2-furyl)glycine (0.47 g, 2.56 mmol) was combined with acetonitrile (10 mL) and cooled to -5°C (ice/salt water bath). Triethylamine (0.26 g, 0.36 mL, 2.56 mmol) was then rapidly added and the mixture stirred at -5°C (3 min). Ethyl chloroformate (0.28 g, 0.25 mL, 2.56 mmol) was added dropwise between -4°C and -3°C , and the resulting suspension was stirred at -4°C (20 min), and then an acetonitrile solution (2 mL) of benzylamine (0.30 g, 0.31 mL, 2.82 mmol) was carefully added. During the addition of benzylamine the temperature of the solution did not go above 0°C . The mixture was stirred at -5°C (1 h) and at room temperature (18 h), and then concentrated in vacuo. The residue was then triturated with hot tetrahydrofuran (5 mL), cooled at -16°C (3 h), and the resulting white precipitate was filtered and identified as triethylamine hydrochloride (^1H NMR, 60 MHz, δ 1.00 (t, J = 7.5 Hz, CH_3), 2.82 (q, J = 7.5 Hz, CH_2), 3.83 (s, NH)). The filtrate was evaporated to dryness in vacuo and the resulting oil purified by flash chromatography (98:2 chloroform/methanol) to give 0.09 g (13%) of the desired product as a white solid: R_f 0.30 (98:2 chloroform/methanol).

mp $178-179^{\circ}\text{C}$.

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.90 (s, CH_3), 4.31 (d, J = 6.0 Hz, CH_2), 5.58 (d, J = 8.1 Hz, CH), 6.27-6.33 (m, C_3^*H), 6.40-6.44 (m, C_4^*H), 7.20-7.36 (m, Ph), 7.60-7.64 (m, C_5^*H), 8.57 (d, J = 8.1 Hz, NH), 8.73 (t, J = 6.0 Hz, NH).

^{13}C NMR (300 MHz, $\text{DMSO}-d_6$): 22.35 (CH_3), 42.27 (CH_2), 50.95 (CH), 107.60 (C_3^*), 110.55 (C_4^*), 126.82 (2C_2^{**} or 2C_3^{**}), 127.08 (2C_2^{**} or 2C_3^{**}), 128.27 (C_4^{**}), 139.05 (C_1^{**}), 142.58 (C_5^*), 151.16 (C_2^*), 168.02 (CH_3CO), 169.30 (NHCO) ppm.

1 IR (KBr): 3230, 1625 (br), 1525 (br), 1375 (br), 1230, 1090,
890 cm^{-1} .

Mass spectrum, m/e (relative intensity): 273 (1), 139 (100),
96 (94), 91 (51), 65 (9).

5 Elemental analysis

Calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$ 66.16% C; 5.83% H; 10.29% N.

Found 65.92% C; 5.83% H; 10.15% N.

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Preparation of D,L-~~α~~-Acetamido-N-benzyl-2-pyrroleacetamide.

2-Acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) was suspended in anhydrous ethyl ether (60 mL), and then boron trifluoride etherate (1.82 g, 1.57 mL, 12.8 mmol) was added in one portion and the resulting solution was stirred (15 min). The pyrrole (2.14 g, 2.22 mL, 32 mmol) was then added in one portion and the solution was stirred at room temperature (48 h) during which time a precipitate formed. Hexanes (80 mL) were then added to the suspension, and the mixture was filtered and the brown semi-solid was triturated with 95:5 chloroform/methanol (30 mL) to furnish a green solid. This material was purified by flash chromatography (95:5 chloroform/methanol) to yield 0.94 g (35%) of the desired product as a white solid: R_f 0.29 (96:4 chloroform/methanol).

mp 174-175°C.

^1H NMR (300 MHz, CD_3CN): δ 1.93 (s, CH_3), 4.35 (d, $J = 6.0$ Hz, CH_2), 5.42 (d, $J = 6.9$ Hz, CH), 6.00-6.18 (m, C_3 -H, C_4 -H), 6.68-6.72 (m, C_5 -H), 7.04 (d, $J = 6.9$ Hz, NH), 7.17 (t, $J = 6.0$ Hz, NH), 7.10-7.47 (m, Ph), 9.10-9.80 (br s, NH).

^{13}C NMR (300 MHz, CD_3CN): 23.02 (CH_3), 43.83 (CH_2), 52.65 (CH), 107.57 (C_3), 108.85 (C_4), 119.33 (C_5), 127.96 (C_2), 128.01 (2C_2 or 2C_3), 128.09 (2C_2 or 2C_3), 129.49 (C_4), 140.01 (C_1), 170.94 (COCH_3), 171.21 (CONH) ppm.

