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(54) Title: α-SUBSTITUTED POLYPEPTIDES HAVING THERAPEUTIC ACTIVITY

(57) Abstract

The compounds of the invention are α-substituted mono-, di-, tri-, tetra-, and pentapeptides useful in treating obesity, anxiety, gastrointestinal ulcers, pain, stroke, and inflammation. They are also useful in blocking the reaction caused by withdrawal from drug or alcohol use and in reducing gastric acid secretion. They are further useful as agents in hypertension, heart failure, stroke, cognition, memory enhancement, spasticity, depression, diabetes, cancer, asthma, bladder dysfunction, psychosis, and arthritis and/or inflammatory pain. Pharmaceutical compositions, novel intermediates, and processes are also included.

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α-SUBSTITUTED POLYPEPTIDES HAVING THERAPEUTIC ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part application of United States Serial Number 07/690,755, filed April 24, 1991.

BACKGROUND OF THE INVENTION

Peptides form the main messenger systems within and between cells and they number more than a thousand. Over a hundred peptides are known to act as hormone, neurohormones, or neurotransmitters, and this number is growing rapidly. The potential for drug development is therefore vast. However, the great majority of peptide messengers are not suitable for use as pharmaceuticals in their natural state.

The problems of natural peptides as drugs are lack of oral activity, failure to penetrate the blood-brain barrier, rapidly metabolized, no selectivity for receptor subclasses, antigenic properties, and expensive to make.

The vast majority of small peptide messengers are not suitable as drugs, particularly where an orally administered and possibly centrally active drug is required. In this situation the development of modified peptides offer significant opportunities. The α,α-disubstituted amino acids are non-genetically coded synthetic analogues of natural mammalian α-amino acids and are incorporated at least once into the neuropeptides of this patent.

Some examples of therapeutic applications of these modified peptides (peptoids) are given in Table I below.

TABLE I

Endogenous Peptide	Peptoid Type*	Therapy
Angiotensin	ANT	Hypertension Heart Failure
Atrial Natriuretic Factor	AG	Heart Failure
Thyrotropin Releasing Factor	AG	Stroke Cognition Spasticity Depression
Neuropeptide-Y	ANT	Hypertension Depression Obesity
Glucagon	ANT	Diabetes
Insulin	AG	Diabetes
Gastrin	ANT	Gastric Ulcer Cancer
Bombesin	ANT	Cancer
Tachykinins SP, NKA, NKB	ANT	Antipsychotic Analgesic Antiinflammatory Antiasthmatic

* ANT = Antagonist; AG = Agonist

These offer completely novel approaches to drug treatment. For example, all of the major tranquilizers block central dopaminergic function indiscriminately. An antipsychotic modified peptide designed to act through the mesolimbic CCK-neuropeptide/Dopamine system may be considerably more selective. An improvement in quality through the ability to modify drug resistant characteristics

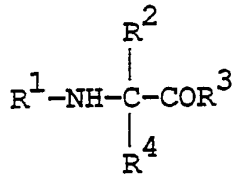
is also expected. In psychosis the blunting of affect leading to general impoverishment of social interactions with schizophrenics is expected to be susceptible to alternate modified peptide therapies. The highly selective behavioral responses elicited by individual neuropeptides is shown in the Table II below.

TABLE II
Behavioral Responses to Peptides

Peptide	Behavior
Angiotensin-II	Dipsogenesis
Cholecystokinin	Cessation of Feeding Drowsiness Enhanced Memory
Adrenocorticotrophic Hormone	Enhanced Alertness Enhanced Cognition
ß-Endorphin	Decreased Awareness Amnesia Reward Analgesia
Dynorphin	Decreased Reward Drowsiness Analgesia
Luteinizing Hormone Releasing Factor	Increased Sexual Receptivity
Corticotrophin Releasing Factor	Anxiety Enhanced Vigilance
Thyrotropin Releasing Factor	Increased Activity Enhanced Awareness
SP or NKA	A dopamine behavioral syndrome, i.e., increased locomotion, rearing
SP	Antidipsogenic activity

SUMMARY OF THE INVENTION

The invention relates to novel compounds of formula



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and the pharmaceutically acceptable salts thereof wherein R^1, R^2, R^3, and R^4 are as defined hereinbelow.

In commonly assigned copending application 07/609,754, filed on April 24, 1991, by Horwell, et al, the disclosure of which is incorporated by reference, CCK analogues containing α,α-disubstituted amino acids are disclosed.

The invention also relates to a pharmaceutical composition containing an effective amount of a compound according to formula I in combination with a pharmaceutically acceptable carrier in unit dosage form for appetite suppression. The invention also relates to a method for suppressing appetite in a mammal.

The compounds of the invention are also useful for blocking the reaction caused by withdrawal from drug or alcohol use. The compounds of the invention are also useful in reducing gastric acid secretion, in treating gastrointestinal ulcers, in treating pain, treating and/or preventing stroke, treating inflammation, and in treating anxiety.

The compounds of the invention are also useful in treating cognitive deficits, small cell lung cancer, colonic cancer, peptic ulcers, and are useful in contraception.

The invention also relates to a pharmaceutical composition for reducing gastric acid secretion containing an effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier in unit dosage form effective for reducing gastric acid secretion.

The invention also relates to a method for reducing gastric acid secretion in mammals which comprises administering an amount effective for gastric acid secretion reduction of the composition described above to a mammal in need of such treatment.

The invention also relates to a pharmaceutical composition containing an effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier in unit dosage form effective for reducing anxiety.

The invention also relates to a method for reducing anxiety in mammals which comprises administering an amount effective for anxiety reduction of the composition described above to a mammal in need of such treatment.

The invention also relates to a pharmaceutical composition containing an effective amount of a compound of formula I in combination with a pharmaceutically acceptable carrier in unit dosage form effective for treating gastrointestinal ulcers.

The invention further relates to a method for treating gastrointestinal ulcers in mammals which comprises administering an amount effective for gastrointestinal ulcer treatment of the composition as described above to a mammal in need of such treatment.

The invention also relates to a pharmaceutical composition containing an effective amount of a

compound of formula I in combination with a pharmaceutically acceptable carrier in unit dosage form effective for treating inflammation.

The invention further relates to a method for treating inflammation in mammals which comprises administering an amount effective of a composition as described above to a mammal in need of such treatment.

The invention also relates to a pharmaceutical composition for preventing the withdrawal response produced by chronic treatment or abuse of drugs or alcohol.

The invention further relates to a method for treating the withdrawal response produced by withdrawal from chronic treatment or withdrawal from abuse of drugs or alcohol. Such drugs include benzodiazepines, especially diazepam, cocaine, caffeine, opioids, alcohol, and nicotine. Withdrawal symptoms are treated by administration of an effective withdrawal treating amount of a compound of the instant invention.

This invention also relates to a pharmaceutical composition containing a therapeutically effective amount of a compound according to formula I in combination with a pharmaceutically acceptable carrier in unit dosage form for treating psychosis.

The invention also relates to a method for treating psychosis in mammals which comprises administering an amount effective for treatment of the composition described above to a mammal in need of such treatment.

This invention also relates to a pharmaceutical composition containing a therapeutically effective amount of a compound according to formula I in

combination with a pharmaceutically acceptable carrier in unit dosage form for treating asthma.

The invention also relates to a method for treating asthma in mammals which comprises administering an amount effective for treatment of the composition described above to a mammal in need of such treatment.

This invention also relates to a pharmaceutical composition containing a therapeutically effective amount of a compound according to formula I in combination with a pharmaceutically acceptable carrier in unit dosage form for treating bladder dysfunction.

The invention also relates to a method for treating bladder dysfunction in mammals which comprises administering an amount effective for treatment of the composition described above to a mammal in need of such treatment.

This invention also relates to a pharmaceutical composition containing a therapeutically effective amount of a compound according to formula I in combination with a pharmaceutically acceptable carrier in unit dosage form for treating arthritis and/or inflammatory pain.

The invention also relates to a method for treating arthritis and/or inflammatory pain in mammals which comprises administering an amount effective for treatment of the composition described above to a mammal in need of such treatment.

The invention further relates to methods of treating hypertension, heart failure, stroke, cognition, memory enhancement, spasticity, depression, and diabetes.

