DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Alcohol, Drug Abuse and
Mental Health Administration
Rockville MD 20857

August 22, 1991

Mr. Carl E. Olsen
P.O. Box 4091
DesMoines, Iowa 50333

Dear Mr. Olsen:

This is in response to your letter of August 4 to Dr. Richard Hawks about the Government's marijuana program. There are two aspects to the program: one is the distribution program to which you refer in your letter and the other is the long-standing program of marijuana research carried out by the National Institute on Drug Abuse and the National Institute of Mental Health.

The use of marijuana as a "medication" to treat a variety of disorders--including the nausea that accompanies cancer or AIDS chemotherapy, increased intraocular pressure from glaucoma, pain, and the muscle spasticity of multiple sclerosis--has been promoted by a number of individuals and groups, both professional and non-professional, over the past 20 years. During this time, the PHS has allowed a very small number of patients (fewer than 15) to use marijuana for these indications.

The program is administered by the Food and Drug Administration (FDA) and is part of what is called the "compassionate" IND (Investigational New Drug) program. The program requires that the patient's physician submit a research protocol to examine the effects of marijuana on the symptoms of his patient. An annual report of results is required. The physician must also obtain a license from the Drug Enforcement Administration (DEA) to dispense Schedule I drugs. The only role of the National Institute on Drug Abuse in this process is the distribution of the actual cigarettes, once appropriate approvals have been obtained from the FDA and the DEA. You may obtain additional information on the compassionate IND program from Ms. Corrine Moody, Pilot Drug Program, Food and Drug Administration, Room 9B-45, 5600 Fishers Lane, Rockville, Maryland 20857.

Recent increased interest in the therapeutic use of marijuana has caused the Public Health Service (PHS) to reexamine its policy on the distribution of marijuana cigarettes. In the past, PHS policy has been to support the study of the therapeutic potential of various active ingredients in marijuana, such as THC, while discouraging the use of the plant material, marijuana. This has allowed the therapeutic potential of cannabinoids to be realized while the campaign against drug abuse continues. Thus, Marinol

(synthetic THC, the principal active ingredient in marijuana) and Nabilone (a synthetic cannabinoid) have been approved by the FDA for the treatment of nausea due to cancer chemotherapy. For a variety of technical reasons having to do with the route of administration of marijuana (smoking) and the complex metabolism and distribution of cannabinoids within the human body, the PHS has decided not to expand the compassionate IND program for use of marijuana. Anyone who is already receiving marijuana cigarettes from the Government will continue to do so. The PHS will continue to encourage physicians to use synthetic THC, which has been proven safe.

Through the National Institute on Drug Abuse and the National Institute of Mental Health, the PHS sponsors an active program of cannabinoid research. Over the last 20 years, many millions of dollars have been spent on hundreds of scientific research projects investigating the properties of marijuana and the cannabinoids. If you would like information on the results of this research, please contact the National Clearinghouse on Alcohol and Drug Abuse Information, 800-729-6686, P.O. Box 2345, Rockville, Maryland 20852.

Sincerely,

Christine R. Hartel

Christine R. Hartel, Ph.D.
Deputy Director
Division of Preclinical Research
National Institute on Drug Abuse

U.S. Department of Justice

Drug Enforcement Administration

Office of the Administrator

Washington, D.C. 20537

AUG 17 1992

Mr. Carl E. Olsen
P.O. Box 4091
Des Moines, Iowa 50333

Dear Mr. Olsen:

This is in response to your letter of July 21, 1992, regarding my decision with respect to the Marijuana Rescheduling Petition.

Your letter correctly states that one of the factors to be considered in determining whether a substance has a currently accepted medical use in treatment is that it is a scientifically established chemical compound capable of reproduction in standardized dosages. While you are also correct in noting that Congress placed coca and opium plant materials in Schedule II, your attempt to analogize those substances to marijuana, and to find inconsistency in their scheduling, fails.

In placing coca leaves and opium plant material in Schedule II, Congress was very much aware that these plant materials have historically been recognized as the source for a variety of accepted and useful medications. Neither of these plants are used medicinally as plant material. In both instances, the medically active alkaloids are extracted from the plant material after which pharmaceutical compounds capable of reproduction in standardized dosages are produced. These compounds are the medications which may then be lawfully marketed in the United States. While indigenous populations in various parts of the world brew coca teas, chew coca leaves, and smoke opium for various purposes, these practices are not permitted in the United States under the Controlled Substances Act.

Unlike pharmaceuticals derived from opium and coca leaves, the petition to reschedule marijuana did not involve the scheduling of any medically useful compound to be extracted from the plant material. Instead, the petition involved unsupported claims for the medical use of smoked marijuana. There is, therefore, no

inconsistency in my finding that such claims did not make a case for accepted medical use in treatment in the United States.

Very truly yours,

Robert C. Bonner

Robert C. Bonner
Administrator of Drug Enforcement

U.S. Department of Justice

Drug Enforcement Administration

Washington, D.C. 20537

OCT 23 1992

Mr. Carl Eric Olsen
P.O. Box 4091
Des Moines, Iowa 50333

Dear Mr. Olsen:

This is in response to your petition to reschedule marijuana from Schedule I to Schedule II of the Controlled Substances Act. The crux of your petition is that marijuana itself need not have an accepted medical use in treatment in the United States if it is shown that marijuana is the source of an accepted and useful medication. To that end, you argue that marijuana should be rescheduled as a source of delta-9-tetrahydrocannabinol because dronabinol, the synthetic form of the same isomer, is controlled in Schedule II.

In a final rule published on May 13, 1986, then Administrator John C. Lawn placed a very specific substance, synthetic dronabinol in sesame oil and encapsulated in soft gelatin capsules, in Schedule II. Administrator Lawn's action did not involve the rescheduling of delta-9-tetrahydrocannabinol itself, nor did it include any form of dronabinol other than the synthetic. Accordingly, pursuant to 21 C.F.R. § 1308.44(c), your petition to reschedule marijuana is not accepted.

Since I am not accepting your petition on the grounds that dronabinol is a wholly synthetic substance, not obtained from marijuana, it is unnecessary for me to consider the broader question of whether the rescheduling of marijuana would be appropriate if accepted medications were indeed obtained from that source. As you are well aware, the issue of whether marijuana itself has any accepted medical use is pending before the United States Court of Appeals for the District of Columbia Circuit. We are confident that the Court will find no merit in the petition and that it will affirm my ruling in that case.

Very truly yours,

Robert C. Bonner
Administrator of Drug Enforcement

UNITED STATES DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In the Matter of PETITION OF CARL ERIC OLSEN	On Remand From the United States Court of Appeals for the District of Columbia Circuit, No. 93-1109

FINAL ORDER

This order is issued pursuant to an Order dated December 9, 1993, from the United States Court of Appeals for the District of Columbia Circuit which remanded the matter of a petition from Carl Eric Olsen to the Drug Enforcement Administration (DEA) for a ruling by the agency.

On September 6, 1992, Carl Eric Olsen (Petitioner) of Des Moines, Iowa, submitted a petition requesting that the controlled substance marijuana, be rescheduled from Schedule I to Schedule II of the Controlled Substances Act of 1970 (CSA). The Petitioner's grounds were based on his evaluation of two prior rescheduling actions by the Administrator. See Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules, 51 Fed. Reg. 17476 (1986) and Marijuana Rescheduling Petition, 57 Fed. Reg. 10499 (1992). On October 23, 1992, then-Administrator of Drug Enforcement, Robert C. Bonner, declined to accept his petition. The Petitioner subsequently filed for review of then-Administrator Bonner's decision with the United States Court of Appeals for the District of Columbia

Circuit. The matter was remanded by Order of that Court to the DEA for a ruling. Pursuant to that Court's Order, and 21 C.F.R. § 1308.44(c), the Deputy Administrator of the Drug Enforcement Administration has considered the matters before him and hereby renders his final decision.

In his Petition for rescheduling, the Petitioner alleged that marijuana need not have an accepted medical use in treatment in the United States in order to be rescheduled from Schedule I, but "it only needs to be shown that marijuana is a source for an accepted and useful medication". This contention was based on Petitioner's own analogies drawn from an earlier DEA marijuana rescheduling case, 57 Fed. Reg. 10499 (1992), and subsequent written statements made to the Petitioner by then-Administrator Bonner regarding coca leaves and opium plant material; and the Petitioner's incorrect contention that the DEA proposed to reschedule dronabinol in a proposed rulemaking. See Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules, 50 Fed. Reg. 42186 (1985). It appears that Petitioner contends that this rescheduling action included delta-9-tetrahydrocannabinol (delta-9-THC), an ingredient in marijuana, and concluded that "since marijuana is now a source for an accepted and useful medication, it must now be rescheduled from Schedule I to Schedule II of the CSA".

The Deputy Administrator finds, for the reasons stated herein, that the grounds upon which the Petitioner relies are not

sufficient to justify the initiation of proceedings for the transfer of marijuana from Schedule I to Schedule II of the CSA.

In July 1992, the Petitioner wrote then-Administrator Bonner regarding his final order of March 26, 1992, (57 Fed. Reg. 10499), in which the Administrator declined to reschedule marijuana to Schedule II, and the apparent "unfair" classification of the marijuana plant as a Schedule I substance, while coca and opium plants remained in Schedule II. Then-Administrator Bonner replied by letter on August 17, 1992, and distinguished the pharmaceuticals or derivative compounds from each plant. Apparently, the Petitioner then created a theory, that given that the Schedule II opium and coca plants were a source for an accepted medication, then if marijuana plants were a source for accepted medications it should also be a Schedule II substance. To further his argument, the Petitioner pointed to the rescheduled drug, which he called dronabinol, as having its source in marijuana. The Petitioner also alluded to inconsistencies of scheduling of delta-9-THC, a component of marijuana, between the CSA and certain multilateral international agreements.

When the CSA was created, Congress specified the initial scheduling of controlled substances and the criteria by which controlled substances could be rescheduled. 21 U.S.C. §§ 811-812. The DEA is bound, by law, to follow this mandate. Congress placed both the tetrahydrocannabinols, which includes delta-9-THC, and the plant marijuana into Schedule I when it enacted the

CSA. See Pub. L. 91-513, § 202(c), Schedule I (c)(17) and (c)(10). Similarly, Congress placed opium poppy and straw and coca leaves into Schedule II. See Pub. L. 91-513, § 202(c), Schedule II (a)(3) and (a)(4). The legislative history indicates that marijuana was placed into Schedule I on its own merits and not because delta-9-THC could be extracted from it. H.R. Rep. No. 1444, 91st Cong., 2d Sess., pt. 1, at 12 (1970).

Whether or not marijuana is a source of delta-9-THC is irrelevant to the status of marijuana under the CSA. With regard to the classification of controlled substances, the Attorney General may, by rule, add to the established schedules or transfer between such schedules any drug or other substance if [s]he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by subsection (b) of Section 812 for the schedule in which such drug is to be placed. 21 U.S.C. § 811(a)(1). The Attorney General has delegated this authority to the Administrator, who has redelegated it to the Deputy Administrator. See 28 C.F.R. §§ 0.100(b) and 0.104. (59 Fed. Reg. 23637 (May 6, 1994)).

In order for a substance to be placed into Schedule II, the Attorney General must find that: "(A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. (C) Abuse of the drug or other substances may lead

to severe psychological or physical dependence." 21 U.S.C. § 812(b)(2).

Then-Administrator John C. Lawn previously determined that marijuana does not have a currently accepted medical use in treatment in the United States and as a result must remain in Schedule I. See Marijuana Rescheduling Petition, 54 Fed. Reg. 53767 (1989). Then-Administrator Lawn's final order was appealed to the United States Circuit Court of Appeals for the D.C. Circuit which returned the matter to the DEA for an explanation of the factors relied upon in determining "currently accepted medical use". See Alliance for Cannabis Therapeutics v. DEA, 930 F.2d 936 (D.C. Cir. 1991).

In response to the remand, then-Administrator Bonner issued a final order in which he determined that for a substance to have a "currently accepted medical use" the following must exist:

a. the drug's chemistry must be known and reproducible;

b. there must be adequate safety studies;

c. there must be adequate and well-controlled studies proving efficacy;

d. the drug must be accepted by qualified experts; and

e. the scientific evidence must be widely available.

Then-Administrator Bonner concluded that marijuana failed to meet all elements of the five-part test and, therefore, did not meet the statutorily prescribed criteria for a Schedule II substance. Marijuana Rescheduling Petition, 57 Fed. Reg. 10499 (1992); See

Alliance for Cannabis Therapeutics v. DEA, et al., 15 F.3d 1131 (D.C. Cir. 1994) upholding the Administrator's decision.

Accordingly, the Deputy Administrator concludes that the Petitioner's contention that marijuana need not have an accepted medical use in treatment in the United States in order to be rescheduled from Schedule I to Schedule II of the CSA is not in accordance with law. DEA may only move a drug from Schedule I if there is a finding of "currently accepted medical use in treatment in the United States".

Although delta-9-THC is the principal psychoactive ingredient in marijuana, it can be synthesized and exist as a chemical. Delta-9-THC is a generic term which refers to four separate chemicals and two mixtures of chemicals, i.e., four stereochemical variants of the parent substance and two racemates. One of the stereochemical variants, the (-) delta-9-trans-THC isomer, is the principal psychoactive ingredient in Cannabis sativa, L., or marijuana. That isomer is also the ingredient in a pharmaceutical product which has been shown to be safe and effective as an anti-emetic for certain patients receiving cancer chemotherapy, and is identified chemically as (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol. The International Nonproprietary name (INN) and the U.S. Adopted Name (USAN) for that isomer of delta-9-THC is dronabinol.

With the development of scientific and medical evidence that demonstrated that a pharmaceutical product which contained

dronabinol was safe and effective for the treatment of nausea and vomiting associated with cancer chemotherapy in certain patients, then-Administrator John C. Lawn rescheduled this pharmaceutical product from Schedule I to Schedule II. See 51 Fed. Reg. 17476 (1986). Only the pharmaceutical product was transferred from Schedule I to Schedule II, i.e., "dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved drug product". No rescheduling action was taken with regard to (-) delta-9-trans-THC, i.e., dronabinol, which remains in Schedule I of the CSA. Tetrahydrocannabinols, including delta-9-THC, one of the synthetic equivalents of the substances contained in the plant or resinous extractives of Cannabis (marijuana) are listed at 21 C.F.R. § 1308.11(d)(25).

Tetrahydrocannabinols and all their isomers, including delta-9-THC, are also the subject of control by international agreement under the United Nations Convention on Psychotropic Substances, 1971, February 21, 1971, 32 U.S.T. 543, T.I.A.S. 9725, 1019 U.N.T.S. 175. Cannabis, cannabis resin and extracts and tinctures of cannabis are regulated as Schedule I substances under the United Nations Single Convention on Narcotic Drugs, 1961, March 30, 1961, 18 U.S.T. 1407, T.I.A.S. 6298, 520 U.N.T.S. 204. The United States is a party to both conventions.

Then-Administrator Lawn also discussed the United States international obligations in his Dronabinol in Sesame Oil and Encapsulated in a Soft Gelatin Capsule, rescheduling action.

See 51 Fed. Reg. 17476 (1986). Since Article 7 of the Convention on Psychotropic Substances, 1971 has strict prohibitions on activities involving Schedule I drugs, in 1987, the United States Government initiated an action to have delta-9-THC transferred to Schedule II to allow the pharmaceutical product to be marketed. See U.N. Doc. E/CN.7/1990/4. Such a transfer was not inconsistent with the substance delta-9-THC remaining in the CSA Schedule I. Under Article 23 of the Convention on Psychotropic Substances, 1971, a party may adopt more strict or severe measures of control if desirable or necessary for the protection of the public health and welfare.

Under the CSA, the regulation of chemicals and the plant material are distinct from each other. The classification of delta-9-THC has no bearing on the classification of marijuana. Under the CSA, a proposed change in the schedule of either a tetrahydrocannabinol or the plant marijuana requires the Attorney General to proceed independently.

Petitioner apparently does not wish to look to the clear construct of the Controlled Substances Act, but to pose alternative theories of the Act. Under the CSA, drugs or other substances may be treated and classified differently, according to the enumerated statutory criteria. 21 U.S.C. § 812(b).

The Deputy Administrator reaffirms that marijuana does not have a currently accepted medical use in treatment in the United States and is thus appropriately listed as a Schedule I controlled substance. The Deputy Administrator finds nothing to

support the petitioner's contention that since marijuana, coca, and opium are all plant materials they must be treated alike in the CSA. The Deputy Administrator further finds that the rescheduling of the pharmaceutical product "dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved drug product", which contains the synthetic chemical ingredient (-) delta-9-trans-THC, did not require that either the plant marijuana or substance delta-9-THC be similarly rescheduled. The Petitioner's request is denied.

Stephen H. Greene
Deputy Administrator

Dated: 5-16-94

STATE OF IOWA

TERRY E. BRANSTAD, GOVERNOR

DEPARTMENT OF GENERAL SERVICES
JANET E. PHIPPS, DIRECTOR

June 2, 1995

Carl E. Olson, Chairperson
P.O. Box 4091
Des Moines, Iowa 50333

Dear Mr. Olson;

The Department of General Services has reserved for your use the West steps of the State Capitol for a rally of Iowans for Medical Marijuana to be held on Sunday, August 5, 1995 beginning at Noon until 2:00 p.m. I appreciate your appointing two marshalls, yourself and John Hartog (515/262-4660) to assist the 50 - 100 people expected to attend the event.