IR (KBr): 3320, 1570 (br), 1470 (br), 1330, 1230, 950, 890, 860, 760, 710, 690, 655 cm^{-1} .

Mass spectrum, m/e (relative intensity): 171 (12), 228 (2), 213 (1), 180 (2), 164 (9), 137 (93), 108 (20), 95 (100), 91 (38), 82 (35), 68 (15).

High resolution mass spectral analysis

Calculated for $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$ 271.13208.

Found 271.13144.

Preparation of D,L-2-Acetamido-N-benzyl-2-ethoxyacetamide.

An ethanolic solution (420 mL) of ethyl 2-acetamido-2-ethoxyacetate (27.92 g, 147 mmol) and benzylamine (23.70 g, 24 mL, 221 mmol) was stirred at 40-45°C for 3 days. The reaction mixture was evaporated in vacuo and the residue recrystallized (1:3.5 tetrahydrofuran/hexanes (650 mL)) to yield 25.80 g (70%) of the desired product as beige crystals: R_f 0.59 (95:5 chloroform/methanol). mp 153-155°C.

^1H NMR (300 MHz, CDCl_3): δ 1.20 (t, $J = 7.0$ Hz, CH_3), 2.07 (s, CH_3), 3.60-3.76 (m, CH_2CH_3), 4.40-4.54 (m, CH_2NH), 5.60 (d, $J = 8.7$ Hz, CH), 6.63 (d, $J = 8.7$ Hz, NH), 7.00 (br s, NH), 7.26-7.36 (m, Ph).

^{13}C NMR (300 MHz, CDCl_3): 15.06 (CH_3CH_2), 23.25 (CH_3CO), 43.60 (CH_2NH), 64.51 (CH_2CH_3), 77.43 (CH), 127.69 ($2\text{C}_2''$ or $2\text{C}_3''$, C_4''), 128.79 ($2\text{C}_2''$ or $2\text{C}_3''$), 137.57 (C_1''), 168.13 (COCH_3), 171.29 (CONH) ppm.

IR (KBr): 3260, 1630 (br), 1550 (sh), 1505 (br), 1380, 1360, 1230, 1115, 1060, 1015, 890, 745, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity): 251 (4), 163 (9), 116 (98), 106 (34), 91 (98), 74 (100).

Elemental analysis

Calculated for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3$ 62.38% C; 7.25% H; 11.19% N.

Found 62.49% C; 7.27% H; 11.24% N.

Preparation of D,L-2-Acetamido-N-benzyl-2-methoxyacetamide.

To a methanolic solution (180 mL) of methyl 2-acetamido-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50°C (3 days) during which time a beige precipitate appeared. The solvent was removed in vacuo and the resulting precipitate was recrystallized from tetrahydrofuran (2x) to give 7.67 g (32%) of the desired product as beige crystals: R_f 0.35 (95:5 chloroform/methanol). mp 145-146°C.

^1H NMR (300 MHz, CDCl_3): δ 2.06 (s, CH_3CO), 3.37 (s, CH_3O), 4.40-4.35 (m, CH_2), 5.52 (d, $J = 8.7$ Hz, CH), 7.12 (d, $J = 8.7$ Hz, NH), 7.20-7.40 (m, Ph, NH).

^{13}C NMR (300 MHz, CDCl_3): 23.03 (CH_3CO), 43.51 (CH_2), 55.84 (CH_3O), 78.94 (CH), 127.62 (C_4), 127.70 (2C_2 or 2C_3), 128.70 (2C_2 or 2C_3), 137.45 (C_1), 166.91 (COCH_3), 171.57 (CONH) ppm.

IR (KBr): 1260, 1825 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1050, 935, 890, 690 cm^{-1} .

Mass spectrum, m/e (relative intensity): 237 (1), 205 (2), 177 (2), 163 (4), 146 (1), 134 (1), 121 (2), 106 (26), 102 (98), 91 (95), 77 (13), 61 (100).

Elemental analysis

Calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_3$ 61.00% C; 6.83% H; 11.86% N.
60.91% C; 6.85% H; 11.66% N.