The invention further provides processes for the preparation of compounds of formula I.

The invention further provides novel intermediates useful in the preparation of compounds of formula I and also provides processes for the preparation of the intermediates.

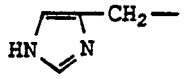
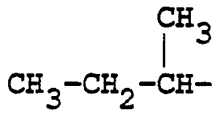
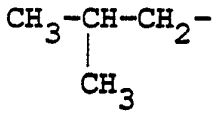
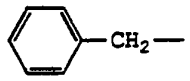
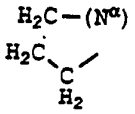
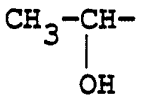
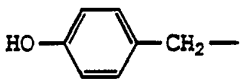
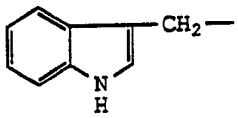
The invention also relates to a pharmaceutical composition for treating pain and to a method of using a compound of formula I for treating pain.

The invention also relates to a pharmaceutical composition for treating and/or preventing stroke and to a method of using a compound of formula I for treating and/or preventing stroke.

DETAILED DESCRIPTION

The following provides a dictionary of the terms used in the description of the invention.

Abbreviation	Side Chain	Amino Acid
ALA	CH_3-	Alanine
ARG	$NH_2-\overset{\overset{NH}{\|\|}}{C}-NH-CH_2-CH_2-CH_2-$	Arginine
ASN	$NH_2-\overset{\overset{O}{\|\|}}{C}-CH_2-$	Asparagine
ASP	$HOOC-CH_2-$	Aspartic Acid
CYS	$HS-CH_2-$	Cysteine
GLU	$HOOC-CH_2-CH_2-$	Glutamic Acid
GLN	$NH_2-\overset{\overset{O}{\|\|}}{C}-CH_2-CH_2-$	Glutamine

Abbreviation	Side Chain	Amino Acid
HIS		Histidine
ILE		Isoleucine
LEU		Leucine
LYS	$NH_2-CH_2-CH_2-CH_2-CH_2-$	Lysine
MET	$CH_3-S-CH_2-CH_2-$	Methionine
PHE		Phenylalanine
PRO		Proline
SER	$HO-CH_2-$	Serine
THR		Threonine
TYR		Tyrosine
TRP		Tryptophan

Abbreviation	Side Chain	Amino Acid
VAL	$CH_3-CH(CH_3)-$	Valine

Abbreviation	N-Terminal Protecting Group
H	Hydrogen
BOC	Tert-butyloxy-carbonyl
CBZ (or Z)	Benzyloxy-carbonyl
IBU	Isobutyryl
IVA	Isovaleryl
NVA	n-Valeryl
1-Adoc	1-Adamantyloxy-carbonyl
2-Adoc	2-Adamantyloxy-carbonyl
Fmoc	9-Fluorenyl-methoxycarbonyl

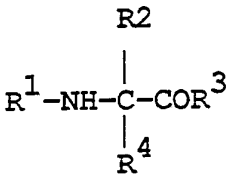
Abbreviation	C-Terminal Substituent/ Side Chain Protecting Group
$-NH_2$	Amide
$-OCH_3$	Methyl ester

Abbreviation	C-Terminal Substituent/ Side Chain Protecting Group
$-OCH_2Ph$	Benzyl ester/ether
$-OC(CH_3)_3$	Tert-butyl ester/ether

The term "N-terminal protecting" as used herein refers to those groups known to the art intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during a synthetic procedure or to prevent the attack of exopeptidases on the compounds or to increase the solubility of the compounds and includes, but is not limited to, sulfonyl, acetyl, pivaloyl, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), benzoyl, or an L- or D-aminoacyl residue, which may itself be N-protected similarly.

The term "C-terminal protecting group" as used herein refers to those groups known to the art intended to protect the C-terminus of an amino acid or peptide, these include but are not limited to an amide, methyl ester, benzyl ester/ether, tert-butyl ester/ether. Other examples of side chains and protecting groups are those known in the art. Any of those could be used.

The compounds of the invention are represented by formula



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and the pharmaceutically acceptable salts thereof, wherein

R^1 is an N-terminal blocking group or from 0 to 4 amino acid residues or hydrogen;

R^2 is a sidechain of a genetically coded amino acid except glycine;

R^3 is a C-terminal blocking group or from 0 to 4 amino acid residues, or -OH, or OR^n where R^n is straight or branched alkyl or cycloalkyl of 1 to 6 carbon atoms;

R^4 is a sidechain of a genetically coded amino acid, except glycine, or

$-HC=CH_2$,

$-C\equiv CH$,

$-CH_2-CH=CH_2$,

$-CH_2C\equiv CH$,

$-CH_2Ar$,

$-CH_2OR$,

$-CH_2OAr$,

$-(CH_2)_nCO_2R$,

$-(CH_2)_nNR^5R^6$ wherein n is an integer of from 0 to 3, R is hydrogen or lower alkyl, Ar is a mono- or polycyclic unsubstituted or substituted carbo- or heterocyclic aromatic or hydroaromatic moiety;

neither R^2 nor R^4 can be hydrogen;

R^1 plus R^3 cannot be greater than 4 amino acid residues in total.

Preferred compounds of the invention are those of formula I selected from:

Formyl-MeMet-Leu-Phe-Obzl,

Formyl-Met-MeLeu-Phe-OBzl,

Formyl-Met-Leu-MePhe-OBzl,

Ac-MeLeu-Leu-Arginal,

Ac-Leu-MeLeu-Arginal,

MeTyr-Arg,

Tyr-MeArg,

MeTyr-Pro-Phe-Pro-NH_2,

Tyr-MePro-Phe-Pro-NH_2,

Tyr-Pro-MePhe-Pro-NH_2,

Tyr-Pro-Phe-MePro-NH_2,

Me-Arg-Lys-Asp-Val-Tyr,

Arg-MeLys-Asp-Val-Tyr,

Arg-Lys-MeAsp-Val-Tyr,

Arg-Lys-Asp-MeVal-Tyr,

Arg-Lys-Asp-Val-MeTyr,

MeArg-Lys-Glu-Val-Tyr,

Arg-MeLys-Glu-Val-Tyr,

Arg-Lys-MeGlu-Val-Tyr,

Arg-Lys-Glu-MeVal-Tyr,

Arg-Lys-Glu-Val-MeTyr,

MeAsp-Leu-Asp-Pro-Arg,

Asp-MeLeu-Asp-Pro-Arg,

Asp-Leu-MeAsp-Pro-Arg,

Asp-Leu-Asp-MePro-Arg,

Asp-Leu-Asp-Pro-MeArg,

MeLys-Trp-Lys,

Lys-MeTrp-Lys,

Lys-Trp-MeLys,

MePhe-Met-Arg-Phe-NH_2,

Phe-MeMet-Arg-Phe-NH_2,

Phe-Met-MeArg-Phe-NH_2,

Phe-Met-Arg-MePhe-NH_2,

MeGlp-His-Pro,
Glp-MeHis-Pro,
Glp-His-MePro,
MeArg-Tyr-Leu-Pro-Thr,
Arg-MeTyr-Leu-Pro-Thr,
Arg-Tyr-MeLeu-ProThr,
Arg-Tyr-Leu-MePro-Thr,
Arg-Tyr-Leu-Pro-MeThr,
MeThr-Lys-Pro-Arg,
Thr-MeLys-Pro-Arg,
Thr-Lys-MePro-Arg,
Thr-Lys-Pro-MeArg,
MeThr-Pro-Arg-Lys,
Thr-MePro-Arg-Lys,
Thr-Pro-MeArg-Lys,
Thr-Pro-Arg-MeLys,
MeThr-Val-Leu,
Thr-MeVal-Leu, and
Thr-Val-MeLeu.