I understand that your organization will again provide your own security arrangements as well as public address system. We can offer you the use of the 110 volt electrical outlet located at the base of the light post immediately east of the Lincoln and Tad statue. There are no charges for the use of the State Capitol grounds or electricity.

Please remember no signs can be hung from the building, lamp posts or trees but signs carried by a single individual are acceptable. I appreciate the efforts outlined in your letter to restrict the use of illegal drugs on the complex. Capitol Police will be informed that two participants, George McMahon and Barbara Douglas are authorized to use marijuana by the federal government as well as the Iowa Board of Pharmacy Examiners.

If you have any questions, please do not hesitate to call me at 242-5120.

Sincerely,

Dean Crocker
Customer Service Center

cc: Janet E. Phipps
Carl Parker
Capitol Police

CUSTOMER SERVICE CENTER / HOOVER BUILDING - A LEVEL / DES MOINES, IOWA 50319
PHONE: 515-242-5120 / FAX: 515-242-5974

STATE OF IOWA

TERRY E. BRANSTAD, GOVERNOR

DEPARTMENT OF GENERAL SERVICES
JANET E. PHIPPS, DIRECTOR

August 16, 1996

Mr. Carl E. Olson, Chairperson
Iowans for Medical Marijuana
P.O. Box 4091
Des Moines, Iowa 50333

Dear Mr. Olson,

The Department of General Services has reserved for your use the West steps of the State Capitol from noon until 3:00 p.m. on Sunday, October 6, 1996. It is understood that the purpose for this rally is to encourage the Iowa Legislature to enact legislation allowing the medical use of marijuana in the state of Iowa. The Iowa Legislature is not in session during your requested time period; please let the Customer Service Center know if there is anything they can assist with in the preparation of this event. There is a 110 volt electrical outlet located at the base of the light post immediately east of the Lincoln and Tad statue. There are no charges for the use of the State Capitol grounds or electricity.

Please remember no signs can be hung from the building, lamp posts or trees, but signs carried by a single individual are acceptable. At no time should signs, pictures or any other form of media be displayed or voiced, that suggest a correlation between the State of Iowa and an individual, group, association or business. The Customer Service Center appreciates the efforts outlined in your letter to restrict the use of illegal drugs on the complex as well as appointing two marshals, yourself and John Hartog (515/ 262-4660) to assist the 50 - 100 people expected to attend this event. Capitol Police has been informed that two participants, George McMahon and Barbara Douglas, have legal prescriptions for marijuana and are approved to use marijuana by the federal government as well as the Iowa Board of Pharmacy Examiners.

Good luck with your event! If you have any questions, please do not hesitate to call me at 242-5120.

Sincerely,

Stephen J. Rodriquez
Customer Service Center

cc: Carl Parker
Capitol Police

CUSTOMER SERVICE CENTER / HOOVER BUILDING - A LEVEL / DES MOINES, IOWA 50319
PHONE: 515-242-5120 / FAX: 515-242-5974

US006630507B1

(12) **United States Patent**
Hampson et al.

(10) **Patent No.: US 6,630,507 B1**
(45) **Date of Patent: Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

(75) Inventors: **Aidan J. Hampson**, Irvine, CA (US); **Julius Axelrod**, Rockville, MD (US); **Maurizio Grimaldi**, Bethesda, MD (US)

(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,028**

(22) PCT Filed: **Apr. 21, 1999**

(86) PCT No.: **PCT/US99/08769**

§ 371 (c)(1),
(2), (4) Date: **Feb. 2, 2001**

(87) PCT Pub. No.: **WO99/53917**

PCT Pub. Date: **Oct. 28, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/082,589, filed on Apr. 21, 1998, and provisional application No. 60/095,993, filed on Aug. 10, 1998.

(51) **Int. Cl.**[7] **A61K 31/35**
(52) **U.S. Cl.** **514/454**
(58) **Field of Search** 514/454

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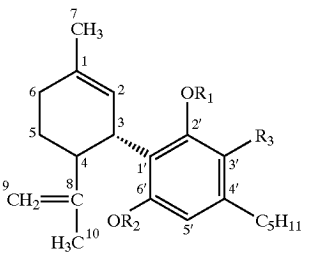
(List continued on next page.)

Primary Examiner—Kevin E. Weddington
(74) *Attorney, Agent, or Firm*—Klarquist Sparkman, LLP

(57) **ABSTRACT**

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidoil, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH_3, and $COCH_3$.

(I)



26 Claims, 7 Drawing Sheets

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* cited by examiner

FIG. 1

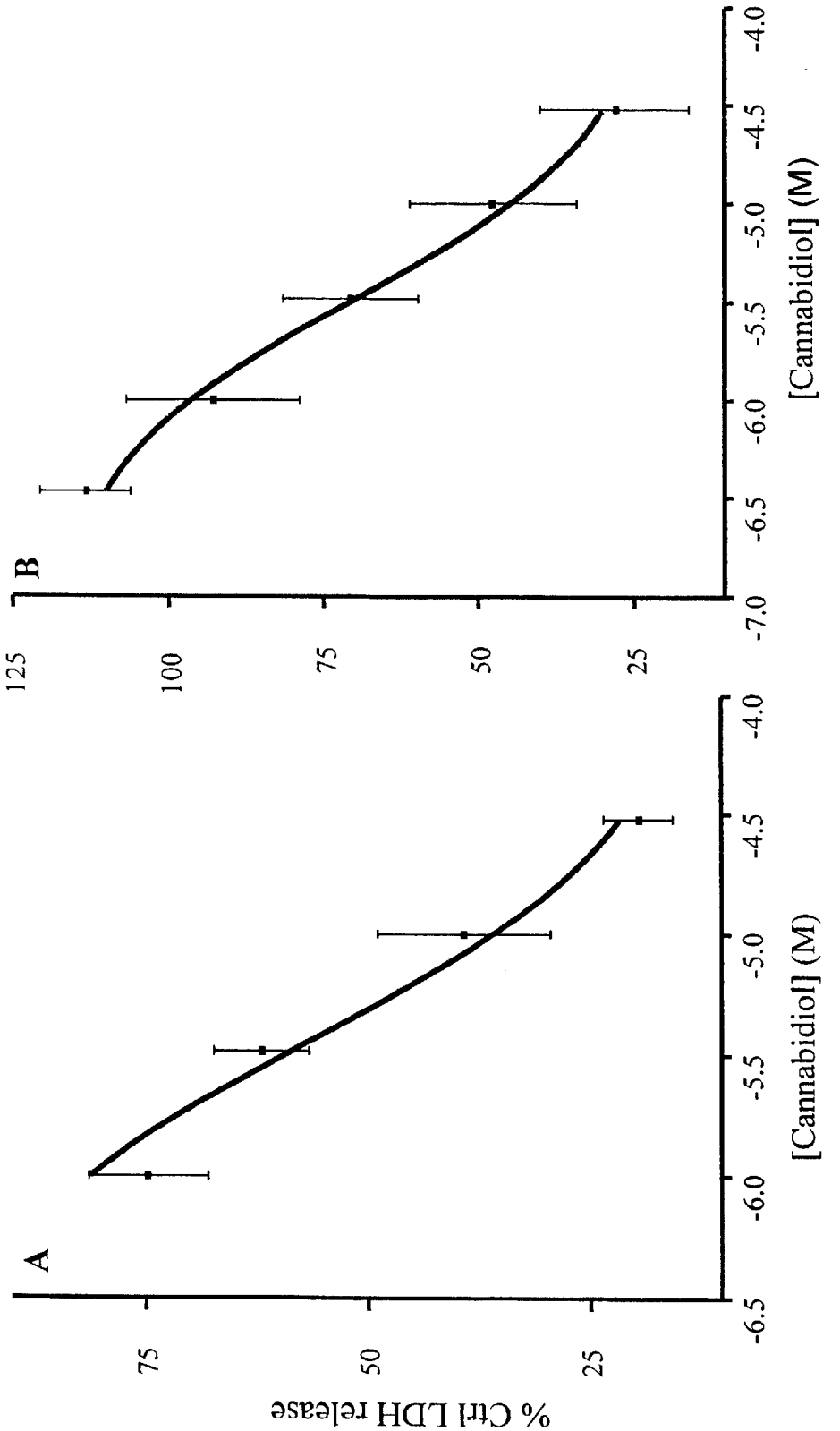

A
B
% Ctrl LDH release
75
50
25
125
100
75
50
25
-6.5
-6.0
-5.5
-5.0
-4.5
-4.0
-7.0
[Cannabidiol] (M)

FIG. 2

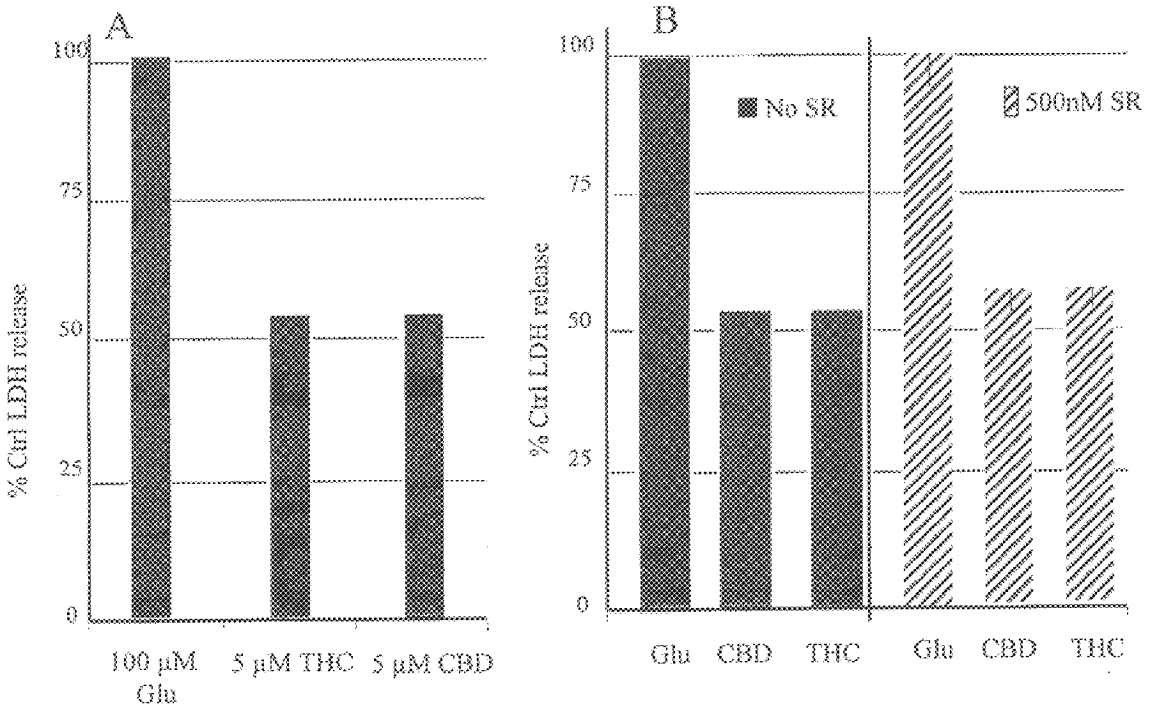

A
100
75
50
25
0
% Ctrl LDH release
100 μM Glu
5 μM THC
5 μM CBD
B
100
75
50
25
0
% Ctrl LDH release
No SR
500nM SR
Glu
CBD
THC
Glu
CBD
THC

FIG. 3

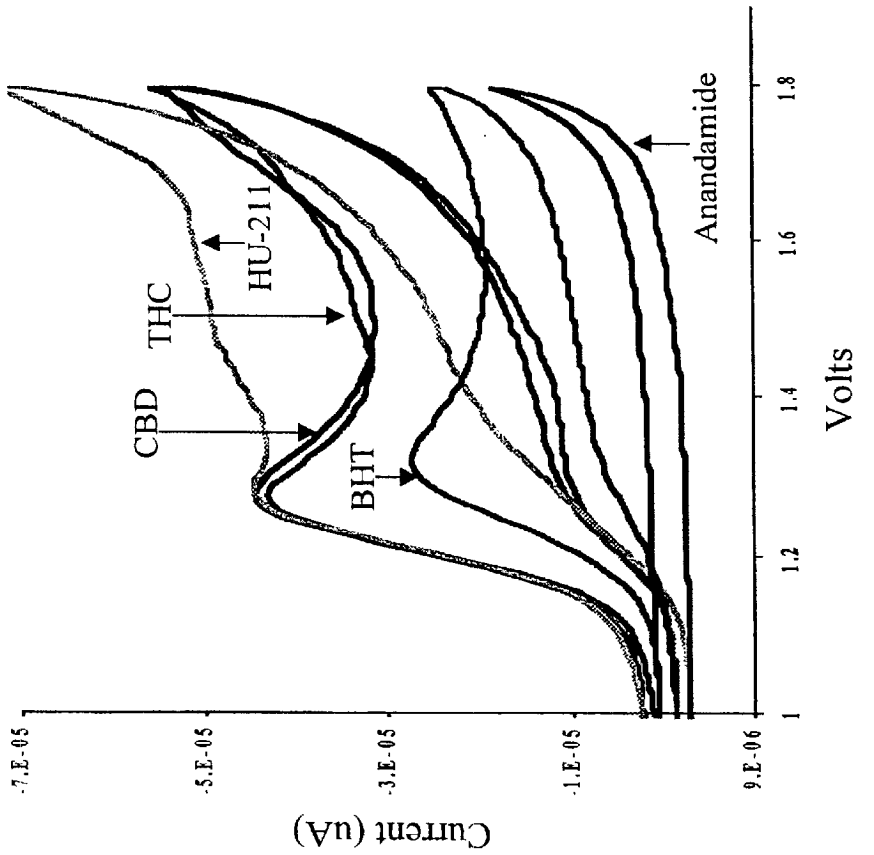

Current (uA)
-7.E-05
-5.E-05
-3.E-05
-1.E-05
9.E-06
1
1.2
1.4
1.6
1.8
Volts
CBD
THC
HU-211
BHT
Anandamide

FIG. 4

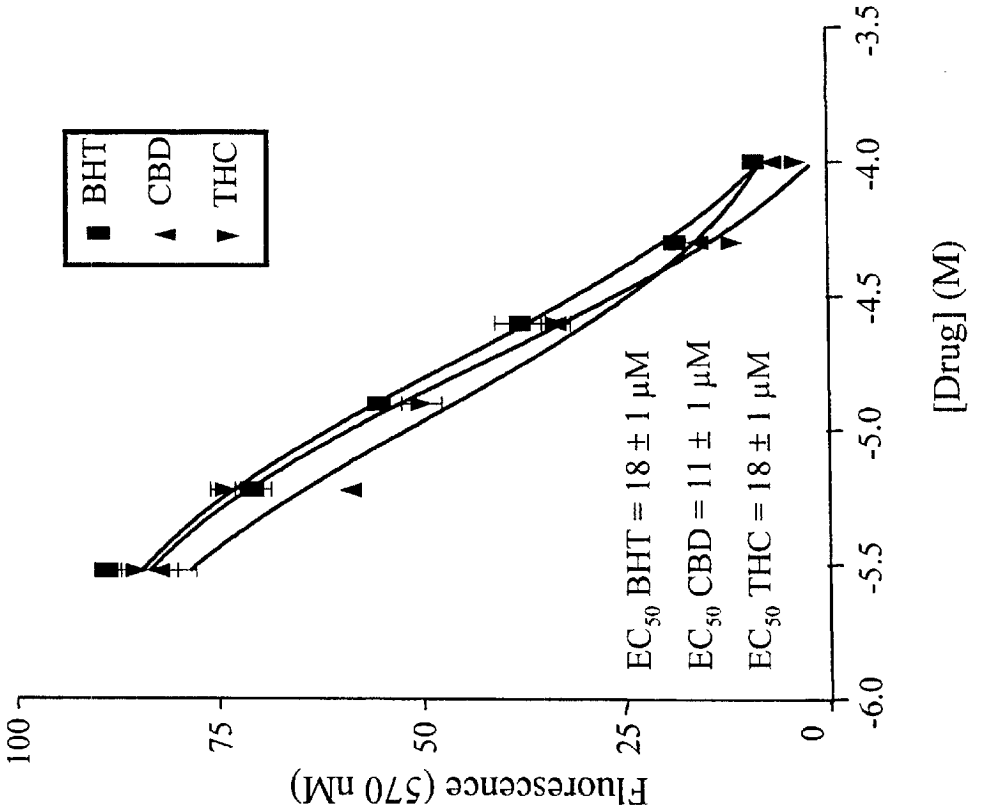

Fluorescence (570 nM)
100
75
50
25
0
-6.0
-5.5
-5.0
-4.5
-4.0
-3.5
[Drug] (M)
BHT
CBD
THC
EC50 BHT = 18 ± 1 µM
EC50 CBD = 11 ± 1 µM
EC50 THC = 18 ± 1 µM

