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Amidinophenol derivatives
Amidophenolderivate
Dérivés d’amidinophénolés

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References cited:
EP A- 0 518 819
US A- 4 514 416
US A- 4 570 006

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Description

The present invention relates to amidinophenol derivatives, processes for their preparation and pharmaceutical compositions containing them.

Phospholipase A₂ (PLA₂) is an enzyme which acts on phospholipids existing in cell membrane and hydrolyzes an ester bond at the second position of the phospholipids. There are known two kinds of PLA₂, i.e., membrane-associated PLA₂ and pancreatic PLA₂.

Membrane-associated PLA₂ acts on phospholipids to release arachidonic acid (AA) from the phospholipids. The AA is converted into prostaglandins, thromboxanes and leukotrienes, which are physiologically active substances inducing various inflammatory diseases and allergic diseases.

On the other hand, pancreatic PLA₂ degrades phospholipids and destructs cell membrane, thereby to produce lysolecithin having strong cytotoxicity. Recently, much importance has been attached to pancreatitis, severity in pancreatitis and multiple organ failure induced by such destructive activity on cell membrane, and it has been more remarkable. Further, it is reported that membrane-associated PLA₂ is also concerned with these diseases.

Accordingly, the inhibition on PLA₂ leads to the suppression of the release of AA, a precursor of various physiologically active substances, and therefore, it is considered to be useful for the prevention and/or the treatment of various inflammatory and allergic diseases. Furthermore, it is considered to be useful for the prevention and/or the treatment of pancreatitis, severity in pancreatitis and multiple organ failure due to the inhibition of destructive activity on cell membrane.

Many compounds having an inhibitory activity on PLA₂ are known. For example, there are known guanidinobenzoic acid derivatives such as camostat mesylate (code no. FOY-305) of the formula (X):

\[
\text{H}_2\text{N} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \\
\text{NH} \quad \text{COO} \quad \text{COO} \quad \text{COOCH}_2\text{CO} \quad \text{N} \quad \text{CH}_3 \\
\text{CH}_3 \quad \text{CH}_3
\]

\[
\text{CH}_3\text{SO}_3\text{H}
\]

and nafamostat mesylate (code no. FUT-175) of the formula (Y):

\[
\text{H}_2\text{N} \quad \text{NH} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{NH}_2 \\
\text{NH} \quad \text{COO} \quad \text{COO} \quad \text{NH} \\
\text{H} \quad \text{H} \quad \text{H}
\]

\[
\text{2CH}_3\text{SO}_3\text{H}
\]


Further, there are known compounds of the formula (Z):
where in $R^{1z}$ is:

(i) C1-4 alkyl,
(ii) C1-4 alkoxy,
(iii) carboxy,
(iv) COOR^{2z} (in which $R^{2z}$ is C1-4 alkyl),
(v) halogen,
(vi) nitro,
(vii) sulfo,
(viii) benzoyle or
(ix) 

$(Z)$

(in which $R^{5z}$ is hydrogen or guanidino).

$R^{2z}$ and $R^{3z}$ each, independently, is:

(i) NHCO-$R^{6z}$ (in which $R^{6z}$ is C1-4 alkyl) or
(ii) 

$(Z)$

(in which $A^{z}$ is bond, methylene or ethylene,

$R^{7z}$ and $R^{8z}$ each, independently, is

1) hydrogen,
2) C1-4 alkyl or
3) amino-protecting group
   (it refers to
   (a) COOR^{9z} in which $R^{9z}$ is t-butyl or benzyl,
   (b) acetyl,
   (c) benzoyle,
   (d) tosyl or
   (e) nitro);
(definitions not related are omitted) (see the specification of the U.S. Patent Nos. 4,514,416 and 4,570,006). It is disclosed that the compounds have an inhibitory activity on protease such as trypsin, plasmin and anti-complement effect, but it is not entirely known that the compounds have an inhibitory activity on PLA₂, 

\[ R^2 \text{ and } R^3 \text{ in the formula } (Z) \text{ hereinbefore depicted can represent } \text{NHCO-R}^6, \text{ but the nitrogen atom in the said group is attached directly to a benzene ring, and further } R^6 \text{ represents only an alkyl group. In the compounds of the present invention, described hereinafter, a benzene ring is substituted by a group } \text{CON}(R^7)(R^8), \text{ CON}(R^9)-\text{CH}(R^7)(R^8) \text{ or a group of the formula:} \]

\[
\text{CON} \quad \text{R}^{10}
\]

the carbon atom in the said group being attached to a benzene ring via a group A which may represent, inter alia, a direct bond.

From the above viewpoint, it can be said that the compounds of the present invention have a chemical structure quite different from the compounds of the formula (Z).

Furthermore, it has never been known that amidinophenol derivatives (compounds of the formula (Z) hereinbefore depicted) have an inhibitory activity on PLA₂ though some guanidinebenzoic acid derivatives (compounds of the formulae (X) and (Y) hereinbefore depicted) have already been known to have the activity.

Accordingly, it is quite unexpected from the related arts, that the amidinophenol derivatives of the present invention have an inhibitory activity on PLA₂.

The present invention relates to:

compounds of the formula (I):

\[
\text{(I)}
\]

wherein \( R^1 \) and \( R^2 \) each, independently, is:

(i) hydrogen,
(ii) C1-4 alkyl,
(iii) C1-4 alkoxy,
(iv) C2-5 acyl,
(v) halogen,
(vi) nitro,
(vii) benzoyl or
(viii) COOR⁴ (in which \( R^4 \) is C1-3 alkyl);

\( A \) is a bond, C1-4 alkyene or

\[
\text{C} = \text{C} \quad \text{R}^5 \quad \text{R}^6
\]

(in which \( R^5 \) and \( R^6 \) each independently, is hydrogen or C1-4 alkyl); \( R^3 \) is
(i) $\text{CON}^{\text{R}^7}_{\text{R}^8}$

(ii) $\text{CON}^{\text{R}^7}_{\text{R}^9}$

or

(iii) $\text{CON}^{\text{R}^9}_{\text{R}^{10}}$

(in which $\text{R}^7$ and $\text{R}^8$ each, independently, is

1. hydrogen,
2. phenyl,
3. C7-10 phenylalkyl,
4. phenyl or C7-10 phenylalkyl each of which is substituted by one or two substituents selected from C1-4 alkyl, halogen and $\text{R}^{11}$-$\text{COOR}^{12}$

(in which $\text{R}^{11}$ is

(a) a bond,
(b) C1-8 alkyne,
(c) C2-8 alkenylene or
(d) C2-8 alkyrylene, and

$\text{R}^{12}$ is

(a) hydrogen,
(b) C1-4 alkyl,
(c) C7-10 phenylalkyl,
(d) phenyl,
(e) allyl (i.e., $\text{-CH}_2\text{CH}=\text{CH}_2$) or
(f) propargyl (i.e., $\text{-CH}_2\text{C}=\text{CH}_2$),

5. C1-10 alkyl,
6. C2-10 alkynyl having one to three double bonds,
7. C2-10 alkynyl having one or two triple bonds,
8. $\text{R}^{11a}$-$\text{COXR}^{12}$

(in which $\text{R}^{11a}$ is

(a) a bond,
(b) C1-8 alkyne,
(c) C2-8 alkenylene in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur and phenylene,
(d) C2-8 alkenylene,
(e) C4-8 alkenylene in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur and
phenylene,
   (f) C2-8 alkyylene, or
   (g) C4-8 alkyylene in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur and
   phenylene,
   X is oxygen or -NH,- and R12 is the same meaning as hereinbefore defined,
   (9) C1-4 alkyl which is substituted by a 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen, or
   (10) C3-7 cycloalkyl;

   R9 is
   (1) hydrogen,
   (2) C1-8 alkyl,
   (3) C7-10 phenylalkyl,
   (4) C2-10 alkenyl having one to three double bonds,
   (5) C2-10 alkynyl having one or two triple bonds,
   (6) R11-COOR12 (in which R11 and R12 are the same meaning as hereinbefore defined), or
   (7) C3-7 cycloalkyl;

   N

   is 4-7 membered, mono-cyclic hetero ring containing one or two nitrogen;
   R10 is
   (1) hydrogen,
   (2) C7-10 phenylalkyl or
   (3) COOR13 (in which R13 is hydrogen, C1-4 alkyl or C7-10 phenylalkyl));
   with the proviso that
   (i) both R7 and R8 do not represent hydrogen at the same time, and
   (ii) when at least one group in R7, R8 and R9 represents the group containing t-butyl ester, the other groups
do not represent the group containing carboxy;

   or an acid-addition salt thereof. The acid addition salts are preferred.

   The compounds of the invention may form hydrates; it is to be understood that such hydrates form part of the
   present invention and that references to the compounds in this specification including the accompanying claims are
to be understood as embracing the hydrates.

   It will be understood that formulae (i) and (ii) may overlap; formula (ii) should be construed as excluding those
   groupings already embraced by formula (i).

   The compounds of the invention possess inhibitory activity on PLA2 and an inhibitory activity on various proteases
   such as trypsin, plasmin, thrombin, kallikrein, especially trypsin.

   Throughout the specification including claims, it may be easily understood by those skilled in the art, that all isomers
are included in the present invention. For example, the alkyl, alkoxy, alkenylene and alkynylene groups include
straight-chain and also branched-chain ones, and the double bonds in the alkenylene group include E, Z and EZ
mixture. Accordingly, all isomers produced by the existence of asymmetric carbon atoms are included in the present
invention when branched-chain alkyl, alkoxy, alkenylene, alkynylene etc. exist.

   In the formula (I), the C1-4 alkyl group represented by R1, R2, R5, R8, R12 and R13, and that in R7 and R9, means,
methyl, ethyl, propyl, butyl and the isomer thereof.

   In the formula (I), the C1-4 alkoxy group represented by R1 and R2, means methoxy, ethoxy, propoxy, butoxy and the
   isomers thereof.

   In the formula (I), the C1-3 alkyl group represented by R4, means methyl, ethyl, propyl and the isomers thereof.

   In the formula (I), the C2-5 acyl group represented by R1 and R2 means acetyl, propionyl, butyryl, valeryl and the
   isomers thereof.

   In the formula (I), the C1-10 alkyl group represented by R7 and R8, means methyl, ethyl, propyl, butyl, pentyl, hexyl,
heptyl, octyl, nonyl, decyl and the isomers thereof.

In the formula (I), the C1-8 alkyl group represented by R^6, means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and the isomers thereof.

In the formula (I), the C7-10 phenylalkyl group represented by R^7, R^8, R^10, R^12 and R^13, means methyl, ethyl, propyl, butyl and the isomers thereof, which are substituted by a phenyl group.

In the formula (I), the halogen atom represented by R^1 and R^2, and that in R^7 and R^8, mean fluorine, chlorine, bromine and iodine atoms.

In the formula (I), the C1-4 alkyne group represented by A, means methylene, ethylene, trimethylene, tetramethylene and the isomers thereof.

In the formula (I), the C1-8 alkyne group represented by R^{11} and R^{11a}, means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene and the isomers thereof. The C2-8 alkenylene group means vinylene propylene, butylene, pentylene, hexylene, heptylene, octylene and the isomers thereof. The C2-8 alkenylene group means ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene and the isomers thereof.

In the formula (I), the C2-8 alkyne in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur and phenylene, represented by R^{11a} means thiaketylene (i.e., -CH=CH-S- and -S-CH=CH), thiatrialkylenes (i.e., -CH=CH=CH-S-, CH=CH-S-CH=CH-S-, S-CH=CH-S-CH=CH-S- and -S-CH=CH=CH-S-), thiattaramine, thiapentamethylene, thiahexamethylene, thiheptamethylene, thiocamethylene and the isomers thereof, or the group in which one of any alkylene groups in the said thiaketylene group, is replaced by a phenylene group (e.g., -CH=CH=CH-S-CH=CH-S-CH=CH=CH-S-).

The C4-8 alkyne in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur and phenylene, means thiabutylene (i.e., -S-CH=CH=CH-S-, thiapentamethylene (i.e., -S-CH=CH=CH=CH-S-), thiapkylene (i.e., -S-CH=CH=CH=CH=CH-S-), thiahexamethylene, thiapentamethylene, thihexamethylene and the isomers thereof, or the group in which one of any alkylene groups in the said thiaketylene group, is replaced by a phenylene group (e.g., -S-CH=CH=CH=CH-S-).

In the formula (I), examples of the 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen, represented by R^7 and R^8, are indole, indoline, quinoline, 1,2,3,4-tetrahydroquinoline, carbazole etc.

In the formula (I), examples of the 4-7 membered, mono-cyclic hetero ring containing one or two nitrogen atoms, represented by:

\[
\text{N}
\]

are pyrrole, pyrrolidine, imidazole, imidazolidine, pyridine, piperidine, pyrazine, piperazine, pyrimidine, etc.

In the formula (I), the C2-10 alkynyl having one to three double bonds, represented by R^7 and R^8, means ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl, hexatrienyl, heptatrienyl, octatrienyl, nonatrienyl, decatrienyl and the isomers thereof.

The C2-10 alkynyl having one or two triple bonds, means ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptyl, octynyl, nonynyl, decynyl, butadiynyl, pentadiynyl, hexadiynyl, heptadiynyl, octadiynyl, nonadiynyl, decadiynyl and the isomers thereof.

In the formula (I), the cycloalkyl group represented by R^7, R^8 and R^9, means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Examples of representative compounds of the present invention are listed as follows:

(1) p-(p-Aminophenoxy)carbonyl)-α-methylocinnamic acid N-(o, m, p)ethoxycarbonylphenyl-N-ethoxycarbonylmethylamide,

(2) p-(p-Aminophenoxy)carbonyl)-α-methylocinnamic acid N-(o, m, p)ethoxycarbonylphenyl-N-benzylxycarbo

(3) p-(p-Aminophenoxy)carbonyl)-α-methylocinnamic acid N-(o, m, p)ethoxycarbonylphenyl-N-allyloxycarbonyl-
methylamide,
(4) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylphenyl-N-propargyloxycarbonylmethylamidine,
(5) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylmethylphenyl-N-ethoxycarbonylmethylamidine,
(6) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylmethylphenyl-N-benzoxycarbonylmethylamidine,
(7) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylmethylphenyl-N-allyloxycarbonylmethylamidine,
(8) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylphenylmethyl-N-ethoxycarbonylmethylamidine,
(9) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylphenylmethyl-N-benzoxycarbonylmethylamidine,
(10) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylphenylmethyl-N-allyloxycarbonylmethylamidine,
(11) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylphenylmethyl-N-allyloxycarbonylmethylamidine,
(12) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylphenylmethyl-N-propargyloxycarbonylmethylamidine,
(13) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylmethylphenylmethyl-N-ethoxycarbonylmethylamidine,
(14) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylmethylphenylmethyl-N-benzoxycarbonylmethylamidine,
(15) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)ethoxycarbonylmethylphenylmethyl-N-allyloxycarbonylmethylamidine,
(16) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-(o, m, p)-ethoxycarbonylmethylphenylmethyl-N-ethoxycarbonylmethylamidine,
(17) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-ethoxycarbonylmethylamidine,
(18) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-benzoxycarbonylmethylamidine,
(19) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-allyloxycarbonylmethylamidine,
(20) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-propargyloxycarbonylmethylamidine,
(21) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-1-methyl-2-ethoxycarbonylethenyl-N-ethoxycarbonylmethylamidine,
(22) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-1-methyl-2-ethoxycarbonylethenyl-N-benzoxycarbonylmethylamidine,
(23) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-1-methyl-2-ethoxycarbonylethenyl-N-allyloxycarbonylmethylamidine,
(24) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-1-methyl-2-ethoxycarbonylethenyl-N-propargyloxycarbonylmethylamidine,
(25) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonyl-1-propenyl-N-ethoxycarbonylmethylamidine,
(26) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonyl-1-propenyl-N-benzoxycarbonylmethylamidine,
(27) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonyl-1-propenyl-N-allyloxycarbonylmethylamidine,
(28) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonyl-1-propenyl-N-propargyloxycarbonylmethylamidine,
(29) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-ethoxycarbonylmethylamidine,
(30) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-benzoxycarbonylmethylamidine,
(31) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-allyloxycarbonylmethylamidine,
(32) p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-2-ethoxycarbonylethenyl-N-propargyloxycarbonylmethylamidine,
(33) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-1-phenylmethyl)methyl-N-ethylxcarbonylmethylamide,
(34) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-benzoxycarbonyl-1-phenylmethyl)methyl-N-benzoxycarbonylmethylamide,
(35) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-1-phenylmethyl)methyl-N-benzoxycarbonylmethylamide,
(36) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-ethylxcarbonylmethylamide,
(37) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-benzoxycarbonylmethylamide,
(38) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl phenyl-1-allyloxycarbonylmethylamide,
(39) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-propargyloxycarbonylmethylamide,
(40) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-ethylxcarbonylmethylamide,
(41) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-benzoxycarbonylmethylamide,
(42) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-allyloxycarbonylmethylamide,
(43) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1-(o, m, p)ethoxycarbonyl]phenyl-1-propargyloxycarbonylmethylamide,
(44) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[2, 3-bis(ethoxycarbonyl)]phenylamid, (45) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[2, 4-bis(ethoxycarbonyl)]phenylamide,
(46) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[2, 5-bis(ethoxycarbonyl)]phenylamide,
(47) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[2, 6-bis(ethoxycarbonyl)]phenylamide,
(48) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[3, 4-bis(ethoxycarbonyl)]phenylamide,
(49) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[3, 5-bis(ethoxycarbonyl)]phenylamide,
(50) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-3-benzoxycarbonyl)propylamid, (51) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-benzoxycarbonyl-3-ethylxcarbonyl)propylamide,
(52) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[1, 2-bis(ethoxycarbonyl)]ethylamide,
(53) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-2-benzoxycarbonyl)ethylamide,
(54) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-benzoxycarbonyl-2-ethylxcarbonyl)ethylamide,
(55) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[bis(ethoxycarbonyl)]methylamide,
(56) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-1-benzoxycarbonyl)methylamide,
(57) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-[bis(ethoxycarbonyl)methyl]methylamide,
(58) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-1-benzoxycarbonyl)ethylamide,
(59) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-bis(1, 3-ethylxcarbonyl)-2-propenylamide,
(60) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-3-benzoxycarbonyl)-2-propenylamide,
(61) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-benzoxycarbonyl-3-ethylxcarbonyl)-2-propenylamide,
(62) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-bis(1, 3-ethylxcarbonyl)-2-butenylamide,
(63) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-3-benzoxycarbonyl)-2-butenylamide,
(64) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-benzoxycarbonyl-3-ethylxcarbonyl)-2-butenylamide,
(65) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-bis[1, 3-ethylxcarbonyl]-2-methylpropenylamide,
(66) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-ethylxcarbonyl-2-methyl-3-benzoxycarbonyl)propenylamide,
(67) p-[(p-Aminophenoxy)carbonyl]-α-methylcinnamic acid N-(1-benzoxycarbonyl-2-methyl-3-ethylxcarbonyl)propenylamide,
(65) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-[ethoxycarbonyl]-1-(3-quinolylmethyl) methylamide,
(66) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-[1-ethoxycarbonyl]-1-(3-carboxyethyl) methylamide,
(67) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-phenylamide,
(68) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-propargylamide,
(69) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-phenylamide,
(70) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-phenylamide,
(71) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-phenylamide,
(72) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-phenylamide,
(73) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-phenylamide,
(74) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-ethoxycarbonyl-N-(4-carboxyphenyl)methylamide,
(75) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-(4-carboxyphenyl)methylamide,
(76) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxy-2-propenyl-N-allylamide,
(77) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-methyl-2-butylnyl-N-carboxymethylamide,
(78) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxy-2-propenyl-N-carboxymethylamide,
(79) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxy-2-propenyl-N-ethoxycarbonyl methylamide,
(80) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxy-2-propenyl-N-carboxymethylamide,
(81) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-ethoxycarbonylpropyl-N-(1-carboxy-1-ethoxycarbonyl)methylamide,
(82) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-ethoxycarbonylpropyl-N-bis(carboxy)methylamide,
(83) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxypropyl-N-bis(ethoxycarbonyl)methylamide,
(84) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxypropynyl-N-(1-ethoxycarbonyl-1-carboxy)methylamide,
(85) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxypropynyl-N-bis(carboxy)methylamide,
(86) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-3-carboxypropynyl-N-allylamide,
(87) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-2,4-hexadienylamidem,
(88) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-2-carboxyethyl-N-2-ethoxycarbonyltylamide,
(89) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N,N-bis(2-carboxyethyl)amide,
(90) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-carboxymethyl-N-propargylamide,
(91) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)-ethoxycarbonyl-2-carboxyethyl-N-2-ethoxycarbonyltylamide,
(92) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)-ethoxycarbonyl-2-carboxyethyl-N-2-ethoxycarbonyltylamide,
(93) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)-2-bis(carboxy)ethyl-N-2-ethoxycarbonyltylamide,
(94) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)-2-bis(ethoxycarbonyl)ethyl-N-2-ethoxycarbonyltylamide,
(95) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)ethoxycarbonyl-2-carboxyethyl-N-2-ethoxycarbonyltylamide,
(96) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)ethoxycarbonyl-2-carboxyethyl-N-2-ethoxycarbonyltylamide,
(97) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)2-bis(carboxy)ethyl-N-2-ethoxycarbonyltylamide,
(98) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)carboxy-3-ethoxycarbonylpropylamide,
(99) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)ethoxycarbonyl-3-carboxypropylamide,
(100) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)3-bis(carboxy)propylamide,
(101) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)carboxy-2-ethoxycarbonyl)ethylamide,
(102) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)ethoxycarbonyl-2-carboxyethylamide,
(103) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)2-bis(carboxy)ethylamide,
(104) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(R)carboxy-3-ethoxycarbonylpropylamide,
(105) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(R)ethoxycarbonyl-3-carboxypropylamide,
(106) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(R)3-bis(carboxy)propylamide,
(107) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)carboxy-2-(ethoxycarbonyl methylthio)) ethylamide,
(108) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)ethoxycarbonyl-2-(carboxymethylthio)) ethylamide,
(109) $p$-(ε-Aminophenoxy)carboxy]α-methylcinnamic acid N-(1-(S)carboxy-2-(carboxymethylthio))ethylamide,
(110) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-carboxy-3-benzoyloxycarbonyl)propylamide,
(111) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-benzoyloxycarbonyl-3-carboxy)propylamide,
(112) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-benzoyloxycarbonyl-2-carboxy)ethylamide,
(113) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-carboxy-2-benzoyloxycarbonyl)ethylamide,
(114) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-carboxy-4-ethoxyacarbonyl)butylamide,
(115) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-ethoxyacarbonyl-4-carboxy)butylamide,
(116) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-1,4-bis(carboxy)butylamide,
(117) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-carboxy-5-ethoxyacarbonyl)pentylamide,
(118) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-ethoxyacarbonyl-5-carboxy)pentylamide,
(119) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-1,5-bis(carboxy)pentylamide,
(120) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-carboxymethylamide,
(121) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-1-carboxymethyl-1-ethoxyacarbonylmethyl methy-
ylamide,
(122) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-1,1-bis(carboxyethyl)methylamide,
(123) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-carboxy-2-(2-ethoxyacarbonyl)ethylthio))
ethylamide,
(124) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-ethoxyacarbonyl-2-(2-carboxyethylthio))
ethylamide,
(125) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-carboxy-2-(2-carboxyethylthio))ethylamide,
(126) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-carboxy-2-(3-ethoxyacarbonyl)propylthio))
ethylamide,
(127) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-ethoxyacarbonyl-2-(3-carboxypropylthio))
ethylamide,
(128) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(S)-carboxy-2-(3-carboxypropylthio))ethyla-
mide,
(129) p-(p-Amidinophenoxyacarbonyl)cinnamic acid N-(1-(S)-carboxy-3-ethoxyacarbonyl)propylamide,
(130) p-(p-Amidinophenoxyacarbonyl)cinnamic acid N-(1-(S)-ethoxyacarbonyl-3-carboxy)propylamide,
(131) p-(p-Amidinophenoxyacarbonyl)cinnamic acid N-(1-(S),3-bis(carboxy)propylamide,
(132) p-(p-Amidinophenoxyacarbonyl)-β-methylcinnamic acid N-(1-(S)-carboxy-3-ethoxyacarbonyl)propylamide,
(133) p-(p-Amidinophenoxyacarbonyl)-β-methylcinnamic acid N-(1-(S)-ethoxyacarbonyl-3-carboxy)propylamide,
(134) p-(p-Amidinophenoxyacarbonyl)-β-methylcinnamic acid N-(1-(S),3-bis(carboxy)propylamide;
and N-benzyl, N-allyl and N-propargyl compounds corresponding to compounds (33) to (66) and (99) to (134)
hereinbefore described; and
(135) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(2-ethoxyacarbonylperhydroazepinyl)amide,
(136) p-(p-Amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(2-ethoxyacarbonylpiperidino)amide;

and further the compounds prepared in Examples hereinafter described.

