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N-PHENYLMETHYLALKADIENAMIDE DERIVATIVES AND
COMPOSITIONS FOR USE AS ANALGESICS

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This invention relates to compositions, containing certain N-phenylmethylalkenamides, having analgesic activity.

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While "pain" is incapable of precise definition due to its basically subjective nature, it can generally be said that the term refers to feelings of distress or suffering caused by stimulation of specialized nerve endings. A great variety of drugs have been developed to reduce pain in man and other animals; some directed to eliminating pain at its source, and others directed to blocking the assimilation of pain by the brain. Among the latter group of drugs that are designed to block the sensation of pain, are the analgesics, which generally relieve pain without causing unconsciousness. Analgesics can be further classified in two main categories: opioid analgesics, including morphine, codeine, levorphanol, and the morphine-like analgesics meperidine, and methadone; and antipyretic analgesics, such as aspirin, phenacetin, acetaminophen, phenylbutazone, and indomethacin.

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Although the precise pharmacological action of these analgesics is uncertain, there are certain effects which readily distinguish the opioid analgesics from the antipyretics. In particular, the antipyretics are weak analgesics, with much of their effect in the peripheral nervous system, so that behavioral changes do not usually occur. Generally, these analgesics relieve only somatic pain originating from muscles, joints, tendons and fasciae, and are ineffective against deep visceral pain. However, the opioid analgesics are quite effective against all types of pain, with broad based action in the central nervous system. Aside from potent analgesia, the opioids, also known as narcotics, often produce effects on mood and other behavioral changes. Perhaps the most notable side effect of the opioid analgesics is the fact that their

repeated use is associated with tolerance as well as psychic and physical dependence.

5 It has been recently discovered that capsaicin, a natural product of certain species of the genus Capsicum, induces analgesia in animals. Capsaicin (8-methyl-N-vanillyl-6E-nonenamide) and "synthetic" capsaicin (N-vanillylnonanamide) are disclosed as analgesics in U.S. Patent 4,313,958, LaHann, issued February 2, 1982. Analgesic activity of capsaicin has also been discussed in the chemical and medical literature, including Yaksh, et al.,
10 Science, 206, 481-483 (1979). The use of capsaicin to prevent dipilatory irritation is also disclosed in U.S. Patent 4,546,112 LaHann, et al., filed December 14, 1981.

Specifically, capsaicin prevents the development of cutaneous hyperalgesia and also provides relief of deep visceral pain and
15 severe pain. In certain tests, capsaicin produces a level of analgesia comparable to morphine, yet it is not antagonized by such narcotic antagonists as nalorphine and naloxone. Thus, capsaicin does not appear to belong to either of the major categories of analgesics, described above.

20 Compounds structurally similar to capsaicin have been described in the chemical literature. These references, though, do not suggest analgesic activity for these compounds. For example, Newman, "Natural and Synthetic Pepper-Flavored Substances (6)," Chemical Products, 102-106 (1954) lists the relative pungency of approximately 164 compounds, including N-vanillyloleamide and other alkenamide derivatives of capsaicin. Ott and Zimmermann, Liebigs Ann., 425, 314-337 (1921) discloses a synthesis for N-vanillyloleamide. A synthesis for N-vanillylino-
25 leamide is disclosed in Ferris, Australian Commonwealth, Dep. Supply, Def. Stand. Lab., No. 89 (1966) (Chem. Abs. 67:22919).

30 U.S. Patent 4,238,505, Nelson, issued December 9, 1980, discloses 3-hydroxyacetanilide for use in producing analgesia in animals. U.S. Patent 4,424,205, LaHann, et al., filed March 18, 1982, describes hydroxyphenylacetamides with analgesic and anti-irritant activity. Similarly, analgesic and

anti-irritant activity is disclosed for N-vanillylsulfonamides in U.S. Patent 4,401,663, Buckwalter, et al

filed March 23, 1982; N-vanillylureas in U.S. Patent 4,460,603,

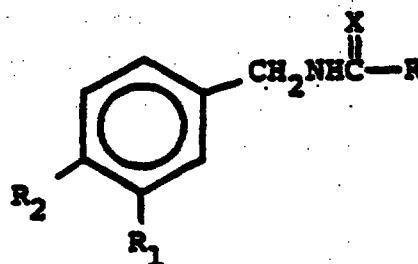
Buckwalter, et al., filed May 25, 1982; and

5 N-vanillylcarbamates in U.S. Patent 4,443,473,

Buckwalter, et al., filed June 3, 1982.

