



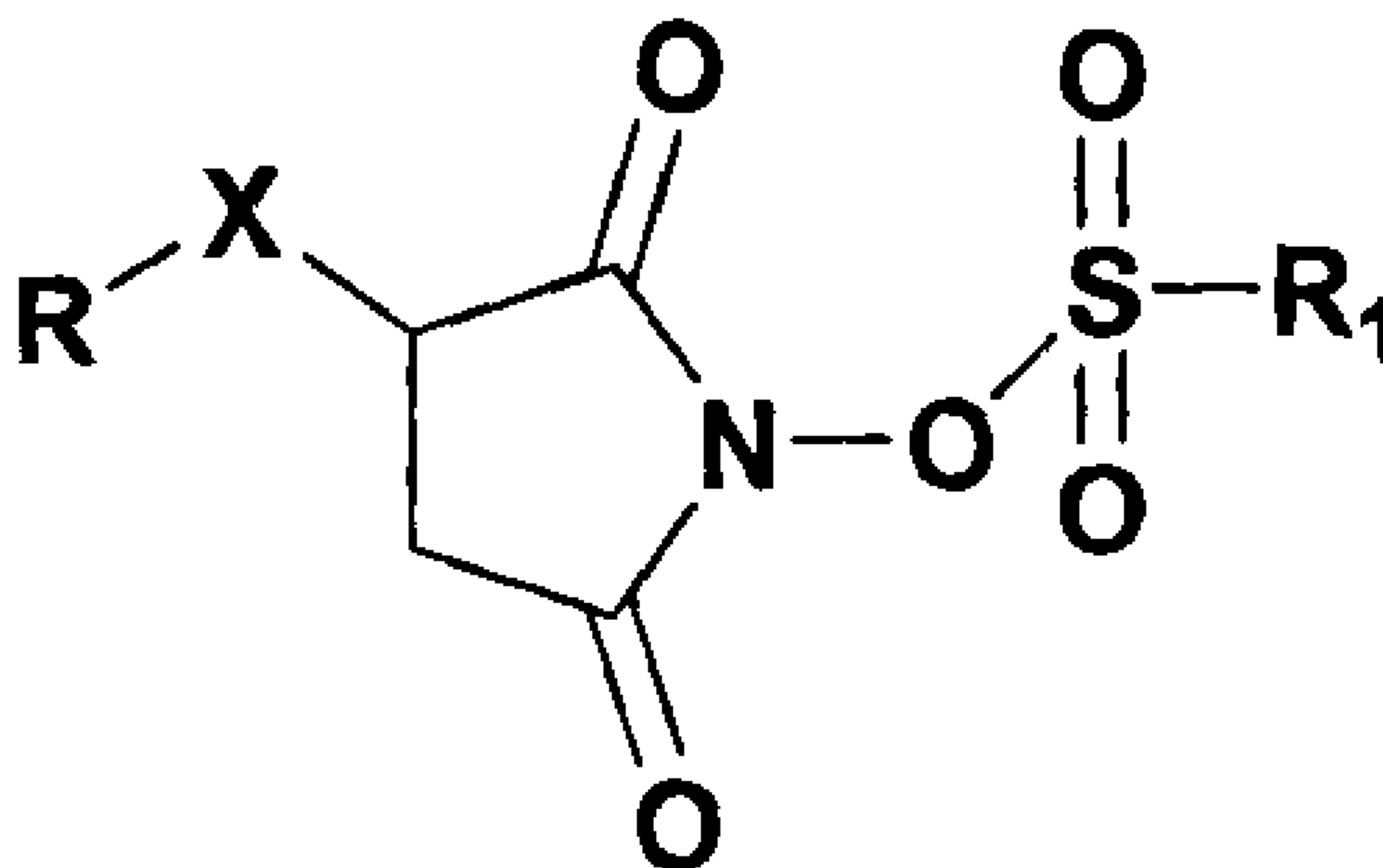
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(54) Titre : NOUVEAUX INHIBITEURS D'ANANDAMIDE AMIDASE UTILES EN TANT QU'AGENTS ANALGESIQUES
(54) Title: NOVEL ANANDAMIDE AMIDASE INHIBITORS AS ANALGESIC AGENTS



(57) Abrégé/Abstract:

Disclosed is a method of inhibiting anandamide amidase in an individual or animal and novel inhibitors of anandamide amidase. Compounds of the invention are represented by Structural Formula (I): R-X-Y (I) wherein R is selected from the group consisting of a methyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, and an optionally substituted heterocyclic group; X is an optionally substituted straight chain hydrocarbonyl group containing from 10-24 carbon atoms if R is a methyl group, and from 4-18 carbon atoms if R is an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted heterocyclic group; and Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme.



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Abstract

Disclosed is a method of inhibiting anandamide amidase in an individual or animal and novel inhibitors of anandamide amidase. Compounds of the invention are represented by Structural Formula (I):



wherein R is selected from the group consisting of a methyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, and an optionally substituted heterocyclic group; X is an optionally substituted straight chain hydrocarbyl group containing from 10-24 carbon atoms if R is a methyl group, and from 4-18 carbon atoms if R is an optionally substituted aryl group, an optionally substituted heteroaryl group, or an optionally substituted heterocyclic group; and Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme.

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NOVEL ANANDAMIDE AMIDASE INHIBITORS AS ANALGESIC AGENTSBackground

Δ^9 -Tetrahydrocannabinol, the psychoactive marijuana derived cannabinoid, binds to the CB1 receptor in the brain and to the CB2 receptor in the spleen. Compounds which stimulate the CB1 receptor have been shown to induce analgesia and sedation, to cause mood elevation, to control nausea and appetite and to lower intraocular pressure (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, FL (1986), Fride and Mechoulam, *Eur. J. Pharmacol.* 231:313 (1993), Crawley et al., *Pharmacol. Biochem. Behav.* 46:967 (1993) and Smith et al., *J. Pharm. Exp. Therap.* 270:219 (1994)). Cannabinoids have also been shown to suppress the immune system (Mechoulam, *Cannabinoids as Therapeutic Agents*, CRC Press, Boca Raton, FL (1986). Thus, compounds which stimulate the CB1 or CB2 receptor, directly or indirectly, are potentially useful in treating glaucoma, preventing tissue rejection in organ transplant patients, controlling nausea in patients undergoing chemotherapy, controlling pain and enhancing the appetite and controlling pain in individuals with AIDS Wasting Syndrome.

Arachidonyl ethanolamide (anandamide) is a naturally-occurring brain constituent that acts as a CB1 and CB2 agonist and exhibits pharmacological activity in mice comparable to cannabinoids (Fride and Mechoulam

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(1993), Crawley et al. (1993) and Smith et al. (1994)).
Anandamide is cleaved *in vivo* by anandamide amidase. Thus,
inhibitors of anandamide amidase have the effect of
indirectly stimulating the CB1 and CB2 receptors by
5 increasing *in vivo* levels of anandamide.

In addition to acting at the CB1 and CB2 receptors,
cannabinoids also affect cellular membranes, thereby
producing undesirable side effects such as drowsiness,
impairment of monoamine oxidase function and impairment of
10 non-receptor mediated brain function. The addictive and
psychotropic properties of cannabinoids also limit their
therapeutic value. Inhibitors of anandamide amidase are
not expected to have the undesired membrane-related side-
effects produced by cannabinoids. By providing an
15 alternate mechanism for stimulating the CB1 and CB2
receptor, anandamide inhibitors might not have the
addictive and psychotropic properties of cannabinoids.
However, present inhibitors of anandamide amidase have
disadvantages. For example, phenylmethanesulfonyl fluoride
20 (PMSF) is toxic to cells. Thus, there is a need for new
and more potent inhibitors of anandamide amidase which have
reduced toxicity towards cells and which do not
significantly interact with the CB1 or CB2 receptor at
inhibitory concentrations.

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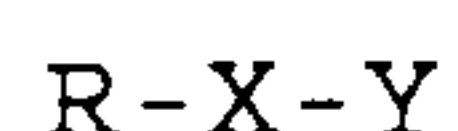
Summary of the Invention

It has now been found that long chain fatty acids and
aromatic acid analogs of long chain fatty acids with head
groups capable of irreversibly binding to a nucleophilic
30 group at an enzyme active site are potent inhibitors of
anandamide amidase. For example, palmitylsulfonyl fluoride
was found to increase the level of undegraded anandamide
55-fold at 10 nM in intact neuroblastoma cells (Example 1)
and is therefore more than 100 fold more potent than

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phenylmethanesulfonyl fluoride at inhibiting anandamide
amidase. At the same time, the inhibitors disclosed herein
have a low affinity for the CB1 receptor (Example 3). For
example, the binding affinity of palmitylsulfonyl fluoride
5 for the CB1 receptor is about 10 times lower than
anandamide. In addition, it has been found that
palmitylsulfonyl fluoride causes some of the same
pharmacological effects in rats as do compounds which
stimulate the CB1 receptor directly, such as
10 Δ^9 -tetrahydrocannabinol. For example, palmitylsulfonyl
fluoride is shown herein to induce analgesia in rats
(Example 4). Based on these results, methods of inhibiting
anandamide amidase, thereby stimulating the CB1 and CB2
receptors, in an individual or animal are disclosed. Also
15 disclosed are novel compounds which inhibit anandamide
amidase.

The present invention is a method of inhibiting
anandamide amidase in an individual or animal. The method
comprises administering to the individual or animal a
20 therapeutically effective amount of a compound represented
by Structural Formula I:



(I)

and physiologically acceptable salts thereof.

25 R is selected from the group consisting of a methyl
group, an aryl group, a substituted aryl group, a
heteroaryl group, a substituted heteroaryl group, a
heterocyclic group and a substituted heterocyclic group.

X is a straight chain hydrocarbyl group or a
30 substituted straight chain hydrocarbyl group containing
from about 4 to about 18 carbon atoms if R is an aryl
group, a substituted aryl group, a heteroaryl group, a

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substituted heteroaryl group, a heterocyclic group or a substituted heterocyclic group.

X is a hydrocarbyl group or a substituted hydrocarbyl group containing from about 10 to about 24 carbon atoms if
5 R is a methyl group.

Y is a moiety capable of irreversibly binding with a nucleophilic group at the active site of an amidase enzyme.

The method and the novel compounds disclosed herein have therapeutic uses. For example, the compounds and
10 methods of the present invention, like cannabinoids, can relieve the pain caused by cancer and the nausea resulting from cancer chemotherapy. They are not expected to have the undesirable membrane-related side-effects associated with cannabinoids. In addition, the methods and compounds
15 disclosed herein are expected to be immunosuppressive and can therefore be used to prevent organ rejection in an individual undergoing an organ transplant. Because the compounds and methods of the present invention enhance the appetite of an individual, they can be used treat patients
20 with AIDS Wasting Syndrome, who are often suffering from malnourishment as a result of appetite loss.

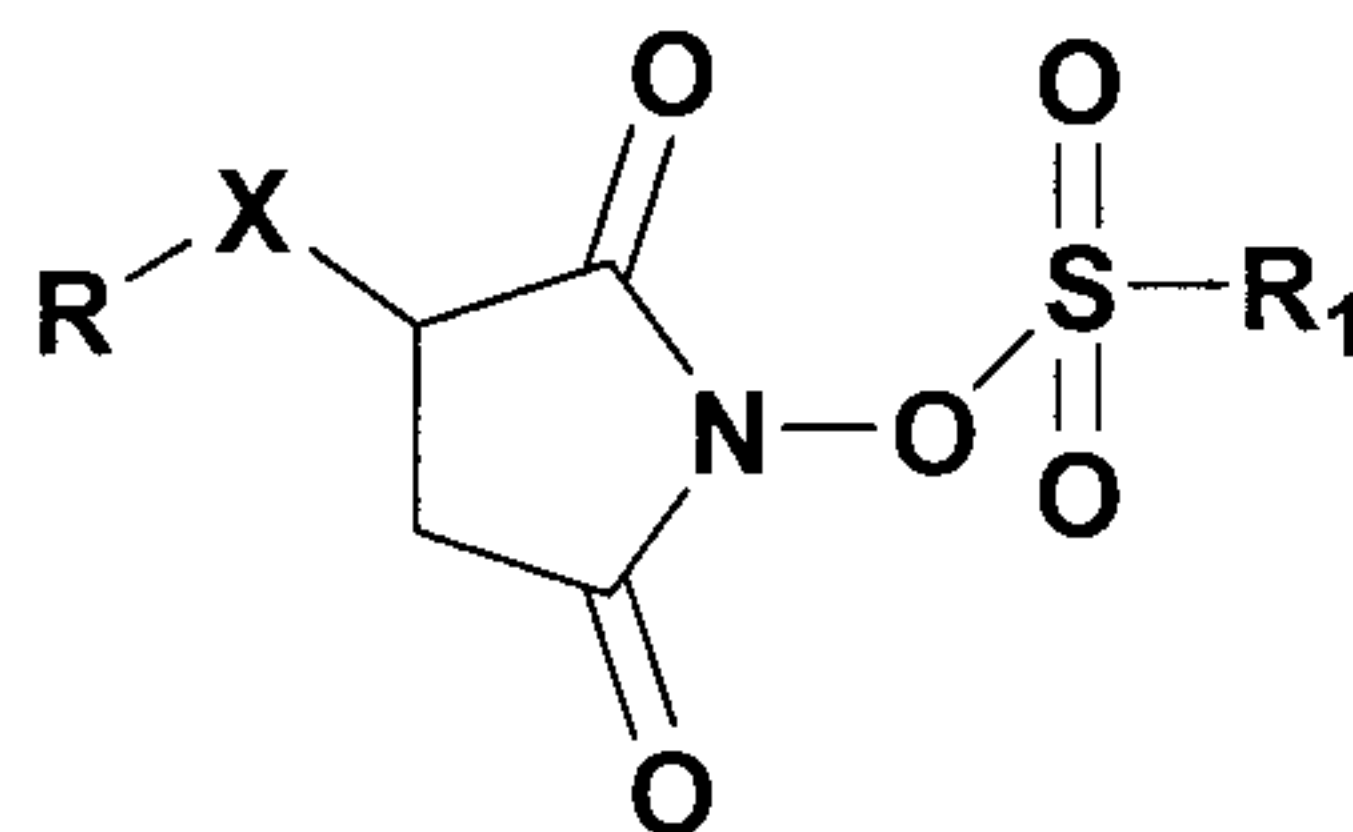
The novel inhibitors of anandamide amidase disclosed herein also have research uses. For example, they can be used to maintain the level of anandamide *in vitro* to study
25 the effect of ananamide on cells and to maintain the level of anandamide *in vivo* to study the effect of anandamide on individuals and animals. They can be used to characterize cells, for example to determine if a cell type has cannabimetic or amidase activity. For example, the
30 inhibitors can be used to determine if a cell population expresses anandamide amidase by contacting the cells with an inhibitor and then determining if there is an increase in the concentration of anandamide. The anandamide inhibitors disclosed herein can also be used as in aid in

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drug design, for example as a control in assays for testing other compounds for their ability to inhibit anandamide amidase and to determine the structure activity requirements of anandamide amidase inhibitors.

5

More particularly, in one aspect the present invention provides a compound represented by the following structural formula:



10

or physiologically acceptable salts thereof, wherein:

R1 is -F or (C1 to C4 straight or branched chain alkyl)O-;

R is selected from the group consisting of:

15

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

20

25

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

-5a-

a heteroaryl group having 5, 6, 9, or 10 members;
a heteroaryl group having 5, 6, 9, or 10 members
wherein said heteroaryl group is substituted by a
substituent selected from the group consisting of:
lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl
or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO,
-CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower
alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or
branched chain alkyl group, said aryl and said
substituted aryl substituents for said heteroaryl
group have 6 or 10 members, said heteroaryl
substituents for said heteroaryl group have 5, 6, 9
or 10 members, and the substituents for said
substituted aryl substituents are as previously
defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent
selected from the group consisting of: lower alkyl,
aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted
aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower
alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂,
-CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or
branched chain alkyl group, said aryl and said
substituted aryl substituents for said heterocyclic
group have 6 or 10 members, said heteroaryl
substituents for said heterocyclic group have 5, 6,
9 or 10 members, and the substituents for said
substituted aryl substituents are as previously
defined;

-5b-

5 X is a straight chain hydrocarbyl group or a substituted
straight chain hydrocarbyl group containing from 4 to 18
carbon atoms if R is an aryl group having 6 or 10
members, a substituted aryl group having 6 or 10 members
wherein the substituents for said aryl group are as
defined above, a heteroaryl group having 5, 6, 9, or 10
members, a substituted heteroaryl group having 5, 6, 9,
or 10 members wherein the substituents for said
10 heteroaryl group are as defined above, a heterocyclic
group, or a substituted heterocyclic group wherein the
substituents for said heterocyclic group are as defined
above; and

15 X is a straight chain hydrocarbyl group or a
substituted straight chain hydrocarbyl group containing
from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain
hydrocarbyl group is substituted by a substituent
selected from the group consisting of: methyl,
20 ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and
ethoxy.