Acid Addition Salts

The compounds of the formula (I), of the present invention may be converted into the corresponding acid addition
salts by known method. Non toxic and water-soluble salts are preferable. Suitable acid addition salts include the salts
with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid and nitric acid, and
the salts with organic acids such as acetic acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, fumaric acid,
maleic acid, citric acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic
acid, isethionic acid, glucuronic acid and gluconic acid.

According to a feature of the present invention, the compounds of the formula (1) of the present invention, in which
all of R⁷, R⁸, R⁹ and R¹⁰, in R³, represent groups not containing COOH and COOt-Bu, i.e., the compounds of the
formula (la):
wherein R¹, R² and A are the same meanings as hereinbefore defined, and R³a is the same meaning as hereinbefore defined for R², provided that all of R⁷, R⁸, R⁹ and R¹⁰, in R², are groups not containing COOH and COOT-Bu, may be prepared by esterification of a compound of the formula (Iia):

wherein R², R³a and A are the same meanings as hereinbefore defined, with a compound of the formula (III):

wherein R¹ is the same meaning as hereinbefore defined. The said esterification is known and can be carried out by methods for example:

(1) using an acid halide,
(2) using a mixed acid anhydride,
(3) using a condensing agent etc.

Each of these methods can be carried out, for example, as follows:

(1) the method using an acid halide may be carried out, for example, by reacting a carboxylic acid with an acid halide (e.g., oxalyl chloride, thionyl chloride etc.) in an inert organic solvent (e.g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.) or without a solvent at from -20°C to the reflux temperature of the solvent, and then by reacting the acid halide obtained with a corresponding alcohol in the presence of a tertiary amine (e.g., pyridine, triethylamine, dimethylaniline, dimethylaminopyridine etc.) in an inert organic solvent (e.g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.), at a temperature of from 0°C to 40°C.

(2) the method using a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid and an acid halide (e.g., pivaloyl chloride, tosyl chloride, mesyl chloride etc.) or an acid derivative (e.g., ethyl chloroformate, isobutyl chloroformate etc.) in the presence of a tertiary amine (e.g., pyridine, triethylamine, dimethylaniline, dimethylaminopyridine etc.) in an inert organic solvent (e.g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.) or without a solvent at a temperature of from 0°C to 40°C, and then by reacting the mixed acid anhydride obtained with a corresponding alcohol in an inert organic solvent (e.g., chloroform, methylene chloride, diethyl ether, tetrahydrofuran etc.), at a temperature of from 0°C to 40°C, and

(3) the method using a condensing agent (e.g., 1,3-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC), 2-chloro-1-methylpyridinium iodide etc.) may be carried out, for example, by reacting...
a carboxylic acid with a corresponding alcohol using a condensing agent in the presence or absence of a tertiary amine (e.g., pyridine, triethylamine, dimethylamine, dimethylaminopyridine etc.) in an inert organic solvent (e.g., chloroform, methylene chloride, dimethyl formamide, diethyl ether etc.) or without a solvent at a temperature of from 0°C to 40°C.

The reactions (1), (2) and (3) hereinbefore described may be preferably carried out in an atmosphere of inert gas (e.g., argon, nitrogen etc.) under anhydrous conditions.

In the compounds of the formula (I), those in which at least one group of R₇, R₈ and R₉ in R₉ represents a group containing COO⁻-Bu and the other groups represent ones not containing COOH, or R₁₀ represents COO⁻-Bu, i.e., the compounds of the formula (Ib):

wherein R¹, R² and A are the same meanings as hereinbefore defined and R³b is the same meaning as hereinbefore defined for R³, provided that at least one group of R₇, R₈ and R₉, in R₃b, is a group containing COO⁻-Bu and the other groups are ones not containing COOH, or R₁₀ is COO⁻-Bu, may be prepared by amidation of a compound of the formula (IIb):

wherein the various symbols are the same meanings as hereinbefore defined, with a compound of the formula (IIib):

wherein R⁷b, R⁸b, R⁹b and R₁₀b are the same meanings as hereinbefore defined for R⁷, R⁸, R⁹ and R₁₀, respectively, provided that at least one group of R⁷b, R⁸b and R⁹b is a group containing COO⁻-Bu and the other groups are ones not containing COOH, or R₁₀b is COO⁻-Bu. The said amidation can be carried out by the same condition as hereinbefore
described for the esterification using an amine of the formula (IIIb) instead of an alcohol of the formula (III).

In the compounds of the formula (I), those in which at least one group of R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> in R<sup>3</sup>, represents a group containing COOH and the other groups represent ones not containing COOH, or R<sup>10</sup> represents COOH, i.e., the compounds of the formula (Ic):

![Chemical Structure](image)

wherein R<sup>1</sup>, R<sup>2</sup> and A are the same meanings as hereinbefore defined and R<sup>3c</sup> is the same meaning as hereinbefore defined for R<sup>3</sup>, provided that at least one group of R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> in R<sup>3</sup>, is a group containing COOH and the other groups are ones not containing COOH, or R<sup>10</sup> is COOH, may be prepared by the hydrolysis of t-butyl ester group, of a compound of the formula (Ib) in which the various symbols are the same meanings as hereinbefore defined. The hydrolysis of t-butyl ester group may be carried out, for example, by using an organic acid (e.g., trifluoroacetic acid etc.) or an inorganic acid (e.g., hydrochloric acid etc.), or the mixture thereof, in an inert organic solvent (e.g., methylene chloride, chloroform, methanol, dioxane, ethyl acetate, anisole etc.) at a temperature of from 0°C to 90°C.

In the compounds of the formula (Ila), those in which all of R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup>, in R<sup>3a</sup>, represent groups not containing benzoxycarbonyl, allyloxy carbonyl and propargyloxy carbonyl, or R<sup>10</sup> in R<sup>3a</sup> represents a group other than benzoxycarbonyl, i.e., the compounds of the formula (Ila-1):

![Chemical Structure](image)

wherein R<sup>2</sup> and A are the same meanings as hereinbefore defined and R<sup>31a</sup> is the same meaning as hereinbefore defined for R<sup>3a</sup>, provided that all of R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> in R<sup>3a</sup>, are groups not containing benzoxycarbonyl, allyloxy carbonyl and propargyloxy carbonyl, or R<sup>10</sup> in R<sup>3a</sup> is not benzoxycarbonyl, may be prepared by methods known per se, for example, by a series of reactions depicted in the following Scheme A.

In the Scheme A, R<sup>2</sup>, A and R<sup>31a</sup> are the same meanings as hereinbefore defined and R<sup>71a</sup>, R<sup>81a</sup> and R<sup>91a</sup> are the same meanings as hereinbefore defined for R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup>, respectively, provided that all of R<sup>7</sup> R<sup>8</sup> and R<sup>9</sup> are groups not containing benzoxycarbonyl, allyloxy carbonyl and propargyloxy carbonyl, or R<sup>101a</sup> is the same meaning as hereinbefore defined for R<sup>10</sup>, provided that R<sup>10</sup> is not benzoxycarbonyl.
In the compounds of the formula (IIa), those in which at least one group of R^7, R^8 and R^9 in R^3a, represents a group containing benzyloxy carbonyl, allyloxy carbonyl or propargyloxy carbonyl, or those in which R^10 in R^3a represents benzyloxy carbonyl, i.e., the compounds of the formula (IIa-2):

\[
\text{HOOC-} \quad \text{A-} \quad \text{R}^{32a}
\]

wherein R^2 and A are the same meanings as hereinbefore defined and R^{32a} is the same meaning as hereinbefore defined for R^{3a}, provided that at least one group of R^7, R^8 and R^9 in R^{3a} is a group containing benzyloxy carbonyl, allyloxy carbonyl or propargyloxy carbonyl, or R^{10} in R^{3a} is benzyloxy carbonyl, may be prepared by methods known per se, for example, by a series of reactions depicted in the following Scheme B.

In the Scheme B, R^2, A and R^{32a} are the same meanings as hereinbefore defined and R^{72a}, R^{82a} and R^{92a} are the same meanings as hereinbefore defined for R^7, R^8 and R^9, respectively, provided that at least one group of R^7, R^8 and R^9 is a group containing benzyloxy carbonyl, allyloxy carbonyl or propargyloxy carbonyl, and R^{102a} is benzyloxy carbonyl.
The compounds of the formula (IIb) may be prepared by methods known per se, for example, by a series of reactions depicted in the following Scheme C.

In the Scheme C, A, R\textsuperscript{1} and R\textsuperscript{2} are the same meanings as hereinbefore defined.
Scheme C

\[
\text{HOOC-} \quad \text{A-COOC(CH}_3\text{)}_3 \\
\text{R}^2
\]

(VII)

\[
\text{HN} \quad \text{condensing agent} \quad \text{OH} \quad \text{HN} \\
\text{H}_2\text{N} \quad \text{R}^1 \quad \text{R}^1 \quad \text{H}_2\text{N}
\]

hydrolysis of t-butyl ester group

\[
\text{HN} \quad \text{O} \quad \text{C} \quad \text{A-COOC(CH}_3\text{)}_3 \\
\text{O} \quad \text{C} \quad \text{A-COOH} \\
\text{R}^1 \quad \text{R}^1 \quad \text{R}^2 \\
\text{R}^2
\]

(IIb)

In the Scheme A, B and C,

\(\text{CH}_3\text{SO}_3\text{H}\) is methanesulfonic acid,

\(\text{CF}_3\text{COOH}\) is trifluoroacetic acid.

The reactions in schemes hereinbefore depicted may be carried out by methods known per se. The compounds of the formulae (IV), (V), (VI) and (VII) used as starting materials in the schemes hereinbefore depicted, are known
(1) Inhibitory activity on PLA₂

A reaction solution including 50 mM tris-HCl buffer (pH 7.5, 874 µl containing 100 mM sodium chloride, 1 mM EDTA), 1M calcium chloride (6 µl), 1% bovine serum albumin (10 µl) and 2.5 mM 10PY-PC (10 µl), was prepared. To the solution were added a test compound in various concentration or water (50 µl), and a solution of 10 mU/ml PLA₂ (derived from hog pancreas) (50 µl). The appearance of fluorescence was measured (Ex=345 nm, Em=396 nm). Percentage (%) of the strength of fluorescence in the presence of a test compound was calculated when the strength of that in the absence thereof was regarded as 100%, and thereafter IC₅₀ value was calculated. The results are shown in the following Table 1.

<table>
<thead>
<tr>
<th>Compound (Example No.)</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.8</td>
</tr>
<tr>
<td>1 (d)</td>
<td>63</td>
</tr>
<tr>
<td>1 (g)</td>
<td>5.3</td>
</tr>
<tr>
<td>1 (i)</td>
<td>28</td>
</tr>
<tr>
<td>1 (k)</td>
<td>3.1</td>
</tr>
<tr>
<td>1 (l)</td>
<td>24</td>
</tr>
<tr>
<td>2 (a)</td>
<td>15</td>
</tr>
<tr>
<td>2 (f)</td>
<td>32</td>
</tr>
</tbody>
</table>

(2) Inhibitory activity on trypsin

To a mixture of a 0.2M HEPES-sodium hydroxide buffer solution (pH 8.0, 100 µl) and distilled water (840 µl), were added a test compound in various concentration or water (10 µl), and a solution of 80 mU/ml trypsin (derived from bovine pancreas) (50 µl) and then the mixture was preincubated for one minute at 30°C. To the solution thus obtained was added 2.5 mM BAPNA (200 µl) and the mixture was incubated for 30 min. The absorbance at 405 nm was measured. Percentage (%) of the absorbance in the presence of a test compound was calculated when the absorbance in the absence thereof was regarded as 100%, and therefrom IC₅₀ value was calculated. The results are shown in the following Table 2.

<table>
<thead>
<tr>
<th>Compound (Example No.)</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.14</td>
</tr>
<tr>
<td>1 (d)</td>
<td>0.13</td>
</tr>
<tr>
<td>1 (g)</td>
<td>0.14</td>
</tr>
<tr>
<td>1 (i)</td>
<td>0.13</td>
</tr>
<tr>
<td>1 (k)</td>
<td>0.22</td>
</tr>
<tr>
<td>1 (p)</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Table 2: (continued)

<table>
<thead>
<tr>
<th>Compound (Example No.)</th>
<th>IC50 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (f)</td>
<td>0.22</td>
</tr>
<tr>
<td>2 (a)</td>
<td>0.14</td>
</tr>
<tr>
<td>2 (f)</td>
<td>0.14</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
</tr>
</tbody>
</table>

In the methods hereinbefore described,

10PY-PC represents 3’-palmitoyl-2-(1-pyrenedecanoyl)-L-α-phosphatidylcholine,
HEPES represents 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, and
BAPNA represents α-N-benzoyl-DL-arginine-p-nitroanilide hydrochloride.

The toxicity of the compounds of the present invention is very weak. Therefore, the compounds of the present invention may be considered to be sufficiently safe and suitable for pharmaceutical use.

Application for pharmaceuticals

The inhibition on PLA2 and on various proteases such as trypsin, plasmin, thrombin and kallikrein, especially trypsin in mammals including human beings, especially human beings are useful for the prevention and/or the treatment of various inflammatory diseases, allergic diseases, disseminated intravascular coagulation, pancreatitis, severity in pancreatitis and multiple organ failure.

For the purpose hereinbefore described, the compounds of the formula (f) of the present invention and non-toxic acid addition salts thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration (preferably, intravenously) up to several times per day, or continuous administration between 1 and 24 hrs. per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

When administering the compounds of the present invention, it is used as solid compositions, liquid compositions or other compositions for oral administration, or as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc.). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate, etc.), stabilizing agents (such as lactose, etc.), and assisting agents for dissolving (such as glutamic acid, asparaginic acid etc.).

The tablets or pills may, if desired, be coated with a film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate etc.), or be coated with more than two films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs. The compositions may also comprise inert diluents commonly used in the art (purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents, etc.), sweetening agents, flavouring agents, perfuming agents, and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfate etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid, etc.). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.
Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsion. In such compositions, one more of active compound(s) is or are admixed with at least one of inert aqueous diluent (s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSORBATE80 (registered trade mark) etc.).

Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose etc.), assisting agents such as assisting agents for dissolving (glutamic acid, asparaginic acid etc.).

They may be sterilized for example, by filtration through a bacteria-retainng filter, by incorporation of sterilizing agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, and which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before used.

Other compositions for parenteral administration include endermic ones such as liquids for external use, ointment, and endermic liniments, and suppositories and pessaries for intrarectal administration which comprise one or more of the active compound(s) and may be prepared by per se known methods.

Examples

The following reference examples and examples illustrate, but not limit, the present invention.

The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations.

Unless otherwise specified, *IR* was measured by KBr method, and *NMR* was measured in a solution of deuteromethanol.

Reference Example 1

p-Benzzyloxyacarbonyl-α-methylcinnamic acid t-butyl ester

\[
\text{C}_6\text{H}_5\text{O} - \text{C} - \text{C}_6\text{H}_4\text{CH}_3 \quad \text{COOC}(\text{CH}_3)_3
\]

To a suspension of sodium hydride (0.8 g, containing 60% oil) in tetrahydrofuran (25 ml) was added slowly dropwise a solution of 2-(diethylphosphono) propionic acid t-butyl ester (4.8 g) in tetrahydrofuran (6 ml) under cooling with ice, and the mixture was stirred for 30 min. at room temperature. After the reaction mixture was cooled with ice, a solution of p-benzzyloxyacarbonylbenzaldehyde (4.0 g) in tetrahydrofuran (15 ml) was added slowly dropwise thereto. The mixture was stirred for 30 min. at room temperature, water was added thereto, and then the reaction mixture was extracted with ethyl acetate. The extract was washed with water, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=20:1→15:1) to give the title compound (5.2 g) having the following physical data:

TLC: Rf 0.34 (hexano : ethyl acetate=10:1).
Reference Example 2

p-Benzoyloxycarbonyl-α-methylcinnamic acid

To a solution of the compound prepared in Reference Example 1 (56.0 g) in anisole (40 ml) was added trifluoroacetic acid (75 ml) under cooling with ice. After stirred for two hours at room temperature, the reaction mixture was concentrated under reduced pressure. Thus obtained white solid was washed with isopropanol ether, filtered, and dried under reduced pressure to give the title compound (39.57 g) as white crystal having the following physical data:

TLC: Rf 0.26 (hexane : ethyl acetate : acetic acid=12 : 4 : 1).

Reference Example 3

p-(Benzoyloxycarbonyl)acetophenone

To a solution of p-acetylbenzoic acid (16.4 g) in dimethylformamide (100 ml) were added successively potassium carbonate (27.6 g) and benzyl bromide (13 ml). The mixture was stirred for 13 hours at room temperature. After quenched by addition of water, the reaction mixture was extracted with a mixture of hexane and ethyl acetate (3 : 1). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=9 : 1→6 : 1) to give the title compound (16 g) having the following physical data:

TLC : Rf 0.63 (hexane : ethyl acetate : acetic acid=12 : 4 : 1).

Reference Example 4

p-(Benzoyloxycarbonyl)-β-methylcinnamic acid

By the same procedure as a series of reactions of Reference Example 1→Reference Example 2, using the compound prepared in Reference Example 3 instead of p-benzoyloxycarbonylbenzaldehyde, the title compound having the following physical data was given:

TLC: Rf 0.45 (hexane : ethyl acetate : acetic acid=12 : 4 : 1).
Reference Example 5

p-[(T-butoxycarbonyl)benzaldehyde

To a solution of p-[(T-butoxycarbonyl)]benzoic acid (13.32 g) in tetrahydrofuran (100 ml) and triethylamine (10 ml), was added slowly dropwise ethyl chloroformate (6.8 ml) under cooling with ice, under an atmosphere of argon. After the mixture was stirred for two hours at room temperature, triethylamine-hydrochloride precipitated was filtered off. To the filtrate thus obtained were added slowly sodium borohydride (4.54 g) and water (20 ml) under cooling with ice. After stirred for one hour at room temperature, the reaction mixture was quenched by addition with water. The reaction mixture was extracted with a mixture of hexane and ethyl acetate (1:1). The extract was washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=10:1→4:1).

To a solution of p-[(T-butoxycarbonyl)]benzyl alcohol (7.28 g) thus obtained in dimethyl sulfoxide (90 ml) and triethylamine (25 ml) was added a solution of sulfur trioxide-pyridine complex (19.75 g) in dimethyl sulfoxide (70 ml). After stirred for 30 min. at room temperature, the reaction mixture was quenched by addition of water. The reaction mixture was acidified by addition of 1N hydrochloric acid, and then extracted with a mixture of hexane and ethyl acetate (3:1). The extract was washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and evaporated to give the title compound (7.2 g) having the following physical data:

TLC : Rf 0.59 (hexane : ethyl acetate=2:1).

Reference Example 6

p-[(T-butoxycarbonyl)]-α-methylcinnamic acid ethyl ester

By the same procedure as Reference Example 1, using the compound prepared in Reference Example 5 instead of p-benzylxycarbonylbenzaldehyde, the title compound having the following physical data was given:

TLC : Rf 0.58 (hexane : ethyl acetate=4:1).

Reference Example 7

p-[(T-butoxycarbonyl)]-α-methylcinnamic acid

To a solution of the compound prepared in Reference Example 6 (6.1 g) in ethanol (60 ml) was added 5N aqueous solution of sodium hydroxide (6 ml) under cooling with ice. After stirred overnight at room temperature, the reaction
mixture was quenched by addition of 2N hydrochloric acid (15 ml), and then evaporated till the volume of the solution became 1/2. An aqueous solution thus obtained was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and evaporated to give the title compound (7.3 g) having the following physical data:

TLC: Rf 0.41 (hexane : ethyl acetate : acetic acid=12 : 6 : 1).

Reference Example 8
p-(p-Methoxybenzyl)oxycarbonyl)cinnamic acid

![Chemical Structure](image)

To a solution of (p-carboxy)benzaldehyde (15 g) in dimethylformamide (200 ml) were added successively potassium carbonate (27.6 g) and p-methoxybenzyl chloride (15 ml). After stirred for 17 hours at room temperature, the reaction mixture was quenched by addition of water and then extracted twice with a mixture of hexane and ethyl acetate (2 : 1). The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. To a solution of the aldehyde compound thus obtained in pyridine (100 ml) were added successively malonic acid (20.8 g) and piperidine (5 ml). After stirred for one hour at 80°C, the reaction mixture was quenched by addition of ice-water, and then neutralized by addition of 1N hydrochloric acid. The crystals thus obtained were filtered, washed with water and ether, successively, and then dried to give the title compound (17.4 g) as white solid having the following physical data:

TLC: Rf 0.37 (chloroform : methanol=9 : 1).

Reference Example 9
p-Benzylxycarbonyl-α-methylcinnamic acid N-ethoxycarbonylmethyl-N-phenylmethylamidine

![Chemical Structure](image)

A suspension of the compound prepared in Reference Example 2 (4 g) in methylene chloride (15 ml) was added oxalyl chloride (5.8 ml) at room temperature. The mixture was stirred for one hour at room temperature and then evaporated. A solution of acid chloride thus obtained, in methylene chloride (20 ml) was added slowly dropwise to a solution of N-ethoxycarbonylmethyl-N-phenylmethylamine (2.61 ml) in a mixture of methylene chloride (28 ml) and pyridine (2.2 ml) under cooling with ice. The reaction mixture was stirred for 30 min. at room temperature, water was added thereto and then the reaction mixture was extracted with ether. The extract was washed with 1N hydrochloric acid, 1N aqueous solution of sodium hydroxide and a saturated aqueous solution of sodium chloride, successively dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=9 : 1→3 : 1) to give the title compound (5.76 g) having the following physical data:

TLC: Rf 0.39 (hexane : ethyl acetate=2:1).
Reference Example 10

p-Carboxy-α-methylcinnamic acid N-ethoxycarbonylmethyl-N-phenylmethylamide

To a solution of the compound prepared in Reference Example 9 (5.7 g) in anisole (60 ml), was added methanesulfonic acid (33 ml) under cooling with ice. The reaction mixture was stirred for two hours at room temperature and evaporated. To the residue were added ice-water and ether, and the mixture was separated into two layers. The organic layer was further extracted with water and a saturated aqueous solution of sodium bicarbonate. All aqueous layers were collected and were acidified by addition of 1N hydrochloric acid under cooling with ice, and then extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively dried over anhydrous magnesium sulfate, and evaporated to give the title compound (3.79 g) having the following physical data:

TLC : Rf 0.18 (hexane : ethyl acetate : acetic acid=12 : 4 : 1).

Reference Example 11

p-(p-methoxybenzyloxycarbonyl)cinnamic acid N'-phenylmethylpiperazinylamide

To a solution of the compound prepared in Reference Example 8 (4.22 g) in dimethylformamide (40 ml), were added successively N-benzylpiperazine (2.35 ml) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (3.1 g). After the reaction mixture was stirred for two hours at room temperature, ice-water was added thereto. The mixture was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate=2 : 1→1 : 2) to give the title compound (3.4 g) having the following physical data:

TLC : Rf 0.67 (ethyl acetate).

Reference Example 12

p-Carboxycinnamic acid N'-phenylmethylpiperazinylamide hydrochloride

By the same procedure as Reference Example 2, using the compound prepared in Reference Example 11 instead of that prepared in Reference Example 1, the free compound of the title compound was obtained. The free compound was converted into the corresponding hydrochloride salt by a conventional manner to give the title compound having
the following physical data:
TLC : Rf 0.21 (ethyl acetate).