It has now been discovered that certain N-phenylmethyl
alkadienamides have analgesic activity in humans and lower ani-
mals. In particular, these alkenamides have potent analgesic
10 activity similar to that of capsaicin, but are substantially less
toxic.

The present invention provides compounds useful for pro-
ducing analgesia in humans and lower animals, of the formula:

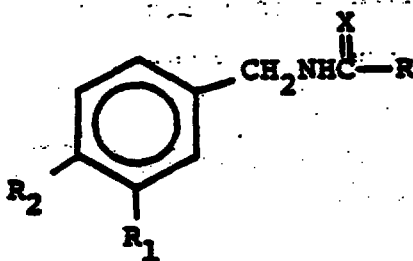


wherein X is O or S, R is straight or branched diene
having from 11 to 23 carbon atoms, the stereochemistry
of said diene being ZE, EZ or EE, R_1 is OH or OCH_3 , and
 R_2 is OH or a $C_1 - C_6$ ester;

and pharmaceutically-
acceptable salts thereof.

This invention also provides compositions for producing
analgesia in humans or lower animals.

The compositions of this invention incorporate certain N-[(substituted phenyl)methyl]-diunsaturated amides (e.g., N-vanillyl-diunsaturated amides), or pharmaceutically-acceptable salts thereof, (herein "alkadienamides") of the formula:



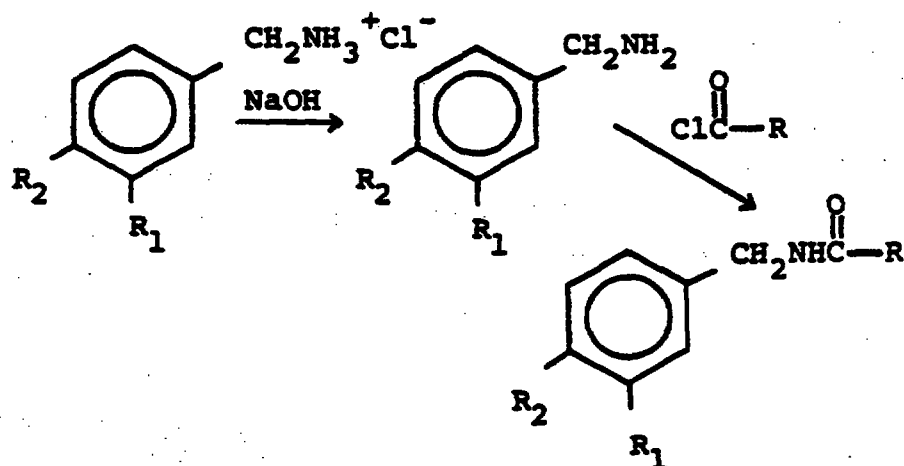
wherein X is O or S; R is straight or branched diene having from 11 to 23 carbon atoms; R_1 is OH or OCH_3 ; and R_2 is OH or a $C_1 - C_6$ ester.

R preferably contains from 16 to 21 carbon atoms and, preferably, unsaturated bonds are at position six or greater, i.e., wherein R is a (m,n-alkadiene), m is at least six. Also preferred are alkadienamides wherein X is O, alkadienamides wherein R_1 is OCH_3 and R_2 is OH, and alkadienamides wherein R_2 is a short-chain (i.e., $C_1 - C_6$) ester, e.g., acetoxy.

Preferred alkadienamides include those where R is derived from such diunsaturated fatty acids as (Z,Z)-9,12-octadecadienoic (linoleic) acid, (E,E)-9-12-octadecadienoic (linoelaidic) acid, (Z,E)-9-12-octadecadienoic acid, (Z,E)-9,11-octadecadienoic acid, (E,E)-10,13-nonadecadienoic acid, and (E,E)-11,14-eicosadienoic acid. Preferred pharmaceutically-acceptable alkadienamide salts include the sodium, potassium, calcium, magnesium, and ammonium salts.

The alkadienamides described herein can be readily prepared by the following general synthetic scheme:





The fatty acids used in the synthesis of preferred alkadienamides are commercially-available.