In another aspect, the invention provides for the use of
a compound represented by the following structural formula:

25
$$R-X-Y$$

or physiologically acceptable salts thereof, to inhibit
anandamide amidase, wherein:

R is selected from the group consisting of:
a methyl group;
30 an aryl group having 6 or 10 members;

-5c-

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;
a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

-5d-

5 a heterocyclic group substituted by a substituent
selected from the group consisting of: lower alkyl,
aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted
aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower
alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂,
-CF₃, -CN, and (lower alkyl)-S-,

10 wherein lower alkyl is a C1 to C5 straight or
branched chain alkyl group, said aryl and said
substituted aryl substituents for said heterocyclic
group have 6 or 10 members, said heteroaryl
substituents for said heterocyclic group have 5, 6,
9 or 10 members, and the substituents for said
substituted aryl substituents are as previously
15 defined;

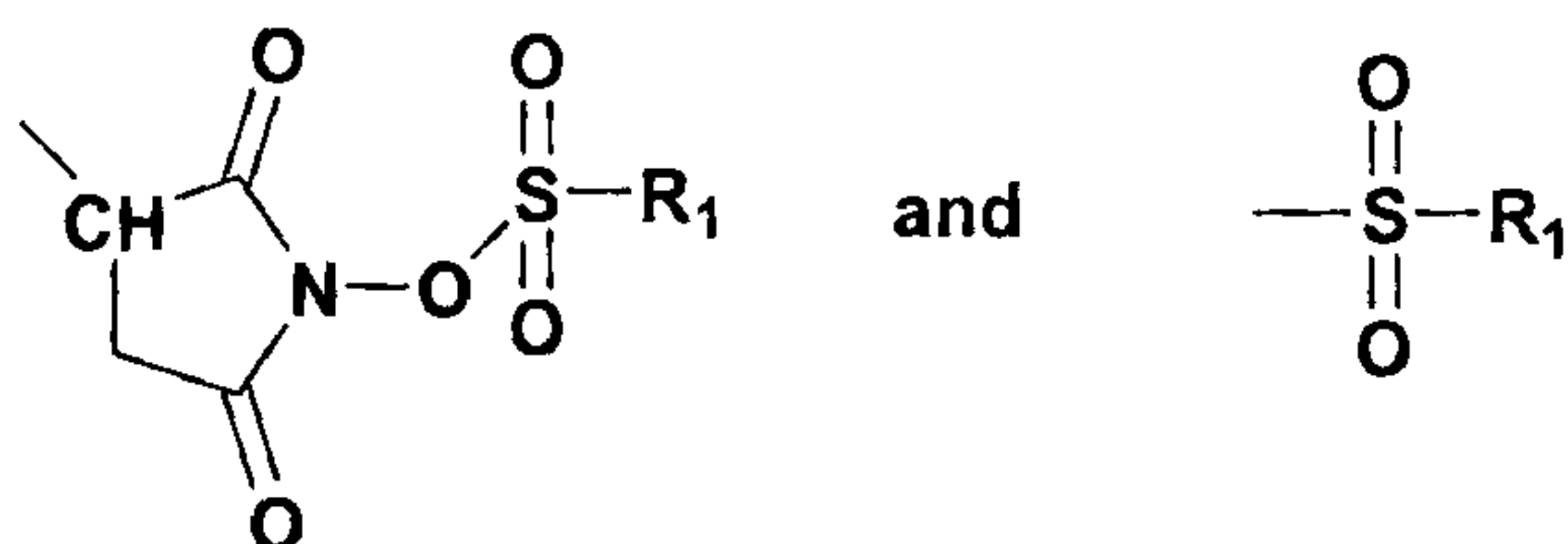
X is a straight chain hydrocarbyl group or a
substituted straight chain hydrocarbyl group containing
from 4 to 18 carbon atoms if R is an aryl group having 6
or 10 members, a substituted aryl group having 6 or 10
20 members wherein the substituents for said aryl group are
as defined above, a heteroaryl group having 5, 6, 9, or
10 members, a substituted heteroaryl group having 5, 6,
9, or 10 members wherein the substituents for said
heteroaryl group are as defined above, a heterocyclic
25 group, or a substituted heterocyclic group wherein the
substituents for said heterocyclic group are as defined
above; and

X is a straight chain hydrocarbyl group or a
substituted straight chain hydrocarbyl group containing
30 from 10 to 24 carbon atoms if R is a methyl group;

-5e-

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:

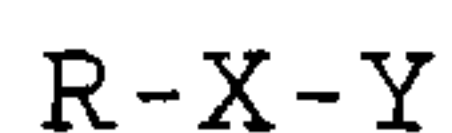


wherein:

R1 is selected from the group consisting of -F and -O(C1 to C4 straight or branched chain alkyl group).

In another aspect, the invention provides for the use of a therapeutically effective amount of a compound represented by the structural formula R-X-Y as described above, or physiologically acceptable salts thereof, in the preparation of a medicament for inhibiting anandamide amidase.

In yet another aspect, the invention provides for the use of a compound represented by the following structural formula:



-5f-

or physiologically acceptable salts thereof, in a therapeutically effective amount for inducing analgesia, wherein:

5 R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

10 an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

15 wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

20 a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of:
25 lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

-5g-

5 wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

10 a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

20 wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

25 X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 30 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the

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substituents for said heterocyclic group are as defined above; and

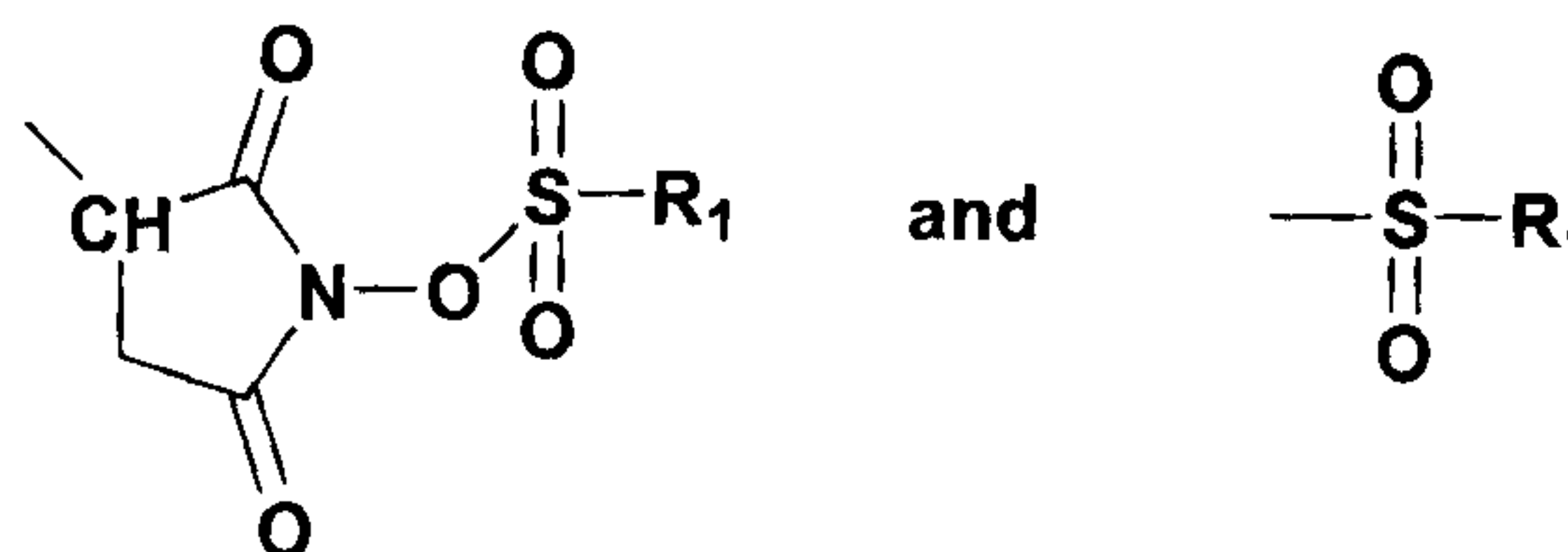
X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

10

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:

15



wherein:

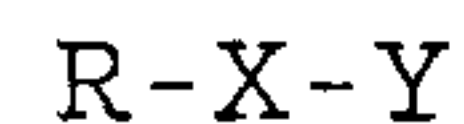
R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

In another aspect, the invention provides for the use of a therapeutically effective amount of a compound represented by the structural formula R-X-Y as described above, or physiologically acceptable salts thereof, in the preparation of a medicament for inducing analgesia.

25

-5i-

In yet another aspect, the invention provides for the use of a compound represented by the following structural
 5 formula:



or physiologically acceptable salts thereof, in a therapeutically effective amount for increasing anandamide levels, wherein:

10 R is selected from the group consisting of:
 a methyl group;
 an aryl group having 6 or 10 members;
 an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from
 15 the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

20 wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted
 25 aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;
 a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of:
 30 lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl),

-5j-

-CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

5 wherein lower alkyl is a C1 to C5 straight or
 branched chain alkyl group, said aryl and said
 substituted aryl substituents for said heteroaryl
 group have 6 or 10 members, said heteroaryl
 substituents for said heteroaryl group have 5, 6, 9
10 or 10 members, and the substituents for said
 substituted aryl substituents are as previously
 defined;

 a heterocyclic group; and

 a heterocyclic group substituted by a substituent
 selected from the group consisting of: lower alkyl,
15 aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted
 aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower
 alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂,
 -CF₃, -CN, and (lower alkyl)-S-,

 wherein lower alkyl is a C1 to C5 straight or
20 branched chain alkyl group, said aryl and said
 substituted aryl substituents for said heterocyclic
 group have 6 or 10 members, said heteroaryl
 substituents for said heterocyclic group have 5, 6,
 9 or 10 members, and the substituents for said
25 substituted aryl substituents are as previously
 defined;

 X is a straight chain hydrocarbyl group or a
 substituted straight chain hydrocarbyl group containing
 from 4 to 18 carbon atoms if R is an aryl group having 6
30 or 10 members, a substituted aryl group having 6 or 10
 members wherein the substituents for said aryl group are
 as defined above, a heteroaryl group having 5, 6, 9, or
 10 members, a substituted heteroaryl group having 5, 6,
 9, or 10 members wherein the substituents for said

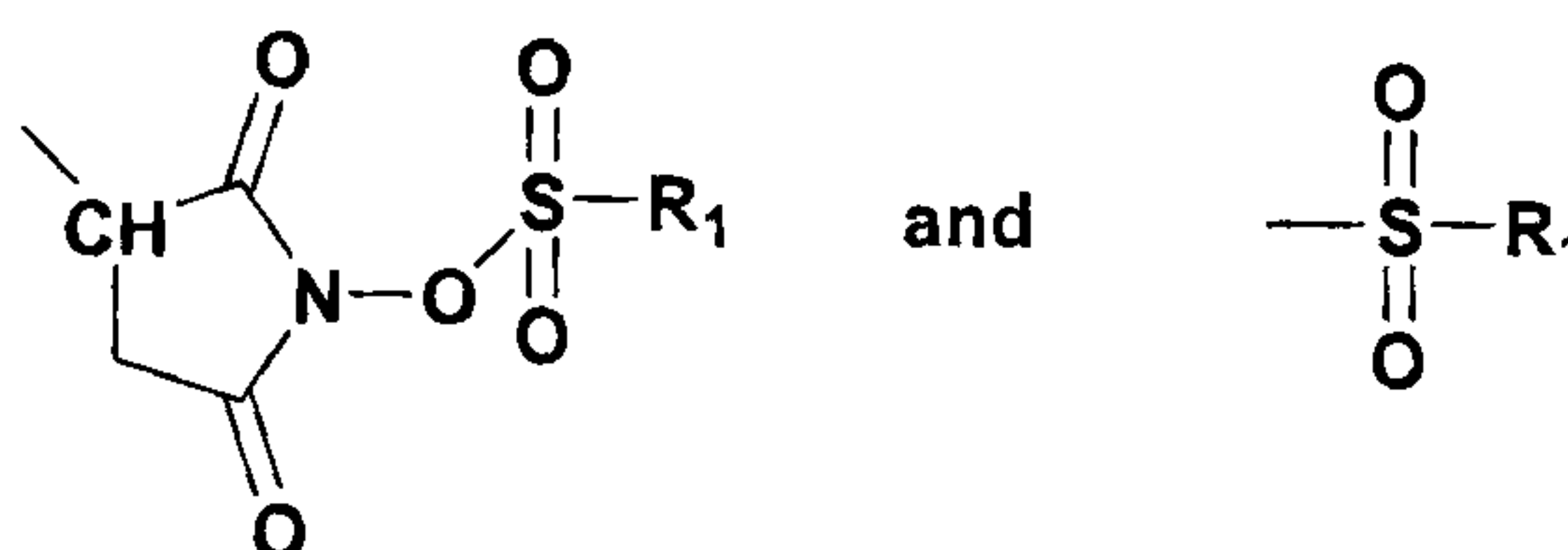
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heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

5 X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

10 Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

20 R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

In still another aspect, the invention provides for the use of a therapeutically effective amount of a compound represented by the structural formula R-X-Y as described above, or physiologically acceptable salts thereof, in the preparation of a medicament for increasing anandamide levels.

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In another aspect, the invention provides for the use of a compound represented by the following structural formula:

5

R-X-Y

or physiologically acceptable salts thereof, in a therapeutically effective amount for stimulating a cannabinoid receptor, wherein:

R is selected from the group consisting of:

10

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

15

20

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

25

a heteroaryl group having 5, 6, 9, or 10 members;

30

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl),

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-CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

5 wherein lower alkyl is a C1 to C5 straight or
 branched chain alkyl group, said aryl and said
 substituted aryl substituents for said heteroaryl
 group have 6 or 10 members, said heteroaryl
 substituents for said heteroaryl group have 5, 6, 9
 or 10 members, and the substituents for said
10 substituted aryl substituents are as previously
 defined;

 a heterocyclic group; and

 a heterocyclic group substituted by a substituent
 selected from the group consisting of: lower alkyl,
15 aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted
 aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower
 alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂,
 -CF₃, -CN, and (lower alkyl)-S-,

 wherein lower alkyl is a C1 to C5 straight or
20 branched chain alkyl group, said aryl and said
 substituted aryl substituents for said heterocyclic
 group have 6 or 10 members, said heteroaryl
 substituents for said heterocyclic group have 5, 6,
 9 or 10 members, and the substituents for said
25 substituted aryl substituents are as previously
 defined;

 X is a straight chain hydrocarbyl group or a
 substituted straight chain hydrocarbyl group containing
 from 4 to 18 carbon atoms if R is an aryl group having 6
30 or 10 members, a substituted aryl group having 6 or 10
 members wherein the substituents for said aryl group are
 as defined above, a heteroaryl group having 5, 6, 9, or
 10 members, a substituted heteroaryl group having 5, 6,
 9, or 10 members wherein the substituents for said

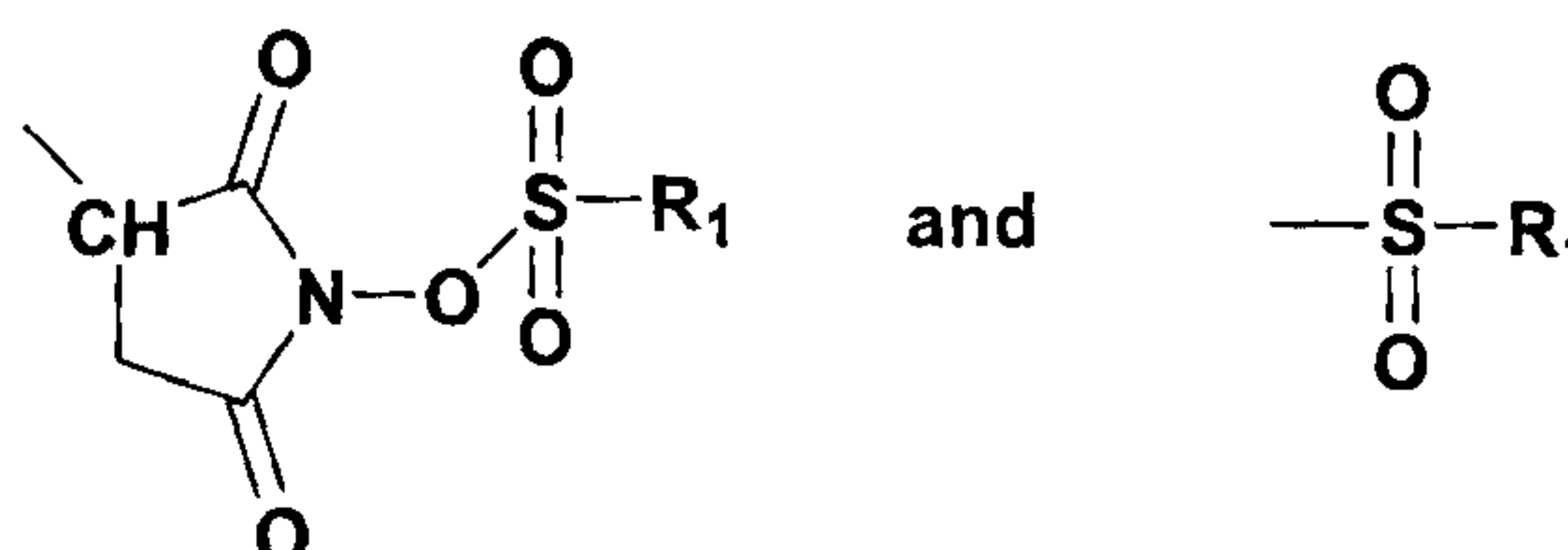
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heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

5 X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

15 Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



20 wherein:

R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

25 In yet another aspect, the invention provides for the use of a therapeutically effective amount of a compound represented by the structural formula R-X-Y as described above, or physiologically acceptable salts thereof, in the preparation of a medicament for stimulating a cannabinoid receptor.

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Brief Description of the Figures

Fig. 1 is a graph showing the effect of
palmitylsulfonyl fluoride and phenylmethanesulfonyl fluoride
5 on anandamide levels in neuroblastoma cells (N18TG2).