Reference Example 13

p-(1-Butoxycarbonyl)cinnamic acid

\[\text{(CH}_3\text{)_3COOC}-\text{COOH}\]

To a solution of p-(1-butoxycarbonyl)benzaldehyde (4.05 g) in pyridine (16 ml), were added successively malonic acid (4.16 g) and piperidine (0.6 ml). The reaction mixture was stirred for four hours at 80°C, and then diluted with ethyl acetate. The mixture was washed with water and a saturated aqueous solution of sodium chloride, successively dried over anhydrous magnesium sulfate and evaporated. The residue thus obtained was washed with n-hexane and dried to give the title compound (4.65 g) having the following physical data:
TLC: Rf 0.28 (hexane : ethyl acetate : acetic acid=2 : 1 : 1 drop).

Reference Example 14

3-(p-(1-butoxycarbonyl)phenyl)propionic acid

\[\text{(CH}_3\text{)COOC}-\text{COOH}\]

To a solution of the compound prepared in Reference Example 12 (4.65 g) in a mixture of methanol (50 ml) and chloroform (50 ml) was added 10% palladium-carbon (0.5 g). The mixture was stirred overnight at room temperature under an atmosphere of hydrogen. The catalyst was filtered off and the solution was evaporated. To a solution of the residue thus obtained, in dioxane (30 ml) was added 1N aqueous solution of sodium hydroxide (20 ml) and the mixture was stirred for one hour at 50°C. The reaction mixture was concentrated and the residue thus obtained was washed with n-hexane and then dried to give the title compound (3.67 g) having the following physical data:
TLC: Rf 0.14 (hexane : ethyl acetate=2 : 1).

Example 1

p-(p-Amidinophenoxy carbonyl)-a-methylcinnamic acid N-ethoxycarbonylmethyl-N-phenylmethylamide hydrochloride

\[\begin{align*}
\text{HN} & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{C} \\
\text{COOC}_2\text{H}_5 & \quad \text{CH}_3 \\
\end{align*}\]

To a solution of the compound prepared in Reference Example 10 (2.67 g) in pyridine (35 ml), were added successively p-amidinophenol hydrochloride (1.21 g) and 1,3-dicyclohexylcarbodiimide (1.73 g). After stirred overnight at room temperature, the reaction mixture was filtered. The filtrate was evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol : acetic acid=30 : 2 : 1) to give the title compound (2.29 g) as white
powder having the following physical data:
TLC : Rf 0.43 (chloroform : methanol : acetic acid=15 : 2 : 1);
IR : ν 3352, 1741, 1678, 1606, 1480, 1411, 1375, 1267, 1214, 1176, 1067, 1015, 975, 888, 736, 699, 630, 521 cm⁻¹;
NMR : δ 8.10 (2H, d, J=8.0 Hz), 7.95 (2H, d, J=8.0 Hz), 7.55 (4H, brd, J=7.5 Hz), 7.40 (5H, brs), 6.75 (1H, brs), 4.82-4.70
(2H, m), 4.21-4.00 (4H, m), 2.15 (3H, s), 1.35-1.20 (3H, m).

Example 1(a)→(vvv)

By the same procedure as a series of reactions of Reference Example 9→Reference Example 10→Example 1,
using, as starting materials, the compound prepared in Reference Example 2, that prepared in Reference Example 4
p-benzoyloxycarbonylbenzoic acid or p-methoxycarbonylbenzoic acid, using proper amines instead of N-ethoxycarbo-
nymethyl-N-phenylmethylamine, and further using p-amidimophenol or its derivatives, the compounds of the present
invention shown in Table 3 were given.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(a)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-&lt;br&gt;α-methylcinnamic acid N-ethoxycarbonylmethyl-N-phenylamide hydrochloride</td>
<td>0.54 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.10 (2H, d), 7.90 (2H, d), 7.50 (2H, d), 7.45-7.30 (5H, m), 7.25 (2H, d), 6.68 (1H, brs), 4.55 (2H, s), 4.22 (2H, q), 1.90 (3H, d), 1.30 (3H, t).</td>
</tr>
<tr>
<td>1(b)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-&lt;br&gt;α-methylcinnamic acid N-((1-(S)-ethoxycarbonyl-2-phenyl)ethyl)amide hydrochloride</td>
<td>0.43 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.10 (2H, d), 7.95 (2H, d), 7.58 (2H, d), 7.57 (2H, d), 7.30 (5H, brs), 7.18 (1H, brs), 4.75 (1H, dd), 4.20 (2H, q), 3.25 (1H, dd), 3.10 (1H, dd), 2.04 (3H, brs), 1.22 (3H, t).</td>
</tr>
<tr>
<td>1(c)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-&lt;br&gt;α-methylcinnamic acid N-[1-(S)-ethoxycarbonyl-2-(3-indolyl)ethyl]amide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>(CDCl$_3$+CD$_3$OD+d6-DMSO) 8.18 (2H, d), 7.92 (2H, d), 7.60 (1H, d), 7.55-7.35 (5H, m), 7.21 (1H, s), 7.19-7.00 (3H, m), 4.85 (1H, t), 4.18 (2H, q), 3.50-3.30 (2H, m), 2.05 (3H, s), 1.95 (3H, s), 1.26 (3H, t).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
<td>NMR</td>
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<tr>
<td>1(d)</td>
<td><img src="" alt="Structure" /></td>
<td>p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-[1-(S),3-bis(ethoxycarbonyl)]-propylamide hydrochloride</td>
<td>0.45 (chlooroform: methanol: acetic acid =15:2:1)</td>
<td>8.22 (2H, d), 7.95 (2H, d), 7.60 (2H, d), 7.56 (2H, d), 7.38 (1H, s), 4.55 (1H, dd), 4.21 (2H, q), 4.15 (2H, q), 2.58-2.42 (2H, m), 2.40-1.98 (2H, m), 2.17 (3H, s), 1.28 (3H, t), 1.23 (3H, t).</td>
</tr>
<tr>
<td>1(e)</td>
<td><img src="" alt="Structure" /></td>
<td>p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N'-(phenylmethyl)piperazinylamide dimethanesulfonate</td>
<td>0.5 (chlooroform: methanol =8:2)</td>
<td>8.21 (2H, d), 7.92 (2H, d), 7.63-7.45 (9H, m), 6.77 (1H, brs), 4.60-4.32 (2H, m), 4.41 (2H, s), 3.60-3.10 (6H, m), 2.70 (6H, s), 2.15 (3H, brs).</td>
</tr>
<tr>
<td>1(f)</td>
<td><img src="" alt="Structure" /></td>
<td>p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-(R)-phenyl-1-ethoxycarbonyl)methylamide methanesulfonate</td>
<td>0.4 (chlooroform: methanol: acetic acid =15:2:1)</td>
<td>8.20 (2H, d), 7.92 (2H, d), 7.60 (2H, d), 7.53 (2H, d), 7.55-7.38 (5H, m), 7.33 (1H, brs), 5.60 (1H, s), 4.20 (2H, dt), 2.70 (3H, s), 2.12 (3H, brs), 1.21 (3H, t).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
<td>NMR</td>
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<tr>
<td>1(g)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(p-fluorophenyl)-N-ethoxy-carbonylmethylamide methanesulfoate</td>
<td>0.26</td>
<td>8.13 (2H, d), 7.91 (2H, d), 7.51 (2H, d), 7.47-7.40 (2H, m), 7.29 (2H, d), 7.15 (2H, t), 6.70 (1H, s), 4.52 (2H, s), 4.24 (2H, q), 2.72 (3H, s), 1.91 (3H, s), 1.30 (3H, t).</td>
</tr>
<tr>
<td>1(h)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(p-methylphenyl)-N-ethoxy-carbonylmethylamide methanesulfonate</td>
<td>0.31</td>
<td>8.11 (2H, d), 7.92 (2H, d), 7.51 (2H, d), 7.26 (2H, d), 7.25 (4H, s), 6.70 (1H, s), 4.50 (2H, s), 4.23 (2H, q), 2.72 (3H, s), 2.33 (3H, s), 1.89 (3H, s), 1.30 (3H, t).</td>
</tr>
<tr>
<td>1(i)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-allyl-N-ethoxy-carbonylmethylamide acetate</td>
<td>0.55</td>
<td>8.22 (2H, d), 7.94 (2H, d), 7.57-7.49 (4H, m), 6.74 (1H, br), 5.90 (1H, br), 5.33 and 5.27 (2H, br), 4.26-4.14 (6H, m), 2.15 (3H, s), 1.30 (3H, t).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
<td>NMR</td>
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<tr>
<td>1(j)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-((p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-propargyl-N-ethoxycarbonylmethylamide acetate)</td>
<td>0.55 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.22 (2H, d), 7.94 (2H, d), 7.60-7.52 (4H, m), 6.89 and 6.70 (1H, br), 4.38 (4H, s), 4.24 (2H, q), 2.89 (1H, br), 2.12 (3H, s), 1.28 (3H, t).</td>
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<tr>
<td>1(k)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-((p-amidino-phenoxycarbonyl)-β-methylcinnamic acid N-phenyl-N-ethoxycarbonylmethylamide hydrochloride</td>
<td>0.44 (chloroform: methanol: acetic acid = 15:2:1)</td>
<td>8.10 (2H, d), 7.92 (2H, d), 7.50 (2H, d), 7.41 (5H, s), 7.40 (2H, d), 6.10 (1H, drs), 4.50 (2H, s), 4.22 (2H, q), 2.42 (3H, s), 1.30 (3H, t).</td>
</tr>
<tr>
<td>1(l)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-((p-amidino-phenoxycarbonyl)-β-methylcinnamic acid N-phenylmethyl-N-ethoxycarbonylmethylamide methanesulfonate</td>
<td>0.45 (chloroform: methanol: acetic acid = 15:2:1)</td>
<td>8.20 (0.6H, d), 8.18 (1.4H, d), 7.90 (2H, d), 7.70 (0.6H, d), 7.65 (1.4H, d), 7.52 (2H, d), 7.42-7.20 (5H, m), 6.61 (0.7H, s), 6.55 (0.3H, s), 4.75 (1.4H, s), 4.72 (0.6H, s), 4.24-4.02 (4H, m), 2.70 (3H, s), 2.35 (2.1H, s), 2.30 (0.9H, s), 1.25 (2.1H, t), 1.19 (0.9H, t).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
<td>NMR</td>
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<tr>
<td>1(n)</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>p-(p-amidino-phenoxy-carbonyl)-β-methylaminooacid N-phenyl-methyl-piperazine dihydrochloride</td>
<td>0.31 (chloroform: methanol = 8:2)</td>
<td>8.20 (2H, d, 7.95 (2H, d, 7.78 (2H, d, 7.70-7.43 (2H, m), 6.60 (2H, d, 7.25 (2H, s), 6.40-6.18 (2H, m), 3.40-3.05 (3H, m), 3.80-3.40 (3H, m), 2.31 (3H, s))</td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>p-(p-amidino-phenoxy-carbonyl)-N-ethoxy-carbonyl-methyl-amine hydrochloride</td>
<td>0.64 (chloroform: methanol/acetic acid = 10:2:1)</td>
<td>8.24 (2H, d, 7.70, 2H, d, 7.90 (2H, d, 7.70, 1.20 (1H, 7.30, 1.20 (1H, 7.20 (1H, 7.20 (2H, s), 4.23 (1H, 4.18 (2H, d, 4.20 (1H, 1.30 (1H, 1.22 (0.9H, 1.30</td>
</tr>
<tr>
<td></td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>p-(p-amidino-phenoxy-carbonyl)-N-ethoxy-carbonyl-methyl-amine hydrochloride</td>
<td>0.64 (chloroform: methanol/acetic acid = 10:2:1)</td>
<td>8.24 (2H, d, 7.90 (2H, d, 7.70, 2H, d, 7.70, 1.20 (1H, 7.30, 1.20 (1H, 7.20 (1H, 7.20 (2H, s), 4.23 (1H, 4.18 (2H, d, 4.20 (1H, 1.30 (1H, 1.22 (0.9H, 1.30</td>
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</table>

Table 3 (continued)
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (RI)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(p)</td>
<td><img src="structure1.png" alt="" /></td>
<td>p-(p-amidino-o-methoxycarbonyl-phenoxycarbonyl)-benzoic acid N-phenyl-N-ethoxy-carbonylmethylamide acetate</td>
<td>0.30 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.46 (1H, d), 8.10-8.00 (3H, m), 7.55-7.49 (3H, m), 7.30-7.20 (5H, m), 4.62 (2H, s), 4.26 (2H, q), 3.69 (3H, s), 1.31 (3H, t).</td>
</tr>
<tr>
<td>1(q)</td>
<td><img src="structure2.png" alt="" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-benzoic acid N-[1-ethoxycarbonyl-2-(3-indolyl)]ethylamide acetate</td>
<td>0.33 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d), 8.00-7.85 (4H, m), 7.65-7.50 (3H, m), 7.35 (1H, d), 7.25-6.95 (4H, m), 4.95 (1H, m), 4.20 (2H, q), 3.45 (2H, m), 2.00 (3H, s), 1.20 (3H, t).</td>
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<tr>
<td>1(r)</td>
<td><img src="structure3.png" alt="" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-benzoic acid N-(2-(S)-ethoxycarbonyl)pyrrolidinylamide acetate</td>
<td>0.31 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.30 and 8.25 (2H, d), 7.95 (2H, d), 7.75 and 7.60 (2H, d), 7.55 (2H, d), 4.60 and 4.45 (1H, m), 4.25 and 4.00 (2H, q), 3.75 and 3.60 (2H, m), 2.40 (1H, m), 2.20-1.85 (3H, m), 2.00 (3H, s), 1.30 and 1.10 (3H, t).</td>
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<td>TLC (Rf)</td>
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<td>1(s)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-benzoic acid N-(2-(R)-ethoxycarbonyl)pyrrolidinylamide acetate</td>
<td>0.31</td>
<td>8.30 and 8.25 (2H, d), 7.95 (2H, d), 7.75 and 7.60 (2H, d), 7.55 (2H, d), 4.60 and 4.45 (1H, m), 4.25 and 4.00 (2H, q), 3.75 and 3.60 (2H, m), 2.40 (1H, m), 2.20-1.85 (3H, m), 2.00 (3H, s), 1.30 and 1.10 (3H, t).</td>
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<td>1(t)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-benzoic acid N'-phenylmethylpiperazinylamide dihydrochloride</td>
<td>0.50</td>
<td>8.28 (2H, d), 7.92 (2H, d), 7.60 (2H, d), 7.53 (2H, d), 7.33-7.24 (5H, m), 3.80 (2H, br), 3.44 (2H, br), 2.59 (2H, br), 2.48 (2H, br).</td>
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<td>1(u)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-3,5-bis(ethoxycarbonyl)phenylamide hydrochloride</td>
<td>0.35</td>
<td>(CDCl₃+CD₃OD) 8.59 (2H, d, J=1.5Hz), 8.42 (1H, d, J=1.5Hz), 8.26 (2H, d, J=8.2Hz), 7.93 (2H, d, J=8.8Hz), 7.64 (2H, d, J=8.2Hz), 7.53 (2H, d, J=8.8Hz), 7.47 (1H, s), 4.43 (4H, q, J=7.0Hz), 2.25 (3H, d, J=1.4Hz), 1.44 (6H, d, J=7.0Hz).</td>
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<td>Ex. No.</td>
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<td>Name</td>
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<td>1(v)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-1-(S),2-bis(ethoxycarbonyl)-ethylamide hydrochloride</td>
<td>0.5</td>
<td>(d6-DMSO+CDCl₃) 9.80-9.00 (3H, m), 8.20 (2H, d, J=8.0Hz), 8.00 (2H, d, J=8.0Hz), 7.57 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz), 7.38 (1H, brs), 4.82 (1H, dd, J=6.0Hz,13Hz), 4.20, 4.17 (2H each, q each, J=8.0Hz each), 2.98 (1H, dd, J=6.0Hz, 15Hz), 2.83 (1H, dd, J=6.0Hz, 15Hz), 2.13 (3H, s), 1.24, 1.23 (3H each, t each, J=8.0Hz each).</td>
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<td>1(w)</td>
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<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-ethoxy-carbonylmethyl-N-(4-ethoxycarbonyl-phenyl)methylamide acetate</td>
<td>0.49</td>
<td>8.18 (2H, d, J=8.4Hz), 8.03 (2H, d, J=8.0Hz), 7.92 (2H, d, J=8.4Hz), 7.51 (4H, d, J=8.4Hz), 7.45 (2H, d, J=8.0Hz), 6.73 (1H, s), 4.82 (2H, s), 4.37 (2H, q, J=7.2Hz), 4.30-4.10 (4H, m), 2.14 (3H, s), 1.92 (3H, s), 1.38 (3H, t, J=7.2Hz), 1.35-1.14 (3H, m).</td>
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<td>1(x)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-bis(ethoxycarbonyl)methylamide hydrochloride</td>
<td>0.63</td>
<td>(d6-DMSO+CDCl₃) 10.0-9.00 (3H, m), 8.20 (2H, d, J=8.0Hz), 8.00 (2H, d, J=8.0Hz), 7.57 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.5Hz), 7.43 (1H, brs), 5.27 (1H, brs), 4.40-4.20 (4H, m), 2.18 (3H, s), 1.32 (6H, brt, J=8.0Hz).</td>
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<td>1(a)</td>
<td>0.42</td>
<td>p-(p-aminoxy carbonyl) methoxy carbonyl phenyl p-carboxy N-ethyl N-phenyl methyl amide</td>
<td><img src="image" alt="Structure 1" /></td>
<td>8.20 (2H, d, J = 8Hz), 7.90 (2H, d, J = 8Hz), 7.70 (2H, d, J = 8Hz), 3.20 (2H, m, CH2CO2H), 2.40 (2H, m, CH2), 1.80 (2H, m, CH2), 1.85 (1H, s, CH3)</td>
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<td>1(b)</td>
<td>0.36</td>
<td>p-(p-aminoxy carbonyl) methoxy carbonyl p-carboxy N-ethyl N-propyl methyl amide</td>
<td><img src="image" alt="Structure 2" /></td>
<td>8.20 (2H, d, J = 8Hz), 7.60 (2H, d, J = 8Hz), 7.35 (1H, s, CH3), 2.50 (2H, m, CH2), 1.55 (1H, m, CH2), 1.25 (1H, s, CH3)</td>
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<tr>
<td>1(c)</td>
<td>0.46</td>
<td>p-(p-aminoxy carbonyl) methoxy carbonyl p-carboxy N-ethyl N-methoxycarbonyl methyl amide</td>
<td><img src="image" alt="Structure 3" /></td>
<td>8.20 (2H, d, J = 8Hz), 7.93 (2H, d, J = 8Hz), 7.75 (2H, d, J = 8Hz), 6.20 (1H, s, CH3), 4.20 (2H, m, CH2)</td>
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Table 3 (continued)
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<td>1(bb)</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-((1-(S)-ethoxycarbonyl-2-ethoxycarbonylmethylthio)ethyl)amide methanesulfonate</td>
<td>0.47 (chloroform: methanol: acetic acid = 10:1:1)</td>
<td>8.24 (2H, d, J=8.4Hz), 7.94 (2H, d, J=8.8Hz), 7.61 (2H, d, J=8.4Hz), 7.54 (2H, d, J=8.8Hz), 7.39 (1H, s), 4.80-4.70 (1H, m), 4.24 (2H, q, J=7.0Hz), 4.20 (2H, q, J=7.2Hz), 3.50-3.00 (5H, m), 2.72 (3H, s), 2.15 (3H, s), 1.31 (3H, t, J=7.0Hz), 1.29 (3H, t, J=7.2Hz).</td>
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<td>1(cc)</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1,4-bis(ethoxycarbonyl)butyl)amide hydrochloride</td>
<td>0.47 (chloroform: methanol: acetic acid = 15:2:1)</td>
<td>8.22 (2H, d, J=8.0Hz), 7.92 (2H, d, J=8.0Hz), 7.60 (2H, d, J=8.0Hz), 7.55 (2H, d, J=8.0Hz), 7.34 (1H, s), 4.49 (1H, dd, J=8.5 Hz, 5.0Hz), 4.20 (2H, q, J=7.5Hz), 4.12 (2H, q, J=7.5Hz), 2.40 (2H, t, J=8.0Hz), 2.12 (3H, s), 2.10-1.60 (4H, m), 1.27 (3H, t, J=7.5Hz), 1.23 (3H, t, J=7.5Hz).</td>
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<td>1(dd)</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1,5-bis(ethoxycarbonyl)pentyl)amide hydrochloride</td>
<td>0.49 (chloroform: methanol: acetic acid = 15:2:1)</td>
<td>8.21 (2H, d, J=8.0Hz), 7.92 (2H, d, J=8.0Hz), 7.60 (2H, d, J=8.0Hz), 7.55 (2H, d, J=8.0Hz), 7.34 (1H, s), 4.45 (1H, dd, J=8.5Hz, 5.0Hz), 4.20 (2H, q, J=7.5Hz), 4.10 (2H, q, J=7.5Hz), 2.36 (2H, t, J=7.5Hz), 2.00-1.80 (2H, m), 1.80-1.58 (2H, m), 1.58-1.38 (2H, m), 1.30 (3H, t, J=7.5Hz), 1.22 (3H, t, J=7.5Hz).</td>
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Table 3 (continued)