FIG. 5

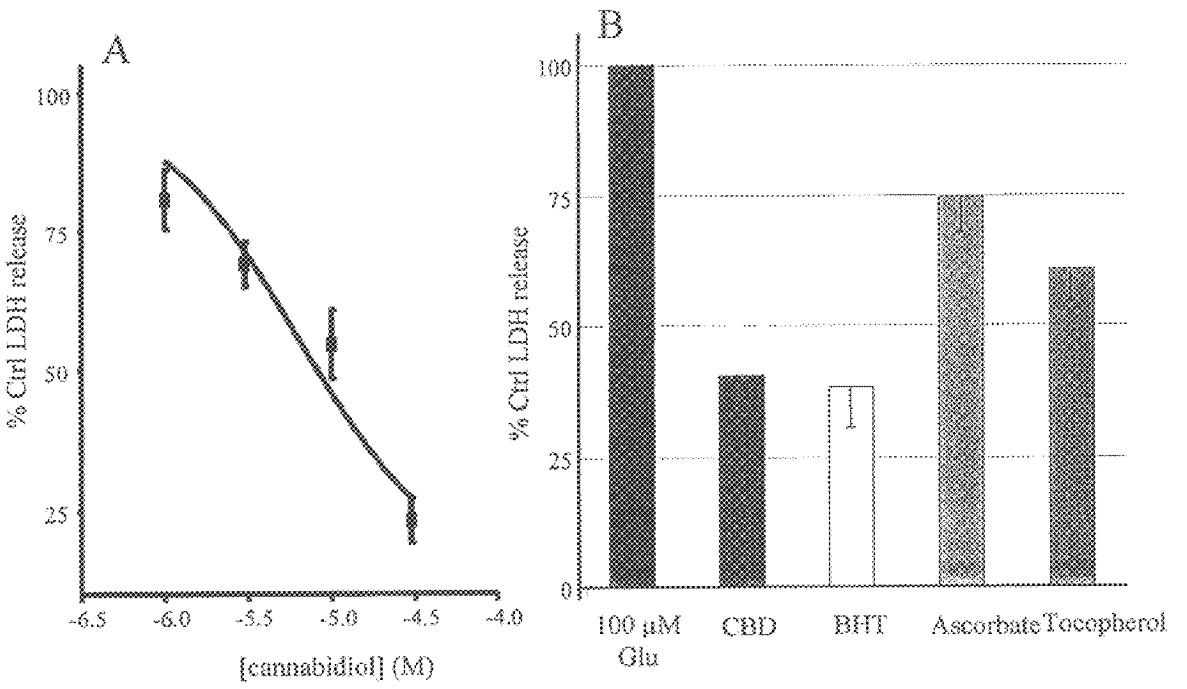

A
100
75
50
25
% Ctrl LDH release
-6.5
-6.0
-5.5
-5.0
-4.5
-4.0
[cannabidiol] (M)
B
100
75
50
25
0
% Ctrl LDH release
100 µM Glu
CBD
BHT
Ascorbate
Tocopherol

FIG. 6

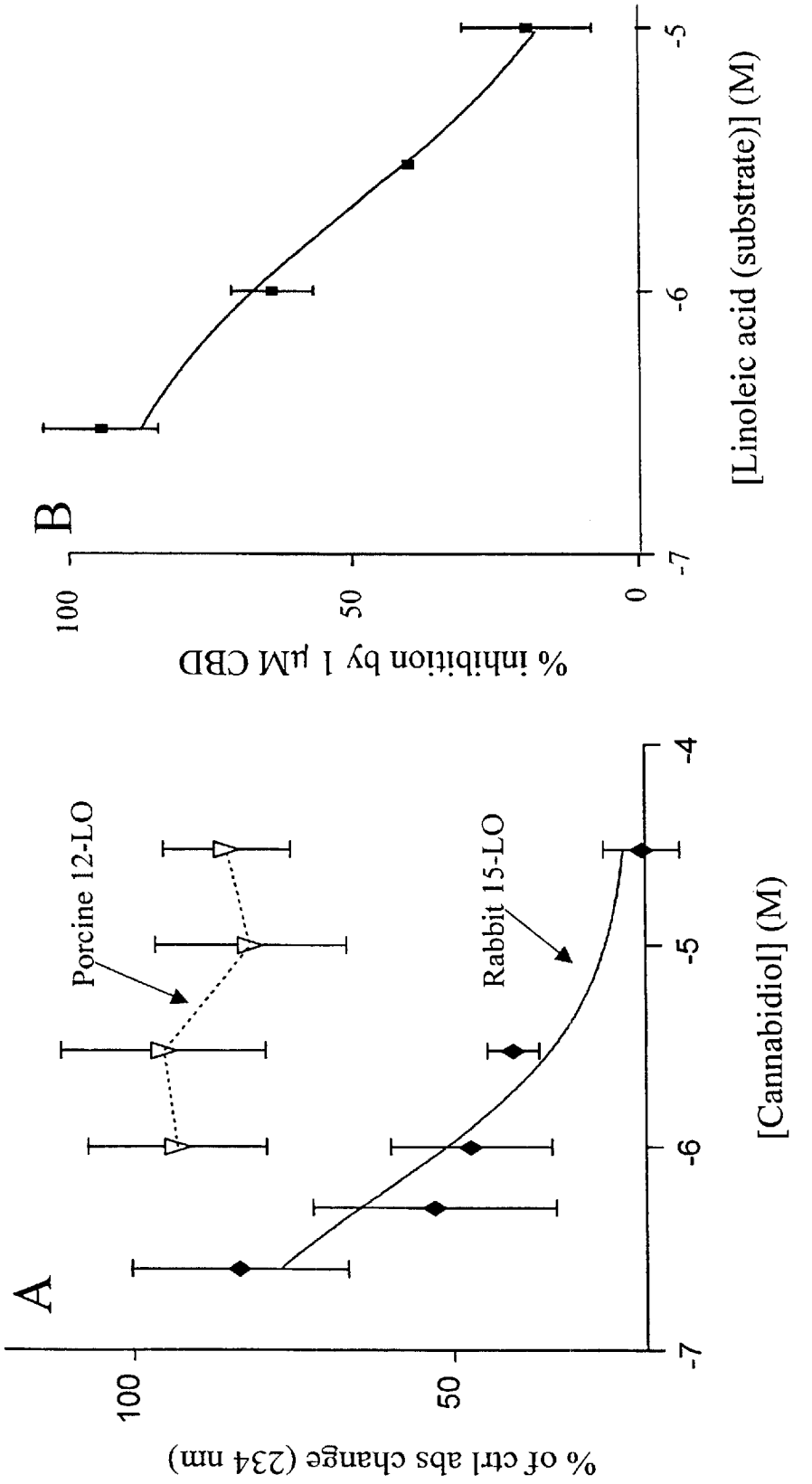

A
% of ctrl abs change (234 nm)
100
50
-7
-6
-5
-4
[Cannabidiol] (M)
Porcine 12-LO
Rabbit 15-LO
B
% inhibition by 1 μM CBD
100
50
0
-7
-6
-5
[Linoleic acid (substrate)] (M)

FIG. 7

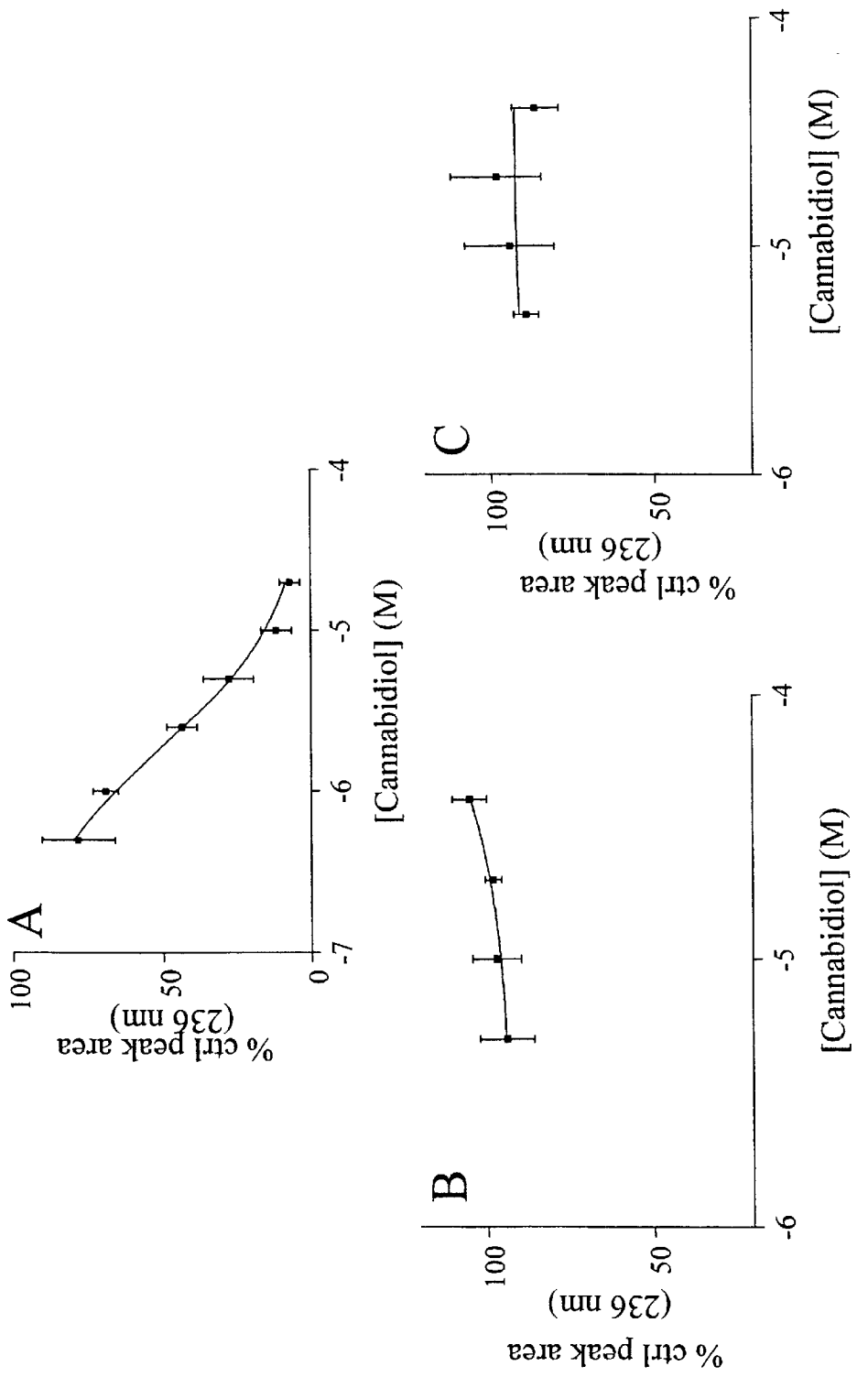
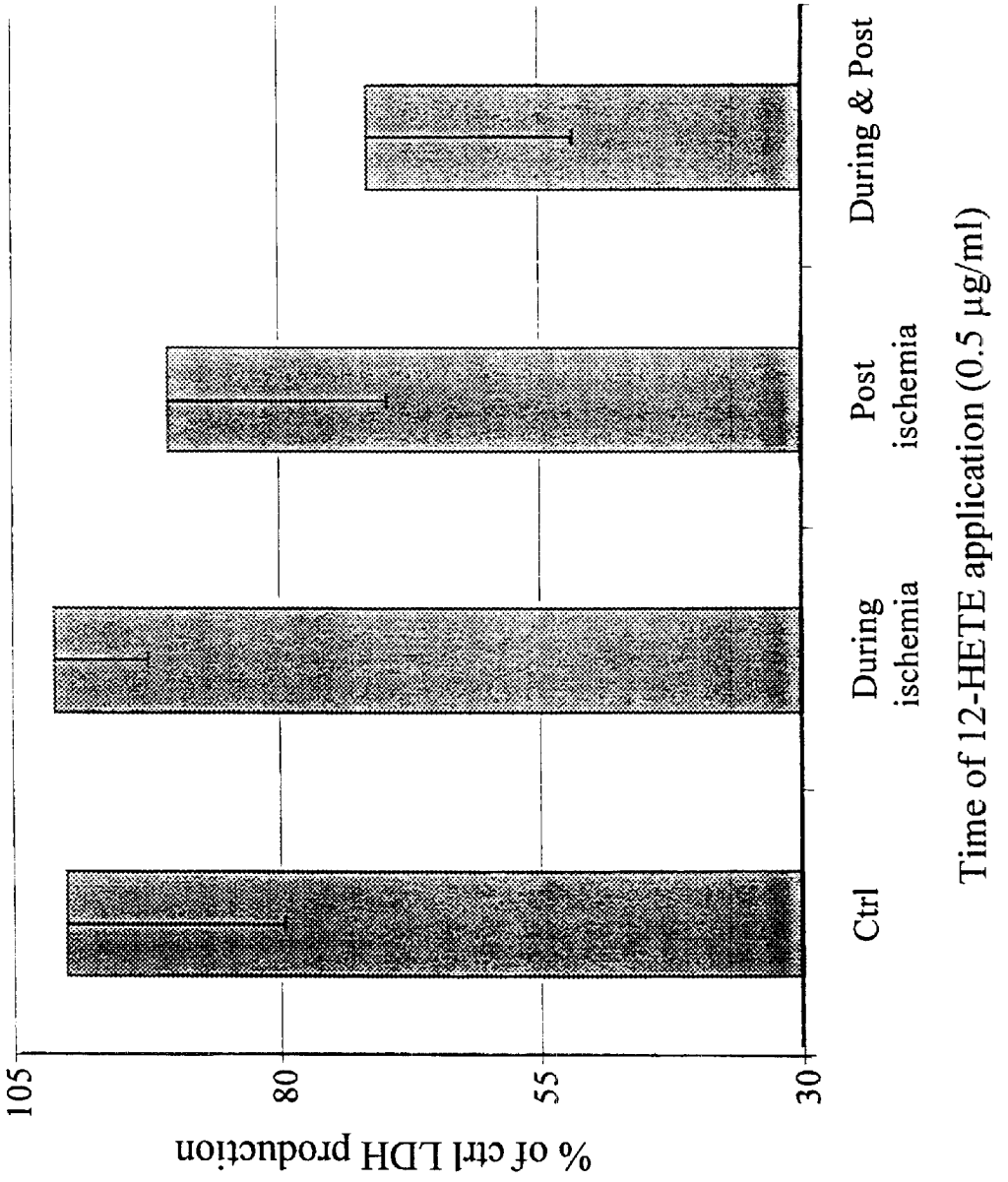


FIG. 8


105
80
55
30
% of ctrl LDH production
Ctrl
During ischemia
Post ischemia
During & Post
Time of 12-HETE application (0.5 µg/ml)

CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS

This application is a 371 of PCT/US99/08769 filed Apr. 21, 1999, which claims benefit of No. 60/082,589 filed Apr. 21, 1998, which claims benefit of No. 60/095,993 filed Aug. 10, 1998.

FIELD OF THE INVENTION

The present invention concerns pharmaceutical compounds and compositions that are useful as tissue protectants, such as neuroprotectants and cardioprotectants. The compounds and compositions may be used, for example, in the treatment of acute ischemic neurological insults or chronic neurodegenerative diseases.

BACKGROUND OF THE INVENTION

Permanent injury to the central nervous system (CNS) occurs in a variety of medical conditions, and has been the subject of intense scientific scrutiny in recent years. It is known that the brain has high metabolic requirements, and that it can suffer permanent neurologic damage if deprived of sufficient oxygen (hypoxia) for even a few minutes. In the absence of oxygen (anoxia), mitochondrial production of ATP cannot meet the metabolic requirements of the brain, and tissue damage occurs. This process is exacerbated by neuronal release of the neurotransmitter glutamate, which stimulates NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) and kainate receptors. Activation of these receptors initiates calcium influx into the neurons, and production of reactive oxygen species, which are potent toxins that damage important cellular structures such as membranes, DNA and enzymes.

The brain has many redundant blood supplies, which means that its tissue is seldom completely deprived of oxygen, even during acute ischemic events caused by thromboembolic events or trauma. A combination of the injury of hypoxia with the added insult of glutamate toxicity is therefore believed to be ultimately responsible for cellular death. Hence if the additive insult of glutamate toxicity can be alleviated, neurological damage could also be lessened. Anti-oxidants and anti-inflammatory agents have been proposed to reduce damage, but they often have poor access to structures such as the brain (which are protected by the blood brain barrier).

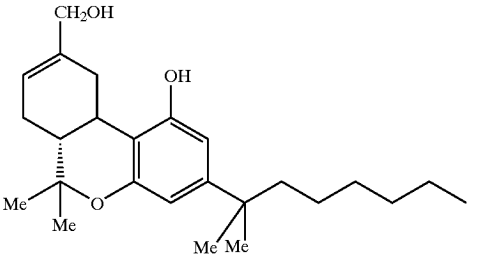
Given the importance of the NMDA, AMPA and kainate receptors in the mechanism of injury, research efforts have focused on using antagonists to these receptors to interfere with the receptor mediated calcium influx that ultimately leads to cellular death and tissue necrosis. In vitro studies using cultured neurons have demonstrated that glutamate receptor antagonists reduce neurotoxicity, but NMDA and AMPA/kainate receptor antagonists have different effects. Antagonists to NMDAr prevent neurotoxicity if present during the glutamate exposure period, but are less effective if added after glutamate is removed. In contrast, AMPA/kainate receptor antagonists are not as effective as NMDA antagonists during the glutamate exposure period, but are more effective following glutamate exposure.