Figs. 2A-2E are graphs showing the IC_{50} values for the
inhibition of anandamide amidase by (A) laurylsulfonyl
fluoride; (B) myristylsulfonyl fluoride; (C)
palmitylsulfonyl fluoride; (D) stearyl sulfonyl fluoride;
10 and (E) arachidylsulfonyl fluoride.

Fig. 3 is a graph showing the log dose-response curves
for palmitylsulfonyl fluoride (K_i is 350.4), arachidonyl
trifluoromethyl (K_i is 1325) ketone and arachidonoyl
ethanolamide (K_i is 70.03) in competition with [H^3] CP-55940
15 binding to CB1.

Fig. 4 is a graph showing the effect in rats of
anandamide, palmitylsulfonyl fluoride and anandamide co-
administration of palmitylsulfonyl fluoride on the time
taken for a lightly restrained mouse to flick its tail away
20 from radiant heat stimulus ("rat flick" test), measured by
the percent maximum possible effect.

Detailed Description of the Invention

One embodiment of the present invention is directed to
a method of inhibiting anandamide amidase in an individual
25 or animal. The inhibition of anandamide amidase results in
increased levels of anandamide in the individual or animal,
thereby causing increased stimulation of cannabinoid
receptors in the individual or animal, e.g., the CB1
receptor in the brain and the CB2 receptor in the spleen.
30 Thus, the present invention is also a method of stimulating

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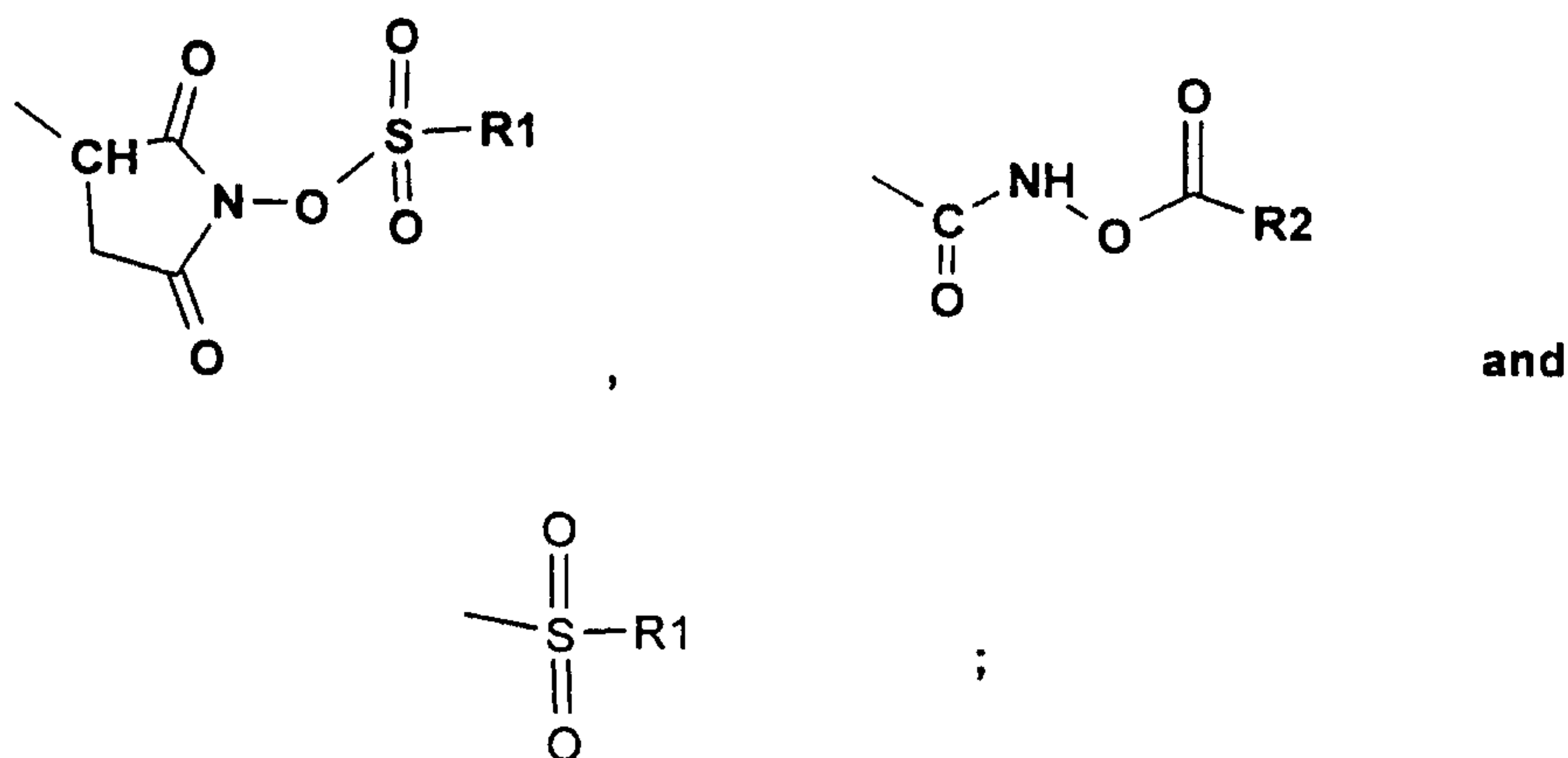
cannabinoid receptors in an individual or animal. It is to be understood that the present invention can also be used to stimulate receptors not yet discovered for which anandamide and/or a cannabinoid acts as an agonist.

5 "Y" in Structural Formula I is a moiety capable of irreversibly binding with a nucleophilic group at the active site of an amidase enzyme. Thus, Y is capable of forming a stable covalent bond with the nucleophilic group at the active site of an amidase enzyme. Suitable
10 structures for Y therefore do not encompass moieties, such as trifluoromethyl ketones, which are capable of acting as a transition state analog of an amidase enzyme and which bind reversibly to these enzymes. As used herein, an "amidase" is an enzyme involved in the hydrolysis of an
15 amide bond.

A nucleophilic group at the active site of an amidase enzyme is a heteroatom-containing functional group on the side chain of an amino acid found at the enzyme active site and includes the hydroxyl group of serine or threonine, the
20 thiol group of cysteine, the phenol group of tyrosine and the amino group of lysine, ornithine or arginine or the imidazole group of histidine.

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Examples of suitable structures for Y include:



R1 is selected from the group consisting of -F and
 -O(C1 to C4 straight or branched chain alkyl group). R2 is
 5 a C1 to C4 straight or branched chain alkyl group.

As used herein, "a straight chain hydrocarbyl group"
 includes a polyalkylene, i.e., $-(CH_2)_n-$. "n" is a positive
 integer from about 10 to about 24, when R is methyl, and
 from about 4 to about 18, when R is aryl, substituted aryl,
 10 heteroaryl, substituted heteroaryl, heterocyclic or
 substituted heterocyclic. A straight chain hydrocarbyl
 group also includes two or more polyalkylene groups
 connected by one or more ether, thioether ether,
 cis-alkenyl, trans-alkenyl or alkynyl linkage such that the
 15 total number of methylene carbon atoms is from about 10 to
 about 24 when R is methyl and from about 4 to 18 when R is
 aryl, substituted aryl, heteroaryl, substituted heteroaryl,
 heterocyclic or substituted heterocyclic. Examples include
 $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_m-S-(CH_2)_o-$, $-(CH_2)_m-CH=CH-(CH_2)_o-$,
 20 $-(CH_2)_m-C\equiv C-(CH_2)_o-$, wherein m and o are each a positive
 integer such that the sum of m and o is equal to n.

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Specific examples include where X is $-(CH_2)_4-(cis-CH=CHCH_2-$
 $)_4-CH_2CH_2-$, $-(CH_2)_4-(cis-CH=CHCH_2)_3-(CH_2)_5-$ and where R-X- is a
 docosatetraenyl or a homo- γ -linolenyl moiety.

In one aspect of the present invention, R in the
 5 compound being administered to inhibit anandamide amidase is
 methyl and Y is a sulfonyl fluoride or a C1 to C4 straight or
 branched chain sulfonyl ester. Preferably, Y is a sulfonyl
 fluoride. Specific examples of sulfonyl fluorides and
 sulfonyl esters include where R-X- is archidyl, Δ^8 , Δ^{11} , Δ^{14} -
 10 eicosatrienyl, docosatetraenyl, homo- γ -linolenyl and CH_3-
 $(CH_2)_n-$, wherein n is 10 (lauryl), 11, 12 (myristyl), 13, 14
 (palmityl), 15 or 16 (stearyl).

As used herein, an "aryl" group is a carbocyclic
 aromatic ring system having 6 or 10 members such as phenyl,
 15 1-naphthyl or 2-naphthyl. A "heteroaryl" group is an
 aromatic ring system having 5-6 or 9-10 members containing
 one or more heteroatoms such as nitrogen, oxygen or sulfur.
 Examples of heteroaryl groups include 2-furanyl, 3-furanyl,
 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl,
 20 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-
 pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-
 imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl,
 5-oxazolyl, 2-thiazolyl, 4-thiazolyl and 5-thiazolyl.
 "Heteroaryl" groups also include fused polycyclic systems in
 25 which one or more monocyclic aryl or monocyclic heteroaryl
 group is fused to another heteroaryl group. Examples include
 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-
 benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl.

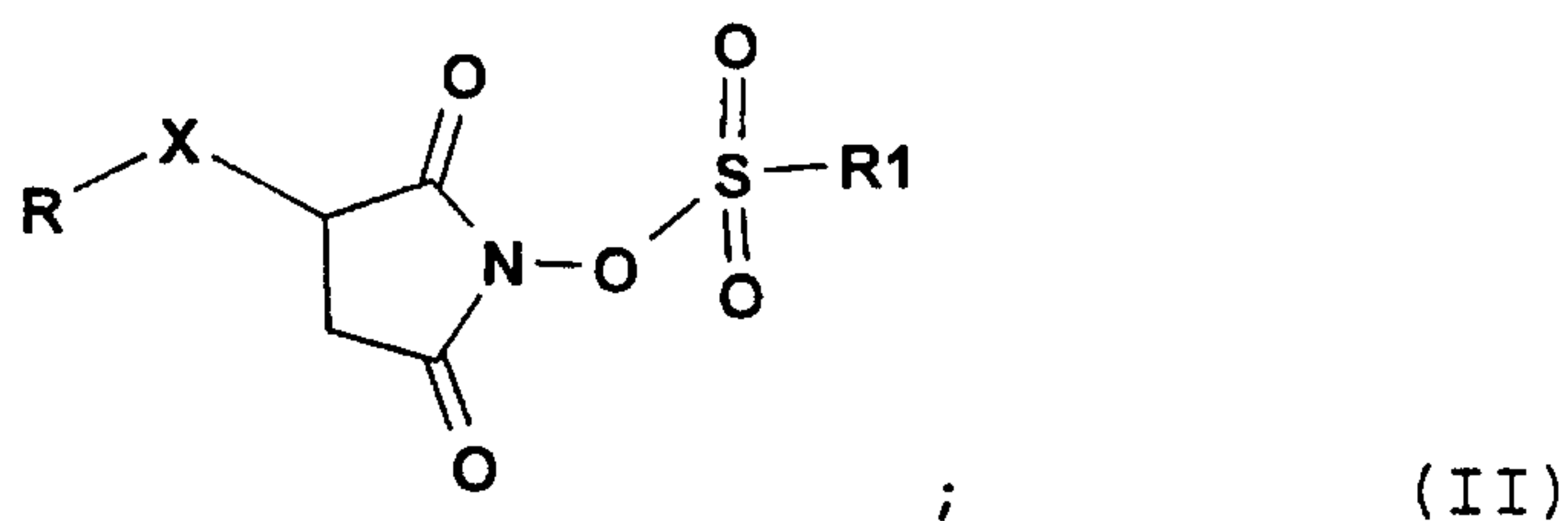
As used herein, a "heterocyclic" group is a C3-C8 non-
 30 aromatic ring system containing one or more heteroatoms such
 as oxygen, nitrogen or sulfur. Examples include 2-
 tetrahydrofuranyl, 3-tetrahydrofuranyl,

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2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

Suitable substituents on a straight chain hydrocarbyl group include methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, ethoxy and hydroxy. Suitable substituents on an aryl, heteroaryl or heterocyclic group include groups such as lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-. A lower alkyl group is a C1 to about C5 straight or branched chain alkyl group.

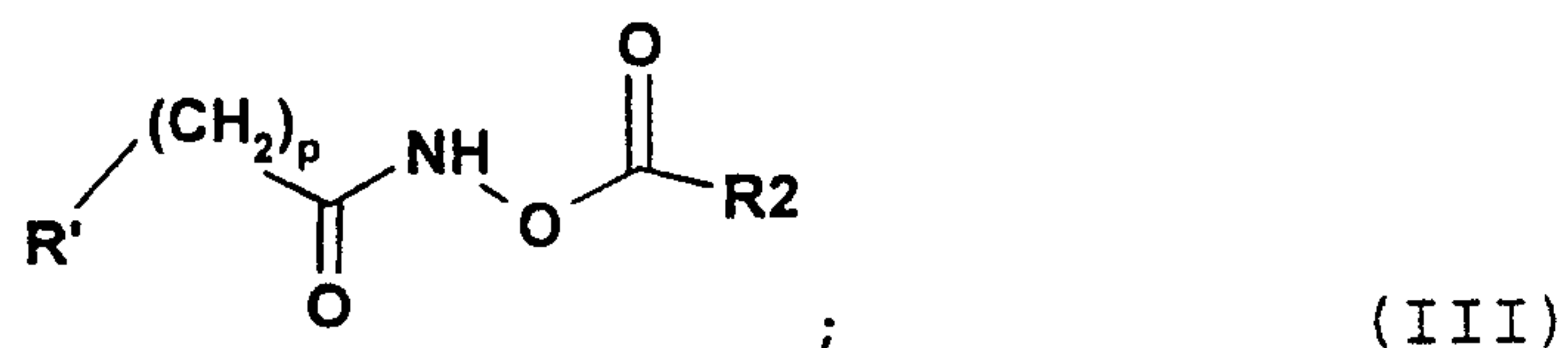
The present invention also refers to novel compounds which can be used to inhibit anandamide amidase. In one embodiment, the compound has a structure represented by Structural Formula (II):



and physiologically acceptable salts thereof. R1 is -F or (C1 to C4 alkyl)O-. R and X are as defined above for Structural Formula (I).

In another embodiment, the novel compound of the present invention has a structure represented by Structural Formula (III):

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and physiologically acceptable salts thereof.

5 R' is selected from the group consisting of an aryl group, a substituted aryl group, a heteroaryl group, a substituted heteroaryl group, a heterocyclic group and a substituted heterocyclic group.

10 R₂ is a C1 to C4 straight or branched chain alkyl group.

p is an integer from about 6 to about 18. In another aspect, p is an integer from about 10 to about 18.

15 A "therapeutically effective amount" of a compound, as used herein, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of anandamide in the individual or animal to cause a discernable increase or decrease in a cellular activity affected or controlled by cannabinoid receptors. For example, anandamide can stimulate receptor-mediated signal transduction that leads to the inhibition of forskolin-stimulated adenylate cyclase (Vogel et al., *J. Neurochem.* 61:352 (1993)). Anandamide also causes partial inhibition of N-type calcium currents via a pertussis toxin-sensitive G protein pathway, independently of cAMP metabolism (Mackie et al., *Mol. Pharmacol.* 47:711 (1993)).

20 A "therapeutically effective amount" of an anandamide inhibitor can also be an amount which results in a sufficiently high level of anandamide in an individual or animal to cause a physiological effect resulting from

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stimulation of cannabinoid receptors. Physiological effects which result from cannabinoid receptor stimulation include analgesia, decreased nausea resulting from chemotherapy, sedation and increased appetite. Other physiological functions include relieving intraocular pressure in glaucoma patients and suppression of the immune system. Typically, a "therapeutically effective amount" of the compound ranges from about 10 mg/day to about 1000 mg/day.

10 As used herein, an "individual" refers to a human. An "animal" refers to veterinary animals, such as dogs, cats, horses, and the like, and farm animals, such as cows, pigs, guinea pigs and the like.

The compounds of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular or subcutaneous administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles may include saline, sterile water, Ringer's solution, and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

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General methods of preparing the sulfonyl fluorides, the N-[(alkyl-sulfonyl)oxy] succinimides and the N-O-diacylhydroxylamines of the present invention are provided in Example 5, Example 6 and Example 7, respectively.

The invention will now be further and specifically described by the following examples.

EXEMPLIFICATION

Example 1 - Increased [³H]Anandamide Levels in Neuroblastoma Cells in the Presence of Palmityl Sulfonyl Fluoride

The assay of the anandamide amidase in intact neuroblastoma cells was performed as described previously (Deutsch, D. G. and S.A. Chin, *Biochem. Pharmacol.* 46:791-796 (1993)). The experiments were performed with 4 x 10⁶ neuroblastoma cells (N18TG2)/6-cm dish. Experimental cells were incubated in 2 ml of media, consisting of Hams's F-12/Dulbecco's modified Eagle's medium (Life Technologies, Inc.) with penicillin, streptomycin, and gentamicin plus 10% bovine calf serum (HyClone, Logan, UT), plus the indicated concentration of inhibitor for 20 minutes. All cells were grown at 37° in a humidified atmosphere containing 5% CO₂ in air. [³H]Anandamide (0.2 μCi of 221 Ci/mmol of [³H]anandamide) was added and the incubation continued for 1 hour. Control cells contained no inhibitor. At the end of the incubation, the cells were washed once with cell culture media and removed from the plates, after a brief incubation with 2 ml of 0.05% trypsin in 0.53 mM EDTA solution at 37°C. The amounts of [³H]anandamide, [³H]phospholipids, and [³H]arachidonate in the cells and media were quantified by liquid scintillation counting of the silica scraped from the appropriate areas

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of the plate after quenching the reaction with chloroform
methanol (1:1), extraction of the sample from the organic
phase, and TLC analysis on channeled silica gel-coated
plates, with a solvent system consisting of the organic
5 layer of an ethyl acetate:hexane:acetic acid:water
(100:50:20:100) mixture.