Compositions

The compositions of the present invention comprise:

- (a) a safe and effective amount of an alkadienamide; and
- (b) a pharmaceutically-acceptable carrier.

A safe and effective amount of alkadienamide is that amount which provides analgesia, thereby alleviating or preventing the pain being treated at a reasonable benefit/risk ratio, as is intended with any medical treatment. Obviously, the amount of alkadienamide will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), the specific formulation and carrier employed, and the solubility and concentration of alkadienamide therein.

Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well known in the art, may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. The amount of the carrier employed in conjunction with the

alkadienamide is sufficient to provide a practical quantity of material per unit dose of analgesic.

Pharmaceutically-acceptable carriers for systemic administration, that may be incorporated into the compositions of this invention, include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Specific pharmaceutically-acceptable carriers are described in the following U.S. Patents: USP 4,424,205,

LaHann, et al., filed March 18, 1982; USP 4,401,663, Buckwalter, et al., filed March 23, 1982; USP 4,460,602. Buckwalter, et al., filed May 25, 1982; and USP 4,443,473 Buckwalter, et al., filed June 3, 1982. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50% of the alkadienamide. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending

agents, diluents, sweeteners, melting agents, coloring, and
flavdring agents. Preferred carriers for oral administration
include gelatin, propylene glycol, cottonseed oil and sesame oil.
Specific examples of pharmaceutically-acceptable carriers and
excipients that may be used to formulate oral dosage forms, which
may be used in formulating oral dosage forms containing alka-
dienamides, are described in U.S. Patent 3,903,297, Robert,
issued September 2, 1975.

Techniques and compositions for making solid oral dosage forms
are described in Marshall, "Solid Oral Dosage Forms," Modern
Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427
(1979).

The compositions of the present invention can also be admin-
istered topically to a biologic subject, i.e., by the direct laying
on or spreading of the composition on epidermal or epithelial
tissue. Such compositions include lotions, creams, solutions, gels
and solids. These topical compositions comprise a safe and effec-
tive amount, usually at least about 0.5%, and preferably from
about 1% to about 2%, of the alkadienamide. Suitable carriers for
topical administration of the alkadienamide preferably remain in
place on the skin as a continuous film and resist being washed off
easily by perspiration or by immersion in water. Generally, the
carrier is organic in nature and capable of having dispersed or
dissolved therein the alkadienamide. The carrier may include
pharmaceutically-acceptable emollients, emulsifiers, thickening
agents, and solvents.

Specific systemic and topical formulations useful in this invention are described in the following U.S. Patents: USP 4,424,205,

LaHann, et al., filed March 18, 1982; USP 4,401,663 Buck-
walter, et al., filed March 23, 1982; USP 4,460,602, Buck-
walter, et al., filed May 25, 1982; and USP 4,443,473, Buck-
walter, et al., filed June 3, 1982. Topical vehicles, useful
herein, are disclosed in USP 4,557,934 and USP 4,537,776.

Additional formulations, useful for paren-
teral, oral, and topical administration of alkadienamides are
disclosed in USP 4,493,848 USP 4,532,139 and USP 4,544,668.

The compositions of the invention are administered
in safe and effective amount, usually
from about 1 mg to about 3600 mg per day, preferably from about
200 mg to about 2000 mg per day, of an alkadienamide. While
dosages higher than the foregoing are effective to produce anal-
gesia, care must be taken in some individuals to prevent adverse
side effects. The alkadienamides and compositions of this inven-
tion can be used to treat and prevent pain, and to provide
analgesia in various disorders at the deeper structures, muscles,
tendons, bursa and joints associated with disease and trauma, and
in various other conditions in which compounds such as aspirin,
codeine, and morphine have heretofore been used to alleviate pain
and discomfort.

The alkadienamides and compositions of the instant invention can be administered topically or systemically. Systemic application includes any method of introducing the alkadienamide into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, and oral administration.

A preferred method of parenteral administration is through intramuscular injection. As is known and practiced in the art, all formulations for parenteral administration must be sterile. For mammals, especially humans, (assuming an approximate body weight of 70 kg) individual doses of from about 2 mg to about 400 mg of alkadienamide are acceptable. Individual doses of from about 50 mg to about 200 mg are preferred.