Pharmacology. The following compounds were tested for anticonvulsant activity using male Carworth Farms #1 mice:

N-Acetyl-D,L-alanine-N'-benzylamide
N-Acetyl-D-alanine-N'-benzylamide
N-Acetyl-L-alanine-N'-benzylamide
N-Acetyl-D,L-phenylglycine-N'-methanamide
N-Acetyl-L-phenylglycine-N'-methanamide
N-Acetyl-D,L-valine-N-benzylamide
N-Acetyl-D,L-phenylglycine-N-benzylamide
N-Acetyl-D-phenylglycine-N-benzylamide
N-Acetyl-L-phenylglycine-N-benzylamide
N-Acetyl-D,L-alanine-N-(3-methoxy)benzylamide
N-Trimethylacetyl-D,L-alanine-N-benzylamide
N-Acetyl-D,L-methionine-N-benzylamide
N-Acetyl-D,L-alanine-N'-(3-fluoro)benzylamide
D,L- α -Acetamido-N-benzyl-3-thiopheneacetamide
D,L- α -Acetamido-N-benzyl-2-thiopheneacetamide
D,L- α -Acetamido-N-benzyl-2-furanacetamide
D,L- α -Acetamido-N-benzyl-2-pyrroleacetamide
D,L-2-Acetamido-N-benzyl-2-ethoxyacetamide
D,L-2-Acetamido-N-benzyl-2-methoxyacetamide

The compound was given in three dose levels (30, 100, 300 mg) and subsequently compared with phenytoin, phenobarbital, mephentoin and phenacetamide (see Table I). N-Acetyl-D,L-alanine-N'-benzylamide was tested at 600 mg/mL as well. Seizures were then artificially induced by either electroshock or pentylenetetrazole. Maximal electroshock seizures (MES) were elicited with a 60 cycle alternating current of 50 mA intensity (5-7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 sec via corneal electrodes. A drop of 0.9% saline was instilled

1 in the eye prior to application of the electrodes so as to
prevent the death of the animal. Protection in this test was
defined as the abolition of the hind limb tonic extension
component of the seizure. The Subcutaneous Pentylene-
5 tetrazole (Metrazol^R) Seizure Threshold Test (sc Met)
entailed the administration of 85 mg/kg of pentylenetetrazole
as a 0.5% solution subcutaneously in the posterior midline.
This amount of pentylenetetrazole was expected to produce
seizures in greater than 95% of mice. The animal was
10 observed for 30 minutes. Protection was defined as the
failure to observe even a threshold seizure (a single episode
of clonic spasms of at least 5 sec duration). The effects of
the compounds on forced and spontaneous motor activity were
evaluated in mice using the Rotorod Test (Tox) or, in some
15 cases, as indicated herein, a horizontal screen assay (HS).
The animal was placed on a one-inch diameter knurled plastic
rod rotating at 6 rpm after the administration of the drug.
Normal mice can remain on a rod rotating at this speed
..... indefinitely. Neurologic toxicity was defined as the failure
of the animal to remain on the rod for one minute. The MES
20 and sc Met Tests were conducted on single animals while four
mice were utilized for the Tox Test. The dose effect
behavior of the compounds was evaluated using the
above-described procedures by the administration of varying
25 dose levels, treating normally eight mice at each dose.
Table I includes an evaluation of the Median Effective Dose
(ED50) and the Median Toxic Dose (TD50) of representative
compounds. Mice were tested with varying doses of the
anticonvulsant to define the limits of complete protection
(or toxicity) and no protection (or no toxicity), as well as
30 three points in between these limits. The Median Effective
Dose (ED50) was defined as the dose which produced the

desired endpoint in 50% of the animals. The Median Toxicity Dose (TD50) was the dose which elicited evidence of minimal neurological toxicity in 50% of the animals.

N-Acetyl-D,L-phenylglycine-N'-benzylamide, N-acetyl-D-phenylglycine-N'-benzylamide, D,L- α -acetamido-N-benzyl-2-furanacetamide, D,L- α -acetamido-N-benzyl-2-pyrroleacetamide exhibited anticonvulsant activity at doses less than 33 mg/kg. As indicated in Table I, N-acetyl-D,L-phenylglycine-N'-benzylamide, N-acetyl-D,L-alanine-N'-benzylamide and their D isomers, as well as D,L- α -acetamido-N-benzyl-2-thiopheneacetamide, D,L- α -acetamido-N-benzyl-2-furanacetamide, D,L- α -acetamido-N-benzyl-2-pyrroleacetamide and D,L-2-acetamido-N-benzyl-2-ethoxyacetamide, possessed ED50 values in the MES test that compared well with phenobarbital, while their TD50s were of similar magnitude or considerably higher. Only the ED50 (sc Met) of N-acetyl-D-alanine-N'-benzylamide was computed while the TD50 of N-acetyl-D,L-phenylglycine-N'-benzylamide, N-acetyl-D-phenylglycine-N'-benzylamide, N-acetyl-L-phenylglycine-N'-benzylamide, D,L- α -acetamido-N-benzyl-3-thiopheneacetamide, D,L- α -acetamido-N-benzyl-2-thiopheneacetamide, D,L- α -acetamido-N-benzyl-2-furanacetamide, D,L- α -acetamido-N-benzyl-2-pyrroleacetamide, D,L-2-acetamido-N-benzyl-2-ethoxyacetamide and D,L-2-acetamido-N-benzyl-2-methoxyacetamide were evaluated using a horizontal screen assay (HS) as opposed to the Rotorod Test.