Some of the research on these antagonists has focused on cannabinoids, a subset of which have been found to be NMDA receptor antagonists. U.S. Pat. No. 5,538,993 (3S, 4S-delta-6-tetrahydrocannabinol-7-oic acids), U.S. Pat. No. 5,521,215 (sterospecific (+) THC enantiomers), and U.S. Pat. No. 5,284,867 (dimethylheptyl benzopyrans) have reported that these cannabinoids are effective NMDA receptor blockers. U.S. Pat. No. 5,434,295 discloses that the 1,1 dimethylheptyl (DMH) homolog of [3R,4R]-7-hydroxy-

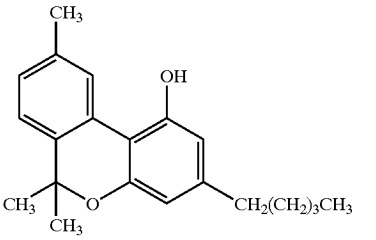
Δ^6THC (known as HU-210) is a superpotent cannabinoid receptor agonist with cannabinomimetic activity two orders of magnitude greater than the natural Δ^9 THC. The HU-210 dimethylheptyl cannabinoid, has severe side effects, including fatigue, thirst, headache, and hypotension. *J. Pharmacol. Sci.* 60:1433–1457 (1971). Subjects who received this synthetic cannabinoid with a dimethylheptyl group experienced marked psychomotor retardation, and were unwilling or incapable of assuming an erect position.

In contrast to HU-210, the (–)(3R,4R) THC-DMH enantiomer (known as HU-211) displays low affinity to the cannabinoid receptors, but retains NMDA receptor antagonist neuroprotective activity.

HU-211

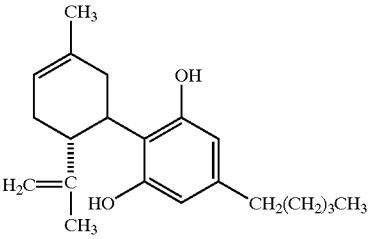


THC (tetrahydrocannabinol) is another of the cannabinoids that has been shown to be neuroprotective in cell cultures, but this protection was believed to be mediated by interaction at the cannabinoid receptor, and so would be accompanied by undesired psychotropic side effects.



THC

Although it has been unclear whether cannabimimetic activity plays a role in neuroprotection against glutamate induced neurological injury, the teaching in this field has clearly been that a cannabinoid must at least be an antagonist at the NMDA receptor to have neuroprotective effect. Hence cannabidiol (2-[3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol or CBD), a cannabinoid devoid of psychoactive effect (*Pharm. Rev.* 38:21–43, 1986), has not been considered useful as a neuroprotectant. Cannabidiol has been studied as an antiepileptic (Carlini et al., *J. Clin. Pharmacol.* 21:417S–427S, 1981; Karler et al., *J. Clin. Pharmacol.* 21:437S–448S, 1981, Consroe et al., *J. Clin Phannacol.* 21:428S–436S, 1981), and has been found to lower intraocular pressure (Colasanti et al, *Exp. Eye Res.* 39:251–259, 1984 and *Gen. Pharmac.* 15:479–484, 1984).



Cannabidiol (CBD)

No signs of toxicity or serious side effects have been observed following chronic administration of cannabidiol to healthy volunteers (Cunha et al., *Pharmacology* 21:175–185, 1980), even in large acute doses of 700 mg/day (Consroe et al., *Pharmacol. Biochem. Behav.* 40:701–708, 1991) but cannabidiol is inactive at the NMDA receptor. Hence in spite of its potential use in treating glaucoma and seizures, cannabidiol has not been considered a neuroprotective agent that could be used to prevent glutamate induced damage in the central nervous system.

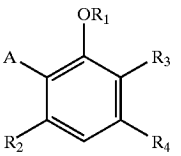
SUMMARY OF THE INVENTION

It is an object of this invention to provide a new class of antioxidant drugs, that have particular application as neuroprotectants, although they are generally useful in the treatment of many oxidation associated diseases.

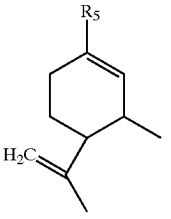
Yet another object of the invention is to provide a subset of such drugs that can be substantially free of psychoactive or psychotoxic effects, are substantially non-toxic even at very high doses, and have good tissue penetration, for example crossing the blood brain barrier.

It has surprisingly been found that cannabidiol and other cannabinoids can function as neuroprotectants, even though they lack NMDA receptor antagonist activity. This discovery was made possible because of the inventor's recognition of a previously unanticipated antioxidant property of the cannabinoids in general (and cannabidiol in particular) that functions completely independently of antagonism at the NMDA, AMPA and kainate receptors. Hence the present invention includes methods of preventing or treating diseases caused by oxidative stress, such as neuronal hypoxia, by administering a prophylactic or therapeutically effective amount of a cannabinoid to a subject who has a disease caused by oxidative stress.

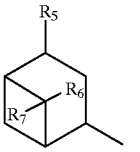
The cannabinoid may be a cannabinoid other than THC, HU-210, or other potent cannabinoid receptor agonists. The cannabinoid may also be other than HU-211 or any other NMDA receptor antagonist that has previously been reported. A potent cannabinoid receptor agonist is one that has an EC_{50} at the cannabinoid receptor of 50 nM or less, but in more particular embodiments 190 nM or 250 nM or less. In disclosed embodiments the cannabinoid is not psychoactive, and is not psychotoxic even at high doses. In some particularly disclosed embodiments, the cannabinoid is selected from the group:



where A is aryl, and particularly

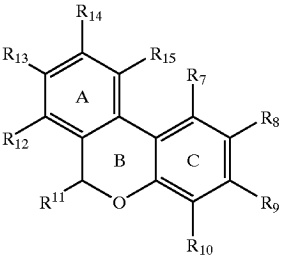


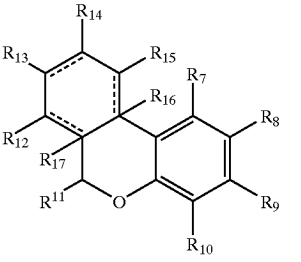
but not a pinene such as:

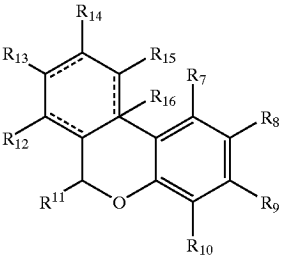


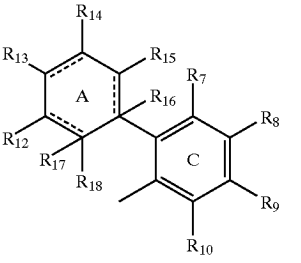
and the R_1–R_5 groups are each independently selected from the groups of hydrogen, lower substituted or unsubstituted alkyl, substituted or unsubstituted carboxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alcohol, and substituted or unsubstituted ethers, and R_6–R_7 are H or methyl. In particular embodiments, there are no nitrogens in the rings, and/or no amino substitutions on the rings.

In other embodiments, the cannabinoid is one of the following:









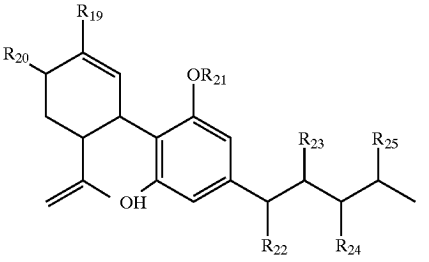
where there can be 0 to 3 double bonds on the A ring, as indicated by the optional double bonds indicated by dashed lines on the A ring. The C ring is aromatic, and the B ring can be a pyran. Particular embodiments are dibenzo pyrans and cyclohexenyl benzenediols. Particular embodiments of the cannabinoids of the present invention may also be highly lipid soluble, and in particular embodiments can be dis-

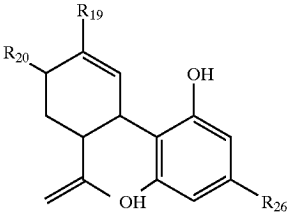
solved in an aqueous solution only sparingly (for example 10 mg/ml or less). The octanol/water partition ratio at neutral pH in useful embodiments is 5000 or greater, for example 6000 or greater. This high lipid solubility enhances penetration of the drug into the CNS, as reflected by its volume of distribution (V_d) of 1.5 L/kg or more, for example 3.5 L/kg, 7 L/kg, or ideally 10 L/kg or more, for example at least 20 L/kg. Particular embodiments may also be highly water soluble derivatives that are able to penetrate the CNS, for example carboxyl derivatives.

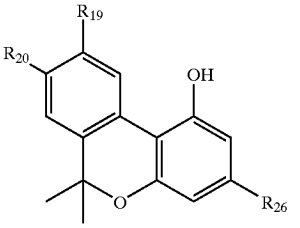
$R_{7\text{-}18}$ are independently selected from the group of H, substituted or unsubstituted alkyl, especially lower alkyl, for example unsubstituted C_1–C_3 alkyl, hydroxyl, alkoxy, especially lower alkoxy such as methoxy or ethoxy, substituted or unsubstituted alcohol, and unsubstituted or substituted carboxyl, for example COOH or $COCH_3$. In other embodiments $R_{7\text{-}18}$ can also be substituted or unsubstituted amino, and halogen.

The cannabinoid has substantially no binding to the NMDAr (for example an IC_{50} greater than or equal to 5 μM or 10 μM), has substantially no psychoactive activity mediated by the cannabinoid receptor (for example an IC_{50} at the cannabinoid receptor of greater than or equal to 300 nM, for example greater than 1 μM and a K_i greater than 250 nM, especially 500–1000 nM, for example greater than 1000 nM), and antioxidant activity, as demonstratable by the Fenton reaction or cyclic voltametry.

In other particular embodiments, the cannabinoids are one of the following:

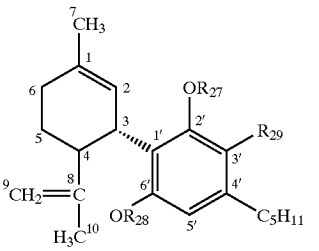




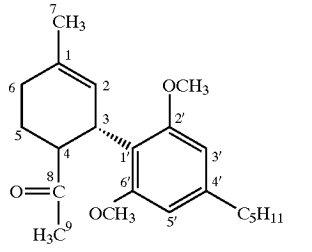


where R_{19} is substituted or unsubstituted alkyl, such as lower alkyl (for example methyl), lower alcohol (such as methyl alcohol) or carboxyl (such as carboxylic acid) and oxygen (as in =O); R_{20} is hydrogen or hydroxy; R_{21} is hydrogen, hydroxy, or methoxy; R_{22} is hydrogen or hydroxy; R_{23} is hydrogen or hydroxy; R_{24} is hydrogen or hydroxy; R_{25} is hydrogen or hydroxy; and R_{26} is substituted or unsubstituted alkyl (for example n-methyl alkyl), substituted or unsubstituted alcohol, or substituted or unsubstituted carboxy.

In yet other embodiments of the invention, the cannabinoids are

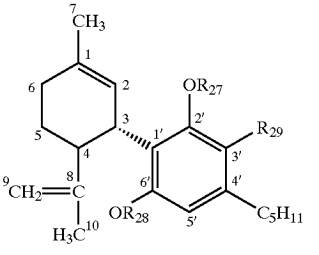


wherein numbering conventions for each of the ring positions are shown, and R_{27}, R_{28} and R_{29} are independently selected from the group consisting of H, unsubstituted lower alkyl such as CH_3, and carboxyl such as $COCH_3$. Particular examples of nonpsychoactive cannabinoids that fall within this definition are cannabidiol and



and other structural analogs of cannabidiol.

In more particular embodiments, the cannabinoid is used to prevent or treat an ischemic or neurodegenerative disease in the central nervous system of a subject, by administering to the subject a therapeutically effective amount of a cannabinoid to protect against oxidative injury to the central nervous system. The cannabinoid may be any of the compounds set forth above, or more specifically



wherein R_{27}, R_{28} and R_{29} are independently selected from the group consisting of H, lower alkyl such as CH_3, and carboxyl such as $COCH_3$, and particularly wherein

a) R_{27}=R_{28}=R_{29}=H

b) R_{27}=R_{29}=H; R_{28}=CH_3

c) R_{27}=R_{28}=CH_3; R_{29}=H

d) R_{27}=R_{28}=$COCH_3$; R_{29}=H

e) R_{27}=H; R_{28}=R_{29}=$COCH_3$

When R_{27}=R_{28}=R_{29}=H, then the compound is cannabidiol. When R_{27}=R_{29}=H and R_{28}=CH_3, the compound is CBD monomethyl ether. When R_{27}=R_{28}=CH_3 and R_{29}=H, the compound is CBD dimethyl ether. When R_{27}=R_{28}=$COCH_3$ and R_{29}=H, the compound is CBD diacetate. When R_{27}=H and R_{28}=R_{29}=$COCH_3$, the compound is CBD monoacetate. The ischemic or neurodegenerative disease may be, for

example, an ischemic infarct, Alzheimer's disease, Parkinson's disease, Down's syndrome, human immunodeficiency virus (HIV) dementia, myocardial infarction, or treatment and prevention of intraoperative or perioperative hypoxic insults that can leave persistent neurological deficits following open heart surgery requiring heart/lung bypass machines, such as coronary artery bypass grafts (CABG).

The invention also includes an assay for selecting a cannabinoid to use in treating a neurological disease by determining whether the cannabinoid is an antioxidant. Once it has been determined that the cannabinoid is an antioxidant, an antioxidant effective amount of the cannabinoid is administered to treat the neurological disease, such as a vascular ischemic event in the central nervous system, for example the type caused by a neurovascular thromboembolism. Similarly, the method of the present invention includes determining whether a disease is caused by oxidative stress, and if the disease is caused by oxidative stress, administering the cannabinoid in a therapeutically effective antioxidant amount.

The invention also includes identifying and administering antioxidant and neuroprotective compounds (such as cannabidiol) which selectively inhibit the enzyme activity of both 5- and 15-lipoxygenase more than the enzyme activity of 12-lipoxygenase. In addition, such compounds posses low NMDA antagonist activity and low cannabinoid receptor activity. Assays for selecting compounds with the desired effect on lipoxygenase enzymes, and methods for using identified compounds to treat neurological or ischemic diseases are also provided. Such diseases may include a vascular ischemic event in the central nervous system, for example a thromboembolism in the brain, or a vascular ischemic event in the myocardium. Useful administration of the compounds involves administration both during and after an ischemic injury.

These and other objects of the invention will be understood more clearly by reference to the following detailed description and drawings.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**A is a graph showing NMDA induced cellular damage in a neuron (as measured by LDH release) in cells that were exposed to glutamate for 10 minutes, which demonstrates that increasing concentrations of cannabidiol in the cell culture protects against cellular damage.

FIG. **1**B is a graph similar to FIG. **1**A, but showing that AMPA/kainate receptor mediated damage (induced by glutamate and the AMPA/kainate receptor potentiating agents cyclothiazide or concanavalin A) is also reduced in a concentration dependent manner by the presence of cannabidiol in the culture medium.

FIG. **2**A is a bar graph showing cellular damage (as measured by LDH release) in the presence of glutamate alone (100 μM Glu), and in the presence of glutamate and 5 μM cannabidiol (CBD) or 5 μM THC, and demonstrates that CBD and THC were similarly protective.

FIG. **2**B is a bar graph similar to FIG. **2**A, but showing the cellular damage assessed in the presence of the cannabinoid receptor antagonist SR 141716A (SR), which was not found to alter the neuroprotective effect of CBD (5 μM) or THC (5 μM), indicating the effect is not a typical cannabinoid effect mediated by the cannabinoid receptor.

FIG. **3** is a graph showing the reduction oxidation potentials determined by cyclic voltametry for some natural and synthetic cannabinoids, the antioxidant BHT, and the non-cannabinoid anandamide (arachidonyl ethanolamide) which is a ligand for the cannabinoid receptor. The voltage at which initial peaks occur is an indication of antioxidant activity.

FIG. **4** is a graph that demonstrates the antioxidant properties of BHT, CBD and THC, by plotting the fluorescence of a fluorescent dye against concentrations of these substances, where declining fluorescence is an indication of greater antioxidant activity.

FIG. **5**A is a graph illustrating decreased t-butyl peroxide induced toxicity (as measured by LDH release) in the presence of increasing concentrations of cannabidiol, demonstrating that cannabidiol is an effective antioxidant in living cells.

FIG. **5**B is a bar graph comparing the antioxidant activity of several antioxidants against glutamate induced toxicity in neurons, showing that CBD has superior antioxidant activity.

FIG. **6**A is a graph showing the effect of CBD (as measured by the change in absorbance at 234 nm) on the enzymatic activity of two lipoxygenase enzymes, rabbit 15-LO and porcine 12-LO, which demonstrates that CBD inhibits 15-LO, but not 12-LO enzyme.

FIG. **6**B is a graph demonstrating that inhibitory effect of CBD on 15-LO is competitive.

FIG. **7**A is a graph similar to FIG. **6**A, but was performed in whole cells rather than purified enzyme preparations, and shows the effect of CBD (as measured by the change in absorbance at 236 nm) on the enzymatic activity of 5-LO from cultured rat basophillic leukemia cells (RBL-2H3), which demonstrates that CBD inhibits 5-LO.