A preferred method of systemic application of the alkadienamides is through oral administration. For mammals, especially humans, (assuming an approximate body weight of 70 kg) individual doses of from about 1 mg to about 900 mg of alkadienamide are acceptable. Individual doses of from about 50 mg to about 600 mg are especially preferred.

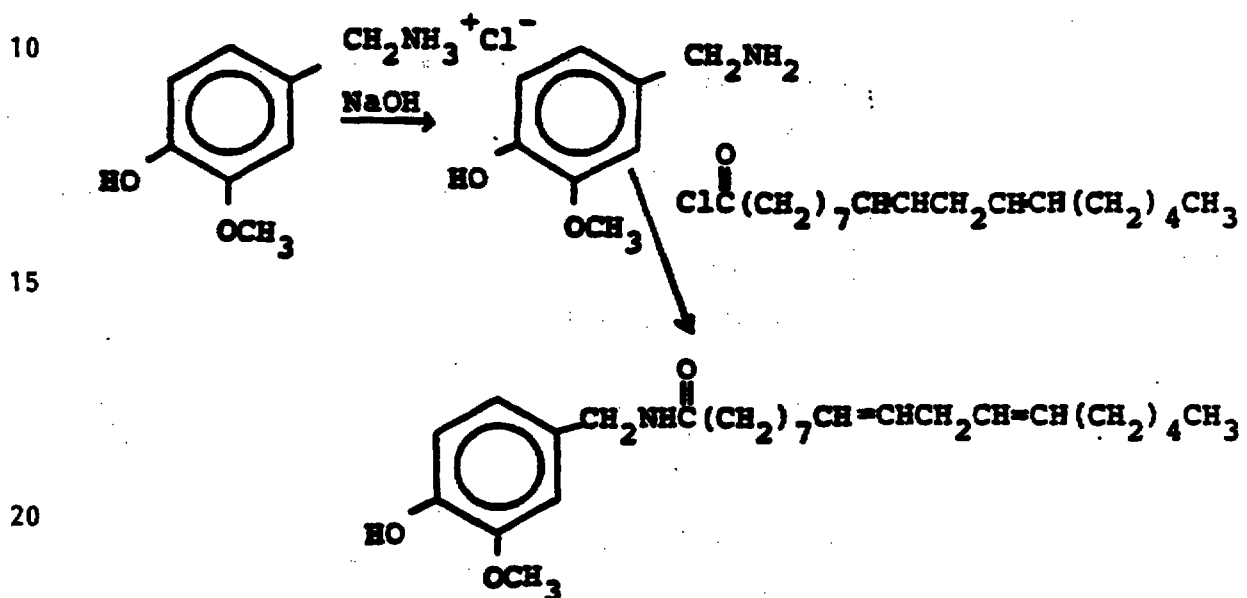
Topical administration can be used to produce local or systemic analgesia, through directly laying on or spreading a safe and effective amount of the alkadienamide, or composition containing an alkadienamide, on epidermal or epithelial tissue, including outer skin and oral, gingival, and nasal tissue. The amount of alkadienamide to be topically administered depends upon such factors as the sensitivity, type and location of tissue to be treated, the composition and carrier (if any) to be administered, and the particular alkadienamide to be administered as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) analgesic effects are desired. The extent of systemic analgesia also depends upon such factors as

the amount of alkadienamide, the area of tissue to be covered, and the ability of the alkadienamide composition to penetrate the skin tissues.

The following non-limiting Examples illustrate the compositions, processes, and uses of the present invention.

EXAMPLE I

N-vanillyl-(E,E)-9,12-octadecadienamide was synthesized by the following method:



Specifically, 6.88 g of 4-hydroxy-3-methoxybenzylamine-HCl was dissolved in 50 ml of tetrahydrofuran (THF), and stirred. Added were 14 ml of a 5N solution of NaOH, and the mixture was stirred for 10 to 15 minutes. Then 10.6 g of (E,E)-9,12 octadecadienoyl chloride (linoelaidoyl chloride), dissolved in THF, was added dropwise. The mixture was then stirred overnight, allowing it to come to room temperature. The solvent was evaporated and the residue partitioned between ethyl ether and water. The organic phase extract was washed with HCl, sodium bicarbonate, water, and brine, and then dried and filtered. 16 g of crude N-vanillyl-(E,E)-9,12-octadecadienamide was obtained. Purification by

recrystallization from ether and pentane gave 9.4 g of analytically pure product. Its structure was confirmed via nuclear magnetic resonance and infrared spectroscopy.