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<td>1(ee)</td>
<td><img src="image" alt="Structure" /> p-(p-aminophenoxycarbonyl)-α-methylcinnamic acid N-(3-ethoxy-carbonylpropyl)-amide acetate</td>
<td>0.31 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.21 (2H, d, J=8.0Hz), 7.95 (2H, d, J=8.0Hz), 7.59 (2H, d, J=8.0Hz), 7.53 (2H, d, J=8.0Hz), 7.31 (1H, brs), 4.12 (2H, q, J=7.5Hz), 3.35 (2H, t, J=8.0Hz), 2.40 (2H, t, J=8.0Hz), 2.10 (3H, d, J=1.0Hz), 2.00 (3H, s), 1.90 (2H, tt, J=8.0Hz), 1.22 (3H, t, J=7.5Hz).</td>
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<td>1(ff)</td>
<td><img src="image" alt="Structure" /> p-(p-aminophenoxycarbonyl)-α-methylcinnamic acid N-ethoxy-carbonylmethylamide methane sulfonate</td>
<td>0.35 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.23 (2H, d, J=8.5Hz), 7.93 (2H, d, J=8.5Hz), 7.60 (2H, d, J=8.5Hz), 7.54 (2H, d, J=8.5Hz), 7.41 (1H, s), 4.21 (2H, q, J=7.0Hz), 4.03 (2H, s), 2.69 (3H, s, MeSO3H), 2.15 (3H, d, J=1.5Hz), 1.30 (3H, t, J=7.0Hz).</td>
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<td>1(gg)</td>
<td><img src="image" alt="Structure" /> p-(p-aminophenoxycarbonyl)-α-methylcinnamic acid N-(1,1-bis-(ethoxycarbonylmethyl)methyl)-amide hydrochloride</td>
<td>0.41 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.21 (2H, d, J=8.0Hz), 7.95 (2H, d, J=8.0Hz), 7.58 (2H, d, J=7.5Hz), 7.53 (2H, d, J=7.5Hz), 7.22 (1H, s), 4.50 (1H, dt, J=7.0Hz), 4.16 (4H, q, J=7.5Hz), 2.69 (4H, d, J=7.0Hz), 2.09 (3H, s), 1.23 (6H, t, J=7.5Hz).</td>
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<td>1(hh)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-ethoxycarbonyl-2-(4-ethoxy carbonyl-phenyl)ethyl)amide hydrochloride</td>
<td>0.43 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.20 (2H, d, J=8.0Hz), 7.98 (2H, d, J=8.0Hz), 7.93 (2H, d, J=8.0Hz), 7.60-7.48 (4H, m), 7.40 (2H, d, J=7.5Hz), 7.18 (1H, s), 4.90-4.70 (1H, m), 4.35 (2H, q, J=8.0Hz), 4.20 (2H, q, J=8.0Hz), 3.50-3.30 (1H, m), 3.18 (1H, dd, J=10.0, 13.0Hz), 2.02 (3H, s), 1.39 (3H, t, J=8.0Hz), 1.25 (3H, t, J=8.0Hz).</td>
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<td>1(ii)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-ethoxycarbonyl-2-(3-ethoxy carbonyl-phenyl)ethyl)amide methanesulfonate</td>
<td>0.44 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>9.38 (1H, brs), 8.83 (1H, brs), 8.22 (2H, d, J=7.5Hz), 8.85-8.00 (4H, m), 7.61-7.35 (6H, m), 7.20 (1H, brs), 4.79 (1H, dd, J=5.0, 8.0Hz), 4.37 (2H, q, J=8.0Hz), 4.21 (2H, q, J=8.0Hz), 3.41-3.25 (1H, m), 3.19 (1H, dd, J=8.0, 13.0Hz), 2.72 (3H, s, MeSO3H), 2.07 (3H, s), 1.37 (3H, t, J=8.0Hz), 1.28 (3H, t, J=8.0Hz).</td>
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<td>1(jj)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1,1-bis-(ethoxycarbonyl)-methyl)-N-allyl amide hydrochloride</td>
<td>0.43 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>(CDCl&lt;sub&gt;3&lt;/sub&gt;+d6-DMSO) 9.40 (3H, brs), 8.18 (2H, d, J=8.0Hz), 8.00 (2H, d, J=8.0Hz), 7.45 (2H, d, J=8.0Hz), 7.40 (2H, d, J=8.0Hz), 6.70 (1H, s), 5.84 (1H, tt, J=5.0, 15.0Hz), 5.48-5.15 (2H, m), 4.98 (1H, brs), 4.23 (4H, q, J=7.0Hz), 4.17 (2H, d, J=5.0Hz), 2.17 (3H, s), 1.31 (3H, t, J=7.0Hz).</td>
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<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-3-ethoxy carbonylpropyl-N-(1,1-bis(ethoxycarbonyl) methyl)amide acetate</td>
<td>0.51 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.23 (2H, d, J=8.4Hz), 7.93 (2H, d, J=8.8Hz), 7.60 (2H, d, J=8.8Hz), 7.52 (2H, d, J=8.4Hz), 6.70 (1H, s), 4.29 (4H, q, J=7.4Hz), 4.20-4.00 (3H, m), 3.60 (2H, m), 2.39 (2H, t, J=7.0Hz), 2.16 (3H, s), 2.05-1.80 (2H, m), 1.94 (3H, s), 1.40-1.15 (9H, m).</td>
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<td>1(ii)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N,N-bis(2-ethoxycarbonyl ethyl)amide hydrochloride</td>
<td>0.59 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8.0Hz), 7.90 (2H, d, J=8.0Hz), 7.58 (2H, d, J=8.0Hz), 7.55 (2H, d, J=8.0Hz), 6.60 (1H, s), 4.15 (4H, q, J=7.5Hz), 3.81-3.60 (4H, m), 2.68 (4H, t, J=7.5Hz), 2.14 (3H, s), 1.22 (6H, t, J=7.5Hz).</td>
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<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-(S)-ethoxycarbonyl-1-(2-ethoxy-carbonylethylthio)methyl)amide hydrochloride</td>
<td>0.48 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 7.40 (1H, br), 4.70 (1H, dd, J=7 Hz), 4.25 (2H, q, J=6.5Hz), 4.15 (2H, q, J=8Hz), 3.15 (1H, dd, J=15 Hz), 3.00 (1H, dd, J=15, 7Hz), 2.85 (2H, t, J=7Hz), 2.65 (2H, t, J=7Hz), 2.20 (3H, s), 1.30 (3H, t, J=6.5Hz), 1.25 (3H, t, J=8Hz).</td>
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<td>1(nn)</td>
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<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-1-(S)-ethoxycarbonyl-1-(3-ethoxycarbonylpropylthio)methylamide hydrochloride</td>
<td>0.48 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 7.35 (1H, br), 4.70 (1H, dd, J=7, 5Hz), 4.25 (2H, q, J=6.5Hz), 4.15 (2H, q, J=8Hz), 3.15 (1H, dd, J=15, 5Hz), 3.00 (1H, dd, J=15, 7Hz), 2.65 (2H, t, J=7.5Hz), 2.45 (2H, t, J=7Hz), 2.20 (3H, s), 1.90 (2H, m), 1.30 (3H, t, J=6.5Hz), 1.25 (3H, t, J=8Hz).</td>
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<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinoo-methoxy carbonyl-phenoxycarbonyl)-α-methylcinnamic acid N-ethoxycarbonylmethyl-N-allylamide acetate</td>
<td>0.47 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.49 (1H, d, J=2.0Hz), 8.21 (2H, d, J=9.0Hz), 8.10 (1H, dd, J=9.0Hz, 2.0Hz), 7.58 (3H, d, J=9.0Hz), 6.69 and 6.75 (1H, m), 5.83-6.00 (1H, m), 5.24-5.33 (2H, m), 4.20 (2H, q, J=7.0Hz), 4.10 (4H, br), 3.78 (3H, s), 2.14 (3H, s), 1.29 (3H, t, J=7.0Hz).</td>
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<td>p-(p-amidinoo-ethoxycarbonyl-phenoxycarbonyl)-α-methylcinnamic acid N-(1-(S), 3-bis-ethoxycarbonylpropyl)amide hydrochloride</td>
<td>0.53 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>(CDCl₃+CD₃OD) 8.51 (1H, d, J=8.0Hz), 8.22 (2H, d, J=8.0Hz), 8.08 (1H, dd, J=2.5, 9.0Hz), 7.57 (2H, d, J=8.0Hz), 7.53 (1H, d, J=9.0Hz), 7.41 (1H, s), 4.61 (1H, dd, J=3.0, 8.0Hz), 4.24, 4.22, 4.18 (2H each, q each, J=7.5Hz each), 2.51 (2H, t, J=7.5Hz), 2.40-2.60 (2H, m), 2.17 (3H, s), 1.32, 1.27, 1.14 (3H each, t each, J=7.5Hz each).</td>
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<td>1(q4)</td>
<td>P-[α-amino-β-ethoxycarbonyl]-α-phenoxycarbonylmethylaminocarbonyl-N-ethylmethylamide hydrochloride</td>
<td><img src="image" alt="Structure" /></td>
<td>8.48 (1H, d, J=2.5Hz), 8.21 (2H, d, J=9.0Hz), 8.08 (1H, d, J=9.0Hz), 7.47 (2H, d, J=8.0Hz), 6.51 (1H, d, J=3.0Hz), 6.00-5.75 (m, 4H, m), 4.38-4.20 (m, 4H, m), 4.20-4.05 (m, 4H, m), 2.18 (3H, brs), 1.31 (3H, t, J=7.5Hz), 1.13 (3H, J=7.5Hz).</td>
<td>0.57 (chloroform: methanol = 10:1)</td>
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Table 3 (Continued)

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<tr>
<th>Ex. No.</th>
<th>Structure</th>
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<th>TLC (Rf)</th>
<th>NMR</th>
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<tr>
<td>1(rr)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1,1-bis-(ethoxycarbonyl))-methyl-N-ethoxycarbonyl-methylamide acetate</td>
<td>0.47 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8Hz), 7.90 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.75 (1H, br.s), 4.45-4.10 (9H, m), 2.20 (3H, br.s), 1.40-1.20 (9H, m).</td>
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<tr>
<td>1(ss)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-(S),2-bis-(ethoxycarbonyl)ethyl)-N-ethoxycarbonyl-methylamide acetate</td>
<td>0.41 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.52 (4H, d, J=9.0Hz), 6.78 and 6.68 (1H, m), 5.39 and 4.80 (1H, m), 4.55-3.93 (2H, m), 4.20 (6H, q, J=7.0Hz), 3.33-2.90 (2H, m), 2.18 and 2.09 (3H, m), 1.28 (9H, t, J=7.0Hz).</td>
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<td>1(tt)</td>
<td><img src="image3" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1,1-bis-(ethoxycarbonyl))-methyl-N-(2-ethoxycarbonyl-ethyl)amide acetate</td>
<td>0.56 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.60 (2H, d, J=8Hz), 7.55 (2H, d, J=9Hz), 6.70 (1H, m), 4.25 (4H, q, J=7Hz), 4.15 (2H, q, J=7Hz), 4.15 (1H, br.s), 3.85 (2H, br.s), 2.75 (2H, t, J=6.5Hz), 2.20 (3H, s), 1.95 (3H, s, CH3COOH), 1.40-1.20 (9H, m).</td>
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<tr>
<td>Ex. No.</td>
<td>Structure</td>
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<td>TLC (Rf)</td>
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<tr>
<td>(µm)</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methyl-L-N-(S)-ethoxy carbonyl-ethyl)amide acetate</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.70 (2H, m), 3.25 and 2.90 (2H, m), 2.15 (6H, s), 1.25 (6H, m)</td>
<td>0.43 (chloroform: methanol: acetic acid = 10:2:1)</td>
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<td>(µm)</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methyl-L-N-(R)-2-bis(ethoxycarbonyl)ethyl)amide acetate</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.65-7.50 (4H, m), 6.75 (1H, m), 5.40-4.00 (6H, m), 3.30-2.20 (12H, m), 2.15 (3H, s), 1.35-1.13 (9H, m)</td>
<td>0.49 (chloroform: methanol: acetic acid = 10:2:1)</td>
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<td>(µm)</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methyl-L-N-(S)-ethoxy carbonyl ethyl)amide hydrochloride</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.70 (2H, m), 3.25 and 2.90 (2H, m), 2.15 (6H, s), 1.25 (6H, m)</td>
<td>0.44 (chloroform: methanol: acetic acid = 10:2:1)</td>
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Table 3 (continued)
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<td>1(xx)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-benzyl-N-(2-ethoxycarbonyl-ethyl)amide acetate</td>
<td>0.38 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.19 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.52 (2H, d, J=9.0Hz), 7.35 (2H, d, J=9.0Hz), 7.50-7.28 (5H, m), 6.67 (1H, s), 4.73 (2H, s), 4.11 (2H, q, J=7.0Hz), 3.69 (2H, t, J=7.0Hz), 2.63 (2H, t, J=7.0Hz), 2.10 (3H, br-s), 1.22 (3H, t, J=7.0Hz).</td>
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<td>1(yy)</td>
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<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-R),2-bis-(ethoxycarbonyl)-ethyl)-N-(2-ethoxycarbonylethyl)amide acetate</td>
<td>0.39 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.58 (2H, d, J=9.0Hz), 7.52 (2H, d, J=9.0Hz), 6.65 (1H, br-s), 4.52 (1H, br), 4.20 and 4.13 (6H, q, J=7.0Hz), 3.97-3.83 (2H, m), 3.22 (1H, br), 2.94 (1H, dd, J=16.0Hz, 7.0Hz), 2.76 (2H, br), 2.12 (3H, s), 1.28 and 1.22 (9H, t, J=7.0Hz).</td>
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<td>1(zz)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-S)-ethoxycarbonyl-ethyl)-N-ethoxycarbonylmethylamide acetate</td>
<td>0.54 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.57 (2H, d, J=9.0Hz), 7.51 (2H, d, J=9.0Hz), 6.69 (1H, s), 4.85-4.69 (1H, m), 4.34 (1H, s), 4.20 (4H, q, J=7.0Hz), 3.92 (0.8H, d, J=18.0Hz), 2.15 and 2.10 (3H, eachS), 1.50 (3H, d, J=7.0Hz), 1.26 (6H, t, J=7.0Hz).</td>
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<td>Ex. No.</td>
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<td>1(aaa)</td>
<td><img src="image" alt="structure" /></td>
<td>p-(p-aminophenoxybenzyl)-α-methylcinnamic acid N-(1-(S)-ethoxycarbonyl-ethyl)-N-(2-ethoxycarbonyl-ethyl)amide acetate</td>
<td>0.55 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.56 (2H, d, J=9.0Hz), 7.50 (2H, d, J=9.0Hz), 6.62 (1H, s), 4.23-4.15 (1H, m), 4.12 (4H, q, J=7.0Hz), 3.82 (2H, br), 2.74 (2H, t-like), 2.12 (3H, s), 1.51 (3H, d, J=7.0Hz), 1.26 (6H, t, J=7.0Hz).</td>
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<td>1(bbb)</td>
<td><img src="image" alt="structure" /></td>
<td>p-(p-aminophenoxybenzyl)-α-methylcinnamic acid N-((1)-(S),2-bis(ethoxycarbonyl)-ethyl)-N-((3-ethoxycarbonylpropyl))-amide acetate</td>
<td>0.44 (chloroform: methanol = 8:2)</td>
<td>8.22 (2H, d, J = 8 Hz), 7.93 (2H, d, J = 8 Hz), 7.59 (2H, d, J = 8 Hz), 7.54 (2H, d, J = 8 Hz), 6.64 (1H, bs), 4.30-3.95 (6H, m), 3.80-3.10 (4H, m), 3.01-2.85 (1H, m), 2.46-2.31 (2H, m), 2.13 (3H, s), 2.13-1.97 (2H, m), 1.91 (3H, s), 1.34-1.09 (9H, m).</td>
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<td>1(ccc)</td>
<td><img src="image" alt="structure" /></td>
<td>p-(p-aminophenoxybenzyl)-α-methylcinnamic acid N-allyl-N-((1)-(R)-ethoxycarbonyl-2-ethoxycarbonyl-methylthio)-ethyl)amide hydrochloride</td>
<td>0.48 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.65-7.50 (4H, m), 6.80 (1H, br.s), 6.00 (1H, br.), 5.45-5.15 (2H, m), 4.50-4.00 (7H, m), 3.50-3.10 (4H, m), 2.15 (3H, br.s), 1.40-1.20 (6H, m).</td>
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<tr>
<td>Ex. No.</td>
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<td>1(ddd)</td>
<td><img src="image" alt="Structure 1(ddd)" /></td>
<td>p-(p-amidinophenoxycarbonyl)-α-methylcinnamic acid N-((1-(R))-2-ethoxy(carbonyl)-methylthio)(ethyl)-N-(3-ethoxy-carbonylpropyl)amide hydrochloride</td>
<td>0.39 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8 Hz), 7.95 (2H, d, J=9 Hz), 7.65-7.50 (4H, m), 6.70 (1H, br.), 4.50-4.00 (7H, m), 3.80-3.20 (6H, m), 2.40 (2H, m), 2.20 (3H, br.s), 2.05 (2H, m), 1.40-1.10 (9H, m).</td>
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<td>1(eee)</td>
<td><img src="image" alt="Structure 1(eee)" /></td>
<td>p-(p-amidinophenoxycarbonyl)-α-methylcinnamic acid N-((1,1-bis(ethoxycarbonyl)methyl)-N-(3-methoxycarbonylpropyl)amide acetate</td>
<td>0.30 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.23 (2H, d, 7.91 (2H, d, J=8 Hz), 7.60 (2H, d, J=8 Hz), 7.53 (2H, d, J=8 Hz), 6.69 (1H, s), 4.90 (1H), 4.27 (4H, q, J=7 Hz), 4.0-4.1 (1H, m), 3.5-3.7 (5H, m), 2.42 (2H, t, J=7 Hz), 2.17 (3H, s), 1.8-2.0 (2H, m), 1.91 (3H, s), 1.32 (6H, t, J=7 Hz)).</td>
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<td>1(fff)</td>
<td><img src="image" alt="Structure 1(fff)" /></td>
<td>p-(p-amidinophenoxycarbonyl)-α-methylcinnamic acid N-((1,3,5)-2-bis(ethoxycarbonyl)propyl)-N-(3-ethoxycarbonylpropyl)amide acetate</td>
<td>0.30 (chloroform: methanol =9:1)</td>
<td>8.22 (2H, d, J = 8 Hz), 7.93 (2H, d, J = 8 Hz), 7.59 (2H, d, J = 8 Hz), 7.53 (2H, d, J = 8 Hz), 6.66 (1H, bs), 4.30-3.90 (6H, m), 3.80-3.15 (3H, m), 2.60-2.30 (4H, m), 2.30-1.80 (4H, m), 2.13 (3H, s), 1.91 (3H, s), 1.35-1.05 (9H, s).</td>
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### Table 3 (continued)

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<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-(1,1-bis-(ethoxycarbonyl)-methyl)-N-isopentylamide acetate</td>
<td>0.41</td>
<td>8.24 (2 H, d, J = 8 Hz), 7.93 (2 H, d, J = 8 Hz), 7.59 (2 H, d, J = 8 Hz), 7.54 (2 H, d, J = 8 Hz), 6.71 (1 H, bs), 4.27 (4 H, q, J = 7 Hz), 3.63-3.35 (2 H, m), 2.16 (3 H, s), 1.91 (3 H, s), 1.67-1.45 (3 H, m), 1.30 (6 H, t, J = 7 Hz), 0.89 (6 H, d, J = 6 Hz).</td>
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<tr>
<td>Ex. No.</td>
<td>Structure</td>
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<td>1(hhh)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy-carbonyl)-α-methylcinnamic acid N-(1,1-bis-(\text{ethoxy-carbonyl})-methyl)-N-(5-(\text{ethoxy-carbonyl-pentyl}))amide acetate</td>
<td>0.41 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.24 (2H, m), 7.92 and 6.94 (2H, d, J=10Hz), 7.72-7.35 (4H, m), 6.71 and 6.59 (1H, br), 4.38-3.99 (6H, m), 3.60-3.37 (2H, br), 2.30 (2H, t, J=7Hz), 2.16 and 2.02 (3H, s), 1.92 (3H, s), 1.80-1.50 (4H, br), 1.48-1.17 (11H, m).</td>
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<td>1(iii)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy-carbonyl)-α-methylcinnamic acid N-(1-(\text{R})-ethoxy-carbonyl-2-(\text{phenylethyl}))-N-(3-(\text{ethoxy-carbonyl-propyl}))amide acetate</td>
<td>0.27 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.19 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 7.52 (4H, d, J=8Hz), 7.2-7.3 (5H, br), 6.41 and 6.07 (1H, s), 4.1-4.4 (3H, m), 3.9-4.1 (2H, m), 3.3-3.5 (2H, m), 2.2-2.9 (2H, br), 2.0-2.2 (5H, m), 1.93 (3H, s), 1.5-1.8 (2H, m), 1.30 (3H, t, J=7Hz), 1.17 (3H, t, J=7Hz).</td>
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<td>1(jjj)</td>
<td><img src="image3" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy-carbonyl)-α-methylcinnamic acid N-(1-(\text{S})-ethoxy-carbonyl-3-methyl-butyl)-N-(3-(\text{ethoxy-carbonyl-propyl}))amide hydrochloride</td>
<td>0.70 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.65-7.50 (4H, m), 6.65 (1H, br.), 4.50-4.00 (5H, m), 3.80-3.30 (2H, m), 2.40 (2H, t, J=7Hz), 2.15 (3H, s), 2.10-1.60 (5H, m), 1.35-1.10 (6H, m), 1.00 (6H, m).</td>
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<td>Ex. No.</td>
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<td>1(kkk)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methyl cinnamic acid N-(1,1-bis(ethoxy carbonyl)-methyl)methyl)-N-(3-methylbutyl) amide acetate</td>
<td>0.36 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=8Hz), 7.93 (2H, d, J=8Hz), 7.57 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 6.63 (1H, bs), 4.25-4.00 (5H, m), 3.50-3.20 (2H, m), 3.10-2.60 (4H, m), 2.13 (3H, s), 1.91 (3H, s), 1.70-1.42 (3H, m), 1.36-1.07 (6H, m), 1.07-0.80 (6H, m).</td>
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<td>1(III)</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methyl cinnamic acid N-(1,1-bis(ethoxy carbonyl)-methyl)methyl)-N-propyl amide acetate</td>
<td>0.32 (chloroform: methanol: acetic acid =20:2:1)</td>
<td>8.23 (2H, d, J=8 Hz), 7.93 (2H, d, J=8 Hz), 7.58 (2H, d, J=8 Hz), 7.54 (2H, d, J=8Hz), 6.64 (1H, bs), 4.24-4.04 (4H, m), 3.45-3.20 (2H, m), 3.10-2.60 (4H, m), 2.13 (3H, s), 1.91 (3H, s), 1.75-1.53 (2H, m), 1.40-1.15 (6H, m), 1.05-0.83 (3H, m).</td>
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<td>1(mmm)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methyl cinnamic acid N-(1,1-bis(ethoxy carbonyl)-methyl)methyl)-N-cyclohexyl amide acetate</td>
<td>0.36 (chloroform: methanol: acetic acid =20:2:1)</td>
<td>8.22 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 7.56 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 6.60 (1H, bs), 4.23-4.00 (5H, m), 3.80-3.55 (1H, m), 3.20-2.65 (4H, m), 2.12 (3H, s), 1.92 (3H, s), 1.95-1.50 (7H, m), 1.50-1.10 (9H, m).</td>
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<td>Ex. No.</td>
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<td>1(nnn)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidinophenoxycarbonyl)-α-methylcinnamic acid N-ethoxy-carbonylmethyl-N-hexylamide acetate</td>
<td>0.35 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 7.56 (4H, t, J=8Hz), 6.70 and 6.61 (1H, s), 4.22 (2H, q, J=7 Hz), 4.15 (2H, s), 3.49 (2H, t, J=7 Hz), 2.14 and 2.09 (3H, s), 1.93 (3H, s), 1.80-1.50 (2H, m), 1.50-1.20 (9H, m), 0.8-1.0 (3H, br).</td>
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<td>p-(p-amidinophenoxycarbonyl)-α-methylcinnamic acid N-ethoxy-carbonylmethyl-N-1-propylbutylamide acetate</td>
<td>0.35 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.23 (2H, d, J=8Hz), 7.91 (2H, d, J=8Hz), 7.56 (4H, t, J=8Hz), 6.62 and 6.67 (1H, s), 4.30-4.10 (3H, m), 3.98 (2H, s), 2.14 and 2.08 (3H, s), 1.90 (3H, s), 1.60-1.10 (11H, m), 0.92 (6H, t, J=7Hz).</td>
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<td>p-(p-amidinophenoxycarbonyl)-α-methylcinnamic acid N-ethoxy-carbonylmethyl-N-methylamide acetate</td>
<td>0.36 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=7Hz), 7.96 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.65 (1H, m), 4.30-4.10 (4H, m), 2.80 (3H, br), 2.15 (3H, m), 1.95 (3H, s), 1.25 (3H, m).</td>
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<td>Ex. No.</td>
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<td>p-(p-amidino-phenoxycarbonyl)-(\alpha)-methylcinnamic acid N-ethoxy-carbonylmethyl-N-ethylamide acetate</td>
<td>0.45 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.65 (1H, m), 4.30-4.10 (4H, m), 3.45 (2H, m), 2.15 (3H, m), 1.95 (3H, s), 1.25 (3H, m), 0.95 (3H, m).</td>
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<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-(\alpha)-methylcinnamic acid N-ethoxy-carbonylmethyl-N-butylamide acetate</td>
<td>0.50 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 7.56 (4H, t, J=8Hz), 6.70-6.60 (1H, m), 4.22 (2H, q, J=7Hz), 4.15 (2H, s), 3.49 (2H, t, J=7Hz), 2.10 (3H, s), 1.93 (3H, s), 1.80-1.50 (2H, m), 1.5-1.2 (5H, m), 0.93 (3H, brt, J=7Hz).</td>
</tr>
<tr>
<td>1(sss)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-(\alpha)-methylcinnamic acid N-ethoxy-carbonylmethyl-N-cyclobutylamide acetate</td>
<td>0.53 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 7.60-7.50 (4H, m), 6.65 (1H, brs), 4.25-4.05 (5H, m), 2.15 (3H, brs), 1.95 (3H, s), 2.00-1.05 (9H, m).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
<td>NMR</td>
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<tr>
<td>1 (iii)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-o-methylisonicarboxylic acid N-cyclopentamylamide acetate</td>
<td>0.53 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.25 (2H, d, J=9 Hz), 7.90 (2H, d, J=8 Hz), 7.65-7.50 (4H, m), 6.65 (1H, brs), 4.25-4.05 (4H, m), 3.80 (4H, m), 2.15 (3H, brs), 1.95 (3H, s), 1.75-1.05 (TH, m).</td>
</tr>
<tr>
<td>1 (uuu)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-o-methylisonicarboxylic acid N-2-ethoxyethyl N-methylamide acetate</td>
<td>0.37 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, J=7 Hz), 7.96 (2H, d, J=7 Hz), 7.65-7.49 (4H, m), 6.65 (1H, m), 4.50-4.10 (2H, brs), 2.75 (2H, m), 2.5 (3H, m), 1.95 (3H, m), 1.25 (3H, m).</td>
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</table>
Table 3 (continued)

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<th>NMR</th>
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<td><img src="image" alt="Structure Image" /></td>
<td>p-(p-aminophenoxyphenylcarbonyl)-α-methylcinnamic acid N-2-ethoxy-carbonylethyl-N-ethylamide acetate</td>
<td>0.45 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.65 (1H, m), 4.20 (2H, m), 3.80 (2H, m), 3.45 (2H, m), 2.75 (2H, m), 2.15 (3H, m), 1.95 (3H, s), 1.25 (3H, m), 0.95 (3H, m).</td>
</tr>
</tbody>
</table>
Example 2

p-(p-Aminophenoxycarbonyl)cinnamic acid N'-phenylmethyl piperazinylamide bishydrochloride

By the same procedure as Example 1, using the compound prepared in Reference Example 12 instead of that prepared in Reference Example 10, the title compound having the following physical data was given.