FIG. **7**B is a graph showing the effect of CBD (as measured by the change in absorbance at 236 nm) on the formation of 12-HETE (the product of 12-LO) by human leukocytes (12-LO type 1).

FIG. **7**C is a graph similar to FIG. **7**B, showing the effect of CBD (as measured by the change in absorbance at 236 nm) on the formation of 12-HETE by human platelets (12-LO type 2).

FIG. **8** is a bar graph demonstrating that 12-HETE can protect cortical neurons from NMDAr toxicity most effectively when administered during and post ischemia.

DETAILED DESCRIPTION OF SOME SPECIFIC EMBODIMENTS

This invention provides antioxidant compounds and compositions, such as pharmaceutical compositions, that include cannabinoids that act as free radical scavengers for use in prophylaxis and treatment of disease. The invention also includes methods for using the antioxidants in prevention and treatment of pathological conditions such as ischemia (tissue hypoxia), and in subjects who have been exposed to oxidant inducing agents such as cancer chemotherapy, toxins, radiation, or other sources of oxidative stress. The compositions and methods described herein are also used for preventing oxidative damage in transplanted organs, for inhibiting reoxygenation injury following reperfusion of ischemic tissues (for example in heart disease), and for any other condition that is mediated by oxidative or free radical mechanisms of injury. In particular embodiments of the invention, the compounds and compositions are used in the treatment of ischemic cardiovascular and neurovascular conditions, and neurodegenerative diseases. However the present invention can also be used as an antioxidant treatment in non-neurological diseases.

Molecular oxygen is essential for aerobic organisms, where it participates in many biochemical reactions, includ-

ing its role as the terminal electron acceptor in oxidative phosphorylation. However excessive concentrations of various forms of reactive oxygen species and other free radicals can have serious adverse biological consequences, including the peroxidation of membrane lipids, hydroxylation of nucleic acid bases, and the oxidation of sulfhydryl groups and other protein moieties. Biological antioxidants include tocopherols and tocotrieneols, carotenoids, quinones, bilirubin, ascorbic acid, uric acid, and metal binding proteins. However these endogenous antioxidant systems are often overwhelmed by pathological processes that allow permanent oxidative damage to occur to tissue.

Free radicals are atoms, ions or molecules that contain an unpaired electron, are usually unstable, and exhibit short half-lives. Reactive oxygen species (ROS) is a collective term, designating the oxygen radicals (e.g. $.O_2^-$ superoxide radical), which by sequential univalent reduction produces hydrogen peroxide (H_2O_2) and hydroxyl radical (.OH). The hydroxyl radical sets off chain reactions and can interact with nucleic acids. Other ROS include nitric oxide (NO.) and peroxy nitrite (NOO.), and other peroxyl (RO_2.) and alkoxyl (RO.) radicals. Increased production of these poisonous metabolites in certain pathological conditions is believed to cause cellular damage through the action of the highly reactive molecules on proteins, lipids and DNA. In particular, ROS are believed to accumulate when tissues are subjected to ischemia, particularly when followed by reperfusion.

The pharmaceutical compositions of the present invention have potent antioxidant and/or free radical scavenging properties, that prevent or reduce oxidative damage in biological systems, such as occurs in ischemic/reperfusion injury, or in chronic neurodegenerative diseases such as Alzheimer's disease, HIV dementia, and many other oxidation associated diseases.

DEFINITIONS

"Oxidative associated diseases" refers to pathological conditions that result at least in part from the production of or exposure to free radicals, particularly oxyradicals, or reactive oxygen species. It is evident to those of skill in the art that most pathological conditions are multifactorial, and that assigning or identifying the predominant causal factors for any particular condition is frequently difficult. For these reasons, the term "free radical associated disease" encompasses pathological states that are recognized as conditions in which free radicals or ROS contribute to the pathology of the disease, or wherein administration of a free radical inhibitor (e.g. desferroxamine), scavenger (e.g. tocopherol, glutathione) or catalyst (e.g. superoxide dismutase, catalase) is shown to produce detectable benefit by decreasing symptoms, increasing survival, or providing other detectable clinical benefits in treating or preventing the pathological state.

Oxidative associated diseases include, without limitation, free radical associated diseases, such as ischemia, ischemic reperfusion injury, inflammatory diseases, systemic lupus erythematosis, myocardial ischemia or infarction, cerebrovascular accidents (such as a thromboembolic or hemorrhagic stroke) that can lead to ischemia or an infarct in the brain, operative ischemia, traumatic hemorrhage (for example a hypovolemic stroke that can lead to CNS hypoxia or anoxia), spinal cord trauma, Down's syndrome, Crohn's disease, autoimmune diseases (e.g. rheumatoid arthritis or diabetes), cataract formation, uveitis, emphysema, gastric ulcers, oxygen toxicity, neoplasia, undesired cellular apoptosis, radiation sickness, and others. The present invention is believed to be particularly beneficial in the treatment of oxidative associated diseases of the CNS, because of the ability of the cannabinoids to cross the blood brain barrier and exert their antioxidant effects in the brain. In particular embodiments, the pharmaceutical composition of the present invention is used for preventing, arresting, or treating neurological damage in Parkinson's disease, Alzheimer's disease and HIV dementia; autoimmune neurodegeneration of the type that can occur in encephalitis, and hypoxic or anoxic neuronal damage that can result from apnea, respiratory arrest or cardiac arrest, and anoxia caused by drowning, brain surgery or trauma (such as concussion or spinal cord shock).

As used herein, an "antioxidant" is a substance that, when present in a mixture containing an oxidizable substrate biological molecule, significantly delays or prevents oxidation of the substrate biological molecule. Antioxidants can act by scavenging biologically important reactive free radicals or other reactive oxygen species ($.O_2^-$, H_2O_2, .OH, HOCl, ferryl, peroxyl, peroxynitrite, and alkoxyl), or by preventing their formation, or by catalytically converting the free radical or other reactive oxygen species to a less reactive species. Relative antioxidant activity can be measured by cyclic voltametry studies of the type disclosed in Example 5 (and FIG. **3**), where the voltage (x-axis) is an index of relative antioxidant activity. The voltage at which the first peak occurs is an indication of the voltage at which an electron is donated, which in turn is an index of antioxidant activity.

"Therapeutically effective antioxidant doses" can be determined by various methods, including generating an empirical dose-response curve, predicting potency and efficacy of a congener by using quantitative structure activity relationships (QSAR) methods or molecular modeling, and other methods used in the pharmaceutical sciences. Since oxidative damage is generally cumulative, there is no minimum threshold level (or dose) with respect to efficacy. However, minimum doses for producing a detectable therapeutic or prophylactic effect for particular disease states can be established.

As used herein, a "cannabinoid" is a chemical compound (such as cannabinol, THC or cannabidiol) that is found in the plant species *Cannabis saliva* (marijuana), and metabolites and synthetic analogues thereof that may or may not have psychoactive properties. Cannabinoids therefore include (without limitation) compounds (such as THC) that have high affinity for the cannabinoid receptor (for example K_i<250 nM), and compounds that do not have significant affinity for the cannabinoid receptor (such as cannabidiol, CBD). Cannabinoids also include compounds that have a characteristic dibenzopyran ring structure (of the type seen in THC) and cannabinoids which do not possess a pyran ring (such as cannabidiol). Hence a partial list of cannabinoids includes THC, CBD, dimethyl heptylpentyl cannabidiol (DMHP-CBD), 6,12-dihydro-6-hydroxy-cannabidiol (described in U.S. Pat. No. 5,227,537, incorporated by reference); (3S,4R)-7-hydroxy-Δ^6-tetrahydrocannabinol homologs and derivatives described in U.S. Pat. No. 4,876,276, incorporated by reference; (+)-4-[4-DMH-2,6-diacetoxy-phenyl]-2-carboxy-6,6-dimethylbicyclo[3.1.1]hept-2-en, and other 4-phenylpinene derivatives disclosed in U.S. Pat. No. 5,434,295, which is incorporated by reference; and cannabidiol (−)(CBD) analogs such as (−)CBD-monomethylether, (−)CBD dimethyl ether; (−)CBD diacetate; (−)3'-acetyl-CBD monoacetate; and ±AF11, all of which are disclosed in Consroe et al., *J. Clin. Phannacol.*

21:428S–436S, 1981, which is also incorporated by reference. Many other cannabinoids are similarly disclosed in Agurell et al., *Pharmacol. Rev.* 38:31–43, 1986, which is also incorporated by reference.

As referred to herein, the term "psychoactivity" means "cannabinoid receptor mediated psychoactivity." Such effects include, euphoria, lightheadedness, reduced motor coordination, and memory impairment. Psychoactivity is not meant to include non-cannabinoid receptor mediated effects such as the anxiolytic effect of CBD.

The "lipoxygenase enzyme activity" refers to the relative level of lipoxygenase enzyme activity for a particular lipoxgenase, such as 5-, 15- or 12-lipoxygenase, as measured in Example 8. A compound would be said to "selectively inhibit a lipoxgenase enzyme" if the concentration of inhibitor required to reduce enzyme activity by 50% was at least about 5 times less than the amount required to reduce activity of a second lipoxgenase enzyme by the same degree (under the same conditions, i.e. temperature, substrate concentration, etc.)

An "antagonist" is a compound that binds and occupies a receptor without activating it. In the presence of a sufficient concentration of antagonist, an agonist cannot activate its receptor. Therefore, antagonists may decrease the neurotoxicity mediated by NMDA (as described in Example 3) or AMPA and Kainate (as described in Example 4).

An "agonist" is a compound that activates a receptor. When the receptor is activated for a longer than normal period of time, this may cause neurotoxicity, as in the case of NMDA, AMPA and kainate receptors (see Examples 3 and 4).

The term "alkyl" refers to a cyclic, branched, or straight chain alkyl group containing only carbon and hydrogen, and unless otherwise mentioned contains one to twelve carbon atoms. This term is further exemplified by groups such as methyl, ethyl, n-propyl, isobutyl, t-butyl, pentyl, pivalyl, heptyl, adamantyl, and cyclopentyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, e.g. halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, aryloxy, aryl, arylalkyl, heteroaryl, amino, alkylamino, dialkylamino, morpholino, piperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality.

The term "lower alkyl" refers to a cyclic, branched or straight chain monovalent alkyl radical of one to seven carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), cyclopropylmethyl, i-amyl, n-amyl, hexyl and heptyl. Lower alkyl groups can also be unsubstituted or substituted, where a specific example of a substituted alkyl is 1,1-dimethyl heptyl.

"Hydroxyl" refers to —OH.

"Alcohol" refers to R—OH, wherein R is alkyl, especially lower alkyl (for example in methyl, ethyl or propyl alcohol). An alcohol may be either linear or branched, such as isopropyl alcohol.

"Carboxyl" refers to the radical —COOH, and substituted carboxyl refers to —COR where R is alkyl, lower alkyl or a carboxylic acid or ester.

The term "aryl" or "Ar" refers to a monovalent unsaturated aromatic carbocyclic group having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl or anthryl), which can optionally be unsubstituted or substituted with, e.g., halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, aryl, arylalkyl, heteroaryl, amino, alkylamino, dialkylamino, morpholino, piperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality.

The term "alkoxy" refers to a substituted or unsubstituted alkoxy, where an alkoxy has the structure —O—R, where R is substituted or unsubstituted alkyl. In an unsubstituted alkoxy, the R is an unsubstituted alkyl. The term "substituted alkoxy" refers to a group having the structure —O—R, where R is alkyl which is substituted with a non-interfering substituent. The term "arylalkoxy" refers to a group having the structure —O—R—Ar, where R is alkyl and Ar is an aromatic substituent. Arylalkoxys are a subset of substituted alkoxys. Examples of useful substituted alkoxy groups are: benzyloxy, naphthyloxy, and chlorobenzyloxy.

The term "aryloxy" refers to a group having the structure —O—Ar, where Ar is an aromatic group. A particular aryloxy group is phenoxy.

The term "heterocycle" refers to a monovalent saturated, unsaturated, or aromatic carbocyclic group having a single ring (e.g. morpholino, pyridyl or faryl) or multiple condensed rings (e.g. indolizinyl or benzo[b]thienyl) and having at least one heteroatom, defined as N, O, P, or S, within the ring, which can optionally be unsubstituted or substituted with, e.g. halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, aryl, arylakyl, heteroaryl, amino, alkylamino, dialkylamino, morpholino, piperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality.

"Arylalkyl" refers to the groups —R—Ar and —R—HetAr, where Ar is an aryl group. HetAr is a heteroaryl group, and R is a straight-chain or branched chain aliphatic group. Example of arylaklyl groups include benzyl and furfuryl. Arylalkyl groups can optionally be unsubstituted or substituted with, e.g., halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, acyloxy, hydroxy, mercapto, carboxy, aryloxy, aryl, arylalkyl, heteroaryl, amino, alkylamino, dialkylamino, morpholino, peperidino, pyrrolidin-1-yl, piperazin-1-yl, or other functionality.

The term "halo" or "halide" refers to fluoro, bromo, chloro and iodo substituents.

The term "amino" refers to a chemical functionality —NR'R" where R' and R" are independently hydrogen, alkyl, or aryl. The term "quaternary amine" refers to the positively charged group —N^+R'R", where R'R" and R" are independently selected and are alkyl or aryl. A particular amino group is —NH_2.

A "pharmaceutical agent" or "drug" refers to a chemical compound or composition capable of inducing a desired therapeutic or prophylactic effect when properly administered to a subject.

All chemical compounds include both the (+) and (−) stereoisomers, as well as either the (+) or (−) stereoisomer.

Other chemistry terms herein are used according to conventional usage in the art, as exemplified by *The McGraw-Hill Dictionary of Chemical Terms* (1985) and *The Condensed Chemical Dictionary* (1981).

The following examples show that both nonpsychoactive cannabidiol, and psychoactive cannabinoids such as THC, can protect neurons from glutamate induced death, by a mechanism independent of cannabinoid receptors. Cannabinoids are also be shown to be potent antioxidants capable of preventing ROS toxicity in neurons.

EXAMPLE 1

Preparation of Cannabinoids and Neuronal Cultures

Cannabidiol, THC and reactants other than those specifically listed below were purchased from Sigma Chemical,

Co. (St. Louis, Mo.). Cyclothiazide, glutamatergic ligands and MK-801 were obtained from Tocris Cookson (UK). Dihydrorhodamine was supplied by Molecular Probes (Eugene, Oreg.). T-butyl hydroperoxide, tetraethylammonium chloride, ferric citrate and sodium dithionite were all purchased from Aldrich (WI). All culture media were Gibco/BRL (MD) products.

Solutions of cannabinoids, cyclothiazide and other lipophiles were prepared by evaporating a 10 mM ethanolic solution (under a stream of nitrogen) in a siliconized microcentrifuge tube. Dimethyl sulfoxide (DMSO, less than 0.05% of final volume) was added to ethanol to prevent the lipophile completely drying onto the tube wall. After evaporation, 1 ml of culture media was added and the drug was dispersed using a high power sonic probe. Special attention was used to ensure the solution did not overheat or generate foam. Following dispersal, all solutions were made up to their final volume in siliconized glass tubes by mixing with an appropriate quantity of culture media.

Primary neuronal cultures were prepared according to the method of Ventra et al. (J. Neurochem. 66:1752–1761, 1996). Fetuses were extracted by Cesarian section from a 17 day pregnant Wistar rat, and the feral brains were placed into phosphate buffered saline. The cortices were then dissected out, cut into small pieces and incubated with papain for nine minutes at 37° C. After this time the tissue was dissociated by passage through a fire polished Pasteur pipette, and the resultant cell suspension separated by centrifugation over a gradient consisting of 10 mg/ml bovine serum albumin and 10 mg/ml ovomucoid (a trypsin inhibitor) in Earls buffered salt solution. The pellet was then re-suspended in high glucose, phenol red free Dulbeco's modified Eagles medium containing 10% fetal bovine serum, 2 mM glutamine, 100 IU penicillin, and 100 μg/ml streptomycin (DMEM). Cells were counted, tested for vitality using the trypan blue exclusion test and seeded onto poly-D-lysine coated 24 multiwell plates. After 96 hours, 10 μM fluoro-deoxyuridine and 10 μM uridine were added to block glial cell growth. This protocol resulted in a highly neuron-enriched culture.

EXAMPLE 2

Preparation of Astrocytes and Conditioned Media

Astrocyte conditioned DMEM was used throughout the AMPA/kainate toxicity procedure and following glutamate exposure in the NMDAr mediated toxicity protocol. Media was conditioned by 24 hour treatment over a confluent layer of type I astrocytes, prepared from two day old Wistar rat pups. Cortices were dissected, cut into small pieces, and enzymatically digested with 0.25% trypsin. Tissue was then dissociated by passage through a fire polished Pasteur pipette and the cell suspension plated into untreated 75 cm^2 T-flasks. After 24 hours the media was replaced and unattached cells removed. Once astrocytes achieved confluence, cells were divided into four flasks. Media for experiments was conditioned by a 24 hour exposure to these astrocytes, after which time it was frozen at −20° C. until use. Astrocyte cultures were used to condition DMEM for no longer than two months.