In the above example,

5 (Z,E)-9,12-octadecadienoyl chloride, (Z,E)-9,11-octadecadienoyl chloride, (E,E)-10,13-nonadecadienoyl chloride, and (E,E)-11,14-eicosadienoyl chloride are substituted, respectively, for (E,E)-9,12-octadecadienoyl chloride, thereby obtaining each respective N-vanillyl-alkadienamide.

10 EXAMPLE II

An analgesic composition, according to the present invention, was made comprising:

N-vanillyl-(E,E)-9,12-octadecadienamide	127.2 mg
ethanol	0.75 ml
15 pyrrolidone	0.75 ml

The composition was made by simple dissolution of the alkadienamide in the liquid solvents. A mouse weighing 30 g, was injected subcutaneously with 0.1 ml of the composition, producing analgesia.

20 EXAMPLE III

A composition, according to the instant invention, for parenteral administration, is made with the following ingredients:

N-vanillyl-(E,E)-9,12-octadecadien-	
amide	100mg/ml of carrier

25 carrier (percent-by-weight):

propylene glycol	72%
polyethylene glycol	17%
water	10%
benzyl alcohol	1%

30 The alkadienamide is dissolved in the carrier and a human subject, weighing 70 kg, is injected subcutaneously with 1.0 ml of

the composition thereby prepared, producing analgesia. At eight-hour intervals, two more subcutaneous injections are made, of 1.0 ml of the composition per administration, for a total of 300 mg N-vanillyl-(E,E)-9,12-octadecadienamide administered over a twenty-four-hour period.

In the above example, N-vanillyl-(Z,Z)-9,12-octadecadienamide, N-vanillyl-(Z,E)-9,12-octadecadienamide, N-vanillyl-(Z,E)-9,11-octadecadienamide, N-vanillyl-(E,E)-10,13-nonadecadienamide, N-vanillyl-(Z,Z)-11,14-eicosadienamide, and N-vanillyl-(E,E)-11,14-eicosadienamide are substituted, respectively, for N-vanillyl-(E,E)-9,12-octadecadienamide, with substantially similar results.

EXAMPLE IV

A composition, according to the instant invention, for parenteral administration, is made with the following components:

N-vanillyl-(E,E)-9,12-octadecadienamide	100mg/ml of carrier
<u>carrier (percent-by-weight):</u>	
sesame oil	98%
benzyl alcohol	2%

A human subject, weighing 70 kg, is injected via deep-intramuscular injection, with 1.0 ml of the composition prepared above, producing analgesia.

In the above example, N-vanillyl-(Z,Z)-9,12-eicosadienamide, N-vanillyl-(E,E)-9,12-octadecadienethioamide, and N-[(3,4-dihydroxyphenyl)methyl]-(E,E)-9,12-octadecadienamide and are substituted, respectively, for N-vanillyl-(E,E)-9,12-octadecadienamide, with substantially similar results.

EXAMPLE V

A composition, according to the instant invention, for parenteral administration, is made with the following components:

N-vanillyl-(Z,Z)-9,12-octadeca-

5	dienamide	100 mg/ml of carrier
	<u>carrier</u> : sodium citrate buffer	
	with (percent-by-total weight):	
	lecithin	0.48%
	carboxymethylcellulose	0.53%
10	povidone	0.50%
	methyl paraben	0.11%
	propyl paraben	0.011%

The above ingredients are admixed, forming a suspension. A human subject, weighing approximately 70 kg, is injected, via intramuscular injection, with 2.0 ml of the composition formed above, producing analgesia.

EXAMPLE VI

A composition, according to the instant invention, for parenteral administration, is made by admixing the following components:

20	N-[(4-acetoxy-3-methoxyphenyl)-methyl]-(E,E)-9,12-octadecadienamide	100 mg/ml of carrier
	<u>carrier</u> (percent by weight):	
	ethyl oleate	98.0%
25	benzyl alcohol	2.0%

A human subject, weighing 70 kg, is injected via intramuscular injection, with 2.0 ml of the composition prepared above, producing analgesia.