TLC : Rf 0.24 (chloroform : methanol=8 : 2);

IR: v 3402,1741, 1678, 1644, 1606, 1479, 1415, 1263, 1216, 1174, 1123, 1070, 1016, 951, 872, 844, 765, 753, 703, 538 cm⁻¹;

NMR (CD₃OD+D₂O-DMSO) : δ 8.10 (2H, d), 7.95 (2H, d), 7.86 (2H, d), 7.70 (1H, d), 7.62-7.45 (7H, m), 7.40 (1H, d), 4.80-4.50 (2H, m), 3.80-3.40 (3H, m), 3.50-3.00 (3H, m).

Example 2(a)~2(ll)

By the same procedure as a series of reactions of Reference Example 11→Reference Example 12→Example 2, using, as starting materials, the compound prepared in Reference Example 7, that prepared in Reference Example 8, that prepared in Reference Example 14 or p-t-butoxycarbonylbenzoic acid, and further using proper amines instead of N-benzylpiperazine, the compounds of the present invention shown in Table 4 were given.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(a)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) cinnamic acid-N-phenyl-N-ethoxy carbonylmethyl amide hydrochloride</td>
<td>0.59 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.15 (2H, d), 7.90 (2H, d), 7.69 (1H, d), 7.60-7.40 (9H, m), 6.58 (1H, d), 4.52 (2H, s), 4.20 (2H, q), 1.25 (3H, t).</td>
</tr>
<tr>
<td>2(b)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) cinnamic acid-N-(2-(S)-ethoxy carbonyl) pyrrolidinyl amide</td>
<td>0.31 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d), 8.00-7.50 (7H, m), 7.15 and 6.95 (1H, d), 4.55 (1H, m), 4.20 (2H, q), 3.90 (2H, m), 2.30 (1H, m), 2.20-2.00 (3H, m), 2.00 (3H, s), 1.30 (3H, t).</td>
</tr>
<tr>
<td>2(c)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) cinnamic acid-N-(2-(R)-ethoxy carbonyl) pyrrolidinyl amide</td>
<td>0.31 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d), 8.00-7.50 (7H, m), 7.15 and 6.95 (1H, d), 4.55 (1H, m), 4.20 (2H, q), 3.90 (2H, m), 2.30 (1H, m), 2.20-2.00 (3H, m), 2.00 (3H, s), 1.30 (3H, t).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
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<tr>
<td>2(d)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) cinnamic acid-N-phenylmethyl-N-ethoxy carbonyl methyl amide acetic acid</td>
<td>0.48 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, m), 7.90 (2H, d), 7.85-7.70 (3H, m), 7.55 (2H, d), 7.40-7.20 (6H, m), 4.95 and 4.75 (2H, s), 4.40 and 4.20 (2H, s), 4.20 (2H, m), 2.00 (3H, s), 1.25 (3H, m).</td>
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<tr>
<td>2(e)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-(2-((S)-benzyl oxycarbonyl) pyrrolidinyl amide acetic acid</td>
<td>0.26 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.21 (1.4H, d), 8.13 (0.6H, d), 7.92 (2H, d), 7.53 (3H, m), 7.45-7.20 (5H, m), 6.77 (0.7H, s), 6.62 (0.3H, s), 5.20 (2H, m), 4.61-4.54 (1H, m), 3.73 (2H, m), 2.11 (3H, s), 2.01 (3H, m), 1.93 (3H, s).</td>
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<td>2(f)</td>
<td><img src="image3" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) benzoic acid-N-(2-(R)-benzyl o xo c arboxyl)-pyrrolidinyl amide acetic acid</td>
<td>0.36 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.30 and 8.10 (2H, d), 7.95 (2H, d), 7.70 and 7.45 (2H, d), 7.55 (2H, d), 7.45-7.25 (5H, m), 5.30 and 5.10 (1H, d), 5.20 and 4.95 (1H, d), 4.70 and 4.50 (1H, m), 3.75 and 3.60 (2H, m), 2.40 (1H, m), 2.20-1.80 (3H, m), 2.00 (3H, s).</td>
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<tr>
<td>Ex. No.</td>
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<td>Name</td>
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<td>2(g)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) cinnamic acid-N-1-(S),3-bis (ethoxy carbonyl) propyl amide hydrochloride</td>
<td>0.39 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.20 (2H, d, J=8.0 Hz), 7.93 (2H, d, J=8.0 Hz), 7.80 (2H, d, J=8.5 Hz), 7.62 (1H, d, J=15 Hz), 7.55 (2H, d, J=8.5 Hz), 6.83 (1H, d, J=15 Hz), 4.58 (1H, dd, J=5.0, 8.0 Hz), 4.20 (2H, q, J=8.0 Hz), 4.25 (2H, q, J=8.0 Hz), 2.45 (2H, t, J=8.0 Hz), 2.56-1.95 (2H, m), 1.28 (3H, t, J=8.0 Hz), 1.23 (3H, t, J=8.0 Hz).</td>
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<tr>
<td>2(h)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl cinnamic acid-N-(1-(S)-benzyloxycarbonyl propyl amide acetic acid</td>
<td>0.68 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8.0 Hz), 7.95 (2H, d, J=8.0 Hz), 7.60-7.50 (4H, m), 7.40-7.30 (5H, m), 5.25 (1H, d, J=11 Hz), 5.20 (1H, d, J=11 Hz), 4.60 (1H, m), 4.15 (2H, q, J=7 Hz), 2.50 (2H, t, J=7 Hz), 2.40-2.00 (2H, m), 2.15 (3H, s), 1.95 (3H, s), 1.25 (3H, t, J=7 Hz).</td>
</tr>
<tr>
<td>2(j)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl cinnamic acid-N-(1-(S)-ethoxycarbonyl propyl amide acetic acid</td>
<td>0.70 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8.0 Hz), 7.95 (2H, d, J=8.0 Hz), 7.60-7.50 (4H, m), 7.40-7.30 (5H, m), 5.15 (2H, s), 4.55 (1H, m), 4.20 (2H, q, J=7 Hz), 2.60 (2H, t, J=7.5 Hz), 2.40-2.00 (2H, m), 2.15 (3H, s), 1.95 (3H, s), 1.30 (3H, t, J=7 Hz).</td>
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Table 4 (continued)

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<td>p-(p-amidino phenoxyacarbonyl)-α-methyl-cinnamic acid-N-(1-(S)-benzylxoyxycarbonyl-2-ethoxycarbonyl) ethyl amide hydrochloride</td>
<td>0.48 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=9.0Hz), 7.94 (2H, d, J=9.0Hz), 7.55 (2H, d, J=9.0Hz), 7.52 (2H, d, J=9.0Hz), 7.35 (5H, s), 7.31 (1H, s), 4.95 (1H, t, J=6.0Hz), 4.14 (2H, q, J=7.0Hz), 2.86-3.08 (2H, m), 2.13 (3H, s), 1.22 (3H, t, J=7.0Hz).</td>
</tr>
<tr>
<td>2(k)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxyacarbonyl)-α-methyl-cinnamic acid-N-(1-(S)-benzylxoyxycarbonyl-2-isobutylxoy carbonyl)ethyl amide acetic acid</td>
<td>0.49 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.10 (2H, d, J=9.0Hz), 7.79 (2H, d, J=9.0Hz), 7.40 (2H, d, J=9.0Hz), 7.36 (2H, d, J=9.0Hz), 7.23 (6H, s), 5.12 (2H, s), 4.88 (1H, t, J=6.0Hz), 3.76 (2H, d, J=7.0Hz), 2.92 (2H, t, J=6.0Hz), 2.02 (3H, d, J=1.0Hz), 1.78 (1H, sep, J=7.0Hz), 0.90 (6H, d, J=7.0Hz).</td>
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<td>2(l)</td>
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<td>p-(p-amidino phenoxyacarbonyl)-α-methyl-cinnamic acid-N-(1-(S)-ethoxycarbonyl-2-benzylxoyxycarbonyl) ethyl amide acetic acid</td>
<td>0.46 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=9.0Hz), 7.93 (2H, d, J=9.0Hz), 7.57-7.48 (4H, m), 7.36 (6H, s), 5.18 (2H, s), 4.95 (1H, t, J=6.0Hz), 4.22 (2H, q, J=7.0Hz), 3.04 (2H, d, J=6.0Hz), 2.11 (3H, s), 1.26 (3H, t, J=7.0Hz).</td>
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<tr>
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<td>2(m)</td>
<td><img src="image" alt="Structure" /> p-(p-amidino phenoxy-carbonyl)-α-methyl-cinnamic acid-N-(2-ethoxy carbonyl)ethyl-N-allyl amide acetic acid</td>
<td>0.37 (chloroform: methanol: acetic acid = 10:1:1)</td>
<td>8.21 (2H, d, J=8.4Hz), 7.93 (2H, d, J=8.8Hz), 7.57 (2H, d, J=8.4Hz), 7.53 (2H, d, J=8.8Hz), 6.92 (1H, dt, J=15.8, 5.2Hz), 6.70 (1H, s), 5.96 (1H, d, J=15.8Hz), 6.00-5.80 (1H, m), 5.35-5.20 (2H, m), 4.20 (2H, q, J=7.2Hz), 4.23 (2H, d, J=5.2Hz), 4.11 (2H, d, J=5.2Hz), 2.15 (3H, s), 1.93 (3H, s), 1.29 (3H, t, J=7.2Hz).</td>
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<tr>
<td>2(n)</td>
<td><img src="image" alt="Structure" /> p-(p-amidino phenoxy-carbonyl)-α-methyl-cinnamic acid-N-(1-(S)-ethoxy-carbonyl-2-(4-ethoxy-carbonyl phenylmethylthio)) ethyl amide methane sulfonic acid</td>
<td>0.69 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.22 (2H, d, J=9.0Hz), 7.99 (2H, d, J=9.0Hz), 7.43 (2H, d, J=9.0Hz), 7.56 (2H, d, J=9.0Hz), 7.50 (2H, d, J=9.0Hz), 7.45 (2H, d, J=9.0Hz), 7.34 (1H, s), 4.70-4.80 (1H, m), 4.36 (2H, q, J=7.0Hz), 4.22 (2H, q, J=7.0Hz), 3.83 (2H, s), 3.00 (1H, dd, J=14.0, 5.0Hz), 2.85 (1H, dd, J=14.0, 9.0Hz), 2.17 (3H, s), 1.39 (3H, s), 1.30 (3H, t, J=7.0Hz).</td>
<td></td>
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<td>2(o)</td>
<td><img src="image" alt="Structure" /> p-(p-amidino phenoxy-carbonyl)-α-methyl-cinnamic acid-N-(1-(S)-ethoxy-carbonyl-2-(3-ethoxy-carbonyl phenylmethylthio)) ethyl amide methane sulfonic acid</td>
<td>0.69 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.23 (2H, d, J=9.0Hz), 8.02 (1H, s), 7.91 (3H, d, J=9.0Hz), 7.57 (2H, d, J=9.0Hz), 7.52 (2H, d, J=9.0Hz), 7.42-7.58 (2H, m), 7.39 (1H, s), 4.78-4.70 (1H, m), 4.38 (2H, q, J=7.0Hz), 4.21 (2H, q, J=7.0Hz), 3.86 (2H, s), 3.01 (1H, dd, J=14.0, 5.0Hz), 2.88 (1H, dd, J=14.0, 9.0Hz), 2.16 (3H, d, J=2.0Hz), 1.40 (3H, t, J=7.0Hz), 1.28 (3H, t, J=7.0Hz).</td>
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<tr>
<td>Ex. No.</td>
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<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-1-(3-ethoxy carbonyl-2-(3-ethoxy carbonyl-2-propenylthio)) ethyl amide methane sulfonic acid</td>
<td>0.69 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=9 Hz), 7.92 (2H, d, J=9 Hz), 7.60 (2H, d, J=9 Hz), 7.52 (2H, d, J=9 Hz), 7.37 (1H, s), 6.88 (1H, dd, J=15.0, 7.5, 7.5 Hz), 5.98 (1H, d, J=15.0 Hz), 4.66 (1H, dd, J=9.0, 5.0 Hz), 4.22 (2H, q, J=7.0 Hz), 4.18 (2H, q, J=7 Hz), 3.36 (2H, d, J=7.5 Hz), 3.08 (1H, dd, J=14.0, 5 Hz), 2.88 (1H, dd, J=14.0, 9 Hz), 2.15 (3H, d, J=2.0 Hz), 1.31 (3H, t, J=7 Hz), 1.27 (3H, t, J=7 Hz).</td>
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<td>2(q)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-1-(3-ethoxy carbonyl-2-(2-ethoxy carbonyl phenylthio)) ethyl amide methane sulfonic acid</td>
<td>0.41 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=9.0 Hz), 7.92 (2H, d, J=9.0 Hz), 7.84-7.90 (1H, m), 7.58-7.49 (6H, m), 7.29-7.20 (2H, m), 4.78 (1H, dd, J=8.0, 5.0 Hz), 4.37 (2H, q, J=7.0 Hz), 4.21 (2H, q, J=7.0 Hz), 3.61 (1H, dd, J=15.0, 5.0 Hz), 3.42 (1H, dd, J=15.0, 8.0 Hz), 2.09 (3H, d, J=2.0 Hz), 1.39 (3H, t, J=7.0 Hz), 1.30 (3H, t, J=7.0 Hz).</td>
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<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-2-(3-methyl-2-butenyl amide hydrochloride</td>
<td>0.59 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8 Hz), 7.90 (2H, d, J=8 Hz), 7.60-7.50 (4H, m), 6.70 (1H, br), 5.25 (1H, br), 4.30-4.00 (6H, m), 2.15 (3H, brs), 1.80 (3H, brs), 1.65 (3H, s), 1.30 (3H, t, J=7.5 Hz).</td>
</tr>
<tr>
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<tr>
<td>2(s)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-aminophenoxycarbonylmethyl-N-allyl) phenoxycarbonylamide</td>
<td>0.58</td>
<td>8.18 (2H, br), 7.79 (1H, d, J=7.5 Hz), 7.51 (2H, d, J=5.0 Hz), 7.39 (2H, d, J=9.0 Hz), 7.30 (2H, d, J=5.0 Hz), 7.12 (2H, m), 5.98 (2H, m), 5.08 (2H, m), 4.95 (2H, s), 4.80 (2H, d, J=6.0 Hz), 2.17 (3H, s), 1.38 (3H, d, J=7.0 Hz).</td>
</tr>
<tr>
<td>2(t)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-aminophenoxycarbonylamide-N,N-allyl) phenoxycarbonylamide</td>
<td>0.39</td>
<td>8.20 (2H, d, J=8.0 Hz), 7.93 (4H, m), 6.71 (1H, s), 6.00 (2H, m), 4.75 (2H, s), 4.08 (2H, d, J=7.0 Hz), 2.16 (3H, s), 1.39 (3H, d, J=7.0 Hz).</td>
</tr>
<tr>
<td>2(u)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-aminophenoxycarbonylamide-N,N-allyl) phenoxycarbonylamide</td>
<td>0.39</td>
<td>8.20 (2H, d, J=8.0 Hz), 7.93 (4H, m), 6.71 (1H, s), 6.00 (2H, m), 4.75 (2H, s), 4.08 (2H, d, J=7.0 Hz), 2.16 (3H, s), 1.39 (3H, d, J=7.0 Hz).</td>
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</table>

Table 4 (continued)
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<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
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</thead>
<tbody>
<tr>
<td>2(v)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxycarbonyl)-α-methyl-cinnamic acid-N-(3-ethoxy carbonyl-2-propenyl)-N-ethoxy carbonylmethyl amide acetic acid</td>
<td>0.48 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.21 (2H, d, J=8.2Hz), 7.93 (2H, d, J=8.8Hz), 7.56 (2H, d, J=8.2Hz), 7.53 (2H, d, J=8.8Hz), 7.05-6.85 (1H, m), 6.72 (1H, s), 6.20-5.90 (1H, m), 4.40-4.00 (8H, m), 2.14 (3H, s), 1.93 (3H, s), 1.35-1.10 (6H, m).</td>
</tr>
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<td>2(w)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxycarbonyl)-α-methyl-cinnamic acid-N-3-ethoxy carbonylpropyl-N-allyl amide acetic acid</td>
<td>0.47 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.22 (2H, d, J=8.4Hz), 7.92 (2H, d, J=8.8Hz), 7.56 (2H, d, J=8.8Hz), 7.52 (2H, d, J=8.4Hz), 6.64 (1H, s), 6.00-5.80 (1H, m), 5.35-5.20 (2H, m), 4.10 (4H, m), 3.48 (2H, t, J=7.0Hz), 2.38 (2H, brt), 2.13 (3H, s), 2.00-1.85 (2H, m), 1.94 (3H, s), 1.24 (3H, s).</td>
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<td>p-(p-amidino phenoxycarbonyl)-α-methyl-cinnamic acid-N-ethoxy carbonylmethyl-N-2,4-hexadienyl amide hydrochloride</td>
<td>0.56 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8.5Hz), 7.94 (2H, d, J=8.5Hz), 7.55 (2H, d, J=8.0Hz), 7.51 (2H, d, J=8.0Hz), 6.70 (1H, brs), 6.20 (1H, dd, J=5.0, 15.0Hz), 6.07 (1H, t, J=15.0Hz), 5.75 (1H, ddd, J=7.5, 15.0Hz), 5.62-5.40 (1H, m), 4.20 (2H, q, J=7.5Hz), 4.15 (2H, d, J=7.5Hz), 2.18 (3H, s), 1.78 (3H, d, J=5.0Hz), 1.28 (3H, t, J=7.5Hz).</td>
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<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>2(y)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino phenoxycarbonyl)-α-methyl-cinnamic acid-N-1-(S), 2-bis (ethoxycarbonyl) ethyl-N-allyl amide hydrochloride</td>
<td>0.45 (chloroform: methanol: acetic acid =15:2:1)</td>
<td>8.21 (2H, d, J=8.0Hz), 7.94 (2H, d, J=8.0Hz), 7.59 (2H, d, J=7.5Hz), 7.57 (2H, d, J=7.5Hz), 6.71 (1H, brs), 6.10-5.80 (1H, m), 5.50-5.10 (2H, m), 4.60-4.40 (1H, m), 4.40-4.00 (2H, m), 4.16 (4H, q, J=7.5Hz), 3.40-3.15 (1H, m), 2.89 (1H, dd, J=5.0, 15.0Hz), 2.17 (3H, s), 1.28 (6H, t, J=7.5Hz).</td>
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<tr>
<td>2(z)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino-o-methoxybenzylphenoxyacarbonyl)-α-methyl-cinnamic acid-N-1-(S), 3-bis (ethoxycarbonyl) propyl amide acetic acid</td>
<td>0.54 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.49 (1H, d, J=2.0Hz), 8.22 (2H, d, J=9.0Hz), 8.10 (1H, dd, J=9.0, 2.0Hz), 7.62 (2H, d, J=9.0Hz), 7.58 (1H, d, J=9.0Hz), 7.35 (1H, s), 4.54 (1H, dd, J=9.5, 5.0Hz), 4.21 (2H, q, J=7.0Hz), 4.14 (2H, q, J=7.0Hz), 3.79 (3H, s), 2.49 (2H, t, J=7.0Hz), 2.02-2.37 (2H, m), 2.15 (3H, s), 1.29 (3H, t, J=7.0Hz), 1.25 (3H, t, J=7.0Hz).</td>
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<td>2(aa)</td>
<td><img src="image3" alt="Structure" /></td>
<td>p-(p-amidino phenoxycarbonyl)-α-methyl-cinnamic acid-N-ethoxy carbonylmethyl-N-isopropyl amide acetic acid</td>
<td>0.38 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=9.0Hz), 7.94 (2H, d, J=9.0Hz), 7.58 (2H, d, J=9.0Hz), 7.53 (2H, d, J=9.0Hz), 6.68 (1H, s), 4.33 (1H, m), 4.20 (2H, q, J=7.0Hz), 4.06 (2H, s), 2.15 (3H, s), 1.29 (3H, t, J=7.0Hz), 1.22 (6H, d, J=7.0Hz).</td>
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<tr>
<td>Ex. No.</td>
<td>Structure</td>
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<td>2(bb)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-(1-(S)-ethoxy carbonyl-3-methyl)butyloamide hydrochloride</td>
<td>0.40 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>9.38 (1H, brs), 8.83 (1H, brs), 8.21 (2H, d, J=8.0Hz), 7.95 (2H, d, J=8.0Hz), 7.60 (2H, d, J=8.0Hz), 7.56 (2H, d, J=8.0Hz), 7.73 (1H, s), 4.60-4.48 (1H, m), 4.20 (2H, q, J=7.5Hz), 2.13 (3H, s), 1.90-1.60 (3H, m), 1.25 (3H, t, J=7.5Hz), 1.00 (3H, d, J=7.5Hz).</td>
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<td>2(cc)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) phenylpropionic acid-N-ethoxy carbonylmethyl-N-allyl amide acetic acid</td>
<td>0.37 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.11 (2H, d, J=8.4Hz), 7.91 (2H, d, J=8.8Hz), 7.51 (2H, d, J=8.8Hz), 7.46 (2H, d, J=8.4Hz), 6.00-5.70 (1H, m), 5.22-5.11 (2H, m), 4.18 (2H, q, J=7.0Hz), 4.06 (4H, brs), 3.06 (2H, t, J=7.0Hz), 2.81 (2H, m), 1.92 (3H, s), 1.26 (3H, t, J=7.0Hz).</td>
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<td>2(dd)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-1-(S), 2-bis (ethoxy carbonyl) ethyl-N-2-ethoxy carbonyl ethyl amide hydrochloride</td>
<td>0.49 (chloroform: methanol: acetic acid =10:1:1)</td>
<td>8.21 (2H, d, J=8.0Hz), 7.95 (2H, d, J=8.0Hz), 7.59 (2H, d, J=7.5Hz), 7.56 (2H, d, J=7.5Hz), 6.65 (1H, s), 4.60-4.40 (1H, m), 4.30-4.02 (6H, m), 4.05-3.60 (2H, m), 3.30-3.15 (1H, m), 2.96 (1H, dd, J=7.5, 17.0Hz), 2.82-2.60 (2H, m), 2.15 (3H, s), 1.28 (6H, t, J=7.5Hz), 1.22 (3H, t, J=7.5Hz).</td>
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</table>
### Table 4 (continued)