EXAMPLE 3

NMDA Mediated Toxicity Studies

Glutamate neurotoxicity can be mediated by NMDA, AMPA or kainate receptors. To examine NMDAr mediated toxicity, cultured neurons (cultured for 14–18 days) were exposed to 250 μM glutamate for 10 minutes in a magnesium free saline solution. The saline was composed of 125 mM NaCl, 25 mM glucose, 10 mM HEPES (pH 7.4), 5 mM KCl, 1.8 mM calcium chloride and 5% bovine serum albumin. Following exposure, cells were washed twice with saline, and incubated for 18 hours in conditioned DMEM. The level of lactate dehydrogenase (LDH) in the media was used as an index of cell injury.

Toxicity was completely prevented by addition of the NMDAr antagonist, MK-801 (500 nM, data not shown). However, FIG. **1A** shows that cannabidiol also prevented neurotoxicity (maximum protection 88±9%) with an EC_{50} of 2–4 μM (specifically about 3.5 μM).

EXAMPLE 4

AMPA and Kainate Receptor Mediated Toxicity Studies

Unlike NMDA receptors, which are regulated by magnesium ions, AMPA/kainate receptors rapidly desensitize following ligand binding. To examine AMPA and kainate receptor mediated toxicity, neurons were cultured for 7–13 days, then exposed to 100 μM glutamate and 50 μM cyclothiazide (used to prevent AMPA receptor desensitization). Cells were incubated with glutamate in the presence of 500 nM MK-801 (an NMDAr antagonist) for 18–20 hours prior to analysis. Specific AMPA and kainate receptor ligands were also used to separately examine the effects of cannabinoids on AMPA and kainate receptor mediated events. Fluorowillardiine (1.5 μM) was the AMPA agonist and 4-methyl glutamate (10 μM) was the kainate agonist used to investigate receptor mediated toxicity. When specifically examining kainate receptor activity, cyclothiazide was replaced with 0.15 mg/ml Concanavalin-A.

Cannabidiol protection against AMPA/kainate mediated neurotoxicity is illustrated in FIG. **1B**, where LDH in the media was used as an index of cell injury. The neuroprotective effect of cannabidiol was similar to that observed in the NMDA mediated toxicity model (FIG. **1A**). Cannabidiol prevented neurotoxicity (maximum protection 80±17%) with an EC_{50} of 2–4 μM (specifically about 3.3 μM). Comparable results were obtained with either the AMPA receptor ligand, fluorowillardiine or the kainate receptor specific ligand, 4-methyl-glutamate (data not shown). Hence cannabidiol protects similarly against toxicity mediated by NMDA, AMPA or kainate receptors.

Unlike cannabidiol, THC is a ligand (and agonist) for the brain cannabinoid receptor. The action of THC at the cannabinoid receptor has been proposed to explain the ability of THC to protect neurons from NMDAr toxicity in vitro. However in AMPA/kainate receptor toxicity assays, THC and cannabidiol were similarly protective (FIG. **2A**), indicating that cannabinoid neuroprotection is independent of cannabinoid receptor activation. This was confirmed by inclusion of cannabinoid receptor antagonist SR-141716A in the culture media (SR in FIG. **2B**). See Mansbach et al., *Psychopharmacology* 124:315–22, 1996, for a description of SR-141716A. Neither THC nor cannabidiol neuroprotection was affected by cannabinoid receptor antagonist (FIG. **2B**).

EXAMPLE 5

Cyclic Voltametery Studies or ReDox Potentials

To investigate whether cannabinoids protect neurons against glutamate damage by reacting with ROS, the anti-

oxidant properties of cannabidiol and other cannabinoids were assessed. Cyclic voltametry, a procedure that measures the ability of a compound to accept or donate electrons under a variable voltage potential, was used to measure the oxidation potentials of several natural and synthetic cannabinoids. These studies were performed with an EG&G Princeton Applied Research potentiostat/galvanostat (Model 273/PAR 270 software, NJ). The working electrode was a glassy carbon disk with a platinum counter electrode and silver/silver chloride reference. Tetraethylammonium chloride in acetonitrile (0.1 M) was used as an electrolyte. Cyclic voltametry scans were done from +0 to 1.8 V at scan rate of 100 mV per second. The reducing ability of cannabidiol (CBD), THC, HU-211, and BHT were measured in this fashion. Anandamide, a cannabinoid receptor ligand without a cannabinoid like structure, was used as a non-responsive control. Each experiment was repeated twice with essentially the same results.

Cannabidiol, THC and the synthetic cannabinoid HU-211 all donated electrons at a similar potential as the antioxidant BHT. Anandamide (arachidonyl ethanolamide) did not undergo oxidation at these potentials (FIG. **3**). Several other natural and synthetic cannabinoids, including cannabidiol, nabilone, and levanantrodol were also tested, and they too exhibited oxidation profiles similar to cannabidiol and THC (data not shown).

EXAMPLE 6

Iron Catalyzed Dihydrorhodamine Oxidation (Fenton Reaction)

The ability of cannabinoids to be readily oxidized, as illustrated in Example 5, indicated they possess antioxidant properties comparable to BHT. The antioxidant activity of BHT was examined in a Fenton reaction, in which iron is catalyzed to produce ROS. Cannabidiol (CBD) and tetrahydrocannabinol (THC) were evaluated for their ability to prevent oxidation of dihydrorhodamine to the fluorescent compound rhodamine. Oxidant was generated by ferrous catalysis (diothionite reduced ferric citrate) of t-butyl hydroperoxide in a 50:50 water:acetonitrile (v/v) solution. Dihydrorhodamine (50 μM) was incubated with 300 μM t-butyl hydroperoxide and 0.5 μM iron for 5 minutes. After this time, oxidation was assessed by spectrofluorimetry (Excit= 500 nm, Emiss=570 nm). Various concentrations of cannabinoids and BHT were included to examine their ability to prevent dihydrorhodiamine oxidation.

Cannabidiol, THC and BHT all prevented dihydrorhodamine oxidation in a similar, concentration dependent manner (FIG. **4**), indicating that cannabinoids have antioxidant potency comparable to BHT.

To confirm that cannabinoids act as antioxidants in the intact cell, neurons were also incubated with the oxidant t-butyl hydroperoxide and varying concentrations of cannabidiol (FIG. **5**A). The t-butyl hydroperoxide oxidant was chosen for its solubility in both aqueous and organic solvents, which facilitates oxidation in both cytosolic and membrane cell compartments. Cell toxicity was assessed 18–20 hours after insult by measuring lactate dehydrogenase (LDH) release into the culture media. All experiments were conducted with triple or quadruple values at each point and all plates contained positive (glutamate alone) and baseline controls. The assay was validated by comparison with an XTT based metabolic activity assay. As shown in FIG. **5**A, cannabidiol protected neurons against ROS toxicity in a dose related manner, with an EC_{50} of about 6 μM. The maximum protection observed was 88±9%.

Cannabidiol was also compared with known antioxidants in an AMPA/kainate toxicity protocol. Neurons were exposed to 100 μM glutamate and equimolar (5 μM) cannabidiol, α-tocopherol, BHT or ascorbate (FIG. **5**B). Although all of the antioxidants attenuated glutamate toxicity, cannabidiol was significantly more protective than either α-tocopherol or ascorbate. The similar antioxidant abilities of cannabidiol and BHT in this chemical system (FIG. **4**), and their comparable protection in neuronal cultures (FIG. **5**B), implies that cannabidiol neuroprotection is due to an antioxidant effect.

EXAMPLE 7

In vivo Rat Studies

The middle cerebral artery of chloral hydrate anesthetized rats was occluded by insertion of suture thread into it. The animals were allowed to recover from the anesthetic and move freely for a period of two hours. After this time the suture was removed under mild anesthetic and the animals allowed to recover for 48 hours. Then the animals were tested for neurological deficits, sacrificed, and the infarct volume calculated. To examine the infarct volume, animals were anesthetized, ex-sanguinated, and a metabolically active dye (3-phenyl tetrazolium chloride) was pumped throughout the body. All living tissues were stained pink by the dye, while morbid regions of infarcted tissue remained white. Brains were then fixed for 24 hours in formaldehyde, sliced and the infarct volumes measured.

One hour prior to induction of ischemia 20 mg/kg of cannabidiol was administered by intra-peritoneal injection (ip) in a 90% saline:5% emulphor 620 (emulsifier):5% ethanol vehicle. A second ip 10 mg/kg dose of cannabidiol was administered 8 hours later using the same vehicle. Control animals received injections of vehicle without drug. IV doses would be expected to be 3–5 times less because of reduction of first pass metabolism.

The infarct size and neurological assessment of the test animals is shown Table 1.

TABLE 1

Cannabidiol protects rat brains from ischemia damage

	Volume of Infarct (mm3)		Behavioral Deficit Score	
Animal	Drug	Control	Drug	Control
1	108.2	110.5	3	2
2	83.85	119.6	4	4
3	8.41	118.9	3	4
4	75.5	177.7	1	4
5	60.53	33.89	1	3
6	27.52	255.5	1	5
7	23.16	143	1	4
Mean	55.3	137.0	2.0	3.7
SEM	13.8	25.7	0.5	0.4
	p = 0.016 significant		p = 0.015 significant	

*Neurological scoring is performed on a subjective 1–5 scale of impairment. 0 = no impairment, 5 = severe (paralysis)

This data shows that infarct size was approximately halved in the animals treated with cannabidiol, which was also accompanied by a substantial improvement in the neurological status of the animal.

These studies with the nonpsychotropic marijuana constituent, cannabidiol, demonstrate that protection can be achieved against both glutamate neurotoxicity and free radical induced cell death. THC, the psychoactive principle

of cannabis, also blocked glutamate neurotoxicity with a potency similar to cannabidiol. In both cases, neuroprotection is unaffected by the presence of a cannabinoid receptor antagonist. These results therefore surprisingly demonstrate that cannabinoids can have useful therapeutic effects that are not mediated by cannabinoid receptors, and therefore are not necessarily accompanied by psychoactive side effects. Cannabidiol also acts as an anti-epileptic and anxiolytic, which makes it particularly useful in the treatment of neurological diseases in which neuroanatomic defects can predispose to seizures (e.g. subarachnoid hemorrhage).

A particular advantage of the cannabinoid compounds of the present invention is that they are highly lipophilic, and have good penetration into the central nervous system. The volume of distribution of some of these compounds is at least 100 L in a 70 kg person (1.4 L/kg), more particularly at least 250 L, and most particularly 500 L or even 700 L in a 70 kg person (10 L/kg). The lipophilicity of particular compounds is also about as great as that of THC, cannabidiol or other compounds that have excellent penetration into the brain and other portions of the CNS.

Cannabinoids that lack psychoactivity or psychotoxicity are particularly useful embodiments of the present invention, because the absence of such side effects allows very high doses of the drug to be used without encountering unpleasant side effects (such as dysphoria) or dangerous complications (such as obtundation in a patient who may already have an altered mental status). For example, therapeutic antioxidant blood levels of cannabidiol can be 5–20 mg/kg, without significant toxicity, while blood levels of psychoactive cannabinoids at this level would produce obtundation, headache, conjunctival irritation, and other problems. Particular examples of the compounds of the present invention have low affinity to the cannabinoid receptor, for example a K_i of greater than 250 nM, for example $K_i \geqq 500$–1000 nM. A compound with a $K_i \geqq 1000$ nM is particularly useful, which compound has essentially no psychoactivity mediated by the cannabinoid receptor.

Cannabidiol blocks glutamate toxicity with equal potency regardless of whether the insult is mediated by NMDA, AMPA or kainate receptors. Cannabidiol and THC have been shown to be comparable to the antioxidant BHT, both in their ability to prevent dihydrorhodamine oxidation and in their cyclic voltametric profiles. Several synthetic cannabinoids also exhibited profiles similar to the BHT, although anandamide, which is not structurally related to cannabinoids, did not. These findings indicate that cannabinoids act as antioxidants in a non-biological situation, which was confirmed in living cells by showing that cannabidiol attenuates hydroperoxide induced neurotoxicity. The potency of cannabidiol as an antioxidant was examined by comparing it on an equimolar basis with three other commonly used compounds.

In the AMPA/kainate receptor dependent neurotoxicity model, cannabidiol neuroprotection was comparable to the potent antioxidant, BHT, but significantly greater than that observed with either α-tocopherol or ascorbate. This unexpected superior antioxidant activity (in the absence of BHT tumor promoting activity) shows for the first time that cannabidiol, and other cannabinoids, can be used as antioxidant drugs in the treatment (including prophylaxis) of oxidation associated diseases, and is particularly useful as a neuroprotectant. The therapeutic potential of nonpsychoactive cannabinoids is particularly promising, because of the absence of psychotoxicity, and the ability to administer higher doses than with psychotropic cannabinoids, such as THC. Previous studies have also indicated that cannabidiol is not toxic, even when chronically administered to humans or given in large acute doses (700 mg/day).

EXAMPLE 8

Effect of Cannabidiol on Lipoxygenase Enzymes

This example describes in vitro and in vivo assays to examine the effect of cannabidiol (CBD) on three lipoxygenase (LO) enzymes: 5-LO, 12-LO and 15-LO.

In vitro Enzyme Assay

The ability of CBD to inhibit lipoxygenase was examined by measuring the time dependent change in absorption at 234 nM following addition of 5 U of each lipoxygenase (rabbit 15-LO purchased from Biomol (PA), porcine 12-LO purchased from Cayman chemicals (MI)) to a solution containing 10 μM (final concentration) linoleic acid.

Enzyme studies were performed using a u.v. spectrophotometer and a 3 ml quartz cuvette containing 2.5 ml of a stirred solution of 12.5 μM sodium linoleic acid (sodium salt) in solution A (25 mM Tris (pH 8.1), 1 mM EDTA 0.1% methyl cellulose). The reaction was initiated by addition of 0.5 ml enzyme solution (10 U/ml enzyme in solution A) and recorded for 60 seconds. Lipoxygenase exhibits non-Michaelis-Menten kinetics, an initial "lag" (priming) phase followed by a linear phase which is terminated by product inhibition. These complications were reduced by assessing enzyme activity (change in absorption) over the "steepest" 20 second period in a 60 second run time. Recordings examined the absorption at 234 nm minus the value at a reference wavelength of 280 nm. Linoleic acid was used as the substrate rather than arachidonic acid, because the products are less inhibitory to the enzyme, thereby providing a longer "linear phase".

Cell Purification and Separation

Human platelets and leukocytes were purified from buffy coat preparations (NIH Blood Bank) using a standard Ficoll based centrifugation method used in blood banks. Prior to use, cells were washed three times to eliminate contaminating cell types. Cultured rat basophillic leukemia cells (RBL-2H3) were used as a source of 5-lipoxygenase.

In vivo Determination of Lipoxygenase Activity

Cells were incubated with arachidonic acid and stimulated with the calcium ionophore A23187. Lipids were extracted and separated by reverse phase HPLC. Product formation was assessed as the area of a peak that co-eluted with an authentic standard, had a greater absorbance at 236 nm than at either 210 or 280 nm, and the formation of which was inhibited by a lipoxygenase inhibitor.

Cell pellets were triturated in DMEM culture media, aliquoted and pre-incubated for 15 minutes with 20 μM arachidonic acid and varying concentrations of cannabidiol and/or 40 μM nordihydroguaiaretic acid (a lipxygenase inhibitor). Platelets and leukocytes were also pre-incubated with 80 μM manoalide (Biomol) to prevent phospholipase A2 activation. Product formation was initiated by addition of 5 μM A23187 and incubation for 10 minutes at 37° C. At the end of the incubation, the reaction was stopped by addition of 15% 1M HCl and 10 ng/ml prostaglandin B2 (internal standard). Lipids were extracted with 1 volume of ethyl ether, which was dried under a stream of nitrogen. Samples were reconstituted in 50% acetonitrile:50% H_2O and separated by reverse phase HPLC using a gradient running from 63% acetonitrile: 37% H_2O:0.2% acetic acid to 90% acetonitrile (0.2% acetic acid) over 13 minutes.

Measurement of NMDAr Toxicity

The ability of 12-HETE (12-(s)-hydroxy-eicosatetraenoic acid, the product of the action of 12-lipoxygenase on arachi-

donic (eicosatetraenoic) acid) to protect cortical neurons from NMDAr toxicity was measured as described in Example 3. The 12-HETE (0.5 μg/ml) was added either during ischemia (co-incubated with the glutamate), during post-ischemia (co-incubated with the DMEM after washing the cells), or during both ischemia and post-ischemia.

Results

Using semi-purified enzyme preparations, the effect of CBD on rabbit 15-LO and porcine 12-LO was compared. As shown in FIGS. **6**A and B, CBD is a potent competitive inhibitor of 15-LO with an EC_{50} of 598 nM. However, CBD had no effect on the 12-LO enzyme.

Using whole cell preparations, the effect of CBD on 5- and 12-LO enzymes was investigated. As shown in FIG. **7**A, CBD inhibited 5-LO in cultured rat basophillic leukemia cells (RBL-2H3) with an EC_{50} of 1.92 μM. However, CBD had no effect on 12-LO, as monitored by the production of 12-HETE (the product of 12-LO), in either human leukocytes or platelets (FIGS. **7**B and C). The leukocyte 12-LO is similar, while the platelet 12-LO is structurally and functionally different, from the porcine 12-LO used in the in vitro enzyme study.