TABLE I

Comparative Median Effective Dosage

5	Compound	Tox TD50 mg/kg	MES ED50 mg/kg	sc Met ED50 mg/kg
	N-acetyl-D,L-alanine- N'-benzylamide	454 (417-501) *	77 (67-89) *	≠
10	N-acetyl-D-alanine- N'-benzylamide	214 (148-262) *	55 (50-60) *	55 (43-67) *
	N-acetyl-L-alanine- N'-benzylamide	841 (691-594) *	548 (463-741) *	≠
15	N-acetyl-D,L- phenylglycine-N'- benzylamide	>>40	32.1	≠
	N-acetyl-D-phenyl- glycine-N'-benzyl- amide	>>80	26.1	≠
20	N-acetyl-L-phenyl- glycine-N'-benzyl- amide	100-300	>300	≠
	D,L- α -acetamido-N- benzyl-3-thiophene- acetamide	>100	87.80	≠
25	D,L- α -acetamido-N- benzyl-2-thiophene- acetamide	30-100	44.80	≠
	D,L- α -acetamido-N- benzyl-2-furan- acetamide	40	10.33	≠

TABLE I - cont'd.

Comparative Median Effective Dosage

Compound	Tox TD50 mg/kg	MES ED50 mg/kg	sc Met ED50 mg/kg
5 D,L- α -acetamido-N-benzyl-2-pyrrole-acetamide	> 100	16.10	≠
D,L-2-acetamido-N-benzyl-2-ethoxy-acetamide	> 112	62.01	≠
10 D,L-2-acetamido-N-benzyl-2-methoxy-acetamide	< 300	98.30	≠
phenytoin	66	10	not effective
15 phenobarbital	69	22	13
mephentoin	154	61	31
phenacemide	421 (337-549)*	87 (74-100)*	116 (71-150)*

* 95% confidence intervals

≠ The ED50 for this substrate was not computed

Thus, while the invention has been described with reference to certain preferred embodiments, those skilled in the art will realize that changes and modifications may be made thereto without departing from the full and intended scope of the appended claims.

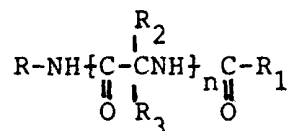
The claims form part of the disclosure of this specification.

The claims defining the invention are as follows:

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1. An anticonvulsant composition comprising an anticonvulsant effective amount of a compound having the following general formula:

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wherein R is aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

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R₁ is H or lower alkyl, unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

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R₂ and R₃, independently, are lower alkenyl, lower alkynyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating 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;

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n is 1 to 4; and

a pharmaceutically acceptable carrier.

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2. The composition according to Claim 1 wherein R₁ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl or hexyl.

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3. The composition in accordance with claims 1 and 2 wherein said methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl or hexyl are unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent.

4. The composition in accordance with claims 1-3 wherein R is benzyl, unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent.

5. The composition in accordance with claims 1-4 wherein said electron withdrawing substituent is halo, nitro, acyl, carboxyl, carboalkoxy, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic, guanidine or quaternary ammonium.

6. The composition in accordance with claims 1-5 wherein said electron donating substituent is hydroxy, alkoxy, alkyl, amino, phenoxy, thiol, sulfide or disulfide.

7. The composition in accordance with claims 1-6 wherein said compound is in the D isomer form, L isomer form, mixtures of the D,L isomer form or D,L racemate form.

8. The composition according to claim 1 wherein the compound is:

N-acetyl-D,L-alanine-N'-benzylamide;

N-acetyl-D-alanine-N'-benzylamide;

N-acetyl-D,L-phenylglycine-N'-benzylamide;

N-acetyl-D-phenylglycine-N'-benzylamide;

D,L- α -acetamido-N-benzyl-3-thiopheneacetamide;

D,L- α -acetamido-N-benzyl-2-thiopheneacetamide;

D,L- α -acetamido-N-benzyl-2-furanacetamide;

D,L- α -acetamido-N-benzyl-2-pyrroleacetamide;

D,L-2-acetamido-N-benzyl-2-ethoxyacetamide; or

D,L-2-acetamido-N-benzyl-2-methoxyacetamide

9. An anticonvulsant composition substantially as hereinbefore described with reference to any one of the Examples.

10. A composition as claimed in any preceding claim, wherein said compound is present as the pharmaceutically acceptable addition salt.

11. The compounds of the general formula set out in claim 1 and pharmaceutically acceptable addition salts thereof.

12. A method of preparing the compounds of claim 11 substantially as hereinbefore described.

DATED this 3 December 1990

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