More preferred compounds of the invention are those of formula I selected from:

Me-Tyr-Gly-Gly-Phe-Met,
MeTyr-Gly-Gly-Phe-Met-NH_2,
MeTyr-Gly-Gly-Phe-Leu-NH_2,
Tyr-Gly-Gly-MePhe-Met,
Tyr-Gly-Gly-MePhe-Met-NH_2,
Tyr-Gly-Gly-MePhe-Leu-NH_2,
Tyr-Gly-Gly-Phe-MeMet,
Tyr-Gly-Gly-Phe-MeMet-NH_2,
Tyr-Gly-Gly-Phe-MeLeu-NH_2,
Z-DMePhe-Phe-Gly,
Z-DPhe-MePhe-Gly,
MeArg-Pro-Tyr-Ile-Leu,
Arg-MePro-Tyr-Ile-Leu,
Arg-Pro-MeTyr-Ile-Leu,

Arg-Pro-Tyr-MeIle-Leu,
Arg-Pro-Tyr-Ile-MeLeu,
MeLeu-Asp-Ile-Ile-Trp,
Leu-MeAsp-Ile-Ile-Trp,
Leu-Asp-MeIle-Ile-Trp,
Leu-Asp-Ile-MeIle-Trp,
Leu-Asp-Ile-Ile-MeTrp,
MeGlu-Cys-Tyr-Phe,
Glu-MeCys-Val-Tyr-Phe,
Glu-Cys-MeVal-Tyr-Phe,
Glu-Cys-Val-MeTyr-Phe, and
Glu-Cys-Val-Tyr-MePhe.

Most preferred compounds of the invention are those of formula I selected from:

MeLys-Trp-Asp-Asn-Gln,
Lys-MeTrp-Asp-Asn-Gln,
Lys-Trp-MeAsp-Asn-Gln,
Lys-Trp-Asp-MeAsn-Gln,
Lys-Trp-Asp-Asn-MeGln,
MeVal-Gly-His-Leu-Met-NH_2,
Val-Gly-MeHis-Leu-Met-NH_2,
Val-Gly-His-MeLeu-Met-NH_2,
Val-Gly-His-Leu-MeMet-NH_2,
MeGlp-His-Trp-Ser-Tyr,
Glp-MeHis-Trp-Ser-Tyr,
Glp-His-MeTrp-Ser-Tyr,
Glp-His-Trp-MeSer-Tyr,
Glp-His-Trp-Ser-MeTyr,
Gly-MeLeu-Arg-Pro-Gly-NH_2,
Gly-Leu-MeArg-Pro-Gly-NH_2,
Gly-Leu-Arg-MePro-Gly-NH_2,
MeTyr-Pro-Ser-Lys-Pro,
Tyr-MePro-Ser-Lys-Pro,
Tyr-Pro-MeSer-Lys-Pro,
Tyr-Pro-Ser-MeLys-Pro,

Tyr-Pro-Ser-Lys-MePro,

MeThr-Arg-Gln-Arg-Tyr-NH_2,

Thr-MeArg-Gln-Arg-Tyr-NH_2,

Thr-Arg-MeGln-Arg-Tyr-NH_2,

Thr-Arg-Gln-MeArg-Tyr-NH_2,

Thr-Arg-Gln-Arg-MeTyr-NH_2,

Gly-MeTrp-Thr-Leu-Asn,

Gly-Trp-MeThr-Leu-Asn,

Gly-Trp-Thr-MeLeu-Asn,

Gly-Trp-Thr-Leu-MeAsn,

MeLeu-Tyr-Gly-Leu-Ala-NH_2,

Leu-MeTyr-Gly-Leu-Ala-NH_2,

Leu-Tyr-Gly-MeLeu-Ala-NH_2,

Leu-Tyr-Gly-Leu-Aib-NH_2,

MePhe-Phe-Trp-Lys-Thr,

Phe-MePhe-Trp-Lys-Thr,

Phe-Phe-MeTrp-Lys-Thr,

Phe-Phe-Trp-MeLys-Thr,

Phe-Phe-Trp-Lys-MeThr,

MePhe-Phe-Gly-Leu-Met-NH_2,

Phe-MePhe-Gly-Leu-Met-NH_2,

Phe-Phe-Gly-MeLeu-Met-NH_2,

Phe-Phe-Gly-Leu-MeMet-NH_2,

and the N^{α}-4-hydroxyphenylacetyl derivatives and the NH_2-CO-$(CH_2)_4$-CO- derivatives of the above four compounds,

N-[[(4-Chlorophenyl)methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide,

N-[[[4-(Trifluoromethyl)phenyl]methoxy]-carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide,

N-[([1,1'-Biphenyl]-4-ylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide,

N-[(9-Anthracenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide,

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide,

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-L-phenylalaninamide,

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-D-phenylalaninamide,

N-[[[4-(Propoxycarbonyl)phenyl]-methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide,

N-[(Phenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalanylglycinamide,

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalanylglycinamide,

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-L-phenylalanylglycinamide, and

N-[[(2,3-Dimethoxyphenyl)methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

The compounds include solvates, hydrates, and pharmaceutically acceptable salts of the compounds of formula I above.

The compounds of the present invention may exist as diastereomers, mixtures of diastereomers, or as the mixed or the individual optical enantiomers. The present invention contemplates all such forms of the compounds. The mixtures of diastereomers are typically obtained as a result of the reactions described more fully below. Individual diastereomers may be separated from mixtures of the diastereomers by conventional techniques such as column chromatography or repetitive recrystallizations. Individual enantiomers may be separated by conventional methods well known in the art such as conversion to a salt with an optically active compound, followed by separation by chromatography or

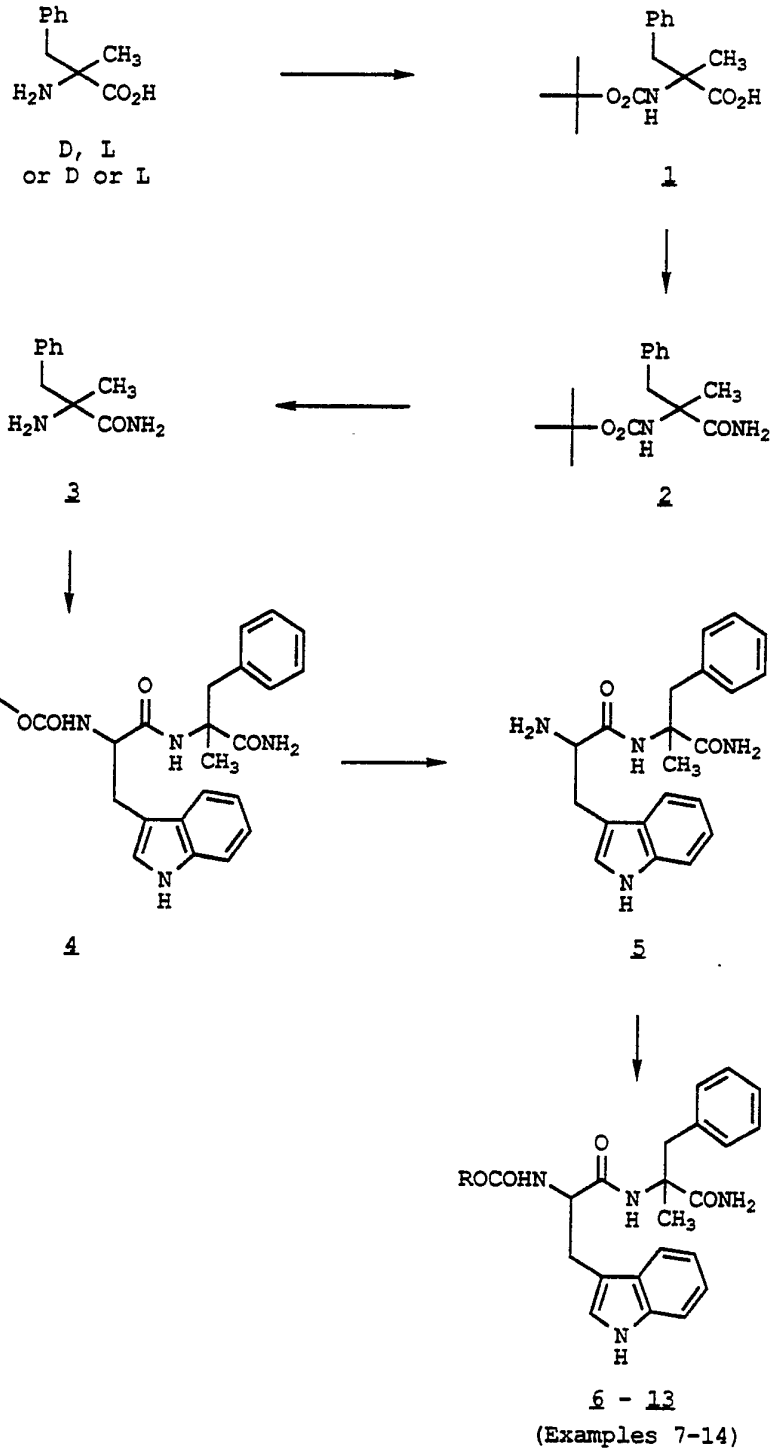
recrystallization and reconversion to the nonsalt form.