The ability of 12-HETE to protect cortical neurons from NMDAr toxicity is shown in FIG. **8**. To achieve best protection from NMDAr toxicity, 12-HETE was administered both during and post ischemia.

Therefore, CBD serves as a selective inhibitor of at least two lipoxygenase enzymes, 5-LO and 15-LO, but had no effect on 12-LO. Importantly, this is the first demonstration (FIG. **8**) that the 12-LO product 12-HETE can play a significant role in protecting neurons from NMDAr mediated toxicity. Although the mechanism of this protection is unknown at the present time, 12-HETE is known to be an important neuromodulator, due to its ability to influence potassium channel activity.

EXAMPLE 9

Methods of Treatment

The present invention includes a treatment that inhibits oxidation associated diseases in a subject such as an animal, for example a rat or human. The method includes administering the antioxidant drugs of the present invention, or a combination of the antioxidant drug and one or more other pharmaceutical agents, to the subject in a pharmaceutically compatible carrier and in an effective amount to inhibit the development or progression of oxidation associated diseases. Although the treatment can be used prophylactically in any patient in a demographic group at significant risk for such diseases, subjects can also be selected using more specific criteria, such as a definitive diagnosis of the condition. The administration of any exogenous antioxidant cannabinoid would inhibit the progression of the oxidation associated disease as compared to a subject to whom the cannabinoid was not administered. The antioxidant effect, however, increases with the dose of the cannabinoid.

The vehicle in which the drug is delivered can include pharmaceutically acceptable compositions of the drugs of the present invention using methods well known to those with skill in the art. Any of the common carriers, such as sterile saline or glucose solution, can be utilized with the drugs provided by the invention. Routes of administration include but are not limited to oral, intracranial ventricular (icv), intrathecal (it), intravenous (iv), parenteral, rectal, topical ophthalmic, subconjunctival, nasal, aural, sublingual (under the tongue) and transdermal. The antioxidant drugs of the invention may be administered intravenously in any conventional medium for intravenous injection such as an aqueous saline medium, or in blood plasma medium. Such medium may also contain conventional pharmaceutical adjunct materials such as, for example, pharmaceutically acceptable salts to adjust the osmotic pressure, lipid carriers such as cyclodextrins, proteins such as serum albumin, hydrophilic agents such as methyl cellulose, detergents, buffers, preservatives and the like. Given the low solubility of many cannabinoids, they may be suspended in sesame oil.

Given the excellent absorption of the compounds of the present invention via an inhaled route, the compounds may also be administered as inhalants, for example in pharmaceutical aerosols utilizing solutions, suspensions, emulsions, powders and semisolid preparations of the type more fully described in *Remington: The Science and Practice of Pharmacy* (19^{th} Edition, 1995) in chapter 95. A particular inhalant form is a metered dose inhalant containing the active ingredient, in a suspension or a dispersing agent (such as sorbitan trioleate, oleyl alcohol, oleic acid, or lecithin, and a propellant such as 12/11 or 12/114).

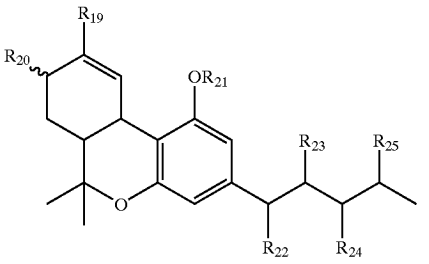
Embodiments of the invention comprising pharmaceutical compositions can be prepared with conventional pharmaceutically acceptable carriers, adjuvants and counterions as would be known to those of skill in the art. The compositions are preferably in the form of a unit dose in solid, semi-solid and liquid dosage forms such as tablets, pills, powders, liquid solutions or suspensions, injectable and infusible solutions, for example a unit dose vial, or a metered dose inhaler. Effective oral human dosage ranges for cannabidiol are contemplated to vary from about 1–40 mg/kg, for example 5–20 mg/kg, and in particular a dose of about 20 mg/kg of body weight.

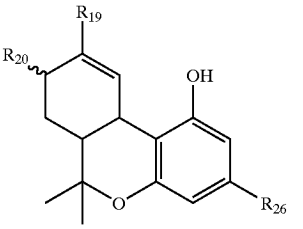
If the antioxidant drugs are to be used in the prevention of cataracts, they may be administered in the form of eye drops formulated in a pharmaceutically inert, biologically acceptable carrier, such as isotonic saline or an ointment. Conventional preservatives, such as benzalkonium chloride, can also be added to the formulation. In ophthalmic ointments, the active ingredient is admixed with a suitable base, such as white petrolatum and mineral oil, along with antimicrobial preservatives. Specific methods of compounding these dosage forms, as well as appropriate pharmaceutical carriers, are known in the art. *Remington: The Science and Practice of Pharmacy,* 19th Ed., Mack Publishing Co. (1995), particularly Part 7.

The compounds of the present invention are ideally administered as soon as a diagnosis is made of an ischemic event, or other oxidative insult. For example, once a myocardial infarction has been confirmed by electrocardiograph, or an elevation in enzymes characteristic of cardiac injury (e.g. CKMB), a therapeutically effective amount of the cannabinoid drug is administered. A dose can also be given following symptoms characteristic of a stroke (motor or sensory abnormalities), or radiographic confirmation of a cerebral infarct in a distribution characteristic of a neurovascular thromboembolic event. The dose can be given by frequent bolus administration, or as a continuous IV dose. In the case of cannabidiol, for example, the drug could be given in a dose of 5 mg/kg active ingredient as a continuous intravenous infusion; or hourly intramuscular injections of that dose.

EXAMPLE 10

The following table lists examples of some dibenzopyran cannabinoids that may be useful as antioxidants in the method of the present invention.

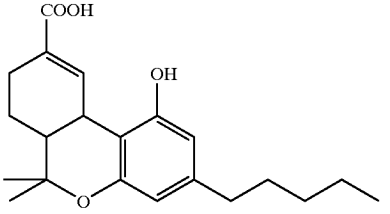




	Compound		R_{19}	R_{20}	R_{21}	R_{22}	R_{23}	R_{24}	R_{25}	R_{26}
H	5	7-OH-Δ^1-THC	CH_2OH	H	H	H	H	H	H	C_5H_{11}
H	6	6α-OH-Δ^1-THC	CH_3	α-OH						
H	7	6β-OH-Δ^1-THC	CH_3	β-OH						
	8	1"-OH-Δ^1-THC	CH_3			OH				
H	9	2"-OH-Δ^1-THC	CH_3				OH			
	10	3"-OH-Δ^1-THC	CH_3					OH		
	11	4"-OH-Δ^1-THC	CH_3						OH	
H	12	6α,7-diOH-Δ^1-THC	CH_2OH	α-OH						
H	13	6v,7-diOH-Δ^1-THC	CH_2OH	β-OH						
	14	1",7-diOH-Δ^1-THC	CH_2OH			OH				
H	15	2",7-diOH-Δ^1-THC	CH_2OH				OH			
H	16	3",7-diOH-Δ^1-THC	CH_2OH					OH		
H	17	4",7-diOH-Δ^1-THC	CH_2OH						OH	
	18	1",6β-diOH-Δ^1-THC	CH_3	β-OH		OH				
	19	1",3"-diOH-Δ^1-THC	CH_3			OH		OH		
	20	1",6α,7-triOH-Δ^1-THC	CH_2OH	α-OH		OH				
H	21	Δ^1-THC-6-one	CH_3	=O						
	22	Epoxyhexahydrocannabinol (EHHC)*	CH_3							
	23	7-oxo-Δ^1-THC	CHO							
H	24	Δ^1-THC-7"-oic acid	COOH							
H	25	Δ^1-THC-3"-oic acid	CH_3							C_2H_4COOH
H	26	1"-OH-Δ^1-THC-7"-oic acid	COOH			OH				
H	27	2"-OH-Δ^1-THC-7"-oic acid	COOH				OH			
H	28	3"-OH-Δ^1-THC-7"-oic acid	COOH					OH		
H	29	4"-OH-Δ^1-THC-7"-oic acid	COOH						OH	
H	30	3",4",5"-trisnor-2"-OH-Δ^1-THC-7-oic acid	COOH							C_2H_4OH
H	31	7-OH-Δ^1-THC-2"-oic acid	CH_2OH							CH_2COOH
H	32	6β-OH-Δ^1-THC-2"-oic acid	CH_3	β-OH						CH_2COOH
H	33	7-OH-Δ^1-THC-3"-oic acid	CH_2OH							C_2H_4COOH
H	34	6β-OH-Δ^1-THC-3"-oic acid	CH_3	β-OH						C_2H_4COOH
H	35	6α-OH-Δ^1-THC-4"-oic acid	CH_3	α-OH						C_3H_6COOH
H	36	2",3"-dehydro-6U-OH-Δ^1-THC-4"-oic acid	CH_3	α-OH						C_3H_4COOH
H	37	Δ^1-THC-1",7-dioic acid	COOH							COOH
H	38	Δ^1-THC-2",7-dioic acid	COOH							CH_2COOH
H	39	Δ^1-THC-3",7-dioic acid	COOH							C_2H_4COOH
H	40	Δ^1-THC-4",7-dioic acid	COOH							C_3H_6COOH
H	41	1",2"-dehydro-Δ^1-THC-3",7-dioic acid	COOH							C_2H_2COOH
H	42	Δ^1-THC-glucuronic acid	CH_3		gluc†					
H	43	Δ^1-THC-7-oic acid glucuronide	COO	gluc†						

*Epoxy group in C-1 and C-2 positions
†Glucuronide
Note: R-group substituents are H if not indicated otherwise.

Chemical structures of some of the dibenzopyran cannabinoids are shown below.



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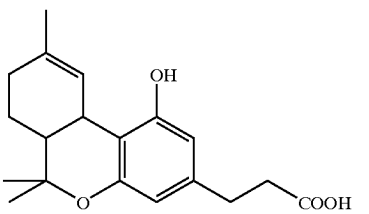

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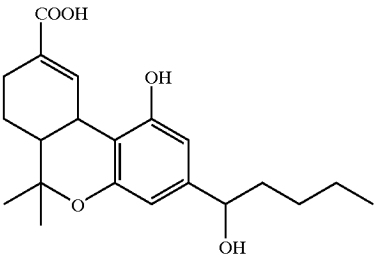

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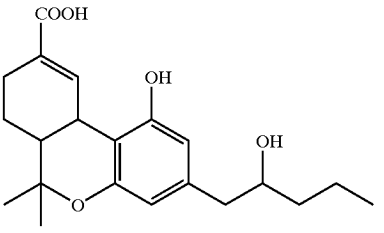

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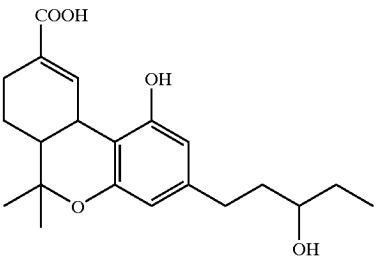

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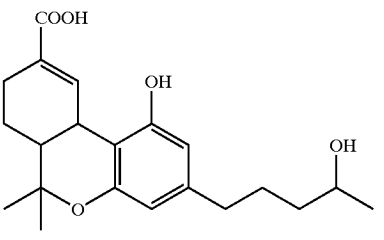

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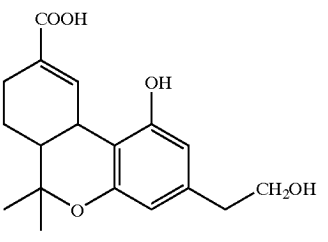

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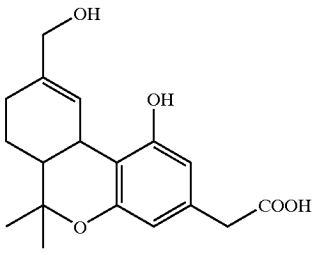

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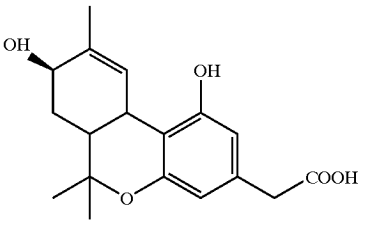

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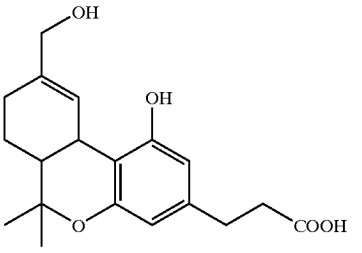

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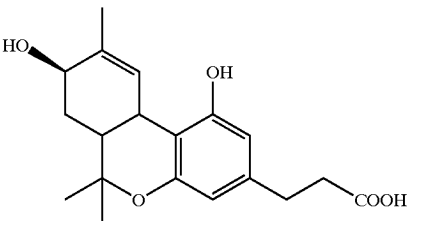

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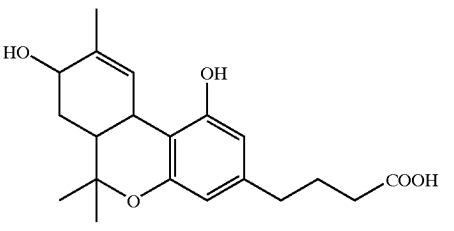

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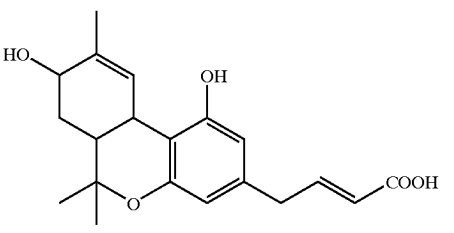

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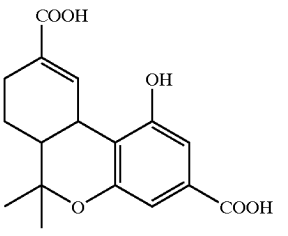

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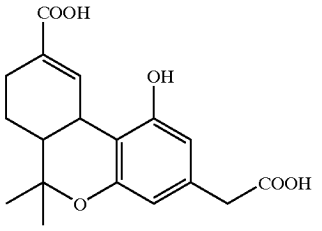

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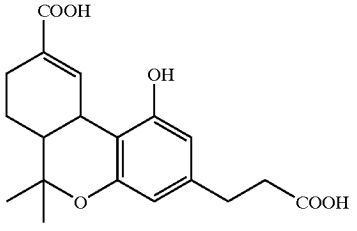

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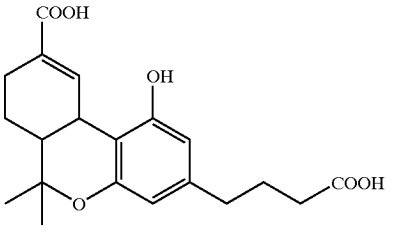

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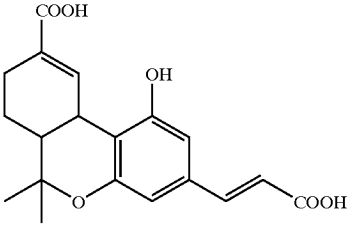
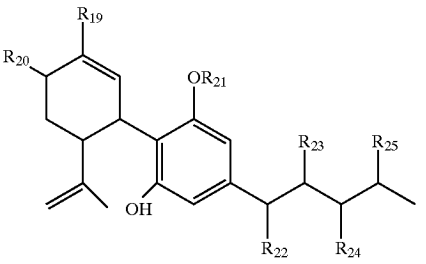
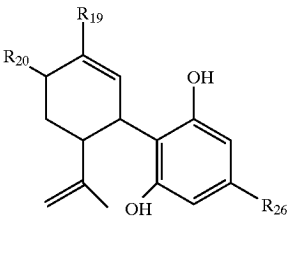


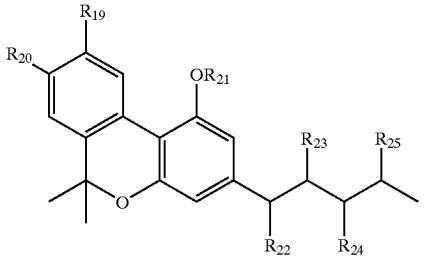
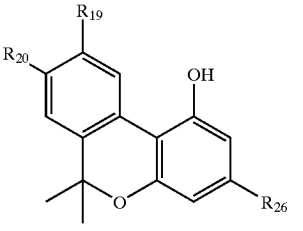
EXAMPLE 11

Examples of Structural Analogs of Cannabidiol

The following table lists examples of some cannabinoids which are structural analogs of cannabidiol and that may be useful as antioxidants in the method of the present invention. A particularly useful example is compound CBD, cannabidiol.