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<th>NMR</th>
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<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-ethoxy carbonylmethyl-N-propyl amide acetic acid</td>
<td>0.46 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.65 (1H, m), 4.30-4.10 (4H, m), 3.45 (2H, m), 2.15 (3H, m), 1.70 (2H, m), 1.25 (3H, m), 0.95 (3H, m).</td>
</tr>
<tr>
<td>2(ff)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-1-(S)-ethoxy carbonyl-2-methyl propyl amide acetic acid</td>
<td>0.46 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8.5Hz), 7.90 (2H, d, J=9Hz), 7.60 (2H, d, J=8.5Hz), 7.55 (2H, d, J=9Hz), 7.30 (1H, brs), 4.40 (1H, d, J=6.5Hz), 4.20 (2H, q, J=7Hz), 2.20 (1H, m), 2.15 (3H, s), 1.95 (3H, s), 1.30 (3H, t, J=7Hz), 1.00 (6H, m).</td>
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<td>2(gg)</td>
<td><img src="image" alt="Structure" /></td>
<td>m-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-ethoxy carbonylmethyl -N-allyl amide acetic acid</td>
<td>0.41 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.15 (2H, m), 7.95 (2H, d, J=8Hz), 7.80-7.60 (2H, m), 7.55 (2H, d, J=8Hz), 6.75 (1H, m), 5.90 (1H, m), 5.40-5.20 (2H, m), 4.30-4.10 (6H, m), 2.15 (3H, br), 1.30 (3H, m).</td>
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<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
<td>NMR</td>
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<tr>
<td>2(hh)</td>
<td><img src="image" alt="Structure" /></td>
<td>m-(p-amidino phenoxy carbonyl)-α-methyl-cinnamic acid-N-1-(S), 3-bis (ethoxycarbonyl) propyl amide hydrochloride</td>
<td>0.41</td>
<td>Chloroform: methanol: acetic acid =10:2:1) 8.25-8.15 (2H, m), 7.95 (2H, d, J= 8Hz), 7.80-7.60 (4H, m), 7.55 (2H, d, J=8Hz), 7.35 (1H, br), 4.55 (1H, dd, J=8.5, 6Hz), 4.20 (2H, q, J= 7.5Hz), 4.15 (2H, q, J=7.5Hz), 2.50 (2H, t, J=7Hz), 2.40-2.00 (2H, m), 2.15 (3H, s), 1.30 (3H, t, J= 7.5Hz), 1.25 (3H, t, J=7.5Hz).</td>
</tr>
<tr>
<td>2(ii)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino phenoxy carbonyl) phenylpropionic acid -N-1-(S), 3-bis (ethoxycarbonyl) propyl amide acetic acid</td>
<td>0.35</td>
<td>Chloroform: methanol: acetic acid =10:1:1) 8.11 (2H, d, J=8.4Hz), 7.92 (2H, d, J=8.8Hz), 7.52 (2H, d, J= 8.8Hz), 7.45 (2H, d, J=8.4Hz), 4.20 (1H, m), 4.16 (2H, q, J= 7.2Hz), 4.10 (2H, q, J=7.2Hz), 3.05 (2H, t, J=7Hz), 2.62 (2H, t, J=7.2Hz), 2.23 (2H, m), 2.20-1.80 (2H, m), 1.93 (3H, s), 1.25 (3H, t, J=7.2Hz), 1.23 (3H, t, J=7.2Hz).</td>
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Table 4 (continued)

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<td>2(jj)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(2-ethoxycarbonylethyl)-N-isopropylamide acetate</td>
<td>0.40 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.57 (2H, d, J=9.0Hz), 7.53 (2H, d, J=9.0Hz), 6.60 (1H, s), 4.29 (1H, m), 4.25 (2H, q, J=7.0Hz), 3.60 (2H, t, J=7.0Hz), 2.69 (2H, t, J=7.0Hz), 2.14 (3H, s), 1.27 (6H, d, J=7.0Hz).</td>
</tr>
<tr>
<td>2(kk)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1,2-bis-(ethoxycarbonyl)-ethyl)-N-3-ethoxycarbonyl-2-propenylamide acetate</td>
<td>0.47 (chloroform: methanol =8:2)</td>
<td>8.23 (2 H, d, J = 8 Hz), 7.93 (2 H, d, J = 8 Hz), 7.65-7.50 (4 H, m), 7.13-6.80 (2 H, m), 6.30-6.10 (1 H, m), 4.60-4.00 (3 H, m), 4.27-4.10 (6 H, m), 3.01-2.84 (2 H, m), 2.13 (3 H, bs), 1.35-1.13 (9 H, m).</td>
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</table>
Table 4 (continued)

<table>
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<tr>
<th>Ex. No.</th>
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<tr>
<td>2(II)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy)carbonyl-α-methylcinnamic acid N-(1-(S),3-bis(ethoxycarbonyl)propyl)-N-allyl amide acetate</td>
<td>0.38 (chloroform: methanol: acetic acid = 20:2:1)</td>
<td>8.22 (2H, d, J=8.5Hz), 7.93 (2H, d, J=8.5Hz), 7.58 (2H, d, J=8.5Hz), 7.53 (2H, d, J=8.5Hz), 6.69 (1H, s), 6.10-5.80 (1H, m), 5.50-5.10 (2H, m), 4.20 (4H, q, J=7.5Hz), 4.30-3.80 (3H, m), 2.60-2.35 (4H, m), 2.13 (3H, s), 1.92 (3H, s), 1.30 (6H, t, J=7.5Hz).</td>
</tr>
</tbody>
</table>
Reference Example 15

p-Methoxycarbonyl-α-methylcinnamic acid t-butyl ester

By the same procedure as Reference Example 1, using p-methoxycarbonylbenzaldehyde instead of p-benzyloxy-carbonylbenzaldehyde, the title compound having the following physical data was given:
TLC : Rf 0.67 (hexane : ethyl acetate = 4 : 1).

Reference Example 16

p-Carboxy-α-methylcinnamic acid t-butyl ester

By the same procedure as Reference Example 7, using the compound prepared in Reference Example 15, the title compound having the following physical data was given:
TLC : Rf 0.42 (ethyl acetate).

Reference Example 17

p-(p-Amidinophenoxy carbonyl)-α-methylcinnamic acid t-butyl ester

By the same procedure as Example 1, using the compound prepared in Reference Example 16, the title compound having the following physical data was given:
TLC : Rf 0.41 (chloroform : methanol : acetic acid=10 : 2 : 1).
Reference Example 18

\[ p-(p\text{-Aminophenoxy})-\alpha\text{-methylcinnamic acid hydrochloride} \]

\[ \begin{array}{c}
\text{HN} \\
\text{H}_2\text{N} \\
\text{O} \\
\text{C} \\
\text{OH} \\
\text{CH}_3
\end{array} \]

To a solution of the compound prepared in Reference Example 17 (4.79 g) in chloroform (100 ml), were added successively a solution of 4N hydrochloric acid in ethyl acetate (50 ml) and dioxane (10 ml). The mixture was stirred for two hours at room temperature and evaporated. The residue thus obtained was washed with ether, filtered and then dried to give the title compound (4.15 g) having the following physical data:

TLC: Rf 0.38 (chloroform : methanol : acetic acid=10 : 2 : 1);
NMR: 6 8.21 (2H, d, J=8.0 Hz), 7.95 (2H, d, J=8.0 Hz), 7.75 (1H, s), 7.60 (2H, d, J=8.0 Hz), 7.54 (2H, d, J=8.0 Hz), 2.12 (3H, s).

Example 3

\[ p-(p\text{-Aminophenoxy})\text{-cinnamoyl})-\alpha\text{-methylcinnamic acid N-t-butoxycarbonylmethyl-N-allylamine acetate} \]

\[ \begin{array}{c}
\text{HN} \\
\text{H}_2\text{N} \\
\text{O} \\
\text{C} \\
\text{O} \\
\text{N} \\
\text{CH}_3
\end{array} \text{CH}_2\text{CO}_2\text{C(CH}_3\text{)_3} \\
\cdot \text{CH}_3\text{COOH}
\]

To a suspension of the compound prepared in Reference Example 18 (3.2 g) in a mixture of pyridine (50 ml) and dimethylformamide (5 ml), were added successively a solution of N-t-butoxycarbonylmethyl-N-allylamine (1.52 g) in pyridine (5 ml) and a solution of 1,3-dicyclohexylcarbodiimide (2.20 g) in pyridine (5 ml). The mixture was stirred overnight at room temperature and evaporated. The residue thus obtained was purified by silica gel column chromatography (chloroform : methanol : acetic acid=50 : 2 : 1→40 : 2 : 1→30 : 2 : 1→10 : 2 : 1) to give the title compound (683 mg) having the following physical data:

TLC: Rf 0.36 (chloroform : methanol : acetic acid=10 : 2 : 1).

Example 3(a)–3(g)

By the same procedure as Example 3, using, as a starting material, the compound prepared in Reference Example 18, and further using a corresponding amine instead of N-t-butoxycarbonylmethyl-N-allylamine, the compounds of the present invention shown in Table 5 were given.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Name</th>
<th>Structure</th>
<th>NMR</th>
<th>TLC (Rf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3(a)</td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylaminocarbonylmethyl-N-tert-butyloxycarbonylamide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>8.20 (2H, d, J=7Hz), 7.95 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.65 (2H, m), 4.40-4.15 (4H, m), 2.00 (3H, s), 1.90 (3H, s), 1.30 (3H, m), 1.00 (6H, d, J=7Hz).</td>
<td>0.378 (chloroform: methanol: acetic acid =100:2:1)</td>
</tr>
<tr>
<td>3(b)</td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylaminocarbonylmethyl-N-tert-butyloxycarbonylamide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>8.20 (2H, d, J=7Hz), 7.95 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.65 (2H, m), 4.40-4.15 (4H, m), 2.00 (3H, s), 1.90 (3H, s), 1.30 (3H, m), 1.00 (6H, d, J=7Hz).</td>
<td>0.378 (chloroform: methanol: acetic acid =100:2:1)</td>
</tr>
<tr>
<td>3(c)</td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylaminocarbonylmethyl-N-tert-butyloxycarbonylamide</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>8.20 (2H, d, J=7Hz), 7.95 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.65 (2H, m), 4.40-4.15 (4H, m), 2.00 (3H, s), 1.90 (3H, s), 1.30 (3H, m), 1.00 (6H, d, J=7Hz).</td>
<td>0.378 (chloroform: methanol: acetic acid =100:2:1)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
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<tr>
<td>3(d)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methyl cinnamic acid N-allyl-N-2-ethoxy carbonyl ethylamide acetate</td>
<td>0.556</td>
<td>8.20 (2H, d, J=7.5 Hz), 7.90 (2H, d, J=7.5 Hz), 7.60 - 7.50 (4H, m), 6.65 (1H, br s), 5.90 (1H, m), 5.40 - 5.20 (2H, m), 4.20 - 4.05 (4H, m), 3.75 (2H, m), 2.70 (2H, m), 2.10 (3H, s), 1.95 (3H, s), 1.25 (3H, m).</td>
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<td>3(e)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methyl cinnamic acid N-2-ethoxy carbonyl ethyl-N-propylamide acetate</td>
<td>0.569</td>
<td>8.25 (2H, d, J=7.5 Hz), 7.95 (2H, d, J=7.5 Hz), 7.60 -7.50 (4H, m), 6.60 (1H, br s), 4.15 (2H, q, J=7 Hz), 3.75 (2H, m), 3.45 (2H, m), 2.70 (2H, m), 2.15 (3H, s), 1.95 (3H, s), 1.70 (2H, m), 1.25 (3H, m), 0.95 (3H, m).</td>
</tr>
<tr>
<td>3(f)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methyl cinnamic acid N-2-ethoxy carbonyl ethyl-N-ethoxy carbonyl methylamide acetate</td>
<td>0.50</td>
<td>8.25 (2H, br d, J=8 Hz), 7.95 (2H, d, J=8 Hz), 7.80 - 7.40 (4H, m), 6.70 (1H, m), 4.45 - 4.05 (6H, m), 3.80 (2H, m), 2.70 (2H, t, J= 7.5 Hz), 2.20 - 2.00 (3H, m), 1.95 (3H, s, CH3COOH), 1.25 (6H, m).</td>
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</tbody>
</table>
Table 5 (continued)

<table>
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<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3(g)</td>
<td>![Structure Image]</td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-cyclohexyl-N-ethoxycarbonylmethylamide acetate</td>
<td>0.55</td>
<td>8.25 (2H, d, J=9.5 Hz), 7.90 (2H, d, J=8 Hz), 7.60-7.50 (4H, m), 6.65 (1H, br.s), 4.25-4.05 (4H, m), 3.80 (1H, m), 2.15 (3H, br.s), 2.00-1.80 (4H, m), 1.75-1.05 (6H, m).</td>
</tr>
</tbody>
</table>
Example 4

p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-carboxymethyl-N-allylamide methanesulfonate

\[
\begin{align*}
\text{HN} & \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{N} \\
\text{H}_2\text{N} & \quad \text{C} \quad \text{CH}_3 \\
& \quad \text{COOH}
\end{align*}
\]

\cdot \text{CH}_3\text{SO}_3\text{H}

To a solution of the compound prepared in Example 3 (683 mg) in chloroform (10 ml), was added a solution of 4N hydrochloric acid in ethyl acetate (6 ml). The mixture was stirred for one hour at room temperature, and then evaporated.

The residue thus obtained was purified by silica gel column chromatography (chloroform : methanol : acetic acid=50 : 2 : 1→40 : 2 : 1→30 : 2 : 1→10 : 2 : 1). To the purified compound thus obtained, was added methanesulfonic acid. The mixture was stirred for 10 min. at room temperature and evaporated. The residue was crystallized from a mixture of ether and acetone. The crystals thus obtained was collected by filtration and dried to give the title compound (286 mg) having the following physical data:

TLC : Rf 0.32 (chloroform : methanol : acetic acid=10 : 2 : 1);
NMR : δ 8.20 (2H, d, J=8.0 Hz), 7.95 (2H, d, J=8.0 Hz), 7.58 (2H, d, J=8.0 Hz), 7.52 (2H, d, J=8.0 Hz), 6.80-6.62 (1H, ml, 6.78-6.00 (1H, m), 5.40-5.20 (2H, m), 4.20-4.05 (4H, m), 2.70 (6H, s), 2.19-2.05 (3H, m).

Example 4(a)

p-(p-Aminophenoxy carbonyl)-α-methylcinnamic acid N-3-carboxypropyl-N-allylamide methanesulfonate

\[
\begin{align*}
\text{HN} & \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{N} \\
\text{H}_2\text{N} & \quad \text{C} \quad \text{CH}_3 \\
& \quad \text{COOH}
\end{align*}
\]

\cdot \text{CH}_3\text{SO}_3\text{H}

By the same procedure as a series of reactions of Example 3→Example 4, using, as a starting material, the compound prepared in Reference Example 18, and further using a corresponding amine, the title compound having the following physical data was given.

TLC : Rf 0.48 (chloroform : methanol : acetic acid=10 : 2 : 1);
NMR : δ 8.21 (2H, d, J=8.0 Hz), 7.90 (2H, d, J=8.0 Hz), 7.58 (2H, d, J=8.0 Hz), 7.55 (2H, d, J=8.0 Hz), 6.62 (1H, s), 6.02-5.79 (1H, m), 5.38-5.20 (2H, m), 4.10 (2H, d, J=5.0 Hz), 3.50 (2H, t, J=7.5 Hz), 2.75 (3H, s, MeSO_3 H), 2.48-2.30 (2H, m), 1.98 (2H, t, J=7.5, 5.0 Hz).
Example 4(b)

\[ \text{p-(p-Aimidophenoxycarbonyl)-\textalpha-methylcinnamic acid N-(1-(S)-ethoxycarbonyl-3-carboxy)propylamide hydrochloride} \]

By the same procedure as a series of reactions of Example 3→Example 4, using, as a starting material, the compound prepared in Reference Example 18, and further using a corresponding amine, the title compound having the following physical data was given.

TLC: Rf 0.32 (chloroform: methanol: acetic acid=10 : 2 : 1);

NMR: δ 8.22 (2H, d, J=9.0Hz), 7.93 (2H, d, J=9.0Hz), 7.60 (2H, d, J=9.0Hz), 7.54 (2H, d, J=9.0Hz), 7.35 (1H, s), 4.52 (1H, dd, J=9.0Hz, 5.0Hz), 4.21 (2H, q, J=7.0Hz), 2.48 (2H, t, J=7.0Hz), 2.35-1.97 (2H, m), 2.13 (3H, s), 1.26 (3H, t, J=7.0Hz).

Example 5(a)~5(gg)

By the same procedure as a series of reactions of Reference Example 2→Example 3 or Reference Example 9→Reference Example 2 (and then purified by silica gel column chromatography (chloroform: methanol: acetic acid = 50 : 2 : 1→40 : 2 : 1→30 : 2 : 1→10 : 2 : 1), and further subjected to salt-exchange reaction, if necessary), using, as a starting material, the compound prepared in Reference Example 17, and further using a corresponding amine, the compounds of the present invention shown in Table 6 were given.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5(a)</td>
<td><img src="image_url" alt="Structure Image" /></td>
<td>p-(p-amidino-phenoxycarbonyl)- ( \alpha )-methylcinnamic acid N-methyl-N-(2-ethoxycarbonyl)ethyamide acetate</td>
<td>0.33 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, ( J = 8 ) Hz), 7.90 (2H, d, ( J = 7 ) Hz), 7.65 (2H, m), 6.75 (1H, m), 4.20 (4H, m), 2.70 (2H, t, ( J = 6 ) Hz), 2.20-2.05 (3H, m), 1.25 (3H, m).</td>
</tr>
<tr>
<td>5(b)</td>
<td><img src="image_url" alt="Structure Image" /></td>
<td>p-(p-amidino-phenoxycarbonyl)- ( \alpha )-methylcinnamic acid N-ethoxycarbonyl-N-(2-carboxyethyl)amide acetate</td>
<td>0.46 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, ( J = 8 ) Hz), 7.90 (2H, d, ( J = 7 ) Hz), 7.65-7.50 (4H, m), 6.70 (1H, m), 4.60-4.15 (4H, m), 2.65 (2H, m), 2.15 (3H, m).</td>
</tr>
<tr>
<td>5(c)</td>
<td><img src="image_url" alt="Structure Image" /></td>
<td>p-(p-amidino-phenoxycarbonyl)- ( \alpha )-methylcinnamic acid N-ethyl-N-(1-((S)-carboxy-3-ethoxypropyl)amide trifluoroacetate</td>
<td>0.27 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.22 (2H, d, ( J = 9.0 ) Hz), 7.93 (2H, d, ( J = 9.0 ) Hz), 7.60 (2H, d, ( J = 9.0 ) Hz), 7.54 (2H, d, ( J = 9.0 ) Hz), 7.38 (1H, s), 4.53 (1H, dd, ( J = 9.0 ) Hz), 7.00 (5H), 4.14 (2H, t, ( J = 7.0 ) Hz), 2.48 (2H, m), 2.15 (3H, s), 1.25 (3H, t, ( J = 7.0 ) Hz).</td>
</tr>
</tbody>
</table>