The compounds of the present invention may be formed by coupling individual substituted α-amino acids by methods well known in the art. (See, for example, standard synthetic methods discussed in the multi-volume treatise The Peptides, Analysis, Synthesis, Biology, by Gross and Meienhofer, Academic Press, New York). If known, the individual substituted alpha amino acid starting materials are synthesized by methods within the skill of the art. (Synthesized racemic [DL]-α-methyl tryptophan methyl ester - see Braña, M. F., et al, J. Heterocyclic Chem., 1980.

In Scheme I below, the α-MePhe was N-terminally protected with $(BOC)_2O$ to afford BOC α-MePhe.(1) Compound 1 was then activated with DCCI and HOBt and reacted with $NH_3(g)$ to give the amide.(2) Removal of the BOC group with TFA gave the amine (3), which was reacted with FMOC-L-TrpOPfp to afford the dipeptide.(4) A further deprotection with piperidine in DMF gave the amine (5), which was reacted with the appropriate chloroformate to give the Examples 7 through 14.(6-13)

SCHEME 1

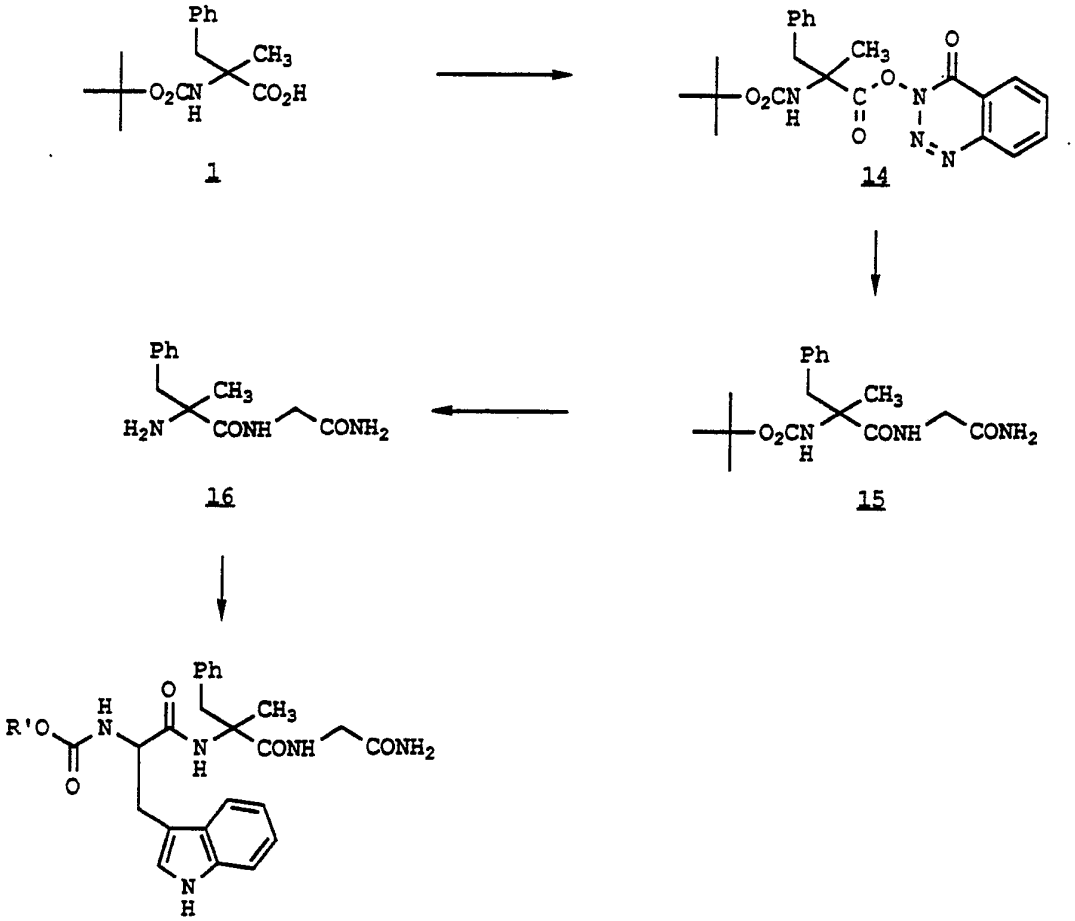
(Examples 2-13)



In Scheme 2 below, Compound 1 was activated with DCCI and HODhbt to give 14, which was reacted with CTlyNH$_2$ in EtOAc to afford the N-protected dipeptide.(15) Removal of the BOC group with TFA gave the amine (16), which was reacted with ROCO(L) Trp activated with HBTU to give the Examples 18 and 19.(17,18)

SCHEME 2

(Examples 2, 14, and 16-19)



(Examples 18 and 19)

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

The powders and tablets preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier

which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsules, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Some of the peptides of the invention were constructed on solid-phase resins designed to produce C-terminal amides either by treatment of the resin with ammonia in methanol or by direct cleavage of an appropriately substituted resin using trifluoroacetic acid, with the required scavengers, giving the amides directly. The latter protocol was used with DuPont RapidAmide® or Nova Biochem Ultrasyn C® resins either in a simple bubbler apparatus (DuPont resin) or automated synthesizer (Nova Biochem resin).

Using a Pharmacia 4170 automated peptide synthesizer and Bioplus® software the peptides were constructed from the C-terminus using Fmoc amino acid pentafluorophenyl or DHBt esters and HOBt catalysis. Each residue was present in a fivefold excess to ensure rapid and complete acylation. On a 0.095 mmol scale the peptide was isolated following TFA cleavage (94% TFA, 5% anisole, 1% ethanedithiol) from the resin (2 hours, room temperature).

The two isomers were separated by RP-HPLC (250 x 25 mm column, gradient elution, Solvent A 0.1% aqueous TFA, Solvent B 0.1% FFA in MeCN, gradient 20% to 80% B over 20 minutes. The peptides of the invention can be made by the above method. Although any compatible resin may be used or, alternatively, solution phase synthesis may be used.

Such peptides include but are not limited to the short chemotactic peptides, for example, formyl-Met-Leu-Phe-OBz, Met-enkephalin, enkephalinamides, leupeptin (Ac-Leu-Leu-Arginol), Kyotorphin (Tyr-Arg), Morphiceptin (Tyr-Pro-Phe-Pro-NH_2), Thymopoetin II (Arg-Lys-Asp-Val-Tyr), Splenopentin (Arg-Lys-Glu-Val-Tyr), Hamburger pentapeptide (Asp-Leu-Asp-Pro-Arg), virus replication inhibiting

peptide (Z-DPhe-Phe-Gly), DNA binding peptide (Lys-Trp-Lys), Molluscan cardioexcitatory peptide (Phe-Met-Arg-Phe-NH_2 and all FMRF-amide analogues), TRH (pGlu-His-Pro), Proctolin (Arg-Tyr-Leu-Pro-Thr), Tuftsin, (Thr-Lys-Pro-Arg), Kentsin (Thr-Pro-Arg-Lys), schizophrenia-related peptide (Tnr-Val-Leu) and short polypeptides or 5-residues or less which are fragments of longer peptides.