The level of [³H] anandamide found in the
neuroblastoma cells incubated with palmitylsulfonyl
fluoride, with phenylmethylsulfonyl fluoride and in control
10 cells is shown in Figure 1. Nanomolar amounts of
palmitylsulfonyl fluoride were sufficient so that over 50%
of the radioactivity was found in anandamide, rather than
in anandamide cleavage products such as arachidonate. This
result indicates that palmitylsulfonyl fluoride is highly
15 effective at inhibiting anandamide amidase. Concentrations
greater than 10 micromolar of phenylmethylsulfonyl fluoride
were required to achieve comparable levels of anandamide
amidase inhibition. Almost complete degradation of [³H]
anandamide was observed in control cells.

20 Example 2 - Determination of IC₅₀ Values for Sulfonyl
Fluoride Inhibitors of Anandamide Amidase

The assay of the anandamide amidase *in vitro* was
performed as described previously (Deutsch, D. G. and S.A.
Chin, *Biochem. Pharmacol.* 46:791-796 (1993)). The
25 indicated amount of each compound was preincubated in a
buffer consisting of 300 µg of crude rat brain homogenate
protein, 500 µg/ml fatty acid-free bovine serum albumin, in
phosphate-buffered saline in a final volume of 1.0 ml, for
10 minutes at 37°C. Crude rat brain homogenate was
30 obtained by decapitating female adult Sprague-Dawley rats,
dissecting the desired tissue and homogenizing in five
volumes of ice-cold TE (10 mM Tris-HCl, 1 mM EDTA, pH 7.6).
Substrate (27.7 µM anandamide + 0.2 µCi of 221 Ci/mmol

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[³H]anandamide ([arachidonyl-5,6,8,9,11,12,14,15-³H]ethanolamide)) (obtained from the National Institute on Drug Abuse) was then added and the samples incubated for 10 minutes. The reaction was quenched by the addition of 5 chloroform:methanol (1:1) and enzyme activity was analyzed by TLC as described in Example 1.

The results for laurylsulfonyl fluoride, myristylsulfonyl fluoride, palmitylsulfonyl fluoride, stearyl sulfonyl fluoride and arachidylsulfonyl fluoride are 10 shown in Figure 2. All compounds were effective inhibitors of anandamide amidase. All compounds except arachidylsulfonyl fluoride had an IC₅₀ of less than 10 nM. Arachidylsulfonyl fluoride was an effective inhibitor of anandamide amidase at concentrations less than 100 nM.

15 Example 3 - Palmitylsulfonyl Fluoride Binds Less Efficiently to the CB1 Receptor than Anandamide

For the CBR1 ligand binding determinations, brain membranes were prepared from frozen rat brains according to the procedure published by Devane et al. (Devane, W.A., et 20 al., *Mol. Pharmacol.* 34:605-613 (1988)). Quantitation of the binding of the fatty acid analogs to CB1 was performed by incubating the analogs at the indicated concentration with 30 µg of membrane protein in a buffer containing 500 pm of the bicyclic cannabinoid analog [³H]CP-55940, 20mM 25 Tris-Cl, pH 7.4, 3 mM MgCl₂, 1 mM Tris-EDTA, and 0.135 mg/ml fatty acid-deficient bovine serum albumin in a final volume of 200 µl in Regisil-treated glass tubes. Specific binding was defined as that which could be displayed by 100 nM desacetyllevonantradol. After 60 minutes at 30°C, the 30 incubation was terminated by the addition of 250 µl of 50 mg/ml bovine serum albumin and the immediate filtration over GF/B filters and washing with ice cold buffer (20 mM Tris-Cl, pH 7.4, 2 mM MgCl₂). The filters were treated

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with 0.1% sodium dodecyl sulfate prior to addition of scintillation mixture and counting in a liquid scintillation counter.

The log dose-response curve for palmitylsulfonyl fluoride, arachidonoyl trifluoromethyl ketone and arachidonoyl ethanolamide in competition with [³H]CP-55940 binding CB1 is shown in Figure 3. This figure shows that palmitylsulfonyl fluoride binds to the CB1 receptor with less than 10% the efficiency of arachidonoyl ethanolamide.

10 Example 4 - Palmitylsulfonyl Fluoride Induces Analgesia in Rats

Drug mixture were prepared by mixing with two parts Tween 80 by weight and dispersing into 0.9% w/v aqueous NaCl solution (saline) as described previously for Δ⁹-THC
15 (Pertwee et al., *Br. J. Pharmacol.* 105:980 (1992)).

Drug mixtures were injected intravenously into male MF1 mice weighing 23-29 grams. Analgesia was measured by means of a "rat flick test" in which the time taken for a lightly restrained mouse to flick it tail away from a
20 radiant heat stimulus was noted. The methods is based on the test described by D'Amour and Smith (D'Amour, F.E., Smith, D. L., *J. Pharmacol. Exp. Ther.*, 72:74-79 (1941)). Mice were subjected to the tail flick at -30 minutes (control latency) and at 12 minutes (test latency). The
25 maximum possible tail flick latency was 10s as mice that did not respond within this time were removed from the apparatus to prevent tissue damage. Analgesia was calculated as percent maximum possible effect by expressing the ratio (test latency - control latency)/(10-s control
30 latency) as a percentage (Compton, D. R., et al., *J. Pharmacol. Exp. Ther.*, 260:201-209 (1992)). Ambient temperature was kept between 20 and 22°C. Values have been expressed as means and limits of error as standard errors.

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Dunnett's test has been used to calculate the significance of differences between the mean effect of each drug treatment and the mean effect of the vehicle, Tween 80.

The results are shown in Figure 4. Palmitylsulfonyl fluoride and anandamide co-administered with
5 palmitylsulfonyl fluoride were about 3x more effective at producing analgesia in the mice than anandamide alone and about 13x more effective than the vehicle.

Example 5 - Alkylsulfonyl Fluorides

10 Alkylmagnesium bromide in dry ether was added to a stirred solution of sulfuryl chloride (2-fold excess) in hexane at 0°C. The reaction mixture was stirred for 1 hour at 0°C and then the ice bath was removed and stirring was continued overnight at room temperature. The solvent was
15 evaporated in vacuo and the product was purified with column chromatography on silica gel to afford the corresponding alkylsulfonyl chloride as white solid.

Alkylsulfonyl chloride was dissolved in acetone and a 10-fold excess of ammonium fluoride was added while
20 stirring at room temperature. The reaction mixture was refluxed for 3 hours. Then it was filtered to remove the insoluble salt, the solvent was evaporated and the product was dried in vacuo. Water was added to hydrolyze any unreacted alkylsulfonyl chloride and the aqueous mixture
25 was extracted with ether. The ethereal extracts were combined, dried, filtered and the solvent was removed in vacuo. The product was purified with column chromatography on silica gel to afford the corresponding alkylsulfonyl fluoride.

30 Example 6 - Alkyl-N-[alkyl-sulfonyl]oxyl Succinimides

Stobbe condensation of aldehydes with diethylsuccinate affords the corresponding alkenylsuccinic acid monoethyl

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esters which are catalytically hydrogenated and subsequently hydrolyzed to give the corresponding alkylsuccinic acids. The acids are mixed with excess of acetic anhydride and refluxed for 1 hour. The excess of
5 acetic anhydride is removed *in vacuo*. Vacuum distillation affords the pure alkylsuccinic anhydrides.

The pure products are dissolved in dry toluene and brought to reflux. An equimolar amount of (benzyloxy)amine in toluene is added and the mixtures are refluxed for 30
10 minutes. The hot solutions are filtered through anhydrous sodium sulfate and the solvent is removed on a rotary evaporator. The residues are dissolved in ethyl acetate and washed with 10% sodium bicarbonate twice and then purified with column chromatography on silica gel.

15 The resulting 3-alkenyl-N-(benzyloxy)succinimides are hydrogenolyzed with 10% Pd-C for 3 hours. The reaction mixtures are then filtered through a Celite pad and the solvent removed *in vacuo*. The produced 3-alkyl-N-hydroxysuccinimides are then dissolved in dry toluene and
20 treated with dry pyridine and various alkylsulfonyl chlorides. The reactions are stirred overnight at room temperature under nitrogen and then quenched with the addition of 2N HCl. The products are extracted with ethyl acetate (twice), dried over anhydrous MgSO₄ and purified
25 with column chromatography.

Example 7 - N,O-diacylhydroxylamines

Methyl esters of various carboxylic acids are treated with excess of hydroxylamine in methanol. Equimolar amounts of KOH and various acid chlorides dissolved in THF
30 are added to aqueous solutions of the hydroxamic acids at 0-5°C in order to afford the corresponding N,O-diacylhydroxylamines.

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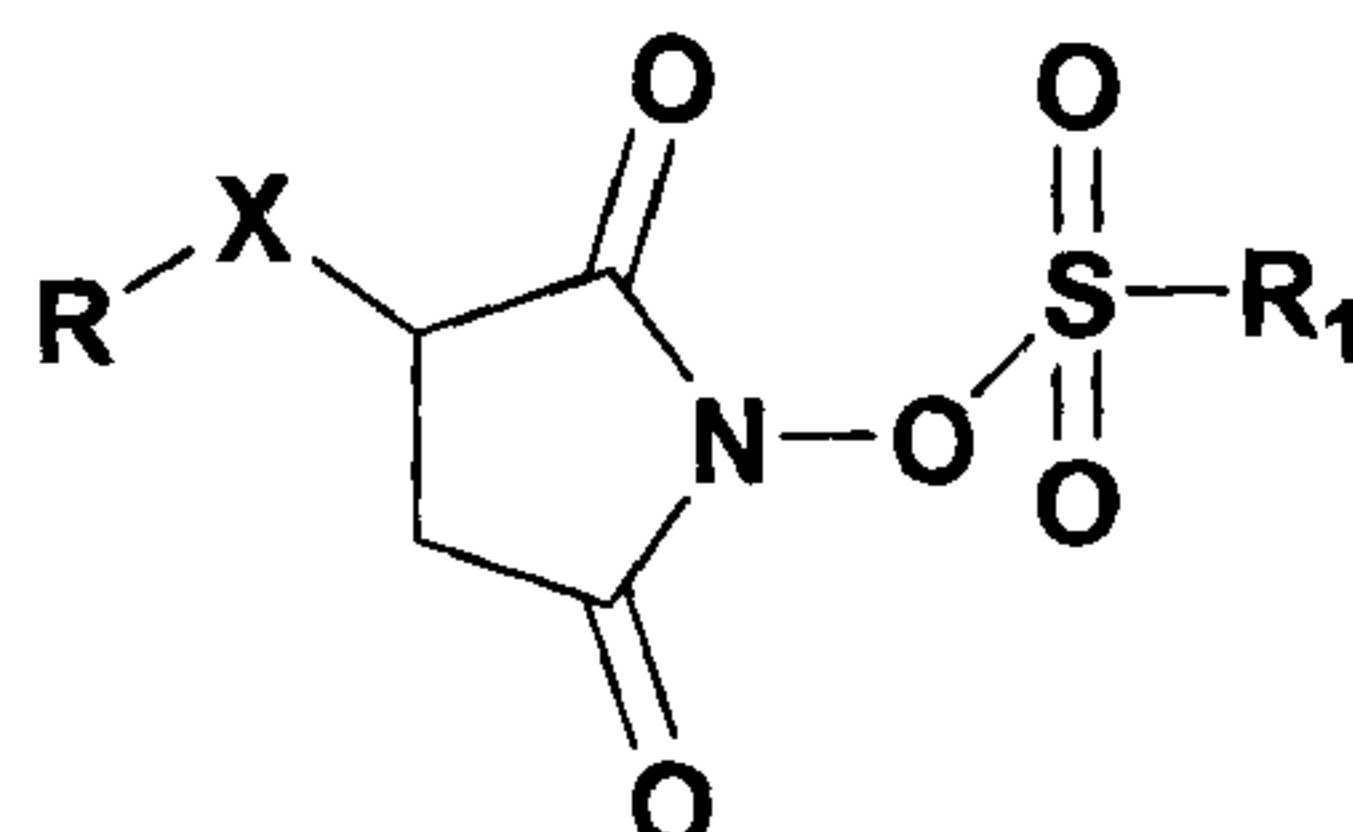
Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to specific embodiments of the invention
5 described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

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CLAIMS

1. A compound represented by the following structural formula:



or physiologically acceptable salts thereof, wherein:

R₁ is -F or (C₁ to C₄ straight or branched chain alkyl)O-;

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C₁ to C₅ straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of:

- 20 -

lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl

- 21 -

group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy.

2. The compound of Claim 1, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-

benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

3. The compound of Claim 1 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

4. The compound of Claim 3 wherein R1 is -F.

5. The compound of Claim 1 wherein:

R is selected from the group consisting of an aryl group, a substituted aryl group, a heteroaryl group, a substituted heteroaryl group, a heterocyclic group and a substituted heterocyclic group;

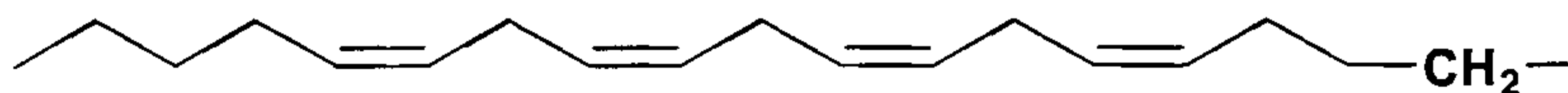
said aryl group, said heteroaryl group, said heterocyclic group, and substituents for said aryl group, said heteroaryl group, and said heterocyclic group being defined as in Claim 1; and

X is $-(\text{CH}_2)_m-$, wherein m is an integer from 4 to 18.

6. The compound of Claim 5 wherein R1 is -F.

7. The compound of Claim 1 wherein R-X- is represented by the following structural formula:

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8. The use of a compound represented by the following structural formula:

R-X-Y

or physiologically acceptable salts thereof, to inhibit anandamide amidase, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl),

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-CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10

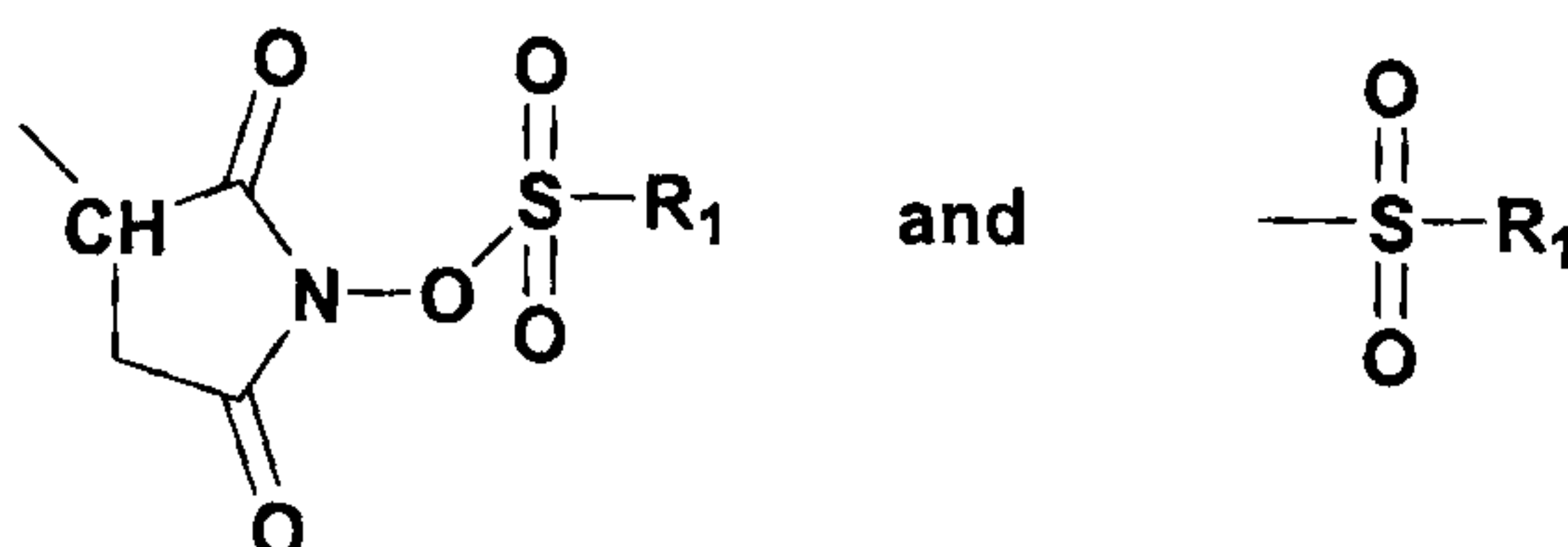
- 25 -

members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

9. The use as claimed in Claim 8, wherein

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said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

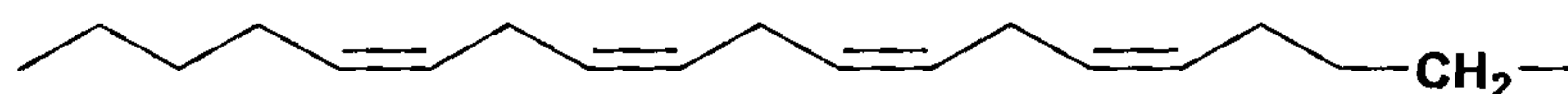
said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

10. The use as defined in Claim 8 wherein Y is $-\text{SO}_2\text{O}(\text{C1 to C4 straight or branched chain alkyl group})$.