**Table 6**
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
</tr>
</thead>
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<td>5(d)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-α-methyl cinnamic acid N-isopropyl-N-carboxymethylamide trifluoroacetate</td>
<td>0.26 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.22-8.14 (2H, m), 7.95-7.88 (2H, m), 7.60-7.50 (4H, m), 6.77 (1H, s), 4.73-4.60 and 4.38-4.24 (1H, m), 3.91 and 3.88 (2H, m), 2.18 and 2.07 (3H, m), 1.23 (6H, d, J = 7.0Hz).</td>
</tr>
<tr>
<td>5(e)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-α-methyl cinnamic acid N-isobutyl-N-carboxymethylamide trifluoroacetate</td>
<td>0.28 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.23-8.15 (2H, m), 7.94-7.88 (2H, m), 7.59-7.49 (4H, m), 6.75 and 6.69 (1H, m), 4.02 and 4.01 (2H, m), 3.35 (2H, d, J = 8.0Hz), 2.15 and 2.10 (3H, m), 2.10-1.95 (1H, m), 0.97-0.90 (6H, m).</td>
</tr>
<tr>
<td>5(f)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-α-methyl cinnamic acid N-propyl-N-carboxymethylamide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20-8.15 (2H, m), 7.91 (2H, d, J = 9.0Hz), 7.60-7.49 (4H, m), 6.74 (1H, s), 4.00 (2H, s), 3.46 (2H, t, J = 7.0Hz), 2.16 and 2.10 (3H, m), 1.73-1.60 (2H, m), 0.97 (3H, t, J = 7.0Hz).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
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<tr>
<td>5(g)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-((1-(R)-ethoxycarbonyl-3-carboxy)propyl)-amide acetate</td>
<td>0.34</td>
<td>8.22 (2H, d, J=9.0Hz), 7.93 (2H, d, J=9.0Hz), 7.60 (2H, d, J=9.0Hz), 7.54 (2H, d, J=9.0Hz), 7.37 (1H, s), 4.54 (1H, dd, J=9.0Hz, 5.0Hz), 4.21 (2H, q, J=7.0Hz), 2.45 (2H, t, J=7.0Hz), 2.34-2.00 (2H, m), 2.15 (3H, s), 1.30 (3H, t, J=7.0Hz).</td>
</tr>
<tr>
<td>5(h)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-allyl-N-((1- (S)-ethoxycarbonyl-2-carboxyethyl)-amide acetate</td>
<td>0.35</td>
<td>8.20 (2H, d, J=9.0Hz), 7.92 (2H, d, J=9.0Hz), 7.56 (2H, d, J=9.0Hz), 7.37 (1H, d, J=9.0Hz), 6.69 (1H, br-s), 6.04-5.89 (1H, m), 5.45-5.20 (2H, m), 4.68 (1H, m), 4.22-4.09 (4H, m), 3.28-3.10 (1H, m), 2.71-2.60 (1H, m), 2.14 (3H, s), 1.28 (3H, t, J=7.0Hz).</td>
</tr>
<tr>
<td>5(i)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-allyl-N-(1-(S),2-dicarboxyethyl)-amide acetate</td>
<td>0.11</td>
<td>8.10 (2H, d, J=9.0Hz), 7.85 (2H, d, J=9.0Hz), 7.56 (2H, d, J=9.0Hz), 7.50 (2H, d, J=9.0Hz), 6.80 and 6.74 (1H, m), 6.04-5.90 (1H, m), 5.33-5.09 (2H, m), 4.65, 4.45, 4.38 and 4.16 (2H, m), 3.78-3.65 (1H, m), 3.22-3.04 (1H, m), 2.80-2.66 (1H, m), 2.18 (3H, s).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
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<tr>
<td>5(j)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-carboxymethyl-N-ethoxycarbonylmethylamidine acetate</td>
<td>0.19 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.75 (1H, m), 4.40-4.15 (6H, m), 2.15 (3H, s), 2.00 (3H, s, CH3COOH), 1.20 (3H, t, J=7Hz).</td>
</tr>
<tr>
<td>5(k)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(2-carboxyethyl)-N-(2-ethoxycarbonyl-ethyl)amide methanesulfonate</td>
<td>0.13 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz), 6.60 (1H, br.), 4.15 (2H, q, J=7Hz), 3.85-3.65 (4H, m), 2.75-2.60 (4H, m), 2.70 (3H, s), 2.15 (3H, s), 1.25 (3H, t, J=7Hz).</td>
</tr>
<tr>
<td>5(l)</td>
<td><img src="image3" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-2,4-hexadienyl-N-carboxymethylamide methanesulfonate</td>
<td>0.30 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.75 (1H, m), 6.30-6.00 (2H, m), 5.85-5.50 (2H, m), 4.20-4.10 (4H, m), 2.75 (3H, s), 2.15 (3H, m), 1.80 (3H, d, J=8Hz).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
<td>NMR</td>
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<tr>
<td>5(m)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N,N-bis-(2-carboxyethyl)amide methanesulfonate</td>
<td>0.58 (chloroform: methanol: acetic acid = 3:1:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz), 6.60 (1H, br.), 3.90-3.65 (4H, br.), 2.70 (3H, s), 2.70-2.60 (4H, m), 2.15 (3H, s).</td>
</tr>
<tr>
<td>5(n)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-(1-(S),3-dicarboxypropyl)amide acetate</td>
<td>0.47 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.21 (2H, d, J=9.0Hz), 7.90 (2H, d, J=9.0Hz), 7.57 (2H, d, J=9.0Hz), 7.50 (2H, d, J=9.0Hz), 7.42 (1H, s), 4.52 (1H, dd, J=7.0Hz, 5.0Hz), 2.53-2.45 (2H, m), 2.37-2.08 (2H, m), 2.16 (3H, s), 2.02 (3H, s, CH3COOH).</td>
</tr>
<tr>
<td>5(o)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-allyl-N-(1-(S)-carboxy-2-ethoxy carbonyl ethyl)amide acetate</td>
<td>0.23 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.80 (1H, m), 5.95 (1H, m), 5.30-5.00 (2H, m), 4.60 (1H, m), 4.15 (2H, m), 3.30-2.70 (2H, m), 2.20 (3H, m), 2.00 (3H, s, CH3COOH), 1.25 (3H, m).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
<td>NMR</td>
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<tr>
<td>5(p)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1-carboxyl-1-ethoxycarbonyl-methyl)-N-(3-ethoxycarbonyl-propyl)amide acetate</td>
<td>0.23 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.21 (2H, d, J=8 Hz), 7.92 (2H, d, J=8 Hz), 7.5-7.6 (4H, m), 6.61 and 6.76 (1H, s, rotamer), 4.95 (1H), 4.0-4.3 (4H, m), 3.5-3.7 (2H, m), 2.35 (2H, t, J=7 Hz), 1.9-2.2 (5H, m), 1.90 (3H, s), 1.1-1.4 (6H, m).</td>
</tr>
<tr>
<td>5(q)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino-phenoxycarbonyl)-α-methylcinnamic acid N-(1,1-bis-(ethoxycarbonyl)-methyl)-N-(3-carboxypropyl)amide acetate</td>
<td>0.38 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>(CD3OD + CDCl3) 8.30-7.30 (8H, m, aromatic, 2 rotamers), 6.72 and 6.61 (1H, s, olefinic, 2 rotamers), 4.40-4.00 (4H, m, COOCH2 X 2, 2 rotamers), 3.70-3.40 (3H, m, NCH2 and NCHCOO, 2 rotamers), 2.40-1.80 (10H, m), 1.44-1.10 (6H, m, CH3 x 2, 2 rotamers).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
<td>NMR</td>
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<tr>
<td>5(r)</td>
<td><img src="image" alt="Structure 5(r)" /></td>
<td>p-(p-amidinophenoxy carbonyl)-(\alpha)-methylcinnamic acid N-carboxy-methyl-N-phenylmethylamide acetate</td>
<td>0.36 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=9Hz), 7.60-7.45 (4H, m), 6.75 (1H, m), 4.75 (2H, m), 4.10 (2H, brs), 2.70 (3H, s), 2.15 (3H, s).</td>
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<td>5(s)</td>
<td><img src="image" alt="Structure 5(s)" /></td>
<td>p-(p-amidinophenoxy carbonyl)-(\alpha)-methylcinnamic acid N-carboxy-methyl-N-1-propylbutylamide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.23 (2H, d, J=8Hz), 7.91 (2H, d, J=8Hz), 7.56 (4H, t, J=8Hz), 6.65 (1H, m), 4.20 (1H, m), 3.98 (2H, s), 2.10 (3H, m), 1.90 (3H, s), 1.60-1.10 (8H, m), 0.92 (6H, t, J=7Hz).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
<td>NMR</td>
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<td>5(t)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-carboxymethyl-N-methylamide acetate</td>
<td>0.25 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=7Hz), 7.96 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.65 (1H, m), 4.20 (2H, m), 2.80 (3H, br), 2.15 (3H, m), 1.95 (3H, s).</td>
</tr>
<tr>
<td>5(u)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-carboxymethyl-N-ethylamide acetate</td>
<td>0.23 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=9Hz), 7.60-7.50 (4H, m), 6.65 (1H, m), 4.20 (2H, m), 3.45 (2H, m), 2.15 (3H, m), 1.95 (3H, s), 0.95 (3H, m).</td>
</tr>
<tr>
<td>5(vl)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-carboxymethyl-N-butylamide acetate</td>
<td>0.29 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 7.56 (4H, t, J=8Hz), 6.70-6.60 (1H, m), 4.22 (2H, q, J=7Hz), 4.15 (2H, s), 3.49 (2H, t, J=7Hz), 2.10 (3H, s), 1.93 (3H, s), 1.80-1.50 (2H, m), 1.50-1.20 (2H, m), 0.93 (3H, br, J=7Hz).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (Rf)</td>
<td>NMR</td>
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<tr>
<td>5(w)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-carboxy-methyl-N-3-methylbutylamide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=7Hz), 7.95 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.65 (1H, m), 4.20 (2H, m), 3.50 (2H, m), 2.15 (3H, m), 1.95 (3H, s), 1.70-1.40 (3H, m), 0.90 (6H, m).</td>
</tr>
<tr>
<td>5(x)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-carboxy-methyl-N-hexylamide acetate</td>
<td>0.25 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.22 (2H, d, J=8Hz), 7.92 (2H, d, J=8Hz), 7.56 (4H, t, J=8Hz), 6.70-6.60 (1H, m), 4.15 (2H, s), 3.49 (2H, t, J=7Hz), 2.10 (3H, m), 1.93 (3H, s), 1.80-1.50 (2H, m), 1.50-1.20 (6H, m), 1.00-0.80 (3H, br).</td>
</tr>
<tr>
<td>5(y)</td>
<td><img src="image" alt="Structure" /></td>
<td>p-(p-amidinophenoxy carbonyl)-α-methylcinnamic acid N-carboxy methyl-N-cyclopropylamide acetate</td>
<td>0.25 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=7Hz), 7.95 (2H, d, J=7Hz), 7.65-7.50 (4H, m), 6.85 (1H, m), 4.20 (2H, s), 3.00 (1H, br), 2.20 (3H, s), 1.95 (3H, s), 0.95-0.90 (4H, m).</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>TLC (RI)</td>
<td>NMR</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>------</td>
<td>----------</td>
<td>-----</td>
</tr>
<tr>
<td>5(z)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-α-methylcinnamic acid N-carboxy-methyl-N-cyclobutylamide acetate</td>
<td>0.22 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.25 (2H, d, J=9.5Hz), 7.90 (2H, d, J=8Hz), 7.60-7.50 (4H, m), 6.65 (1H, brs), 4.25-4.05 (3H, m), 2.15 (3H, brs), 1.95 (3H, s), 2.00-1.05 (6H, m).</td>
</tr>
<tr>
<td>5(aa)</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-α-methylcinnamic acid N-carboxy-methyl-N-cyclopentylamide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.25 (2H, d, J=9.5Hz), 7.90 (2H, d, J=8Hz), 7.60-7.50 (4H, m), 6.65 (1H, brs), 4.25-4.05 (2H, m), 3.80 (1H, m), 2.15 (3H, brs), 1.95 (3H, s), 2.00-1.80 (4H, m), 1.75-1.05 (4H, m).</td>
</tr>
<tr>
<td>5(bb)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>p-(p-amidino-phenoxy carbonyl)-α-methylcinnamic acid N-carboxy-methyl-N-cyclohexylamide acetate</td>
<td>0.25 (chloroform: methanol: acetic acid = 10:2:1)</td>
<td>8.25 (2H, d, J=9.5Hz), 7.90 (2H, d, J=7Hz), 7.60-7.50 (4H, m), 6.85 (1H, m), 4.25-4.05 (2H, m), 3.80 (1H, m), 2.15 (3H, brs), 1.95 (3H, s), 2.00-1.80 (4H, m), 1.75-1.05 (6H, m).</td>
</tr>
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</table>
Table 6 (continued)

<table>
<thead>
<tr>
<th>Ex. No.</th>
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<tr>
<td>5(c)</td>
<td><img src="image" alt="Structure Image" /></td>
</tr>
<tr>
<td>5(dd)</td>
<td><img src="image" alt="Structure Image" /></td>
</tr>
</tbody>
</table>

NMR.

- **5(c)**:
  - 8.20 (2H, d, J=1HHz), 7.95 (2H, dd, J=1Hz), 7.60-7.50 (2H, m), 6.65 (1H, m), 2.75 (2H, m), 2.15 (3H, s), 1.95 (3H, s).

- **5(dd)**:
  - 8.20 (2H, d, J=8Hz), 7.90 (2H, d, J=8Hz), 7.60-7.50 (2H, m), 6.65 (1H, m), 2.75 (2H, m), 2.15 (3H, m), 1.95 (3H, s), 0.95 (2H, m).

TLC (RI).

- **5(c)**: 0.25 (chloroform:methanol:acetic acid =10:2:1).
- **5(dd)**: 0.26 (chloroform:methanol:acetic acid =10:2:1).

Name.

- **5(c)**: \(\text{p-(p-amino-phenoxycarbonyl)-\alpha-methylcinnamic acid N-2-carboxy-ethyl-N-methylamide acetate}\)
- **5(dd)**: \(\text{p-(p-amino-phenoxycarbonyl)-cinnamic acid N-2-carboxy-ethyl-N-ethylamide acetate}\)
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>TLC (Rf)</th>
<th>NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5(ee)</td>
<td><img src="image1" alt="Structure" /></td>
<td>p-(p-amidino- phenoxy carbonyl)- ( \alpha )-methylcinnamic acid N-2-carboxy-ethyl-N-propylamide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.25 (2H, d, J=7Hz), 7.95 (2H, d, J=7Hz), 7.55 (4H, m), 6.60 (1H, m), 3.75 (2H, m), 3.50 (2H, m), 2.70 (2H, m), 2.15 (3H, s), 1.95 (3H, s), 1.70 (2H, m), 0.95 (3H, m).</td>
</tr>
<tr>
<td>5(ff)</td>
<td><img src="image2" alt="Structure" /></td>
<td>p-(p-amidino- phenoxy carbonyl)- ( \alpha )-methylcinnamic acid N-2-carboxy-ethyl-N-1-methyl-cinnamamide acetate</td>
<td>0.28 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=8Hz), 7.95 (2H, d, J=8Hz), 7.58 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz), 6.62 (1H, s), 4.40-4.20 (1H, m), 3.60 (2H, brt, J= 7.5Hz), 2.68 (2H, t, J=7.5Hz), 2.15 (3H, s), 1.92 (3H, s), 1.28 (6H, d, J=6Hz).</td>
</tr>
<tr>
<td>5(gg)</td>
<td><img src="image3" alt="Structure" /></td>
<td>p-(p-amidino- phenoxy carbonyl)- ( \alpha )-methylcinnamic acid N-2-carboxy-ethyl-N-allylalamide acetate</td>
<td>0.26 (chloroform: methanol: acetic acid =10:2:1)</td>
<td>8.20 (2H, d, J=7.5Hz), 7.90 (2H, d, J=7.5Hz), 7.60-7.50 (4H, m), 6.65 (1H, br), 5.90 (1H, m), 5.40-5.20 (2H, m), 4.20-4.05 (2H, m), 3.75 (2H, m), 2.70 (2H, m), 2.10 (3H, s), 1.95 (3H, s).</td>
</tr>
</tbody>
</table>
Formulation Example

Formulation Example 1

The following components were admixed in conventional manner and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

- p-(p-Amidinophenoxy carbonyl)-α-methylcinnamic acid N-allyl-N-ethoxycarbonyl methyl amide acetate 5.0 g
- Carboxymethyl cellulose calcium 0.2 g (disintegrating agent)
- Magnesium stearate (lubricating agent) 0.1 g
- Microcrystalline cellulose 4.7 g

Formulation Example 2

The following components were admixed in conventional manner. The solution was sterilized in conventional manner, placed 5 ml portions into ampoules and freeze-dried to obtain 100 ampoules each containing 20 mg of active ingredient.

- p-(p-Amidinophenoxy carbonyl)-α-methylcinnamic acid N-allyl-N-ethoxycarbonylmethyl amide acetate 2 g
- Anhydrous citric acid 200 mg
- Distilled water 500 ml

Claims

1. A compound of the formula (I):

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{NH} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{A} & \quad \text{R}_3
\end{align*}
\]

wherein 

(i) hydrogen,  
(ii) C1-4 alkyl,  
(iii) C1-4 alkoxy,  
(iv) C2-5 acyl,  
(v) halogen,  
(vi) nitro,  
(vii) benzoyl or  
(viii) COOR^\text{4} \quad \text{(in which R^4 is C1-3 alkyl)};

A is a bond, C1-4 alkyene or

\[
\begin{align*}
\text{C} = \text{C} \\
\text{R}_5 & \quad \text{R}_6
\end{align*}
\]

(in which R^5 and R^6 each independently, is hydrogen or C1-4 alkyl);
(i) \( R^3 \) is
\[
\text{CON} - R^7 - R^8
\]

(ii) \( R^3 \) is
\[
\text{CON} - R^9 - R^7 - R^8
\]

or

(iii) \( R^3 \) is
\[
\text{CON} - R^{10}
\]

(in which \( R^7 \) and \( R^8 \) each, independently, is

1. hydrogen,
2. phenyl,
3. C7-10 phenylaikyl,
4. phenyl or C7-10 phenylaikyl each of which is substituted by one or two substituents selected from C1-4 alkyl, halogen and \( R^{11} \)-COOR^{12}

(in which \( R^{11} \) is

(a) a bond,
(b) C1-8 alkyene,
(c) C2-8 alkenylene or
(d) C2-8 alkynylene, and

\( R^{12} \) is

(a) hydrogen,
(b) C1-4 alkyl,
(c) C7-10 phenylaikyl,
(d) phenyl,
(e) allyl or
(f) propargyl).

(5) C1-10 alkyl,
(6) C2-10 alkenyl having one to three double bonds,
(7) C2-10 alkynyl having one or two triple bonds,
(8) \( R^{11a} \)-COXR^{12}

(in which \( R^{11a} \) is

(a) a bond,
(b) C1-8 alkyene,
(c) C2-8 alkenylene in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur and
phenylene,
(d) C₂-₆ alkenylene,
(e) C₄-₆ alkenylene in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur
and phenylene,
(f) C₂-₈ alkenylene, or
(g) C₄-₈ alkynylene in which one or two carbon atoms in the main chain are replaced by sulfur, or sulfur
and phenylene,

X is oxygen or -NH₂, and R¹² is the same meaning as hereinbefore defined),
(9) C₁-₄ alkyl which is substituted by a 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen, or
(10) C₃-₇ cycloalkyl);

R⁹ is

1) hydrogen,
2) C₁-₈ alkyl,
3) C₇-₁₀ phenylalkyl,
4) C₂-₁₀ alkenyl having one to three double bonds,
5) C₂-₁₀ alkynyl having one or two triple bonds,
6) R¹¹-COOR¹² (in which R¹¹ and R¹² are the same meaning as hereinbefore defined), or
7) C₃-₇ cycloalkyl;

N

is 4-7 membered, mono-cyclic hetero ring containing one or two nitrogen;
R¹⁰ is

1) hydrogen,
2) C₇-₁₀ phenylalkyl or
3) COOR¹³ (in which R¹³ is hydrogen, C₁-₄ alkyl or C₇-₁₀ phenylalkyl);

with the proviso that
(i) both R⁷ and R⁸ do not represent hydrogen at the same time, and
(ii) when at least one group in R⁷, R⁸ and R⁹ represents the group containing t-butyl ester, the other groups
do not represent the group containing carboxy;

or an acid-addition salt thereof.

2. A compound according to claim 1, wherein R³ is

\[
(i) \text{CON}_{\text{R}^7}^{\text{R}^8}
\]

or

(iii)
in which the various symbols are as defined in claim 1.

3. A compound according to claim 1, wherein $R^3$ is

$$
\begin{array}{c}
\text{(iii)} \\
\text{CON} \\
\text{R^9} \\
\text{R^8} \\
\end{array}
$$

in which the various symbols are as defined in claim 1.

4. A compound according to claim 3, wherein

$$
\begin{array}{c}
\text{N} \\
\end{array}
$$

is 4-7 membered, mono-cyclic hetero ring containing one nitrogen.

5. A compound according to claim 3, wherein

$$
\begin{array}{c}
\text{N} \\
\end{array}
$$

is 4-7 membered, mono-cyclic hetero ring containing two nitrogen.

6. A compound according to claim 2, wherein one of $R^7$ and $R^8$ is

(9) C1-4 alkyl which is substituted by a 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen.

7. A compound according to claim 2, wherein one of $R^7$ and $R^8$ is

(2) phenyl,
(3) C7-10 phenylalkyl,
(4) phenyl or C7-10 phenylalkyl which is substituted by one or two substituents optionally selected from C1-4 alkyl, halogen and
$R^11$-COOR$^{12}$
(in which $R^{11}$ and $R^{12}$ are as defined in claim 1)
(5) $R^{11a}$-COX$R^{12a}$
(in which $R^{11a}$

(6) C2-8 alkenylene in which two carbon atoms in the main chain are replaced by sulfur and phenylene,
(7) C4-8 alkenylene in which two carbon atoms in the main chain are replaced by sulfur and phenylene,
(8) C4-8 alkynylene in which two carbon atoms in the main chain are replaced by sulfur and phenylene,
8. A compound according to claim 2, wherein one of R^7 and R^8 is
  5  (5) C1-10 alkyl,
  (6) C2-10 alkenyl having one to three double bonds,
  (7) C2-10 alkylnyl having one or two triple bonds, or
  10  (8) R^{11a}-COXR^{12}
       (in which R^{11a}
       (a) bond,
       (b) C1-6 alkylene,
       (c) C2-8 alkylene in which a carbon atom in the main chain is replaced by sulfur,
       (d) C2-6 alkenylene,
       (e) C4-8 alkenylene in which a carbon atom in the main chain is replaced by sulfur,
       (f) C2-8 alkynylene, or
       (g) C4-8 alkynylene in which a carbon atom in the main chain is replaced by sulfur,

9. A compound according to claim 1, which is p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-allyl-N-ethoxycarbonylmethylamide or an acid addition salt thereof.

10. A compound according to claim 1, which is
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(2-ethoxycarbonylperhydroazepinyl)lamide.

11. A compound according to claim 1, which is
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(2-ethoxycarbonylpiperidino)lamide, or
    p-(p-amidinophenoxyacarbonyl)cinnamic acid N-(2-ethoxycarbonylpyrrolidinyl)lamide.

12. A compound according to claim 1, which is
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N'-phenylmethylpiperazinylamide.

13. A compound according to claim 1, which is
    p-(p-amidinophenoxyacarbonyl)benzoic acid N-[1-ethoxycarbonyl-2-(3-indolyl)ethyl]amide.

14. A compound according to claim 1, which is
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-ethoxycarbonylmethyl-N-phenylamide,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-ethoxycarbonyl-2-phenyl)ethylamide,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-3,5-bis(ethoxycarbonyl)phenylamide,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1-ethoxycarbonyl-2-(4-ethoxycarbonylphenylmethylthio))ethylamide,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-cyclopropyl-N-ethoxycarbonylmethylamide or
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-cyclohexyl-N-carboxymethylamide.

15. A compound according to claim 1, which is
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(2-ethoxycarbonylthiethyl)-N-isopropylamide,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-carboxymethyl-N-allylalmine,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-propargyl-N-ethoxycarbonylmethylalmine,
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-allyl-N-((1-ethoxycarbonyl-2-ethoxycarbonylmethylthio)ethyl)lamide or
    p-(p-amidinophenoxyacarbonyl)-α-methylcinnamic acid N-(1,1-bis(ethoxycarbonyl)ethyl)-N-ethoxycarbonylmethylamide.

16. A compound according to any one of the preceding claims in the form of an acid addition salt.
17. A process for the preparation of the compounds of the formula (I) claimed in claim 1, which is characterized by:

(i) esterification of a compound of the formula (IIa):

```
HOOCH2\[A-R\textsuperscript{3a}\]
R\textsuperscript{2}
```

wherein R\textsuperscript{3a} is the same meaning as hereinbefore defined for R\textsuperscript{2}, provided that all of R\textsuperscript{7}, R\textsuperscript{8}, R\textsuperscript{9} and R\textsuperscript{10}, in R\textsuperscript{2}, are groups not containing COOH and COOi-Bu, and R\textsuperscript{2} and A are as defined in claim 1, with a compound of the formula (III):

```
NH
H\textsubscript{2}N
\[\text{OH}\]
R\textsuperscript{1}
```

wherein R\textsuperscript{1} is as defined in claim 1;

(ii) amidation of a compound of the formula (IIb):

```
HN
H\textsubscript{2}N
\[O\]
R\textsuperscript{1}
\[\text{COOH}\]
R\textsuperscript{2}
```

wherein the various symbols are as defined in claim 1, with a compound of the formula (IIlb):
EP 0 588 655 B1

wherein $R^{7b}$, $R^{8b}$, $R^{9b}$ and $R^{10b}$ are the same meanings as hereinbefore defined for $R^7$, $R^8$, $R^9$ and $R^{10}$, respectively, provided that at least one group of $R^{7b}$, $R^{8b}$ and $R^{9b}$ is a group containing COOt-Bu and the other groups are ones not containing COOH, or $R^{10b}$ is COOt-Bu; or

(iii) hydrolysis of t-butyl ester group, of a compound of the formula (Ib):

wherein $R^1$, $R^2$ and $A$ are as defined in claim 1 and $R^{3b}$ has the same meaning as defined in claim 1 for $R^3$, provided that at least one group of $R^7$, $R^8$ and $R^9$, in $R^2$, is a group containing COOt-Bu and the other groups are ones not containing COOH, or $R^{10}$ is COOt-Bu.

18. A pharmaceutical composition which comprises, as active ingredient, an effective amount of a compound of the formula (I) depicted in claim 1, or an acid addition salt thereof, with a carrier or coating.

19. A compound of the formula (I) or an acid addition salt thereof for use in the manufacture of pharmaceutical composition for the prevention and/or treatment of various inflammatory diseases, allergic diseases, disseminated intravascular coagulation, pancreatitis, severity in pancreatitis or multiple organ failure.

Patentansprüche

1. Verbindung der Formel (I):
worin bedeuten:
$R^1$ und $R^2$ jeweils unabhängig voneinander

(i) Wasserstoff,
(ii) C1-4 Alkyl,
(iii) C1-4 Alkoxy,
(iv) C2-5 Acyl,
(v) Halogen,
(vi) Nitro,
(vii) Benzoyl oder
(viii) COOR^4 (mit $R^4$ gleich C1-3 Alkyl);
A eine Bindung, C1-4 Alkyle oder

\[
\begin{array}{c}
\text{C} = \text{C} \\
R^5 \quad R^6
\end{array}
\]

(mit $R^5$ und $R^6$ jeweils unabhängig voneinander gleich Wasserstoff oder C1-4 Alkyl);
$R^3$

(i) \( \text{CON} < R^7 \),

(ii) \( \text{CON} \quad R^7 \quad R^8 \)

oder

(iii) \( \text{CON} \quad R^{10} \)

(mit $R^7$ und $R^8$ unabhängig voneinander jeweils gleich
(1) Wasserstoff,
(2) Phenyl,
(3) C7-10 Phenylalkyl,
(4) Phenyl oder C7-10 Phenylalkyl, von denen jedes durch einen oder zwei Substituenten, ausgewählt aus C1-4 Alkyl, Halogen und R^11-CHO R^12
(mit R^11 gleich

(a) einer Bindung,
(b) C1-6 Alkylen,
(c) C2-6 Alkenylen oder
(d) C2-6 Alkinylen und

R^12 gleich

(a) Wasserstoff,
(b) C1-4 Alkyl,
(c) C7-10 Phenylalkyl,
(d) Phenyl,
(e) Allyl oder
(f) Propargyl), substituiert sein kann,

(5) C1-10 Alkyl,
(6) C2-10 Alkenyl mit einer bis drei Doppelbindungen(n),
(7) C2-10 Alkinylen mit einer oder zwei Dreifachbindungen,
(8) R^11a-CHO R^12
(mit R^11a gleich

(a) einer Bindung,
(b) C1-6 Alkylen,
(c) C2-6 Alkenylen, worin ein oder zwei Kohlenstoffatom(e) in der Hauptkette durch Schwefel oder Schwefel und Phenyl substituiert ist (sind),
(d) C2-6 Alkinylen,
(e) C4-6 Alkenylen, worin ein oder zwei Kohlenstoffatom(e) in der Hauptkette durch Schwefel oder Schwefel und Phenylen ersetzt ist (sind),
(f) C2-6 Alkinylen oder
(g) C4-6 Alkinylen, worin ein oder zwei Kohlenstoffatom(e) in der Hauptkette durch Schwefel oder Schwefel und Phenylen ersetzt ist (sind),

X gleich Sauerstoff oder -NH- und R^12 in der zuvor angegebenen Bedeutung,
(9) C1-4 Alkyl, welches durch einen 7-14 gliedrigen bi- oder tricyclischen Heteroring mit einem Stickstoff substituiert ist, oder
(10) C3-7 Cycloalkyl;

R^6 gleich

(1) Wasserstoff,
(2) C1-8 Alkyl,
(3) C7-10 Phenylalkyl,
(4) C2-10 Alkenyl mit einer bis drei Doppelbindungen(n),
(5) C2-10 Alkynyl mit einer oder zwei Dreifachbindungen(n),
(6) R^11-CHO R^12 (mit R^11 und R^12 in der zuvor angegebenen Bedeutung) oder
(7) C3-7 Cycloalkyl;
gleich einen 4-7gliedrigen, monocyclischen Heteroring mit einem oder zwei Stickstoff(en);
$R^{10}$ gleich

1. Wasserstoff.
2. C7-10 Phenylalkyl oder
3. COOR$^{13}$ (mit $R^{13}$ gleich Wasserstoff, C1-4 Alkyl oder C7-10 Phenylalkyl);

wobei gilt, daß

(i) beide Reste $R^7$ und $R^8$ nicht gleichzeitig Wasserstoff bedeuten dürfen und
(ii) im Falle, daß mindestens eine Gruppe $R^7$, $R^8$ und $R^9$ eine tert.-butylesterhaltige Gruppe darstellt, die restlichen Gruppen nicht für eine carboxyhaltige Gruppe stehen.

oder ein Säureadditionssalz derselben.