Preferred compounds are:

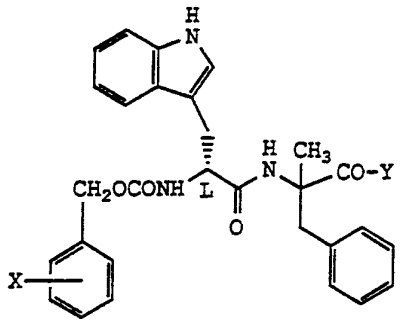
LTyr-Gly-Gly-α-MePhe-LLeu (isomer 1) and LTyr-Gly-Gly-α-MePhe-LLeu (isomer 2) whose full chemical names are N-[α-methyl-N-[N-(N-L-tyrosylglycyl)glycyl]-L-phenylalanyl]-L-leucine trifluoroacetate (1:1 salt) and N-[α-methyl-N-[N-(N-L-tyrosylglycyl)glycyl]-D-phenylalanyl]-L-leucine trifluoroacetate (1:1 salt).

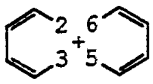
Some of the compounds were evaluated in three tachykinin binding assays:

For the NK_1 receptor - measurement of the binding of [^{125}I]-Bolton Hunter labeled substance P (0.1 nM) to guinea pig cerebral cortex membranes, and for the NK_3 receptor - measurement of the binding of [^{3}H]-senktide (2 nM) to guinea pig cerebral cortex membranes. See Lee, C. M., et al, Eur. J. Pharmacol. 130:209 (1986), and Guard, S., et al, Brit. J. Pharmacol. 99:767 (1990).

For the NK_2 receptor - measurement of the binding of [^{125}I]-iodohistidyl neurokinin A (0.1 nM) to hamster urinary bladder membranes. See Buck and Shatzer, Life Sci. 42:2701 (1988).

TABLE III. Structure of Results



Ex.	X	Y	Stereo-chemistry at α-Me-Phe	Binding IC50 (nM)		
				NK_1	NK_2	NK_3
7	4-CL	NH_2	D,L	$>10^5$	98	$>10^5$
8	4-CF_3	NH_2	D,L	$>10^5$	188	$>10^5$
9	4-Ph	NH_2	D,L	$>10^5$	94	$>10^5$
10		NH_2	D,L	$>10^5$	68	$>10^5$
11		NH_2	D,L	$>10^5$	73	$>10^5$
12		NH_2	L	~10^5	48	$>10^5$
13		NH_2	D	$>10^5$	1850	$>10^5$
14	4-CO_2-n-Pr	NH_2	D,L	$>10^5$	144	$>10^5$
18	H	$NHCH_2CONH_2$	D,L	~10^5	20	$>10^5$
19		$NHCH_2CONH_2$	D,L	$>10^5$	14	$>10^5$
20		$NHCH_2CONH_2$	L	~10^5	6	$>10^5$
21	2,3-di-OCH_3	NH_2	D,L	2900	45	$>10^5$

The data in Table III show that the compounds are selective NK_2 receptor ligands. The compounds of Examples 18 and 19 illustrate NK_2 receptor antagonism. See Table IV. Therefore, they are expected to be useful in treating disorders mediated by tachykinins, e.g., respiratory disorders, inflammation, gastrointestinal disorders, ophthalmic diseases, allergies, pain, circulatory insufficiency, diseases of the central nervous system, and migraine.

NK_2 Functional Data Summary

Tissue	Agonist	Antagonist	Conc.	Dose\ Ratio	pKa
Rat Colon	Eledoisin	Example 18	1 μM	3.1	6.5
		Example 19	1 μM	7.7	6.8
		L659,874	10 μM	10.3	7.0
Hamster Bladder Urinary	NKA	Example 18	3 μM	30	7.0
		Example 19	3 μM	29	6.9
		L659,874	3 μM	29	6.9
Hamster Trachea	NKA	Example 18	1 μM	11	6.9
		Example 18	3 μM	46	7.2
		Example 19	3 μM	31	6.9
		Example 19	10 μM	472	7.2
		L659,874	1 μM	11	7.0
		L659,874	3 μM	41	7.1

[a] L659,874 is a standard NK_2 antagonist. Its chemical name is Glycinamide, N-acetyl-L-leucyl-L-methionyl-L-glutaminyl-L-tryptophyl-L-phenylalanyl-Ac-LLeu-LMet-LGln-LTrp-LPhe-Gly-NH_2

For the hamster trachea, see Maggi, C. A., Patacchini, R., Rovero, P., and Meri, A. Eur. J. Pharmacol., 1989;166:435-440.

For the hamster urinary bladder, see Mizrahi, J., Dion, S., D'Orleans-Juste, P., Escher, B., Drapeau, G., and Regoli, D., Eur. J. Pharmacol., 1985;118:25-36.

For the rat colon, see Bailey, S. J. and Jordan, C. C., Br. J. Pharmacol., 1984;82:441-451.

The following examples illustrate the instant invention but are not intended to limit it in any way.

EXAMPLE 1

Tyr-Gly-Gly-αMePhe-Leu

The peptide was prepared and separated as described above, using solid-phase methodology.

Isomer 1 (L,D,L or L,L,L), LTyr-Gly-Gly-αMePhe-LLeu NMR (D_2O) δ 0.89 (6H, br d), 1.41 (3H, s), 1.57 (3H, br m), 3.18 (2H, 2bq), 3.12 (2H, d), 3.92 (4H, m), 4.25 (2H, m), 6.88 (2H, d), 7.18 (4H, d), 7.46 (3H, m). FAB-MS 57C $(M+H)^+$, 592 $(M+Na)^+$, 608 $(M+K)^+$.

Isomer 2 (L,L,L or L,D,L) LTyr-Gly-Gly-αMePhe-LLeu NMR (D_2O) δ 0.88 (6H, dd), 1.43 (3H, s), 1.57 (3H, br m), 3.20 (4H, m), 3.91 (4H, m), 4.23 (2H, m), 6.88 (2H, d), 7.16 (4H, d), 7.33 (3H, m). FAB-MS 570 $(M+H)^+$, 592 $(M+Na)^+$, 608 $(M+K)^+$.

EXAMPLE 2

N-(t-Butyloxycarbonyl)-DL-α-methylphenylalanine (1)

DL-α-Methylphenylalanine (5.0 g, 28 mmol) was dissolved in warm 10% Na_2CO_3 solution (60 mL) and then cooled to 0°C. t-Butyloxycarbonyl anhydride (6.39 g, 29.3 mmol) in dioxan (50 mL) was added dropwise and the mixture stirred at 0°C for 1 hour. The mixture was then allowed to warm to room temperature and stirred for a further 24 hours. The solvents were then distilled off in vacuo and the residue taken up in H_2O. This was then washed with CH_2Cl_2 (3x), acidified with citric acid, and

extracted with CH_2Cl_2 (3x). The organic extracts were combined, dried ($MgSO_4$), and the solvent distilled off in vacuo to give **1** as a white solid (6.2 g, 25.1 mmol, 90%): ^1H NMR (DMSO-d_6) δ 1.18 (3H, s), 1.41 (9H, s), 2.91 (1H, d, J 13 Hz), 3.31 (1H, d, J 13 Hz), 6.71 (1H, bs), 7.09 (2H, d), 7.25 (3H m), 12.50 (1H, bs).

EXAMPLE 3

N-(t-Butyloxycarbonyl)-DL-α-methylphenylalaninamide (2)

1 (6.7 g, 22 mmol) was dissolved in CH_2Cl_2 (80 mL) and 1,3-dicyclohexylcarbodiimide (4.9 g, 24 mmol) followed by 1-hydroxybenzotriazole monohydrate (3.9 g, 28.8 mmol) added and the mixture stirred for 0.5 hour at room temperature. DMF (15 mL) was then added, the solution cooled to -10°C and a slow stream of NH_3 (g) bubbled through. The mixture thickened almost immediately so a further amount of DMF (50 mL) was added. After 0.5 hour, the addition of NH_3 (g) was stopped and the white precipitate removed by filtration and washed with EtOAc. The washings were combined with the filtrate and the solvent distilled off in vacuo. The residue was partitioned between H_2O (500 mL) and CH_2Cl_2. The aqueous layer was washed with $CHCl_2$ (3x), the organic extracts combined, washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$), and the solvent distilled off in vacuo. The white solid obtained was further purified by flash column chromatography on silica, eluting with a mixture of $CHCl_3$:MeOH (95:5) to give **2** as a white solid (4.4 g, 15.8 mmol, 66%): ^1H NMR (DMSO-d_6) δ 1.33 (3H, s), 1.41 (9H, s), 3.31 (2H, bs), 6.25 (1H, bs), 7.15 (6H, m), 7.41 (1H, bs).