EXAMPLE VII

A composition, according to the instant invention, is made with the following components:

N-vanillyl-(E,E)-9,12-octadeca-

5	dienamide	2000 mg
	sesame oil	50 ml
	benzyl alcohol	6 ml
	8% gelatin in water	100 ml
	tartaric acid	60 mg

10 The alkadienamide is dissolved in the sesame oil and benzyl alcohol. An emulsion is obtained through adding this solution to a mixture of the gelatin and tartaric acid. This emulsion is administered orally to a human subject, weighing approximately 70 Kg, producing analgesia.

15 EXAMPLE VIII

A composition, according to the instant invention, for oral administration, is made with the following components:

N-vanillyl-(E,E)-10,13-nonadeca-

	dienamide	100 mg/ml of carrier
20	<u>carrier</u> (percent-by-weight):	
	propylene glycol	100%

5.0 ml of the syrup thereby prepared is administered orally to a human subject, producing analgesia.

25 In the above example, flavoring agents, sweetening agents such as sucrose, lactose, mannitol and saccharin, and preservatives such as glycerin, methyl paraben, propylparaben, benzoic acid, sodium benzoate and alcohol, are added, singly or in combination, to the composition formed above, with substantially similar results.

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EXAMPLE IX

A composition, according to the instant invention, for oral administration, is made with the following components:

N-vanillyl-(Z,Z)-11,14-eicosadien-

5	amide	100 mg/ml of carrier
	<u>carrier</u> (percent-by-weight):	
	cottonseed oil	99%
	benzyl alcohol	1%

10 Soft gelatin capsules, each having a volume of 0.3 ml, are filled with the composition formed above. Two capsules are administered to a human subject every eight hours, producing sustained analgesic effects.

EXAMPLE X

15 A composition, according to the instant invention, for oral administration, is made with the following components:

	<u>Component</u>	<u>Bulk</u>	<u>Individual Tablet</u>
	N-vanillyl-(E,E)-9,12-octa-		
	decadienamide	70 g	350 mg
	starch	6	30
20	magnesium stearate	1	5
	microcrystalline cellulose	20	100
	colloidal silicon dioxide	0.5	2.5
	povidone	2.5	12.5

25 The above ingredients are admixed into a bulk mixture, totalling 100 g. Compressed tablets are formed, using tableting methods known in the art, each containing 0.5 g of the bulk mixture. A human subject, weighing approximately 70 kg, is orally administered two of the tablets, for a total dose of 700 mg of alka-

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EXAMPLE XI

A composition, according to the instant invention, for oral administration, is made with the following components:

	<u>Component</u>	<u>Bulk</u>	<u>Individual Tablet</u>
5	N-vanillyl-(Z,Z)-9,12-octa-		
	decadienamide	100 g	500 mg
	mannitol	97.2	486
	acacia	5.86	29.3
	starch	9.62	48.1
10	talc	3.2	16.0
	calcium stearate	0.42	2.1
	orange flavor mix	1.06	5.3

The above ingredients are admixed into a bulk mixture totalling 217.4 g. Chewable tablets are formed, using tableting methods known in the art, each containing 1.09 g of the bulk mixture, for a total of 200 tablets formed. A human subject, weighing approximately 70 kg, is orally administered three of the tablets, for a total dose of 1500 mg of alkadienamide, producing analgesia.

EXAMPLE XII

20 A composition, according to the instant invention, for oral administration, is made with the following components:

	N-vanillyl-(E,E)-9,12-octadecadienamide	1000 mg
	starch	10.2
	magnesium stearate	5.1

25 A capsule is made by filling with the above ingredients, and administered to a human subject, weighing approximately 70 kg, producing analgesia.

EXAMPLE XIII

A lotion composition, according to the instant invention, for topical administration, is formed through admixing the following components (percentages-by-weight):

5	N-vanillyl-(E,E)-11,14-eicosadienamide	2.0%
	isopropyl myristate	8.0%
	corn oil	5.0%
	propylene glycol	5.0%
	triethanolamine oleate	5.0%
10	xanthan gum	0.5%
	water	74.5%

Approximately 4 ml of the lotion formed is applied to a 80 cm² portion of the skin of a human subject, producing analgesia.

In the above example, 15-methyl-N-vanillyl-(Z,Z)-9,12-octadecadienamide and 15-ethyl-N-vanillyl-(Z,Z)-9,12-octadecadienamide are substituted for N-vanillyl-(E,E)-11,14-eicosadienamide respectively, with substantially similar results.