11. The use as defined in Claim 8 wherein Y is $-\text{SO}_2\text{OCH}_3$.

12. The use as defined in Claim 11 wherein R-X- is:

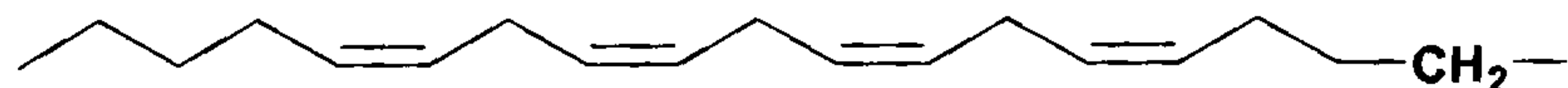


13. The use as defined in Claim 11 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

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14. The use of Claim 8 wherein Y is $-\text{SO}_2\text{F}$.

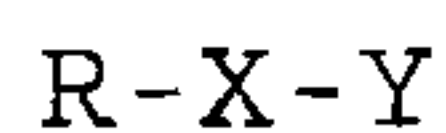
15. The use of Claim 14 wherein R-X- is:



16. The use of Claim 14 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

17. The use of Claim 16 wherein n is 14.

18. The use of a therapeutically effective amount of a compound represented by the following structural formula:



or physiologically acceptable salts thereof, in the preparation of a medicament for inhibiting anandamide amidase, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, $-\text{CO}-\text{O}(\text{lower alkyl})$, $-\text{CHO}$, $-\text{CO}-(\text{lower alkyl})$, $-\text{CO}-\text{NH}(\text{lower alkyl})$, $-\text{CO}-\text{N}(\text{lower alkyl})_2$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CN}$, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

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a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

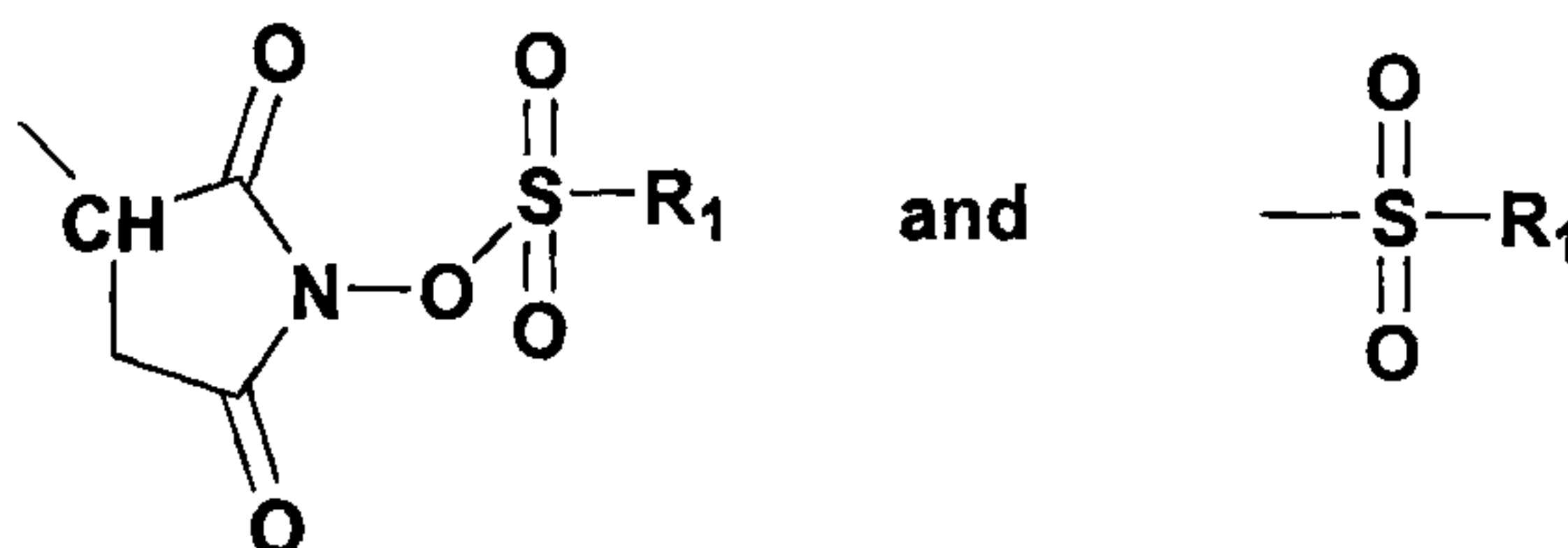
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X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



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wherein:

R1 is selected from the group consisting of -F and -O(C1 to C4 straight or branched chain alkyl group).

19. The use as claimed in Claim 18, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

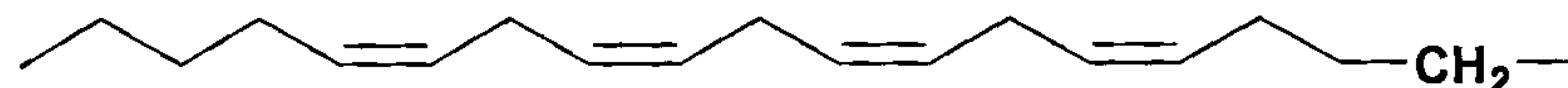
said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

20. The use as defined in Claim 18 wherein Y is -SO₂O(C1 to C4 straight or branched chain alkyl group).

21. The use as defined in Claim 18 wherein Y is -SO₂OCH₃.

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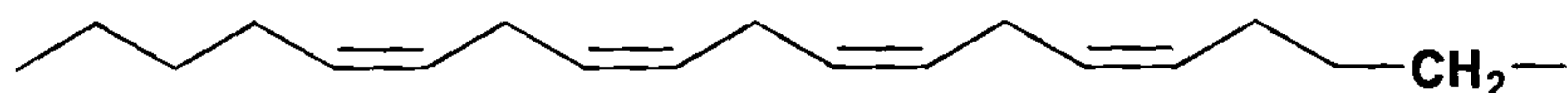
22. The use as defined in Claim 21 wherein R-X- is:



23. The use as defined in Claim 21 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

24. The use of Claim 18 wherein Y is $-\text{SO}_2\text{F}$.

25. The use of Claim 24 wherein R-X- is:

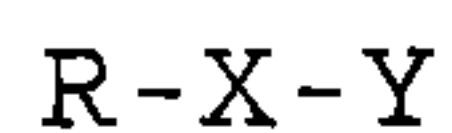


26. The use of Claim 24 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

27. The use of Claim 26 wherein n is 14.

28. The use as claimed in any one of claims 18 to 27, wherein the medicament comprises a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the formula R-X-Y together with a pharmaceutically acceptable carrier.

29. The use of a compound represented by the following structural formula:



or physiologically acceptable salts thereof, in a therapeutically effective amount for inducing analgesia, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

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an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

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a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

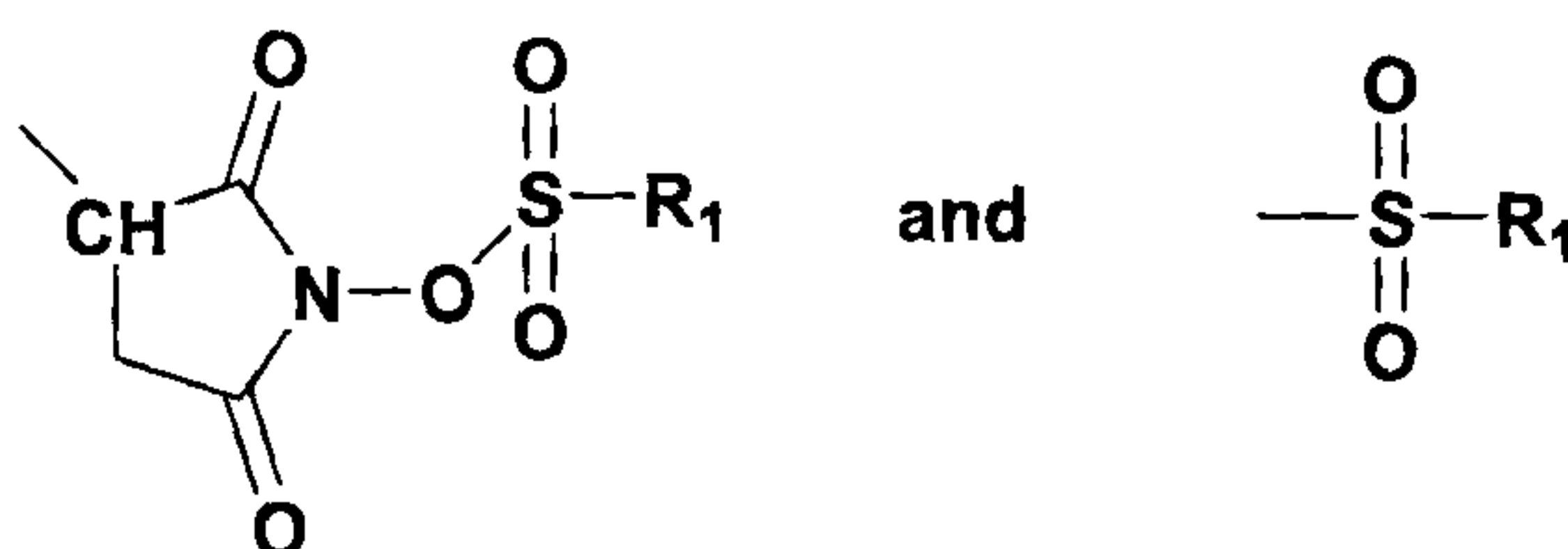
X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent

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selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

30. The use as claimed in Claim 29, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-

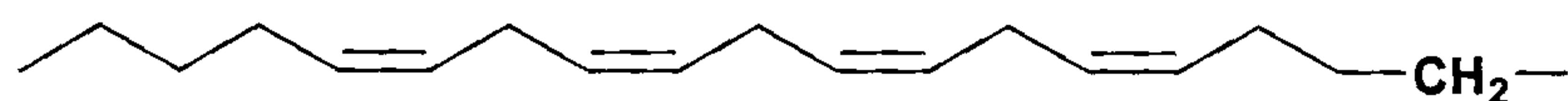
- 35 -

tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

31. The use as defined in Claim 29 wherein Y is $-\text{SO}_2\text{O}$ (C1 to C4 straight or branched chain alkyl group).

32. The use as defined in Claim 29 wherein Y is $-\text{SO}_2\text{OCH}_3$.

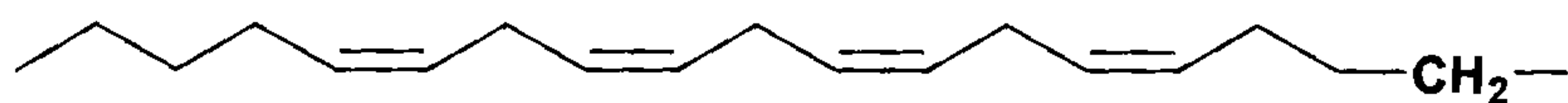
33. The use as defined in Claim 32 wherein R-X- is:



34. The use as defined in Claim 32 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

35. The use of Claim 29 wherein Y is $-\text{SO}_2\text{F}$.

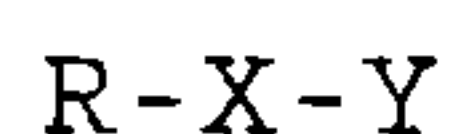
36. The use of Claim 35 wherein R-X- is:



37. The use of Claim 35 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

38. The use of Claim 37 wherein n is 14.

39. The use of a therapeutically effective amount of a compound represented by the following structural formula:



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or physiologically acceptable salts thereof, in the preparation of a medicament for inducing analgesia, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said

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heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

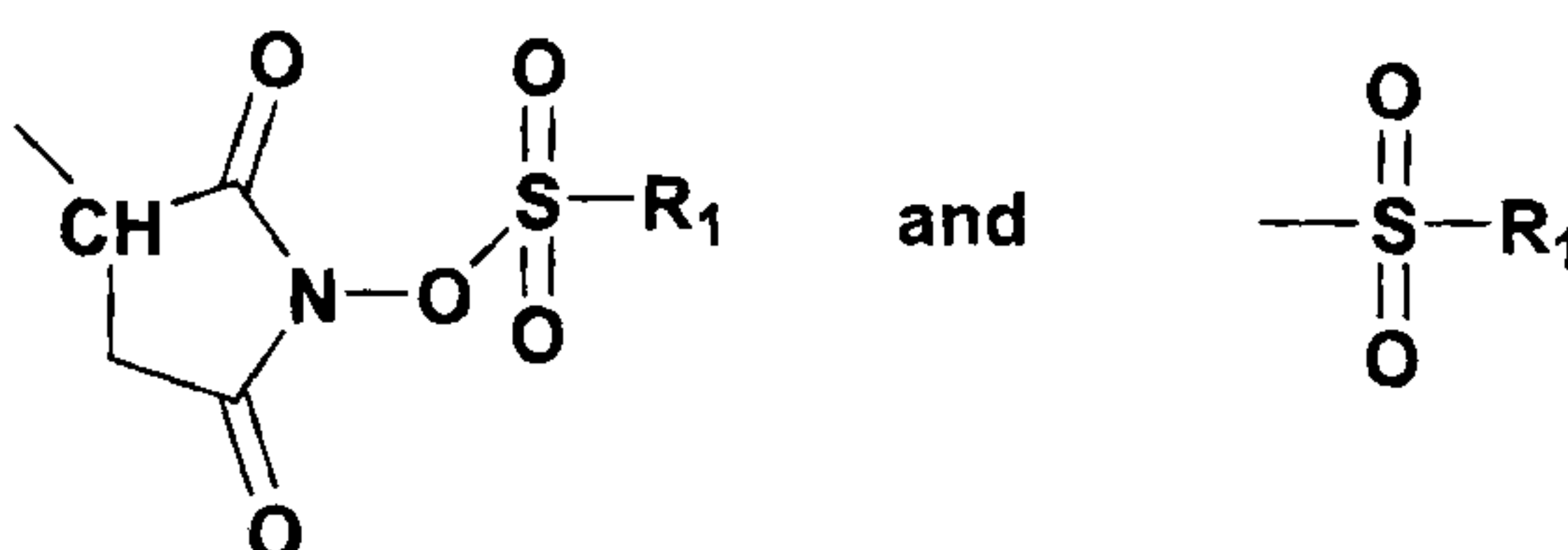
X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

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X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

R1 is selected from the group consisting of -F and -O(C1 to C4 straight or branched chain alkyl group).

40. The use as claimed in Claim 39, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-

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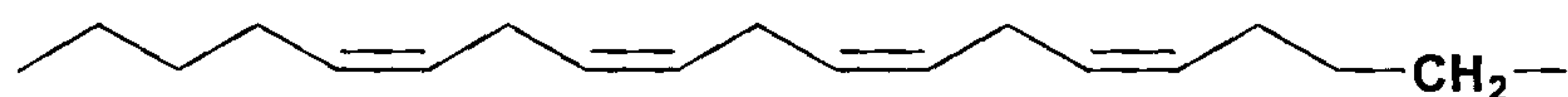
pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

41. The use as defined in Claim 39 wherein Y is $-\text{SO}_2\text{O}(\text{C1 to C4 straight or branched chain alkyl group})$.

42. The use as defined in Claim 39 wherein Y is $-\text{SO}_2\text{OCH}_3$.

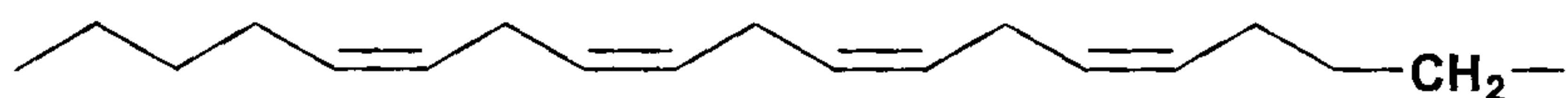
43. The use as defined in Claim 42 wherein R-X- is:



44. The use as defined in Claim 42 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n$; wherein n is an integer from 10 to 24.

45. The use of Claim 39 wherein Y is $-\text{SO}_2\text{F}$.

46. The use of Claim 45 wherein R-X- is:



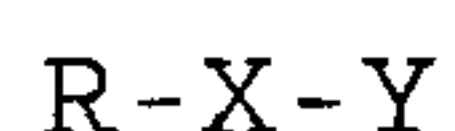
47. The use of Claim 45 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n$, wherein n is an integer from 10 to 24.

48. The use of Claim 47 wherein n is 14.

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49. The use as claimed in any one of claims 39 to 48, wherein the medicament comprises a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the formula R-X-Y together with a pharmaceutically acceptable carrier.