EXAMPLE 4

DL-α-Methylphenylalaninamide (3)

2 (4.4 g, 15 mmol) was stirred in TFA (15 mL) at room temperature for 15 minutes. The TFA was distilled off in vacuo and the residue taken up in EtOAc. The organic solution was carefully washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and the solvent removed in vacuo to give 3 as a white solid (1.9 g, 12.1 mmol, 70%) ^1H NMR (MeOH-d_4) δ 1.40 (3H, s), 2.77 (1H, d, J 13 Hz), 3.21 (1H, d, J 13 Hz), 7.30 (5H, m).

EXAMPLE 5

N-(9H-Fluoren-9-ylmethoxy)carbonyl]-L-tryptophyl-DL-α-methylphenylalaninamide (4)

3 (1.8 g, 10.1 mmol) and N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-tryptophan pentafluorophenyl ester (6.0 g, 10.1 mmol) were stirred together in DMF (50 mL) at room temperature for 18 hours. The solution was concentrated in vacuo and H_2O (400 mL) added. The aqueous suspension was extracted with EtOAc (3x) and the organic extracts combined, dried ($MgSO_4$) and the solvent removed in vacuo to give crude 4.

EXAMPLE 6

L-Tryptophyl-DL-α-methylphenylalaninamide (5)

4 (3.65 g, 6.2 mmol) was dissolved in a 20% solution of piperidine in DMF (20 mL) and stirred at room temperature for 20 minutes. The mixture was then concentrated in vacuo and H_2O (400 mL) added; the white precipitate formed was then removed by filtration. Citric acid was added to the filtrate to pH 3 and washed with EtOAc (3x). The aqueous layer was made alkaline (pH 9) with solid Na_2CO_3 and

extracted with EtOAc (3x). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed in vacuo to give **5** as a pale yellow solid (2.2 g). Purification by flash column chromatography on silica, eluting with CH_2Cl_2:MeOH (10:1) gave the product **5** as a white foam (1.8 g, 4.93 mmol, 80%): ^1H NMR (DMSO-d_6) δ 1.45 (0.5 x 3H, s), 1.51 (0.5 x 3H, s), 1.81 (2H, bs), 2.59 (0.5 x H, dd, J 10.14 Hz), 2.76 (0.5 x H, dd, 9, 14 Hz), 3.15 (2H, m), 3.45 (2H, m), 6.95-7.60 (12H, m), 8.16 (0.5 x H, s), 8.28 (0.5 x H, s), 10.85 (1H, s).

EXAMPLE 7

N-[[(4-Chlorophenyl)methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (6)

Pyridine (0.11 mL, 1.4 mmol) was added dropwise to a stirred solution of 4-chlorobenzyl alcohol (0.20 g, 1.4 mmol) and triphosgene (0.15 g, 0.51 mmol) in CH_2Cl_2 (5 mL) at 0°C and stirred for 5 minutes. The solvent was removed in vacuo and the resulting oil triturated with Et_2O and filtered. The filtrate was added to a solution of **5** (0.26 g, 0.71 mmol) and triethylamine (0.10 mL, 0.71 mmol) in THF (25 mL) and stirred overnight. The solvent was removed in vacuo to give a white solid which was partitioned between EtOAc and 10% citric acid solution. The organic layer was washed with saturated $NaHCO_3$ solution and H_2O and dried ($MgSO_4$). Further purification by flash column chromatography on silica eluting with a mixture of CH_2Cl_2:MeOH (95:5) gave **6** as a white foam (0.23 g, 0.43 mmol, 61%); mp 89-101.3°C; MS (FAB) m/e 533 [M+H]: ^1H NMR (DMSO-d_6) δ 1.38 (0.5 x 3H, s, α-CH_3), 1.40 (0.5 x 3H, s, α-CH_3), 2.80-3.40 (4H, m, CH_2-indole, CH_2Ph), 4.10-4.32 (1H, m, Trp α-H), 4.80-4.99 (2H, m,

CH_2O), 6.90-7.78 (18H, m, Ar, $CONH_2$, CONH, OCONH), 10.70 (1H, s, indole NH); Anal. ($C_{29}H_{29}N_4O_4C \cdot 0.3\ H_2O$) C, H, N.

EXAMPLE 8

N-[[[4-(Trifluoromethyl)phenyl]methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (7)

Prepared by the same method as **6**. White foam (0.092 g, 62%); mp 91-112°C; MS (FAB) m/e 567 [M+H]; ^1H NMR (DMSO-d_6) δ 1.38 (0.5 x 3H, s, α-CH_3), 1.41 (0.5 x 3H, s, α-CH_3), 2.70, 3.46 (4H, m, CH_2-indole, CH_2Ph), 4.12-4.36 (1H, m, Trp α-H), 4.90-5.16 (2H, m, CH_2O), 6.90-7.88 (18H, m, Ar, $CONH_2$ CONH, OCONH), 10.84 (1H, s, indole NH); Anal. ($C_{30}H_{29}N_4O_4F_3 \cdot 0.75\ H_2O$) C, H, N.

EXAMPLE 9

N-[([1,1'-Biphenyl]-4-ylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (8)

Prepared by the same method as **6**. White foam (0.050 g, 32%); mp 92-102°C; MS (FAB) m/e 576 [M+H]; ^1H NMR (DMSO-d_6) δ 1.38 (0.5 x 3H, s, α-CH_3), 1.39 (0.5 x 3H, s, α-CH_3), 2.72-3.40 (4H, m, CH_2-indole, CH_2Ph), 4.12-4.35 (1H, m, Trp α-H), 4.90-5.08 (2H, m, CH_2O), 6.92-7.85 (23H, m, Ar, $CONH_2$, CONH, OCONH), 10.90 (1H, s, indole NH); Anal. ($C_{35}H_{34}N_4O_4 \cdot 0.75\ H_2O$) C, H, N.

EXAMPLE 10

N-[(9-Anthracenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (9)

Prepared by the same method as **6**. Yellow foam (0.10 g, 23%); mp 113-130°C; MS (FAB) m/e 599 [M+H]; ^1H NMR (DMSO-d_6) 1.36 (3H, s, α-CH_3), 2.25-3.20 (2H, m, CH_2-indole), 3.25-3.40 (2H, m, CH_2Ph), 4.20-4.38

(1H, m, Trp α-H), 5.95 (0.5 x 2H, AB, J 12 Hz, CH_2Ar), 6.01 (0.5 x 2H, AB, J 12 Hz, CH_2Ar), 6.85-7.20 (17H, m, Ar, $CONH_2$, OCONH), 7.77 (0.5 x H, s, CONH), 7.83 (0.5 x H, s, CONH), 8.10 (1H, s, Ar), 8.13 (1H, s, Ar), 8.28 (1H, s, Ar), 8.31 (1H, s, Ar), 8.67 (1H, s, Ar), 10.80 (1H, s, indole NH); Anal. ($C_{37}H_{34}N_4O_4 \cdot 0.7\ H_2O$) C, H, N.

EXAMPLE 11

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (10)

Prepared by the same method as 6. White foam (0.13 g, 34%); mp 102-113°C; MS (FAB) m/e 549 [M+H]; ^1H NMR (DMSO-d_6) δ 1.40 (3H, s), 2.87 (1H, m), 3.05-3.45 (3H, m), 4.15-4.40 (1H, m), 5.30-5.50 (2H, m), 6.90-8.00 (21H, m), 10.70 (1H, s); Anal. ($C_{33}H_{32}N_4O_4 \cdot 0.4\ H_2O$) C, H, N.

EXAMPLE 12

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-L-phenylalaninamide (11)

Prepared by the same method as 6, -α-methyl-L-phenylalanine was obtained by the method of Turk, et al (Turk, J., Panse, G. T., Marshall G. R., J. Org. Chem. 40:953 (1975)).

EXAMPLE 13

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-D-phenylalaninamide (12)

Prepared by the same method as 6. D-α-methyl-phenylalanine was obtained by the method of Turk, et al.