EXAMPLE XIV

An ointment composition, according to the instant invention, for topical administration, is formed with the following components (percentages-by-weight):

	N-vanillyl-(E,E)-9,12-octadecadienamide	2.0%
	oleyl alcohol	30.0%
25	cetyl alcohol	40.0%
	propylene glycol	28.0%

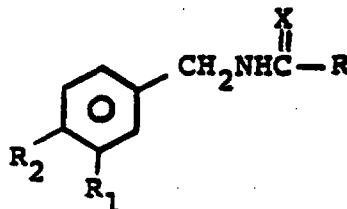
The components are admixed and approximately 6 ml of the ointment is applied to a 100 cm² portion of the skin of a human subject, producing analgesia.



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CLAIMS

1. Alkadienamide compounds, and pharmaceutically-acceptable salts thereof, characterized in that they have the formula:



wherein X is O or S; R is straight or branched diene having from 11 to 23 carbon atoms, the stereochemistry of said diene being ZE, EZ or EE; R₁ is OH or OCH₃; and R₂ is OH or a C₁ - C₆ ester.

2. Alkadienamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 1, characterized in that R₁ is OCH₃ and R₂ is OH.

3. Alkadienamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 1, characterized in that R₂ is a C₁ - C₆ ester.

4. Alkadienamide compounds, and pharmaceutically-acceptable salts thereof, according to Claims 1 or 2, characterized in that they are selected from the group consisting of
N-vanillyl-(Z,E)-9,12-octadecadienamide, N-vanillyl-(E,E)-9,12-octadecadienamide, N-vanillyl-(Z,E)-9,11-octadecadienamide, N-vanillyl-(E,E)-10,13-nonadecadienamide, and N-vanillyl-(E,E)-11,14-eicosadienamide.

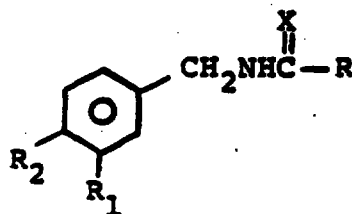


5. The alkadienamide compounds and pharmaceutically-acceptable salts thereof, according to Claims 1 or 3, characterized in that said alkadienamide is N-[(4-acetoxy-3-methoxyphenyl)methyl]-(E,E)-9,12-octadecadienamide.

6. The alkadienamide compound, and pharmaceutically-acceptable salts thereof, according to any of Claims 1, 2 and 4, characterized in that said alkadienamide is N-vanillyl-(E,E)-9,12-octadecadienamide.

7. A composition for producing analgesia in humans or lower animals, characterized in that it comprises:

- (a) a safe and effective amount of an alkadienamide compound or pharmaceutically-acceptable salt thereof, or mixtures thereof, of the formula:



wherein X is O or S; R is straight or branched diene having from 11 to 23 carbon atoms; R_1 is OH or OCH_3 ; and R_2 is OH or a $C_1 - C_6$ ester.

- (b) a pharmaceutically-acceptable carrier.



8. A composition, according to Claim 7, characterized in that the alkadienamide compound is a pharmaceutically-acceptable salt selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

9. A composition, according to Claim 7 or 8, for parenteral administration, characterized in that it comprises at least 90%, by weight, of said pharmaceutically-acceptable carrier.

10. A composition according to Claim 7 or 8, for oral administration, characterized in that it comprises from 25% to 50%, by weight of said alkadienamide.

11. A composition according to any of Claims 7 to 10 characterized in that R_1 is OCH_3 and R_2 is OH.

12. A composition according to any of Claims 7-10 characterized in that R_2 is a $C_1 - C_6$ ester.

13. A composition according to Claim 11 or 12 characterized in that they are selected from the group consisting of N-vanillyl-(Z,Z)-9,12-octadecadienamide, N-vanillyl-(Z,E)-9,12-octadecadienamide, N-vanillyl-(E,E)-9,12-octadecadienamide, N-vanillyl-(Z,E)-9,11-octadecadienamide, N-vanillyl-(E,E)-10,13-nonadecadienamide, N-vanillyl-(Z,Z)-11,14-eicosadienamide, and N-vanillyl-(E,E)-11,14-eicosadienamide.