2. Verbindung nach Anspruch 1, worin $R^3$ für

\[
\text{(i) CON} \overset{R^7}{\underset{R^8}{\text{R}}} \\
\]

oder

\[
\text{(ii) CON} \overset{R^7}{\underset{R^9}{\text{R}}} \\
\]

worin die verschiedenen Symbole, die in Anspruch 1 angegebene Bedeutung besitzen, steht.

3. Verbindung nach Anspruch 1, worin $R^3$ für

\[
\text{(iii) CON} \overset{R^{10}}{\text{R}} \\
\]

worin die verschiedenen Symbole die in Anspruch 1 angegebene Bedeutung besitzen, steht.

4. Verbindung nach Anspruch 3, worin

\[
\text{N} \\
\]

für einen 4-7gliedrigen, monocyclischen Heteroring mit einem Stickstoff steht.

5. Verbindung nach Anspruch 3, worin
für einen 4-7gliedrigen monocyclischen Heteroring mit zwei Stickstoffen steht.

6. Verbindung nach Anspruch 2, worin einer der Reste \( R^7 \) und \( R^8 \) für
(9) C1-4 Alkyl, welches durch einen 7-14gliedrigen bi- oder tricyclischen Heteroring mit einem Stickstoff substituiert ist, steht.

7. Verbindung nach Anspruch 2, worin einer der Reste \( R^7 \) und \( R^8 \) für
(2) Phenyl,
(3) C7-10 Phenylalkyl,
(4) Phenyl oder C7-10 Phenylalkyl, von denen jedes durch einen oder zwei in beliebiger Weise aus C1-4 Alkyl, Halogenen und \( R^{11} \)-COOR^{12} (mit \( R^{11} \) und \( R^{12} \) in der in Anspruch 1 angegebenen Bedeutung) ausgewählten Substituenten substituiert ist,
(8) \( R^{11a} \)-COX\( R^{12} \)
(mit \( R^{11a} \) gleich
(c) C2-8 Alkenyl, worin zwei Kohlenstoffatome in der Hauptkette durch Schwefel und Phenylen ersetzt sind,
(e) C4-8 Alkenylen, worin zwei Kohlenstoffatome in der Hauptkette durch Schwefel und Phenylen ersetzt sind,
(g) C4-8 Alkinyle, worin zwei Kohlenstoffatome in der Hauptkette durch Schwefel und Phenylen ersetzt sind, und
X und \( R^{12} \) in der in Anspruch 1 angegebenen Bedeutung) oder
(10) C3-7 Cycloalkyl steht.

8. Verbindung nach Anspruch 2, worin einer der Reste \( R^7 \) und \( R^8 \) für
(5) C1-10 Alkyl,
(6) C2-10 Alkenyl mit einer bis drei Doppelbindung(en),
(7) C2-10 Alkinyl mit einer oder zwei Dreifachbindung(en) oder
(8) \( R^{11a} \)-COX\( R^{12} \)
(mit \( R^{11a} \) gleich
(a) einer Bindung,
(b) C1-8 Alkenyle,
(c) C2-8 Alkenyl, worin ein Kohlenstoffatom in der Hauptkette durch Schwefel ersetzt ist,
(d) C2-8 Alkenyle,
(e) C4-8 Alkenylen, worin ein Kohlenstoffatom in der Hauptkette durch Schwefel ersetzt ist,
(f) C2-8 Alkinyle, oder
(g) C4-8 Alkinyle, worin ein Kohlenstoffatom in der Hauptkette durch Schwefel ersetzt ist, und
X und \( R^{12} \) in der in Anspruch 1 angegebenen Bedeutung)

steht.

9. Verbindung nach Anspruch 1, nämlich p-\( p\)-(p-Aminophenoxycarbonyl)-\( \alpha \)-methylzimtsäure-N-allyl-N-ethoxycarbonylmethylamid oder ein Säureadditionssalz derselben.

10. Verbindung nach Anspruch 1, nämlich p-\( p\)-(p-Aminophenoxycarbonyl)-\( \alpha \)-methylzimtsäure-N-(2-ethoxycarbonylperhydroazepinyl)amid.

11. Verbindung nach Anspruch 1, nämlich p-\( p\)-(p-Aminophenoxycarbonyl)-\( \alpha \)-methylzimtsäure-N-(2-ethoxycarbonylpiperidino)amid oder
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p-(p-Amidinophenocarbonyl)zimtsäure-N-(2-ethoxycarbonylpyrrolidinyl)amid.

12. Verbindung nach Anspruch 1, nämlich
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N′-phenylmethyl(piperazinyl)amid.

13. Verbindung nach Anspruch 1, nämlich
   p-(p-Amidinophenocarbonyl)-α-benzoësäure-N-[1-ethoxycarbonyl-2-(3-indoly)]ethylamid.

14. Verbindung nach Anspruch 1, nämlich
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-ethoxycarbonyl(methyl-N-phenyl)amid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-(1-ethoxycarbonyl-2-phenyl)ethylamid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-3,5-bis(ethoxycarbonyl)phenylamid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-(1-ethoxycarbonyl-2-(4-ethoxycarbonyl)phenyl)ethylamid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-cyclopropyl-N-ethoxycarbonylmethylamid oder
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-cyclohexyl-N-carboxymethylamid.

15. Verbindung nach Anspruch 1, nämlich
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-(2-ethoxycarbonyl)ethyl-N-isopropylamid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-carboxymethyl-N-allylamid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-propargyl-N-ethoxycarbonylmethylamid,
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-allyl-N-(1-ethoxycarbonyl-2-ethoxycarbonyl)ethylamid oder
   p-(p-Amidinophenocarbonyl)-α-methylzimtsäure-N-(1,1-bis(ethoxycarbonyl)methyl)-N-ethoxycarbonylmet-
   theylamid.

16. Verbindung nach einem der vorhergehenden Ansprüche in Form eines Säureadditionssalzes.

17. Verfahren zur Herstellung von Verbindungen der Formel (I) nach Anspruch 1, gekennzeichnet durch

   (I) Veresterung einer Verbindung der Formel (IIa):

   \[
   \text{HOOC} \quad \text{A} \quad \text{R}^{3a} \\
   \text{R}^2 \\
   \text{ (IIa) }
   \]

   worin \( R^{3a} \) die zuvor angegebene Bedeutung von \( R^3 \) besitzt, wobei gilt, daß sämtliche Reste \( R^7, R^8, R^9 \) und \( R^{10} \) in \( R^3 \) für Gruppen ohne COOH und COO-tet.-Bu stehen, und \( R^2 \) und A die in Anspruch 1 angegebene Bedeutung besitzen, mit einer Verbindung der Formel (III):

   \[
   \text{HN} \\
   \text{H}_2\text{N} \\
   \text{O} \\
   \text{R}^1 \\
   \text{ (III) }
   \]

   worin \( R^1 \) die in Anspruch 1 angegebene Bedeutung besitzt.
(ii) Amidierung einer Verbindung der Formel (I lb):

\[ \text{HN} \quad \text{O} \quad A - \text{COOH} \]
\[ \text{R}^1 \quad \text{R}^2 \]

worin die verschiedenen Symbole die in Anspruch 1 angegebene Bedeutung besitzen, mit einer Verbindung der Formel (IIIb):

\[ \text{(i)} \quad \text{HN} \quad \text{R}^{7b} \quad \text{R}^{8b} \]
\[ \text{(ii)} \quad \text{HN} \quad \text{R}^{7b} \quad \text{R}^{8b} \quad \text{or} \]
\[ \text{(iii)} \quad \text{HN} \quad \text{R}^{10b} \]

worin \( \text{R}^{7b}, \text{R}^{8b}, \text{R}^{9b} \) und \( \text{R}^{10b} \) die zuvor für \( \text{R}^{7}, \text{R}^{8}, \text{R}^{9} \) bzw. \( \text{R}^{10} \) angegebenen Bedeutung besitzen, wobei jedoch mindestens eine der Gruppen \( \text{R}^{7b}, \text{R}^{8b} \) und \( \text{R}^{9b} \) für eine Gruppe mit COO-tert.-Bu steht und die restlichen Gruppen aus solchen ohne COOH bestehen oder \( \text{R}^{10b} \) COO-tert.-Bu ist; oder

(iii) Hydrolyse der tert.-Butyl-Estergruppe einer Verbindung der Formel (Ib),

\[ \text{HN} \quad \text{O} \quad A - \text{R}^{3b} \]
\[ \text{R}^1 \quad \text{R}^2 \]

worin \( \text{R}^1, \text{R}^2 \) und \( A \) die in Anspruch 1 angegebene Bedeutung besitzen und \( \text{R}^{3b} \) der Bedeutung von \( \text{R}^{3} \) gemäß der Definition von Anspruch 1 entspricht, wobei gilt, daß mindestens eine der Gruppen \( \text{R}^{7}, \text{R}^{8} \) und \( \text{R}^{9} \) von \( \text{R}^{3} \) aus einer Gruppe mit COO-tert.-Bu besteht und die anderen Gruppen für solche von COOH stehen, oder für \( \text{R}^{10} \) ist COO-tert.-Bu.

18. Arzneimittelzubereitung, welche als aktiven Bestandteile eine wirksame Menge einer Verbindung der in Anspruch 1 abgebildeten Formel (I) oder eines Säureadditionssalzes derselben zusammen mit einem Träger oder Überzug enthält.

19. Verbindung der Formel (I) oder ein Säureadditionssalz derselben zur Verwendung bei der Herstellung einer Ar-
Revidications

1. Composé de formule (I):

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{NH} & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{A} & \quad \text{R}^3
\end{align*}
\]

(l)

dans laquelle \( \text{R}^1 \) et \( \text{R}^2 \) représentent chacun indépendamment :

(i) un atome d'hydrogène,
(ii) un groupement alkyle en \( \text{C}_1\text{-C}_4 \),
(iii) un groupement alcoxy en \( \text{C}_1\text{-C}_4 \),
(iv) un groupement acyle en \( \text{C}_2\text{-C}_5 \),
(v) un atome d'halogène,
(vi) un groupement nitro,
(vii) un groupement benzoyle ou
(viii) \( \text{COOR}^4 \) (où \( \text{R}^4 \) représente un groupement alkyle en \( \text{C}_1\text{-C}_3 \));

A représente une liaison, un groupement alkylène en \( \text{C}_1\text{-C}_4 \) ou

\[
\begin{align*}
\text{C} & \quad \text{C} \\
\text{R}^5 & \quad \text{R}^6
\end{align*}
\]

(où \( \text{R}^5 \) et \( \text{R}^6 \) représentent chacun indépendamment un atome d'hydrogène ou un groupement alkyle en \( \text{C}_1\text{-C}_4 \));

\( \text{R}^9 \) représente

(i) \[
\begin{align*}
\text{CON} & \quad \text{R}^7 \\
\text{R}^8
\end{align*}
\]

(ii) \[
\begin{align*}
\text{CON} & \quad \text{R}^7 \\
\text{R}^8
\end{align*}
\]

ou
(où R^7 et R^8 représentent chacun indépendamment

(1) un atome d'hydrogène,
(2) un groupement phénylé,
(3) un groupement phénylationyle en C\textsubscript{7}-C\textsubscript{10},
(4) un groupement phénylé ou un groupement phénylationyle en C\textsubscript{7}-C\textsubscript{10}, chacun étant substitué par 1 ou 2 substituants choisis parmi un groupement alkyle en C\textsubscript{1}-C\textsubscript{4}, un atome d'halogène et R\textsuperscript{11}-COOR\textsuperscript{12}
(où R\textsuperscript{11} représente

(a) une liaison,
(b) un groupement alkylène en C\textsubscript{1}-C\textsubscript{4},
(c) un groupement alcénylé en C\textsubscript{2}-C\textsubscript{8} ou
(d) un groupement alcynylène en C\textsubscript{2}-C\textsubscript{8} et

R\textsuperscript{12} représente

(a) un atome d'hydrogène,
(b) un groupement alkyle en C\textsubscript{1}-C\textsubscript{4},
(c) un groupement phénylationyle en C\textsubscript{7}-C\textsubscript{10},
(d) un groupement phénylé,
(e) un groupement allyle ou
(f) un groupement propargyle),

(5) un groupement alkyle en C\textsubscript{1}-C\textsubscript{10},
(6) un groupement alcénylé en C\textsubscript{2}-C\textsubscript{10} ayant de 1 à 3 doubles liaisons,
(7) un groupement alcynylène en C\textsubscript{2}-C\textsubscript{10} ayant 1 ou 2 triples liaisons,
(8) R\textsuperscript{11a}-COX\textsuperscript{12}
(où R\textsuperscript{11a} représente

(a) une liaison,
(b) un groupement alkylène en C\textsubscript{1}-C\textsubscript{4},
(c) un groupement alkylène en C\textsubscript{2}-C\textsubscript{8} dans lequel 1 ou 2 atomes de carbone de la chaîne principale sont remplacés par du soufre ou bien du soufre et du phénylé,
(d) un groupement alcénylé en C\textsubscript{2}-C\textsubscript{8},
(e) un groupement alcénylé en C\textsubscript{4}-C\textsubscript{8} dans lequel 1 ou 2 atomes de carbone de la chaîne principale sont remplacés par du soufre ou bien du soufre et du phénylé,
(f) un groupement alcynylène en C\textsubscript{2}-C\textsubscript{8} ou
(g) un groupement alcynylène en C\textsubscript{4}-C\textsubscript{8} dans lequel 1 ou 2 atomes de carbone de la chaîne principale sont remplacés par du soufre ou bien du soufre et du phénylé,
X représente un atome d’oxygène ou -NH- et R\textsuperscript{12} est tel que défini précédemment),

(9) un groupement alkyle en C\textsubscript{1}-C\textsubscript{4} qui est substitué par un noyau hétérogué bicyclique ou tricyclique, ayant de 7 à 14 chaînons, contenant un atome d’azote, ou
(10) un groupement cycloalkyle en C\textsubscript{2}-C\textsubscript{7},

R\textsuperscript{p} représente

(1) un atome d'hydrogène,
(2) un groupement alkyle en C\textsubscript{1}-C\textsubscript{8},
(3) un groupement phénylationyle en C\textsubscript{7}-C\textsubscript{10},
(4) un groupement alcénylé en C\textsubscript{2}-C\textsubscript{10} ayant de 1 à 3 doubles liaisons,
(5) un groupement alcynylène en C\textsubscript{2}-C\textsubscript{10} ayant 1 ou 2 triples liaisons,

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(6) $R^{11}$-COOR$^{12}$ (où $R^{11}$ et $R^{12}$ sont tels que définis précédemment) ou
(7) un groupement cycloalkyle en C$_2$-C$_7$ ;

représente un noyau hétérogène monocyclique ayant de 4 à 7 chaînons, contenant 1 ou 2 atomes d'azote ;
$R^{10}$ représente

(1) un atome d'hydrogène,
(2) un groupement phénylalkyle en C$_7$-C$_{10}$ ou
(3) COOR$^{13}$ (où $R^{13}$ représente un atome d'hydrogène, un groupement alkyle en C$_1$-C$_4$ ou un groupement
phénylalkyle en C$_7$-C$_{10}$) ;

à condition que

(i) les radicaux $R^7$ et $R^8$ ne représentent pas un atome d'hydrogène en même temps et
(ii) lorsqu'au moins un groupement parmi $R^7$, $R^8$ et $R^9$ représente le groupement contenant l'ester t-butylique,
les autres groupements ne représentent pas le groupement contenant un carboxy ;

ou un de ses sels d'addition d'acides.

2. Composé selon la revendication 1, pour lequel $R^3$ représente

(i) $\text{CON} \begin{array}{c} \overrightarrow{R^7} \\ \overleftarrow{R^8} \end{array}$

ou

(ii) $\text{CON} \begin{array}{c} \overrightarrow{R^7} \\ \overleftarrow{R^8} \\ R^9 \end{array}$

où les divers symboles sont tels que définis dans la revendication 1.

3. Composé selon la revendication 1, pour lequel $R^5$ représente

(iii) $\text{CON} \begin{array}{c} \overrightarrow{R^{10}} \end{array}$

où les divers symboles sont tels que définis dans la revendication 1.

4. Composé selon la revendication 3, pour lequel
représente un noyau hétérogène monocyclique ayant de 4 à 7 chaînons, contenant un atome d’azote.

5. Composé selon la revendication 3, pour lequel

représente un noyau hétérogène monocyclique ayant de 4 à 7 chaînons, contenant 2 atomes d’azote.

6. Composé selon la revendication 2, pour lequel un radical parmi R7 et R8 représente
   (9) un groupement alkyle en C1-C4 qui est substitué par un noyau hétérogène bicyclique ou tricyclique, ayant de 7 à 14 chaînons, contenant un atome d’azote.

7. Composé selon la revendication 2, pour lequel un radical parmi R7 et R8 représente

   (2) un groupement phényle,
   (3) un groupement phénylalkyle en C7-C10,
   (4) un groupement phényle ou un groupement phénylalkyle en C7-C10 qui est substitué par 1 ou 2 substituants choisis éventuellement parmi un groupement alkyle en C1-C4, un atome d’halogène et R11-COOR12
   (où R11 et R12 sont tels que définis dans la revendication 1),
   (8) R11a-COXR12
   (où R11a représente

   (c) un groupement alcénylène en C2-C6 dans lequel 2 atomes de carbone de la chaîne principale sont remplacés par du soufre et du phénylène,
   (e) un groupement alcénylène en C4-C8 dans lequel 2 atomes de carbone de la chaîne principale sont remplacés par du soufre et du phénylène,

   (g) un groupement alcynyénène en C4-C8 dans lequel 2 atomes de carbone de la chaîne principale sont remplacés par du soufre et du phénylène,

   (où X et R12 sont tels que définis dans la revendication 1) ou
   (10) un groupement cycloalkyle en C3-C7.

8. Composé selon la revendication 2, pour lequel un radical parmi R7 et R8 représente

   (5) un groupement alkyle en C1-C10,
   (6) un groupement alcénylène en C2-C10 ayant de 1 à 3 doubles liaisons,
   (7) un groupement alcynyénène en C2-C10 ayant 1 ou 2 triples liaisons ou
   (8) R11a-COXR12
   (où R11a représente

   (a) une liaison,
   (b) un groupement alcénylène en C1-C6,
   (c) un groupement alcénylène en C2-C6 dans lequel 1 atome de carbone de la chaîne principale est remplacé par du soufre,
   (d) un groupement alcénylène en C2-C6,
   (e) un groupement alcénylène en C4-C8 dans lequel 1 atome de carbone de la chaîne principale est remplacé par du soufre,
   (f) un groupement alcynyénène en C2-C6 ou
   (g) un groupement alcynyénène en C4-C8 dans lequel un atome de carbone de la chaîne principale est remplacé par du soufre,
9. Composé selon la revendication 1, qui est le N-allyl-N-éthoxy-carbonylméthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique ou un de ses sols d'addition d'acides.

10. Composé selon la revendication 1, qui est le N-(2-éthoxy-carbonylperhydroazépiny)amide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique.

11. Composé selon la revendication 1, qui est le N-(2-éthoxy-carbonylpipéridino)amide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique ou le N-(2-éthoxy-carbonylpyrrolidino)amide d'acide p-(p-aminophénylacryloxy-carbonyl)-cinnamique.

12. Composé selon la revendication qui est le N-phénylméthylpipérazinylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique.

13. Composé selon la revendication 1, qui est le N-[1-éthoxy-carbonyl-2-(3-indolyl)]éthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)benzoïque.

14. Composé selon la revendication 1, qui est

le N-éthoxy-carbonylméthyl-N-phénylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique,
le N-(1-éthoxy-carbonyl-2-phényl)éthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique,
le N-3,5-bis(éthoxy-carbonyl)phénylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique,
le N-(1-éthoxy-carbonyl-2-(4-éthoxy-carbonylphénylméthylthio))éthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique.
le N-cyclopropyl-N-éthoxy-carbonylméthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique ou
le N-cyclohexyl-N-carboxyméthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique.

15. Composé selon la revendication 1, qui est

le N-(2-éthoxy-carbonylthéthyl)-N-isopropylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique,
le N-carboxyméthyl-N-allylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique,
le N-propargyl-N-éthoxy-carbonylméthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique,
le N-allyl-N-(1-éthoxy-carbonyl-2-éthoxy-carbonylméthylthio)éthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique ou
le N-(1,1-bis(éthoxy-carbonyl)méthyl)-N-éthoxy-carbonylméthylamide d'acide p-(p-aminophénylacryloxy-carbonyl)-α-méthylcinnamique.

16. Composé selon l'une quelconque des revendications précédentes sous la forme d'un sel d'addition d'acide.

17. Procédé de préparation des composés de formule (I) selon la revendication 1, qui est caractérisé par :

(i) l'estérification d'un composé de formule (IIa) :

![Diagramme](image)

(iiia)

(iii)

dans laquelle $R^{3a}$ présente la même signification que $R^3$, à condition que tous les radicaux $R^7$, $R^8$, $R^9$ et $R^{10}$, dans $R^3$, soient des groupements ne contenant pas COOH et COOt-Bu, et $R^2$ et $A$ sont tels que définis dans la revendication 1, avec un composé de formule (III):
dans laquelle \( R^1 \) est tel que défini dans la revendication 1 ;

(ii) l'amidation d'un composé de formule (IIIb) :

\[
\begin{array}{c}
\text{NH} \\
\text{H}_2\text{N}
\end{array}
\begin{array}{c}
\text{OC} \\
\text{A-COOH}
\end{array}
\begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array}
\]

(iii) l'hydrolyse du groupement ester t-butylique d'un composé de formule (Ib)
dans laquelle R¹, R² et A sont tels que définis dans la revendication 1 et R³b présente la même signification que R³ dans la revendication 1, à condition qu'au moins un groupement parmi R⁷, R⁸ et R⁹, dans R⁵, soit un groupement contenant COOt-Bu et les autres groupements soient des groupements ne contenant pas COOH, ou bien R¹⁰ représente COOt-Bu.

18. Composition pharmaceutique qui comprend, en tant que principe actif, une quantité efficace d'un composé de formule (I) décrite dans la revendication 1 ou un de ses sels d'addition d'acides avec un véhicule ou revêtement.

19. Composé de formule (I) ou un de ses sels d'addition d'acides à utiliser dans la préparation d'une composition pharmaceutique destinée à empêcher et/ou traiter diverses maladies inflammatoires, maladies allergiques, la coagulation intravasculaire disséminée, la pancréatite, les cas graves de pancréatite ou la défaillance de multiples organes.