EXAMPLE 14

N-[[[4-(Propoxycarbonyl)phenyl]methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (13)

Propyl 4-(hydroxymethyl)benzoate (0.10 g, 0.5 mmol), 4-nitrophenyl chloroformate (0.10 g, 0.5 mmol) and pyridine (0.04 mL, 0.5 mmol) were stirred for 18 hours in CH_2Cl_2 (8 mL). The solvent was removed in vacuo and the white residue triturated with EtOAc and filtered. The filtrate was added to a solution of **5** (0.10 g, 0.27 mmol) and 1,1,3,3-tetramethylguanidine (0.10 mL, 0.81 mmol) in DMSO (2 mL) and stirred for 3.5 hours. The reaction mixture was poured onto H_2O and extracted with EtOAc. The organic layer was washed with 10% citric acid solution, saturated $NaHCO_3$ solution, H_2O, and dried ($MgSO_4$). Further purification by flash column chromatography on silica, eluting with CH_2Cl_2 (95:5) gave **13** as a white foam (0.02 g, 13%); mp 78-105°C; MS (FAB) m/e 586 [M+H]; ^1H NMR (DMSO-d_6) δ 0.97 (3H, t, J 7 Hz, CH_3CH_2), 1.38 (0.5 x 3H, s, α-CH_3), 1.40 (0.5 x 3H, s, α-CH_2), 1.76 (2H, m, CH_2CH_2), 2.80-3.45 (4H, m, CH_2-indole, CH_2Ph), 4.12-4.35 (3H, m, Trp α-H, CH_2CH_2O), 4.94-5.15 (2H, m, CH_2OCO), 6.95-7.95 (18H, m, Ar, $CONH_2$, CONH, OCONH, 10.82 (1H, s, indole NH); Anal. ($C_{33}H_{36}N_4O_6 \cdot 0.75\ H_2O$) C, H, N.

EXAMPLE 15

Boc(α-Me)-DL-PheODhbt (14)

1,3-Dicyclohexylcarbodiimide (4.95 g, 24 mmol) was added to a solution of **1** (6.70 g, 24 mmol) in THF (100 mL) at -15°C and allowed to stir for 5 minutes. 3-Hydroxy-1,2,3-benzotriazine-4-(3H)-one (3.91 g, 24 mmol) and an additional volume of THF (20 mL) were added and the mixture stirred at -10°C for 1 hour and at 0°C for 4 hours. After leaving overnight at 5°C a

white solid precipitated. This was filtered and dried to give **14** (9.1 g, 89%): ^{1}H NMR (DMSO-d_6) δ 1.44 (3H, s, α-CH_3), 1.49 (9H, s, t-Bu), 3.06 (1H, d, J 13 Hz, CH'HPh), 3.61 (1H, d, J 13 Hz, CH'HPh), 7.15-7.38 (5H, m, Ph), 7.64 (1H, s, OCONH), 8.02 (1H, 5, J 7.5 Hz, Ar), 8.19 (1H, t, J 7.5 Hz, Ar), 8.33 (2H, d, J 8 Hz, Ar).

EXAMPLE 16

Boc-(α-Me)-DLPheGlyNH_2 (15)

14 (4.24 g, 10 mmol), glycinamide hydrochloride (1.11 g, 11 mmol), and triethylamine (1.39 mL, 11 mmol) in EtOAc (100 mL) were stirred overnight at room temperature. The white solid which precipitated was removed by filtration and washed with EtOAc. The filtrate was washed with 10% citric acid solution, saturated $NaHCO_3$ solution, H_2O, and dried ($MgSO_4$). Removal of the solvent in vacuo gave **15** as a white solid (2.05 g, 61%): ^{1}H NMR (DMSO-d_6) δ 1.16 (3H, s, α-CH_3), 1.43 (9H, s, t-Bu), 2.95 (1H, d, J 13 Hz, CH_2Ph), 3.26 (1H, d, J 15 Hz, CH_2Ph), 3.46 (1H, br d, J 16.5 Hz, NHCH_2CO), 3.69 (1H, dd, J 16.5 Hz, 6 Hz, NHCH_2CO), 7.02-7.34 (8H, m, Ar, $CONH_2$, OCONH), 8.17 (1H, bs, NHCO).

EXAMPLE 17

(α-Me)-DLPheGlyNH_2 (16)

15 (2.0 g, 5.7 mmol) was stirred at 0°C in TFA (2 mL) for 15 minutes. The solvent was removed in vacuo and the residue triturated with ET_2O. The white solid formed was filtered and dried to give **16** (1.97 g, 95%): ^{1}H NMR (DMSO-d_6) δ 1.52 (3H, s, α-CH_3), 3.06 (1H, d, J 14 Hz, CH_2Ph), 3.20 (1H, d, J 14 Hz, CH_2Ph), 3.74 (2H, d, J 5.5 Hz, NHCH_2CO),

7.00-7.40 (7H, m, Ph_2CONH_2), 8.09 (3H, bs, NH_3+), 8.62 (1H, J 5.6 Hz, CONH).

EXAMPLE 18

N-[(Phenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalanylglycinamide (17)

Hydrobenzotriazolyl tetramethyluronium hexachlorophosphate (HBTU) (0.19 g, 0.5 mmol) was added to a solution of Z-(L)-Trp (0.15 g, 0.5 mmol), **16** (0.17 g, 0.5 mmol), and N,N-diisopropylethylamine (0.26 mL, 1.5 mmol) in DMF (3 mL) and stirred at room temperature for 45 minutes. Water was added and the mixture extracted with EtOAc. The organic layer was washed with 10% citric acid solution, saturated $NaHCO_3$ solution, H_2O, and dried ($MgSO_4$). Further purification by flash column chromatography on silica, eluting with CH_2Cl_2:MeOH (90:10) gave **17** as a white foam (0.17 g, 61%); mp 92-110°C; MS (FAB) m/e 556 [M+H]; ^1H NMR (DMSO-d_6) δ 1.19 (0.5 x 3H, s, α-CH_3), 1.24 (0.5 x 3H, s, α-CH_3), 2.80-3.30 (4H, m, CH_2-indole, CH_2Ph), 3.40-3.78 (2H, m, $C\underline{H}_2CONH_2$), 4.25-4.48 (1H, m, Trp-α-H), 4.84-5.06 (2H, m, CH_2OCO), 6.88-7.45 (16H, m, Ar, OCONH, $CONH_2$), 7.55-7.75 (2H, m, Ar), 7.80 (0.5 x H, t, $CON\underline{H}CH_2$), 7.88 (0.5 x H, t, $CON\underline{H}CH_2$), 8.35 (0.5 x H, s, $N\underline{H}C(CH_3)$, 8.41 (0.5 x H, s, $N\underline{H}C(CH_3)$, 10.86 (1H, s, indole NH); Anal. ($C_{31}H_{33}N_5O_{35}\cdot 0.5H_2O$) C, H, N.

EXAMPLE 19

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalanylglycinamide (18)

Diisopropylethylamine (52 µL, 0.3 mmol) was added to a stirred solution of N-[(1-naphthylmethoxy)carbonyl]tryptophan (0.117 g, 0.3 mmol) and HBTU (0.114 g, 0.3 mmol) in DMF (5 mL) at room

temperature. The mixture was stirred for 10 minutes, then 16 (0.105 g, 0.3 mmol) in DMF (5 mL) was added, followed by diisopropyl ethylamine (105 μL, 0.6 mmol) and the reaction mixture stirred for a further 18 hours. The mixture was poured into H_2O (100 mL) and extracted with EtOAc (2 x 50 mL). The organic extracts were combined, washed with 10% citric acid solution (1 x 100 mL), saturated $NaHCO_3$ solution (1 x 100 mL), H_2O (2 x 100 mL), and dried ($MgSO_4$). The solvent was removed in vacuo and the residue purified by column chromatography on silica, eluting first with mixtures of EtOAc in hexane (30% to 70%) followed by CH_2Cl_2:MeOH (95:5) to give **18** as a white solid (0.148 g, 81%); MS (FAB) m/e 606 [M+H]: ^1H NMR (DMSO-d_6) δ 1.21 (0.5 x 3H, s, α-CH_3), 1.26 (0.5 x 3H, s, α-CH_3), 2.85-3.78 (6H, m, CH_2-indole, CH_2Ph, Ch_2CONH_2), 4.38 (1H, m, Trp α-H), 5.44 (2H, m, CH_2 naphthyl), 6.92-7.20 (10H, m, Ar/NH), 7.33 (0.5 x H, s, Ar/NH), 7.35 (0.5 x H, s, Ar/NH), 7.52-7.70 (6H, m, Ar/NH), 7.75-8.00 (4H, m, Ar/NH), 8.33 (0.5 x H, s, NH), 8.35 (0.5 x H, s, NH), 10.72 (1H, s, NH indole); Anal. ($C_{35}H_{35}N_5O_5 \cdot 0.5H_2O$) C, H, N.