50. The use of a compound represented by the following structural formula:



or physiologically acceptable salts thereof, in a therapeutically effective amount for increasing anandamide levels, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a

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substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl

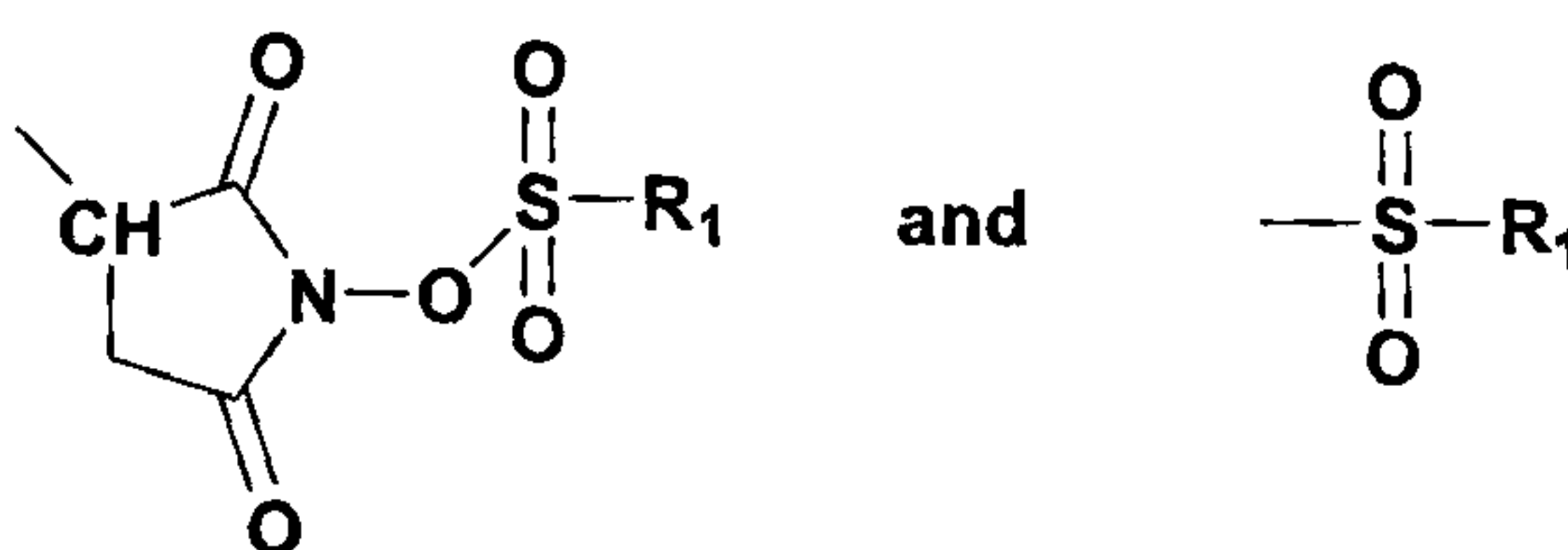
- 42 -

group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

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51. The use as claimed in Claim 50, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

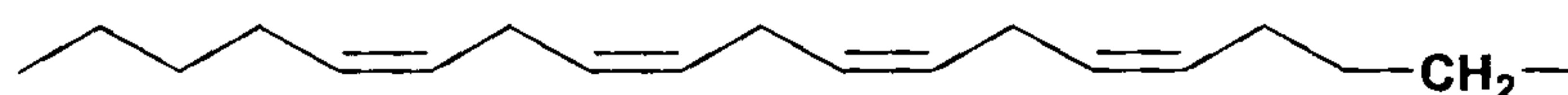
said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

52. The use as defined in Claim 50 wherein Y is $-\text{SO}_2\text{O}(\text{C1 to C4 straight or branched chain alkyl group})$.

53. The use as defined in Claim 50 wherein Y is $-\text{SO}_2\text{OCH}_3$.

54. The use as defined in Claim 53 wherein R-X- is:

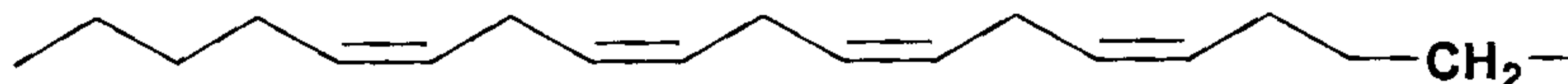


55. The use as defined in Claim 53 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

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56. The use of Claim 50 wherein Y is $-\text{SO}_2\text{F}$.

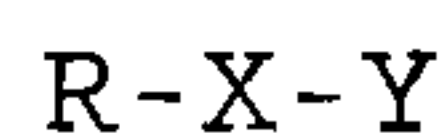
57. The use of Claim 56 wherein R-X- is:



58. The use of Claim 56 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

59. The use of Claim 58 wherein n is 14.

60. The use of a therapeutically effective amount of a compound represented by the following structural formula:



or physiologically acceptable salts thereof, in the preparation of a medicament for increasing anandamide levels, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, $-\text{CO}-\text{O}(\text{lower alkyl})$, $-\text{CHO}$, $-\text{CO}-(\text{lower alkyl})$, $-\text{CO}-\text{NH}(\text{lower alkyl})$, $-\text{CO}-\text{N}(\text{lower alkyl})_2$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CN}$, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

- 45 -

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

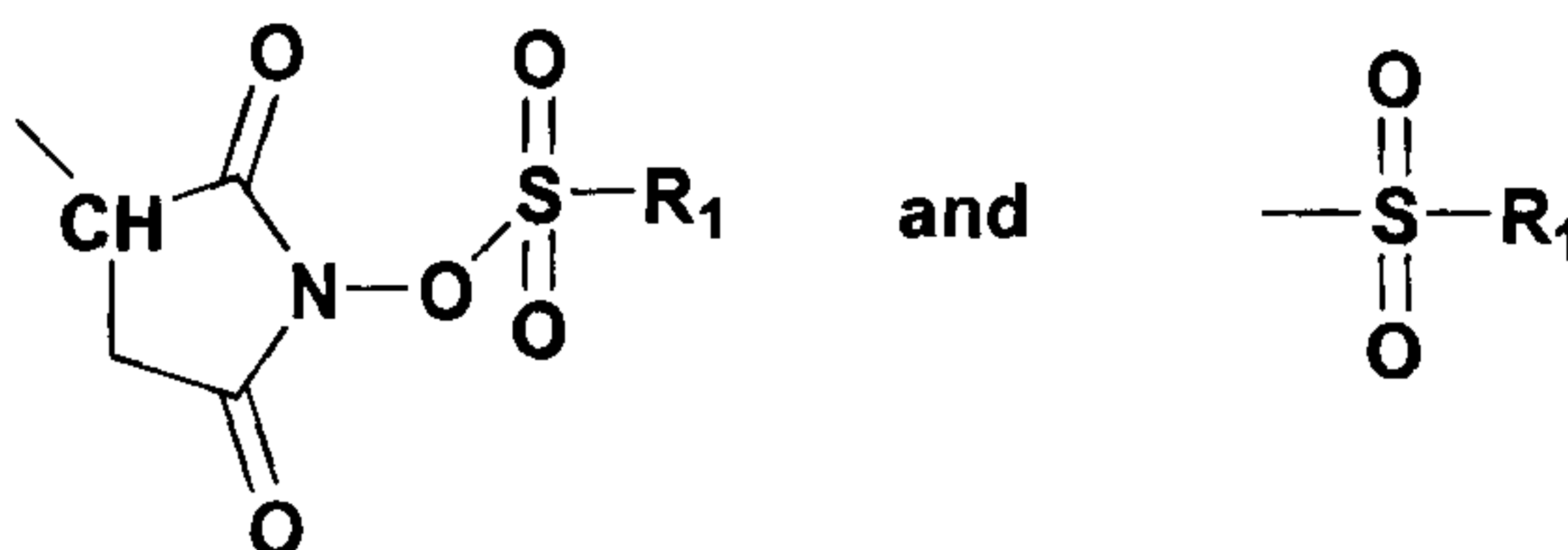
- 46 -

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



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wherein:

R1 is selected from the group consisting of -F and -O(C1 to C4 straight or branched chain alkyl group).

61. The use as claimed in Claim 60, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

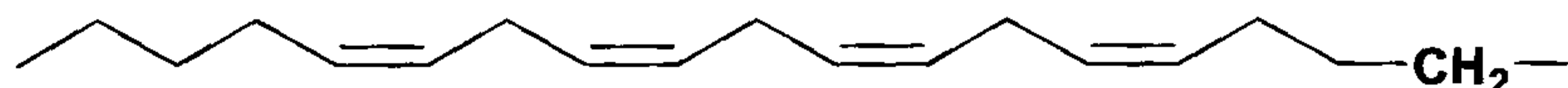
said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

62. The use as defined in Claim 60 wherein Y is -SO₂O(C1 to C4 straight or branched chain alkyl group).

63. The use as defined in Claim 60 wherein Y is -SO₂OCH₃.

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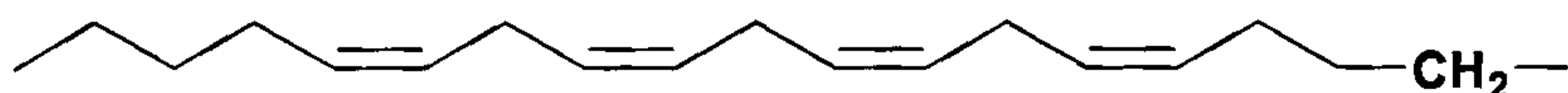
64. The use as defined in Claim 63 wherein R-X- is:



65. The use as defined in Claim 63 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

66. The use of Claim 60 wherein Y is $-\text{SO}_2\text{F}$.

67. The use of Claim 66 wherein R-X- is:

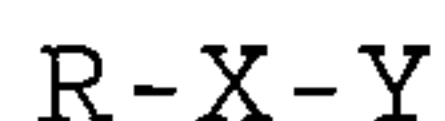


68. The use of Claim 66 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

69. The use of Claim 68 wherein n is 14.

70. The use as claimed in any one of claims 60 to 69, wherein the medicament comprises a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the formula R-X-Y together with a pharmaceutically acceptable carrier.

71. The use of a compound represented by the following structural formula:



or physiologically acceptable salts thereof, in a therapeutically effective amount for stimulating a cannabinoid receptor, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

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an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

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a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

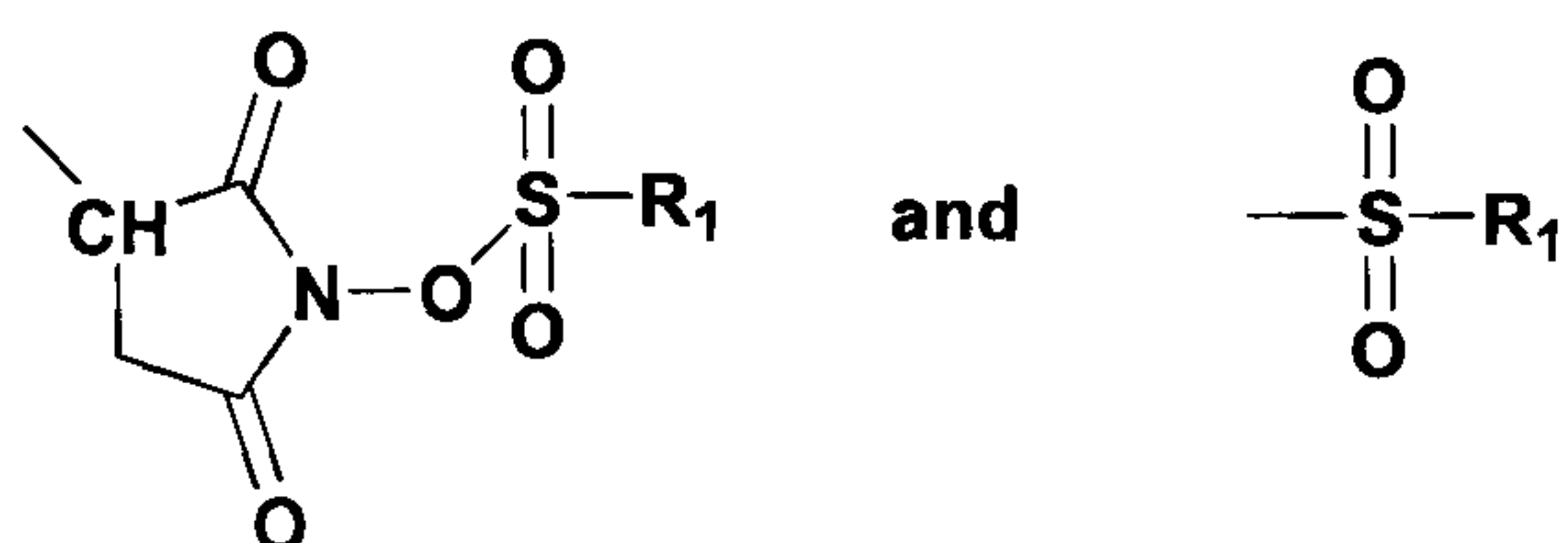
X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent

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selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

R₁ is selected from the group consisting of -F and -O(C₁ to C₄ straight or branched chain alkyl group).

72. The use as claimed in Claim 71, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-

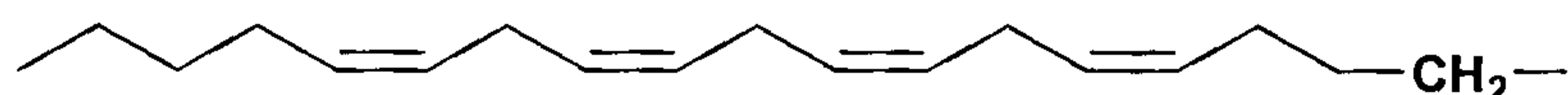
- 52 -

tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

73. The use as defined in Claim 71 wherein Y is $-\text{SO}_2\text{O}(\text{C1 to C4 straight or branched chain alkyl group})$.

74. The use as defined in Claim 71 wherein Y is $-\text{SO}_2\text{OCH}_3$.

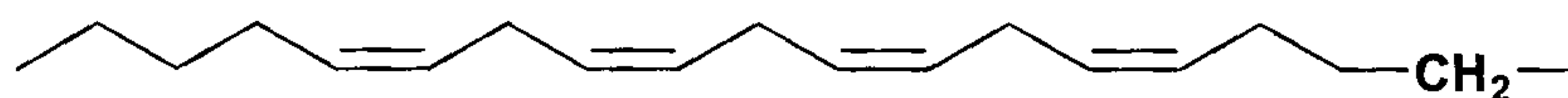
75. The use as defined in Claim 74 wherein R-X- is:



76. The use as defined in Claim 74 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

77. The use of Claim 71 wherein Y is $-\text{SO}_2\text{F}$.

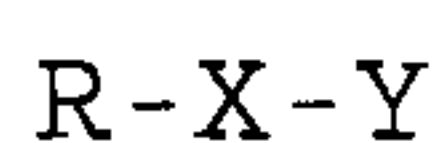
78. The use of Claim 77 wherein R-X- is:



79. The use of Claim 77 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

80. The use of Claim 79 wherein n is 14.

81. The use of a therapeutically effective amount of a compound represented by the following structural formula:



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or physiologically acceptable salts thereof, in the preparation of a medicament for stimulating a cannabinoid receptor, wherein:

R is selected from the group consisting of:

a methyl group;

an aryl group having 6 or 10 members;

an aryl group having 6 or 10 members wherein said aryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents have 6 or 10 members, said heteroaryl substituents have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heteroaryl group having 5, 6, 9, or 10 members;

a heteroaryl group having 5, 6, 9, or 10 members wherein said heteroaryl group is substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heteroaryl group have 6 or 10 members, said

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heteroaryl substituents for said heteroaryl group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

a heterocyclic group; and

a heterocyclic group substituted by a substituent selected from the group consisting of: lower alkyl, aryl, heteroaryl, (lower alkyl)-O-, (aryl or substituted aryl)-O-, halo, -CO-O(lower alkyl), -CHO, -CO-(lower alkyl), -CO-NH(lower alkyl), -CO-N(lower alkyl)₂, -NO₂, -CF₃, -CN, and (lower alkyl)-S-,

wherein lower alkyl is a C1 to C5 straight or branched chain alkyl group, said aryl and said substituted aryl substituents for said heterocyclic group have 6 or 10 members, said heteroaryl substituents for said heterocyclic group have 5, 6, 9 or 10 members, and the substituents for said substituted aryl substituents are as previously defined;

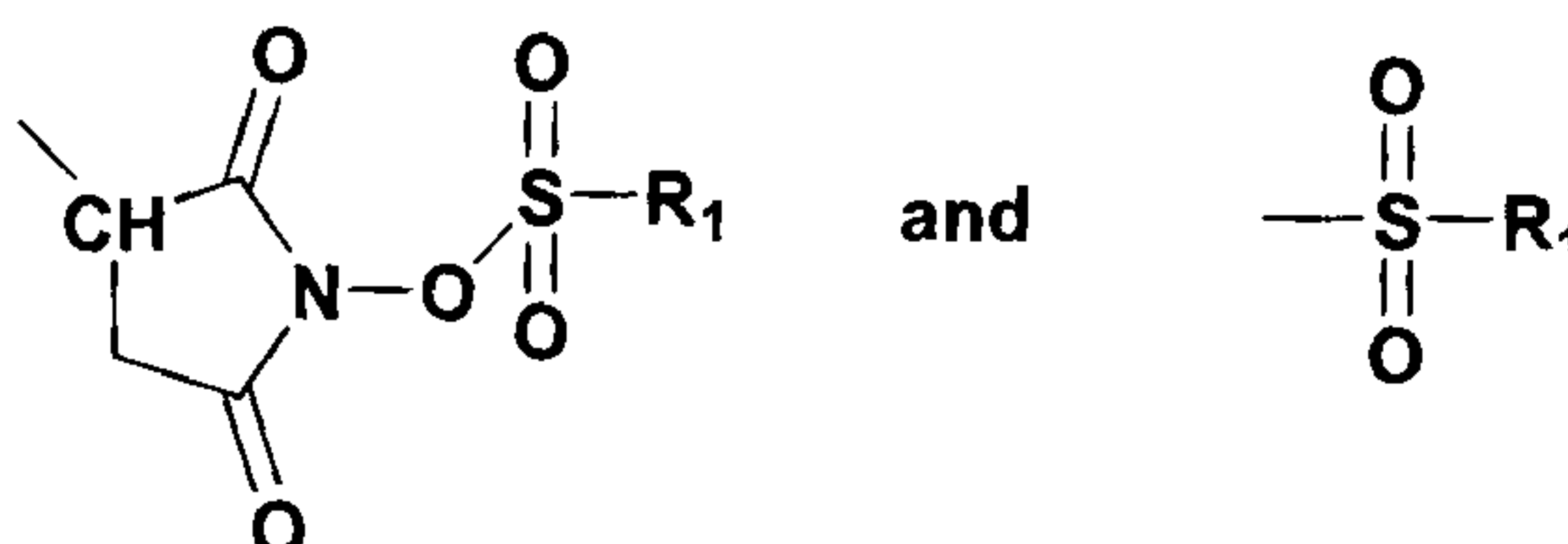
X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 4 to 18 carbon atoms if R is an aryl group having 6 or 10 members, a substituted aryl group having 6 or 10 members wherein the substituents for said aryl group are as defined above, a heteroaryl group having 5, 6, 9, or 10 members, a substituted heteroaryl group having 5, 6, 9, or 10 members wherein the substituents for said heteroaryl group are as defined above, a heterocyclic group, or a substituted heterocyclic group wherein the substituents for said heterocyclic group are as defined above; and

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X is a straight chain hydrocarbyl group or a substituted straight chain hydrocarbyl group containing from 10 to 24 carbon atoms if R is a methyl group;

wherein said substituted straight chain hydrocarbyl group is substituted by a substituent selected from the group consisting of: methyl, ethyl, hydroxy, hydroxymethyl, thiol, methoxy, and ethoxy; and

Y is a moiety capable of irreversibly binding to a nucleophilic group at the active site of an amidase enzyme, wherein Y is selected from the group consisting of:



wherein:

R1 is selected from the group consisting of -F and -O(C1 to C4 straight or branched chain alkyl group).