EXAMPLE 20

N-[(1-Naphthalenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-L-phenylalanylglycinamide (19)

Prepared by the same method as Compound 18 as in Example 19 in methylphenylalanine and obtained by the method of Tuttle, et al.

EXAMPLE 21

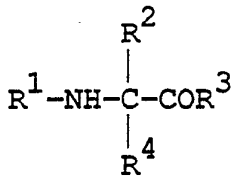
N-[[(2,3-Dimethoxyphenyl)methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide (20)

Prepared by the same method as Compound 6 in Example 7, white foam: mp 87-102°C; MS (FAB) m/e 559

[M+H]; ^{1}H NMR (DMSO-d_6) δ 1.39 (3H,S,α-CH_3), 2.88 (1H, t) and 3.11-3.39 (3H, m, CH_2-indole, CH_2Ph), 3.63 (3H, d, OCH_3), 3.78 (3H, s, OCH_3), 4.21 (1H, m, Trp α-H), 4.93 (2H, s, CH_2O), 6.79-7.78 (17H, m, Ar, $CONH_2$, CONH, OCONH), 10.76 (1H, s, indole NH), and ($C_{31}H_{34}N_4O_6 \cdot 0.5\ H_2O$) C, H, N.

CLAIMS

1. A compound of formula



I

or a pharmaceutically acceptable salt thereof wherein:

R^1 is an N-terminal blocking group, from 0 to 4 amino acid residues or hydrogen;

R^2 is a sidechain of a genetically coded amino acid except glycine;

R^3 is a C-terminal blocking group from 0 to 4 amino acid residues, -OH, or OR^n wherein R^n is straight or branched alkyl or cycloalkyl of from 1 to 6 carbon atoms;

R^4 is a sidechain of a genetically coded amino acid, except glycine, or

$-HC=CH_2$,

$-C\equiv CH$,

$-CH_2-CH=CH_2$,

$-CH_2C\equiv CH$,

$-CH_2Ar$,

$-CH_2OR$,

$-CH_2OAr$,

$-(CH_2)_nCO_2R$, or

$-(CH_2)_nNR^5R^6$ wherein n is an integer of from 0 to 3, R is hydrogen or lower alkyl, Ar is a mono- or polycyclic unsubstituted or substituted carbo- or heterocyclic aromatic or hydroaromatic moiety;

R^4 and R^2 cannot be hydrogen;

R^1 and R^3 together cannot be more than 4 amino acid residues.

2. A compound according to Claim 1 wherein:

R^1 is H,
Boc,
Fmoc,
Z,
1-Adoc,
2-Adoc,
IVA, or
NVA;

R^2 is CH_3- or
HOOC-CH_2- ; and

R^3 is $-NH_2$,
$-OCH_3$, or
$-OCH_2Ph$.

3. A compound according to Claim 1 selected from

MeLys-Trp-Asp-Asn-Gln,
Lys-MeTrp-Asp-Asn-Gln,
Lys-Trp-MeAsp-Asn-Gln,
Lys-Trp-Asp-MeAsn-Gln,
Lys-Trp-Asp-Asn-MeGln,
MeVal-Gly-His-Leu-Met-NH_2,
Val-Gly-MeHis-Leu-Met-NH_2,
Val-Gly-His-MeLeu-Met-NH_2,
Val-Gly-His-Leu-MeMet-NH_2,
MeGlp-His-Trp-Ser-Tyr,
Glp-MeHis-Trp-Ser-Tyr,
Glp-His-MeTrp-Ser-Tyr,
Glp-His-Trp-MeSer-Tyr,
Glp-His-Trp-Ser-MeTyr,
Gly-MeLeu-Arg-Pro-Gly-NH_2,

Gly-Leu-MeArg-Pro-Gly-NH_2,
Gly-Leu-Arg-MePro-Gly-NH_2,
MeTyr-Pro-Ser-Lys-Pro,
Tyr-MePro-Ser-Lys-Pro,
Tyr-Pro-MeSer-Lys-Pro,
Tyr-Pro-Ser-MeLys-Pro,
Tyr-Pro-Ser-Lys-MePro,
MeThr-Arg-Gln-Arg-Tyr-NH_2,
Thr-MeArg-Gln-Arg-Tyr-NH_2,
Thr-Arg-MeGln-Arg-Tyr-NH_2,
Thr-Arg-Gln-MeArg-Tyr-NH_2,
Thr-Arg-Gln-Arg-MeTyr-NH_2,
Gly-MeTrp-Thr-Leu-Asn,
Gly-Trp-MeThr-Leu-Asn,
Gly-Trp-Thr-MeLeu-Asn,
Gly-Trp-Thr-Leu-MeAsn,
MeLeu-Tyr-Gly-Leu-Ala-NH_2,
Leu-MeTyr-Gly-Leu-Ala-NH_2,
Leu-Tyr-Gly-MeLeu-Ala-NH_2,
Leu-Tyr-Gly-Leu-Aib-NH_2,
MePhe-Phe-Trp-Lys-Thr,
Phe-MePhe-Trp-Lys-Thr,
Phe-Phe-MeTrp-Lys-Thr,
Phe-Phe-Trp-MeLys-Thr,
Phe-Phe-Trp-Lys-MeThr,
MePhe-Phe-Gly-Leu-Met-NH_2,
Phe-MePhe-Gly-Leu-Met-NH_2,
Phe-Phe-Gly-MeLeu-Met-NH_2, and
Phe-Phe-Gly-Leu-MeMet-NH_2.

4. A compound named N-[α-methyl-N-[N-(N-L-tyrosylglycyl)glycyl]-L-phenylalanyl]-L-leucine trifluoroacetate (1:1 salt).

5. A compound named N-[α-methyl-N-[N-(N-L-tyrosylglycyl)glycyl]-D-phenylalanyl]-L-leucine trifluoroacetate (1:1 salt).

6. A compound named N-[[(4-chlorophenyl)methoxy]-carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

7. A compound named N-[[[4-(trifluoromethyl)-phenyl]methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

8. A compound named N-[([1,1'-biphenyl]-4-yl-methoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

9. A compound named N-[(9-anthracenylmethoxy)-carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

10. A compound named N-[(1-naphthalenylmethoxy)-carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

11. A compound named N-[(1-naphthalenylmethoxy)-carbonyl]-L-tryptophyl-α-methyl-L-phenylalaninamide.

12. A compound named N-[(1-naphthalenylmethoxy)-carbonyl]-L-tryptophyl-α-methyl-D-phenylalaninamide.

13. A compound named N-[[[4-(propoxycarbonyl)-phenyl]methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

14. A compound named N-[(phenylmethoxy)carbonyl]-L-tryptophyl-α-methyl-DL-phenylalanylglycinamide.

15. A compound named N-[(1-naphthalenylmethoxy)-carbonyl]-L-tryptophyl-α-methyl-DL-phenylalanyl-glycinamide.

16. A compound named N-[(1-naphthalenylmethoxy)-carbonyl]-L-tryptophyl-α-methyl-L-phenylalanylglycinamide.

17. A compound named N-[[(2,3-dimethoxyphenyl)-methoxy]carbonyl]-L-tryptophyl-α-methyl-DL-phenylalaninamide.

18. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat pain in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

19. A method of treating pain in a mammal comprising administering an effective pain treating amount of a compound according to Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03119

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 37/00, 37/02; CO7K 5/00, 7/00

US CL :530/330; 514/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/330; 514/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS TEXT SEARCH, CAS ONLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A, 90/12810 (RIVIER ET AL) 01 NOVEMBER 1990, see entire document.	1-19
Y	US, A, 4,689,318 (KAISER ET AL) 25 AUGUST 1987, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

23 July 1992

Date of mailing of the international search report

29 JUL 1992

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