82. The use as claimed in Claim 81, wherein

said aryl group is selected from the group consisting of: phenyl, 1-naphthyl and 2-naphthyl,

said heteroaryl group is selected from the group consisting of: 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyrazinyl, 2-imidazolyl, 4-imidazolyl, 1-

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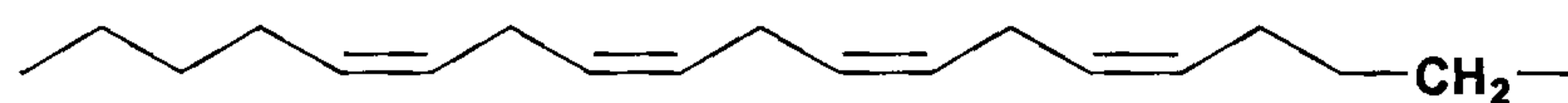
pyrrolyl, 2-pyrrolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-benzothienyl, 3-benzothienyl, 2-benzofuranyl, 3-benzofuranyl, 2-indolyl, 2-quinolinyl and 3-quinolinyl, and

said heterocyclic group is selected from the group consisting of: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl and 4-thiazolidinyl.

83. The use as defined in Claim 81 wherein Y is $-\text{SO}_2\text{O}(\text{C1 to C4 straight or branched chain alkyl group})$.

84. The use as defined in Claim 81 wherein Y is $-\text{SO}_2\text{OCH}_3$.

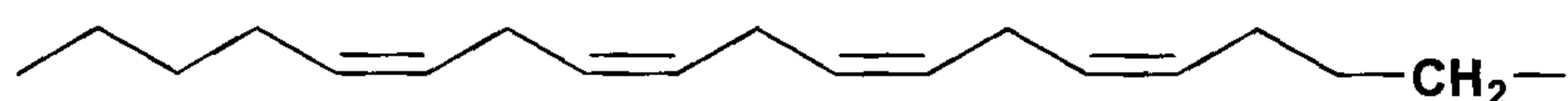
85. The use as defined in Claim 84 wherein R-X- is:



86. The use as defined in Claim 84 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$; wherein n is an integer from 10 to 24.

87. The use of Claim 81 wherein Y is $-\text{SO}_2\text{F}$.

88. The use of Claim 87 wherein R-X- is:



89. The use of Claim 87 wherein R-X- is $\text{CH}_3-(\text{CH}_2)_n-$, wherein n is an integer from 10 to 24.

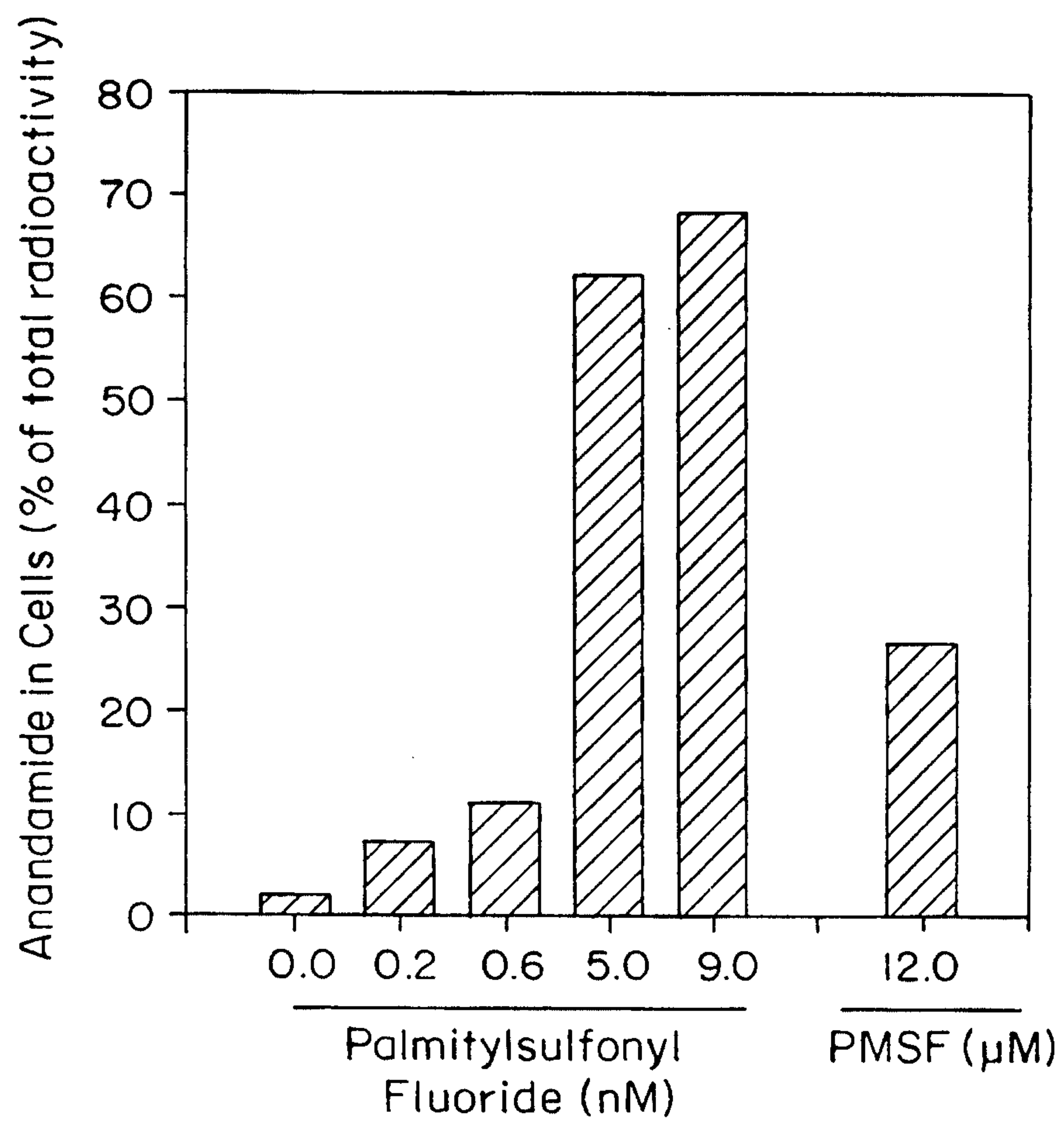
- 57 -

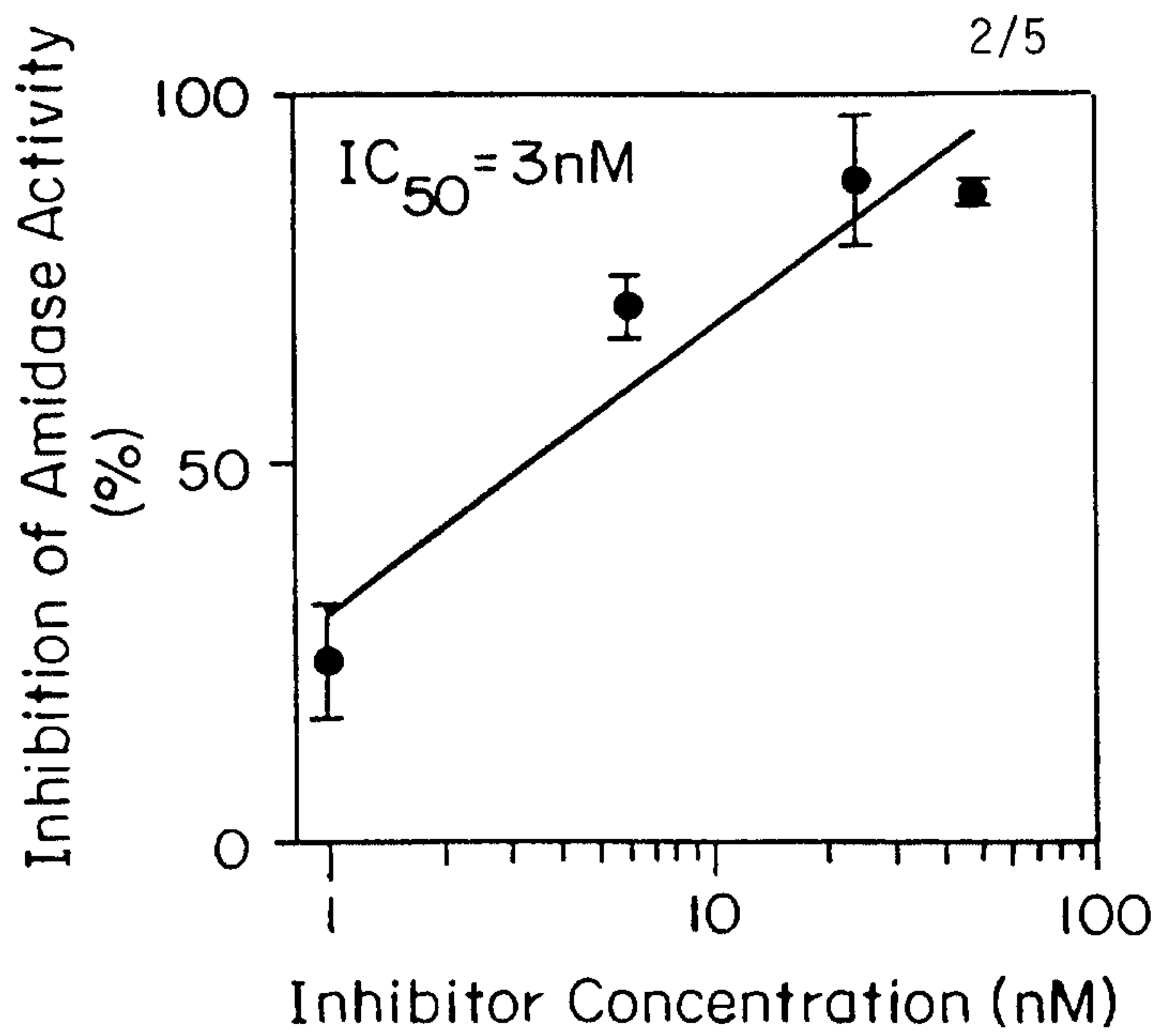
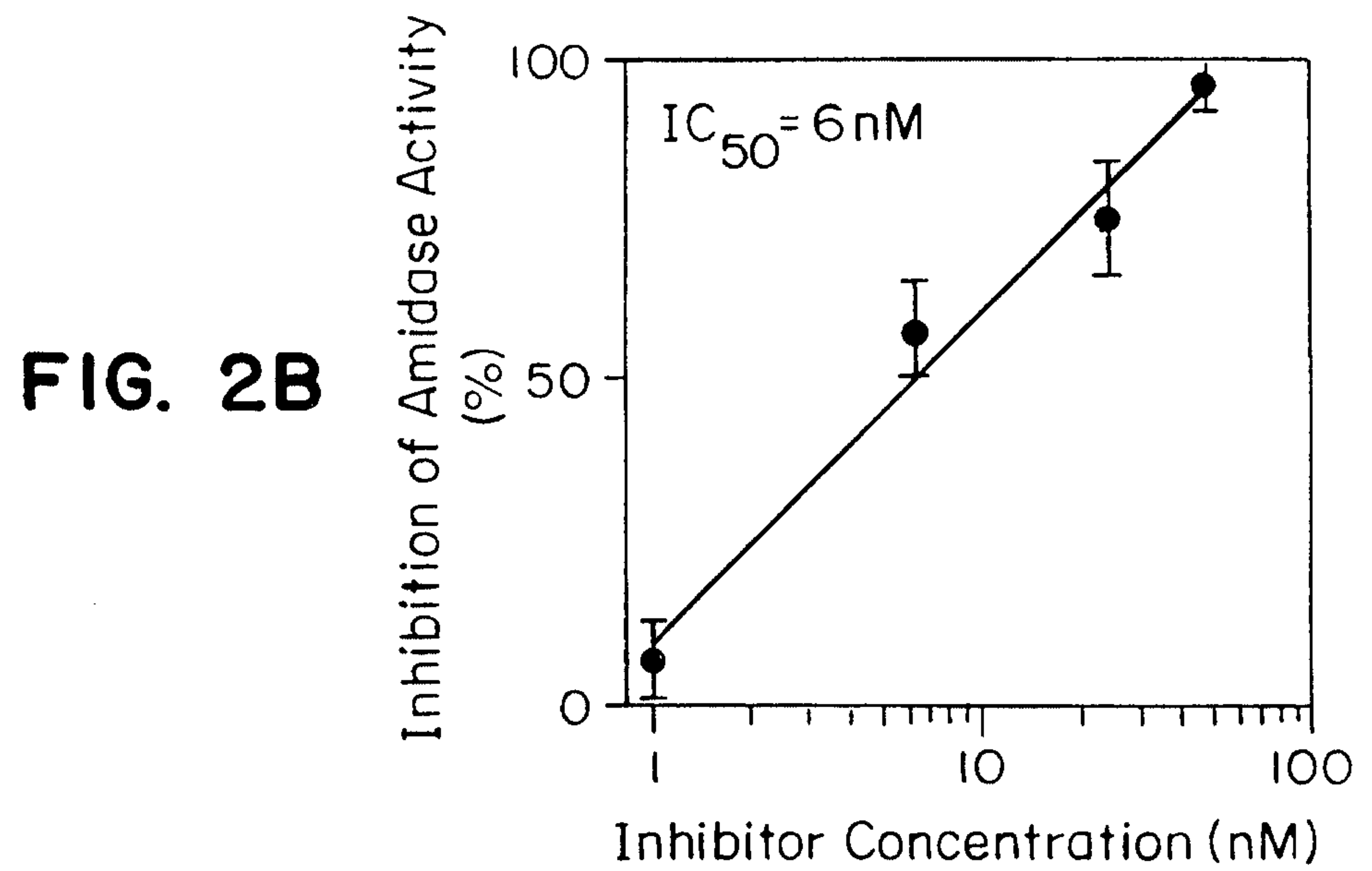
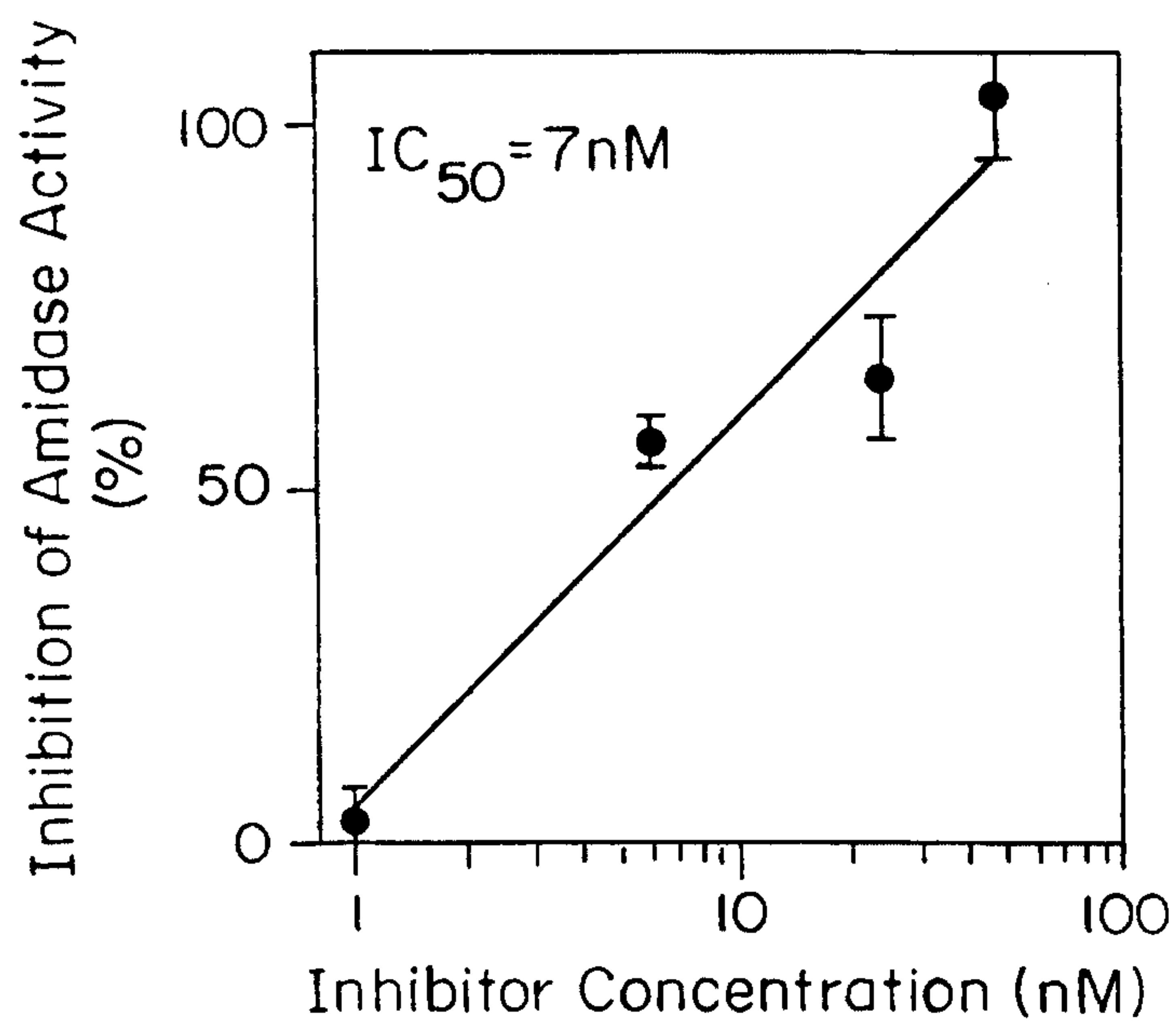
90. The use of Claim 89 wherein n is 14.

91. The use as claimed in any one of claims 81 to 90, wherein the medicament comprises a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the formula R-X-Y together with a pharmaceutically acceptable carrier.

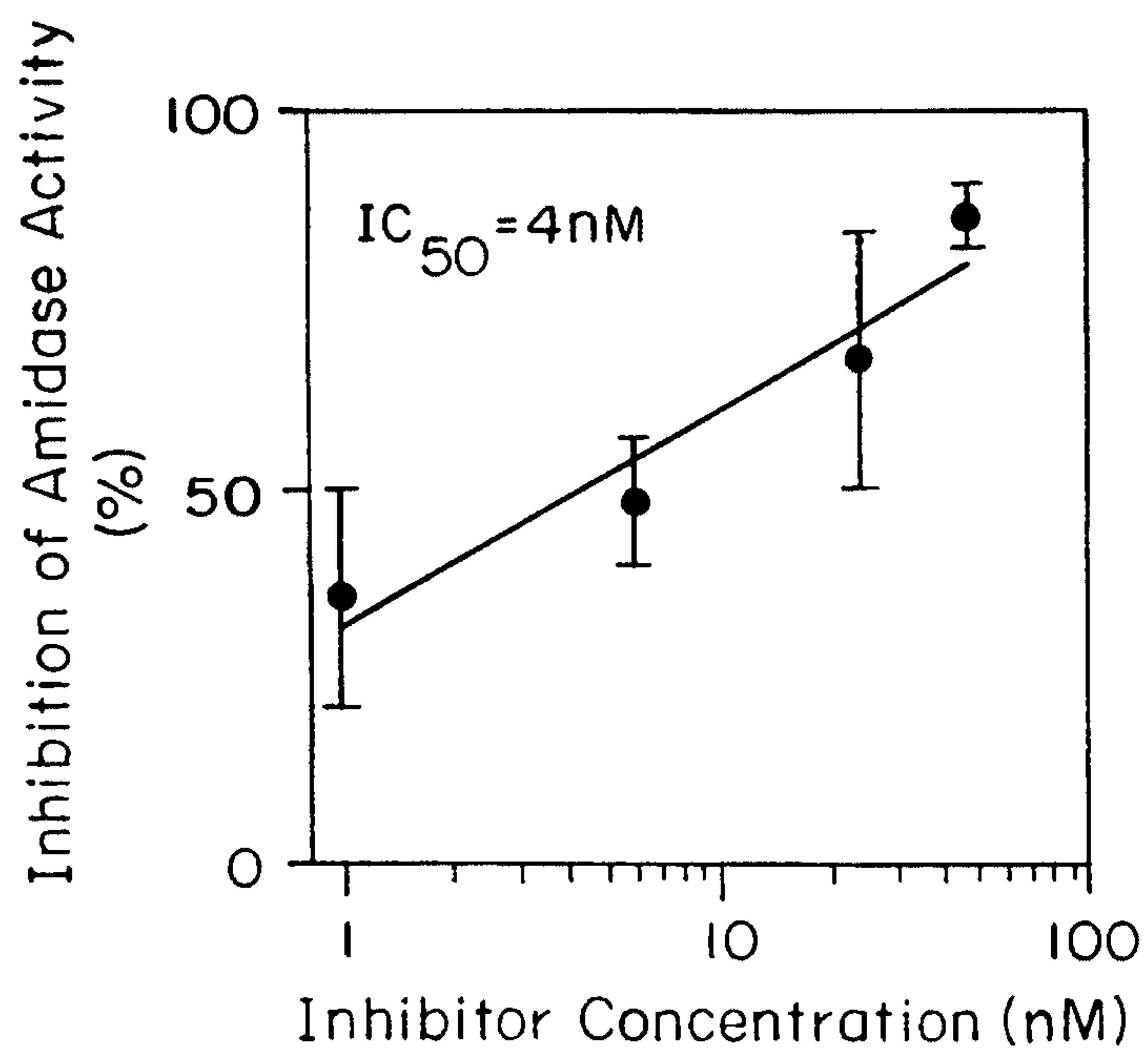
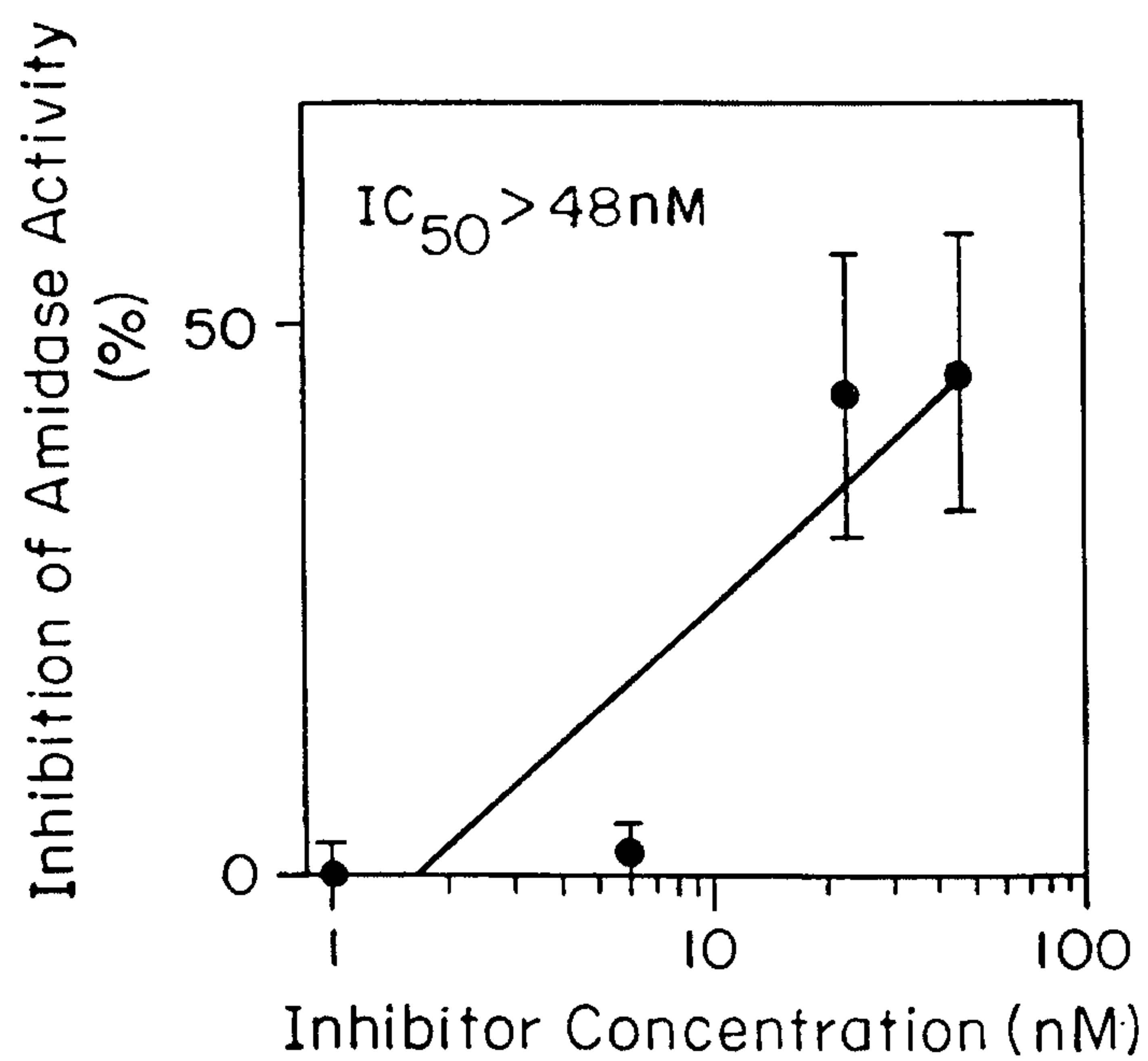
92. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 7 together with a pharmaceutically acceptable carrier.

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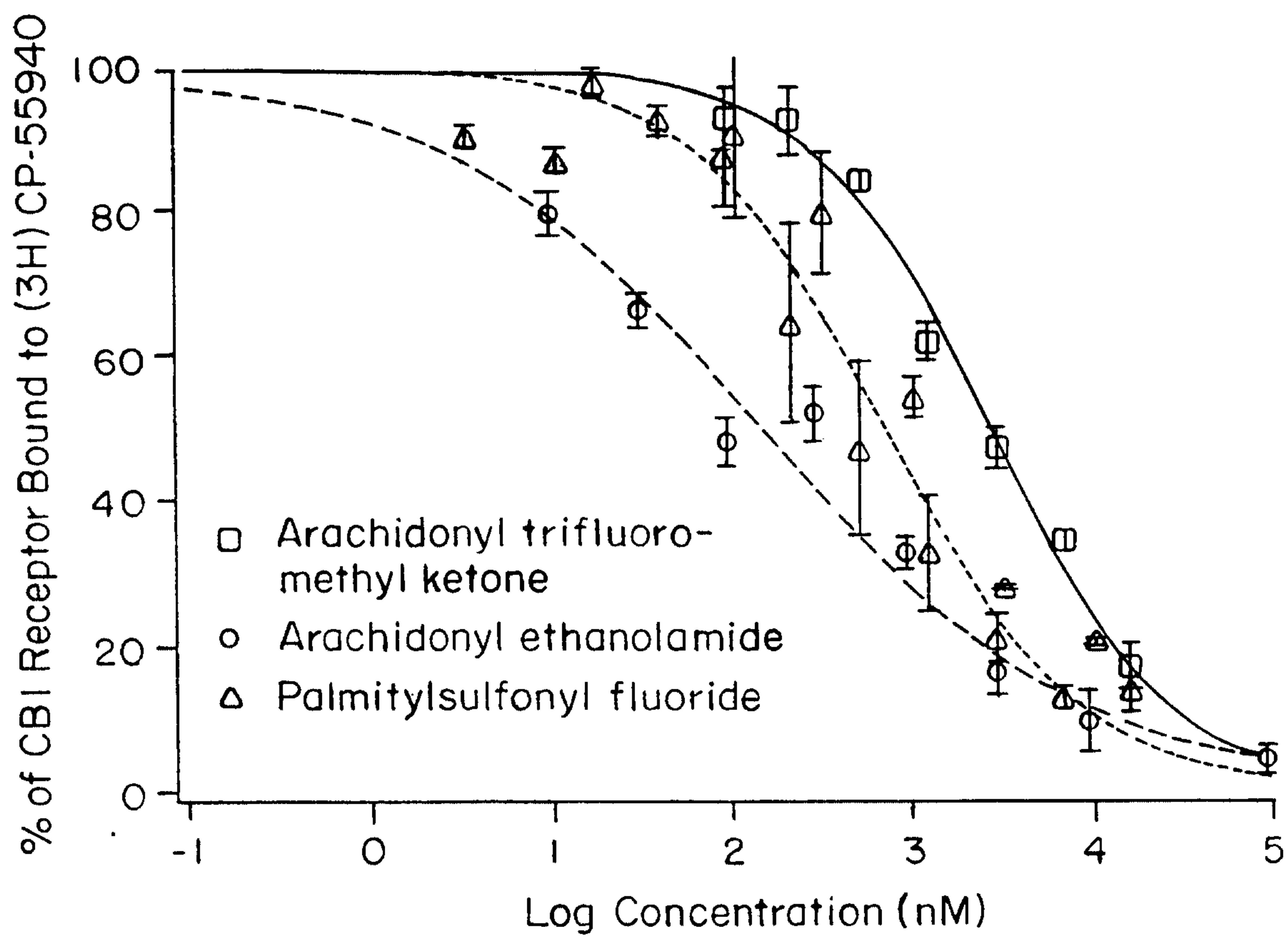
**FIG. I**

**FIG. 2A****FIG. 2B****FIG. 2C**

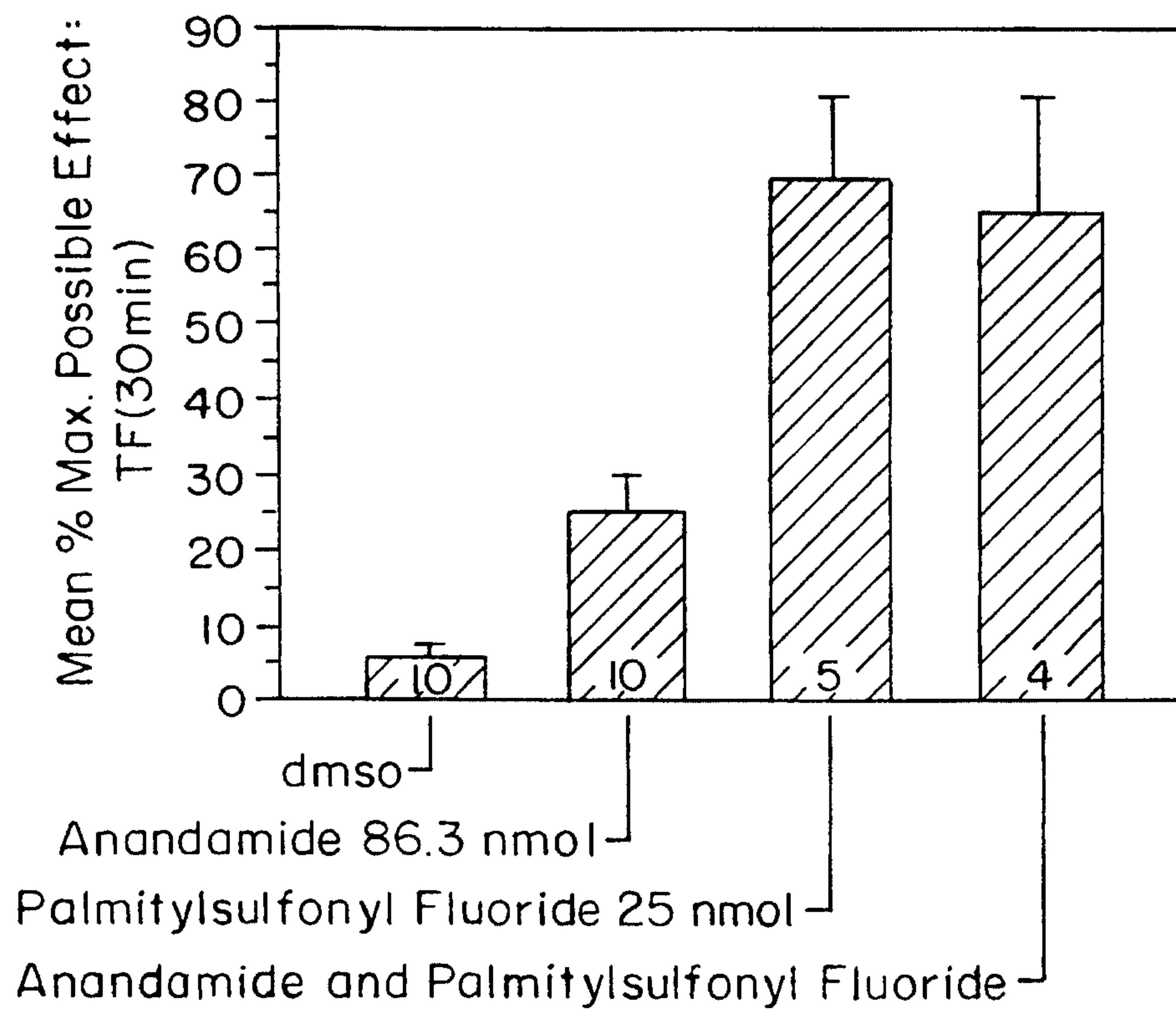
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**FIG. 2D****FIG. 2E**

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**FIG. 3**

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**FIG. 4**