Compound	R_{19}	R_{20}	R_{21}	R_{22}	R_{23}	R_{24}	R_{25}	R_{26}
								
								
44 CBD	CH_3	H	H	H	H	H	H	C_5H_{11}
45 7-OH—CBD	CH_2OH							
46 6α-	CH_3	α-OH						
47 6β-	CH_3	β-OH						
48 1"-	CH_3			OH				
49 2"-	CH_3				OH			
50 3"-	CH_3					OH		
51 4"-	CH_3						OH	
52 5"-	CH_3							$C_4H_8CH_2OH$
53 6,7-diOH—CBD	CH_2OH	OH						
54 3",7-diOH—CBD	CH_2OH					OH		
55 4",7-diOH—CBD	CH_2OH						OH	
56 CBD-7-oic acid	COOH							
57 CBD-3"-oic acid	CH_3							C_2H_4COOH

-continued

Compound	R_{19}	R_{20}	R_{21}	R_{22}	R_{23}	R_{24}	R_{25}	R_{26}
								
58 CBN	CH_3	H	H	H	H	H	H	C_5H_{11}
59 7-OH—CBN	CH_2OH							
60 1"-OH—CBN	CH_3			OH				
61 2"-OH—CBN	CH_3				OH			
62 3"-OH—CBN	CH_3					OH		
63 4"-OH—CBN	CH_3						OH	
64 5"-OH—CBN	CH_3							$C_4H_8CH_2OH$
65 2"-7-diOH—CBN	CH_2OH				OH			
66 CBN-7-oic acid	COOH							
67 CBN-1"-oic acid	CH_3							COOH
68 CBN-3"-oic acid	CH_3							C_2H_4COOH

Note: R-group substituents are H if not indicated otherwise.

The invention being thus described, variation in the materials and methods for practicing the invention will be apparent to one of ordinary skill in the art. Such variations are to be considered within the scope of the invention, which is set forth in the claims below.

We claim:

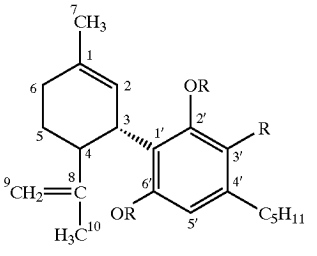
1. A method of treating diseases caused by oxidative stress, comprising administering a therapeutically effective amount of a cannabinoid that has substantially no binding to the NMDA receptor to a subject who has a disease caused by oxidative stress.

2. The method of claim **1**, wherein the cannabinoid is nonpsychoactive.

3. The method of claim **2**, wherein the cannabinoid has a volume of distribution of 10 L/kg or more.

4. The method of claim **1**, wherein the cannabinoid is not an antagonist at the NMDA receptor.

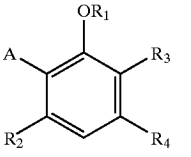
5. The method of claim **1**, wherein the cannabinoid is:



where R is H, substituted or unsubstituted alkyl, carboxyl, alkoxy, aryl, aryloxy, arylalkyl, halo or amino.

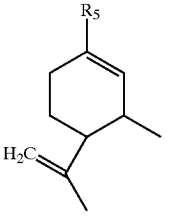
6. The method of claim **5**, wherein R is H, substituted or unsubstituted alkyl, carboxyl or alkoxy.

7. The method of claim **2**, wherein the cannabinoid is:



where

A is cyclohexyl, substituted or unsubstituted aryl, or



but not a pinene;

R_1 is H, substituted or unsubstituted alkyl, or substituted or unsubstituted carboxyl;

R_2 is H, lower substituted or unsubstituted alkyl, or alkoxy;

R_3 is of H, lower substituted or unsubstituted alkyl, or substituted or unsubstituted carboxyl;

R_4 is H, hydroxyl, or lower substituted or unsubstituted alkyl; and

R_5 is H, hydroxyl, or lower substituted or unsubstituted alkyl.

8. The method of claim **7**, wherein

R_1 is lower alkyl, COOH or $COCH_3$;

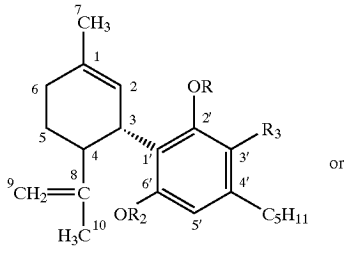
R_2 is unsubstituted C_1–C_5 alkyl, hydroxyl, methoxy or ethoxy;

R_3 is H, unsubstituted C_1–C_3 alkyl, or $COCH_3$;

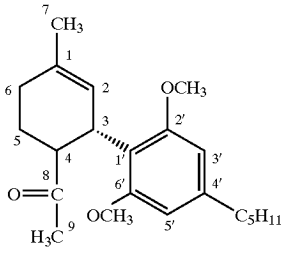
R_4 is hydroxyl, pentyl, heptyl, or diemthylheptyl; and

R_5 is hydroxyl or methyl.

9. The method of claim **1**, wherein the cannabinoid is:

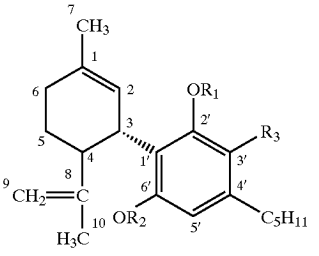


or



where R_1, R_2 and R_3 are independently H, CH_3, or $COCH_3$.

10. The method of claim **9**, wherein the cannabinoid is:



where:

a) R_1=R_2=R_3=H;

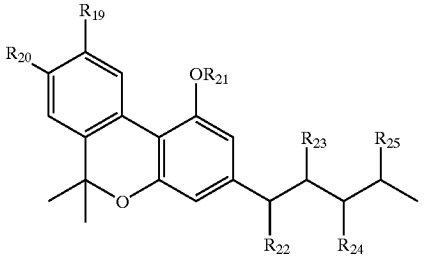
b) R_1=R_3=H, R_2=CH_3;

c) R_1=R_2=CH_3, R_3=H;

d) R_1=R_2=$COCH_3$, R_3=H; or

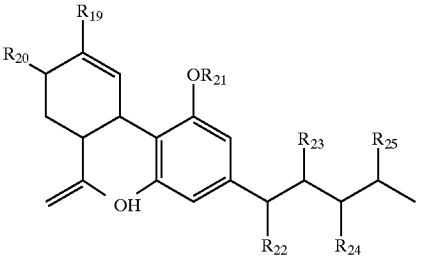
e) R_1=H, R_2=R_3=$COCH_3$.

11. The method of claim **2**, wherein the cannabinoid is:



or

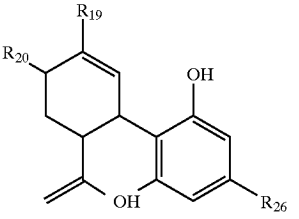
-continued



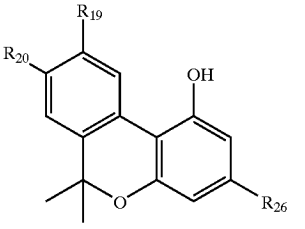
where R_{19} is H, lower alkyl, lower alcohol, or carboxyl; R_{20} is H or OH; and R_{21}–R_{25} are independently H or OH.

12. The method of claim **11**, wherein R_{19} is H, CH_3, CH_2OH, or COOH, and R_{20}–R_{24} are independently H or OH.

13. The method of claim **2**, wherein the cannabinoid is:



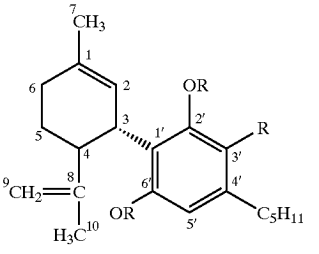
or



where R_{19} and R_{20} are H, and R_{26} is alkyl.

14. The method of claim **10**, wherein the cannabinoid is cannabidiol.

15. A method of treating an ischemic or neurodegenerative disease in the central nervous system of a subject, comprising administering to the subject a therapeutically effective amount of a cannabinoid, where the cannabinoid is



where R is H, substituted or unsubstituted alkyl, carboxyl, alkoxy, aryl, aryloxy, arylalkyl, halo or amino.

16. The method of claim **15**, wherein the cannabinoid is not a psychoactive cannabinoid.

17. The method of claim **15** where the ischemic or neurodegenerative disease is an ischemic infarct, Alzheimer's disease, Parkinson's disease, and human immunodeficiency virus dementia, Down's syndrome, or heart disease.

18. A method of treating a disease with a cannabinoid that has substantially no binding to the NMDA receptor, comprising determining whether the disease is caused by oxi-

dative stress, and if the disease is caused by oxidative stress, administering the cannabinoid in a therapeutically effective antioxidant amount.

19. The method of claim **18**, wherein the cannabinoid has a volume of distribution of at least 1.5 L/kg and substantially no activity at the cannabinoid receptor.

20. The method of claim **19**, wherein the cannabinoid has a volume of distribution of at least 10 L/kg.

21. The method of claim **1**, wherein the cannabinoid selectively inhibits an enzyme activity of 5- and 15-lipoxygenase more than an enzyme activity of 12-lipoxygenase.

22. A method of treating a neurodegenerative or ischemic disease in the central nervous system of a subject, comprising administering to the subject a therapeutically effective amount of a compound selected from any of the compounds of claims **9** through **13**.

23. The method of claim **22** where the compound is cannabidiol.

24. The method of claim **22**, wherein the ischemic or neurodegenerative disease is an ischemic infarct, Alzheimer's disease, Parkinson's disease, and human immunodeficiency virus dementia, Down's syndrome, or heart disease.

25. The method of claim **24** wherein the disease is an ischemic infarct.

26. The method of claim **1**, wherein the cannabinoid is not an antagonist at the AMPA receptor.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,630,507 B1
DATED : October 7, 2003
INVENTOR(S) : Hampson et al.

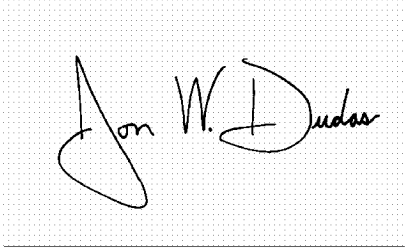
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13,
Line 23, "feral" should read -- fetal --.

Column 30,
Line 16, reads "R_{20}-R_{24}" should read -- R_{20}-R_{25} --.

Signed and Sealed this

Fifteenth Day of June, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

Proposed Rules

Federal Register
Vol. 72, No. 184
Monday, September 24, 2007

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. 2007N–0264]

Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Companion Document to Direct Final Rule; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; correction.

SUMMARY: The Food and Drug Administration is correcting a proposed rule that appeared in the **Federal Register** of August 16, 2007 (72 FR 45993). That document proposed to amend the biologics regulations by removing, revising, or updating specific regulations applicable to blood, blood components, and Source Plasma to be more consistent with current practices in the blood industry and to remove unnecessary or outdated requirements. The proposal published as a companion document to the direct final rule that published in the same issue of the **Federal Register** (August 16, 2007, 72 FR 45883). Both documents published with a typographical error in the codified section. This document corrects the error in the proposed rule. Elsewhere in this issue of the **Federal Register** we are correcting the error in the direct final rule.

DATES: Submit written or electronic comments on the proposed rule by October 30, 2007.

ADDRESSES: You may submit comments on the proposed rule, identified by Docket No. 2007N–0264, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described previously, in the **ADDRESSES** portion of this document under *Electronic Submissions*.

Instructions: All submissions received must include the agency name and docket number for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the ''Request for Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of the proposed rule (72 FR 45993 at 45995).

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: *For information regarding this correction*: Joyce Strong, Office of Policy (HF–27), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7010.

For information regarding the proposed rule: Stephen M. Ripley, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION: In FR Doc. E7–15942, appearing on page 45993, in the **Federal Register** of Thursday, August 16, 2007, the following correction is made:

§ 610.53 [Corrected]

1. On page 45996, in the amendment to § 610.53 *Dating periods for licensed biological products*, in the table in paragraph (c), ''65° C'' is corrected to read ''−65° C'' everywhere it appears.

Dated: September 17, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E7–18802 Filed 9–21–07; 8:45 am]
BILLING CODE 4160–01–S

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–308P]

Technical Amendment to Listing in Schedule III of Approved Drug Products Containing Tetrahydrocannabinols

AGENCY: Drug Enforcement Administration (DEA), Department of Justice.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: Under the current schedules of controlled substances in the DEA regulations, among the substances listed in schedule III is a synthetic isomer of tetrahydrocannabinols (THC) contained in a specific formulation of a drug product approved by the U.S. Food and Drug Administration (FDA). As currently written, the DEA regulation would not necessarily include drug products approved by the FDA under section 505(j) of the Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 355) (commonly referred to as generic drugs) that cite the drug product currently listed in schedule III as the reference listed drug. DEA is hereby proposing to modify the regulation so that certain generic drug products are also included in the schedule III listing.

DATES: Written comments must be postmarked, and electronic comments must be sent, on or before November 23, 2007.

ADDRESSES: Please submit comments, identified by ''Docket No. DEA–308,'' by one of the following methods:

1. *Regular mail:* Deputy Administrator, Drug Enforcement Administration, Washington, DC 20537, Attention: DEA Federal Register Representative/ODL.

2. *Express mail:* DEA Headquarters, Attention: DEA Federal Register Representative/ODL, 2401 Jefferson-Davis Highway, Alexandria, VA 22301.

3. *E-mail comments directly to agency: dea.diversion.policy@usdoj.gov.*

4. *Federal eRulemaking portal: http://www.regulations.gov.* Follow the on-line instructions for submitting comments.

Posting of Public Comments: Please note that all comments received are considered part of the public record and made available for public inspection online at *http://www.regulations.gov* and in the Drug Enforcement Administration's public docket. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place all the personal identifying information you do not want posted online or made available in the public docket in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be posted online or made available in the public docket, you must include the phrase ''CONFIDENTIAL BUSINESS INFORMATION'' in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be posted online or made available in the public docket.

Personal identifying information and confidential business information identified and located as set forth above will be redacted and the comment, in redacted form, will be posted online and placed in the Drug Enforcement Administration's public docket file. If you wish to inspect the agency's public docket file in person by appointment, please see the ''**FOR FURTHER INFORMATION**'' paragraph.

FOR FURTHER INFORMATION CONTACT: Christine A. Sannerud, Ph.D., Chief, Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537; Telephone: (202) 307–7183.

SUPPLEMENTARY INFORMATION:

I. Summary

Under the Controlled Substances Act (CSA), the schedules of controlled substances are published on an updated basis in the DEA regulations.[1] Currently, one of the substances listed in schedule III is the following: ''Dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved product.'' [2] This describes the drug product marketed under the brand name Marinol. As explained below, it is possible that generic versions of Marinol could be approved by the FDA yet not fit within the same schedule III listing as Marinol. The rule being proposed here would correct this situation so that certain generic versions of Marinol that might be approved by the FDA in the future will be in the same schedule as Marinol.

II. Detailed Explanation

Background

Dronabinol is a name of a particular isomer of a class of chemicals known as tetrahydrocannabinols (THC). Specifically, dronabinol is the United States Adopted Name (USAN) for the (-)-isomer of Δ^9-(trans)-tetrahydrocannabinol [(-)-Δ^9-(trans)-THC], which is believed to be the major psychoactive component of the cannabis plant (marijuana).

At present, Marinol is the only drug product containing any form of THC that has been approved for marketing by the FDA.[3] Accordingly, THC, as a general category, is listed in schedule I of the CSA,[4] while dronabinol contained in the Marinol formulation is listed separately in schedule III. Any other formulation containing dronabinol (or any other isomer of THC) remains a schedule I controlled substance.[5]

The current wording of the Marinol formulation in schedule III (21 CFR 1308.13(g)(1)) was added to the DEA regulations in 1986, when the substance was transferred from schedule I to schedule II after the FDA approved Marinol for marketing.[6] The wording of this listing was not specific to Marinol and thereby could include any generic product meeting that description that might be approved by the FDA in the future. However, at the time the regulation was promulgated, DEA did not anticipate the possibility that a generic formulation could be developed that did not fit precisely the wording of the listing that currently appears in schedule III.

Recently, firms have submitted to FDA abbreviated new drug applications (ANDA) for their proposed generic versions of Marinol. As these ANDAs remain pending with the FDA, the precise nature of these formulations is not available for public disclosure. However, these formulations might differ from the Marinol formulation currently listed in schedule III. Nonetheless, the firms that have submitted the ANDAs assert that their formulations would meet the approval requirements under 21 U.S.C. 355(j), because, among other things, they have the same active ingredient, strength, dosage form, and route of administration as Marinol, and are bioequivalent to Marinol. Products are bioequivalent if there is no significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action. 21 CFR 320.1. There is no requirement under 21 U.S.C. 355(j), or FDA's implementing regulations, that solid oral dosage forms such as capsules that are proposed for approval in ANDAs contain the same inactive ingredients as the listed drug referenced. Thus, for example, a sponsor of an ANDA referencing Marinol could propose for approval a capsule formulated with an inactive ingredient other than sesame oil. The generic drug,

[1] 21 U.S.C. 812(a), (c) and n. 1.

[2] 21 CFR 1308.13(g)(1).

[3] The FDA approved Marinol in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, the FDA expanded Marinol's approved indications to include the treatment of anorexia associated with weight loss in patients with AIDS.

[4] 21 U.S.C. 812(c), Schedule I(c)(17). Schedule I contains those controlled substances with ''no currently accepted medical use in treatment in the United States'' and ''a lack of accepted safety for use * * * under medical supervision.'' 21 U.S.C. 812(b)(1).

[5] The introductory language to schedule I(c) states that any material, compound, mixture, or preparation that contains any of the substances listed in schedule I(c) (including ''tetrahydrocannabinols'') is a schedule I controlled substance ''[u]nless specifically excepted or unless listed in another schedule.'' The only material, compound, mixture, or preparation that contains THC but is listed in another schedule is the Marinol formulation, which is listed in schedule III.

[6] 51 FR 17476 (May 13, 1986). DEA subsequently transferred the FDA-approved Marinol formulation from schedule II to schedule III. 64 FR 35928 (July 2, 1999).

therefore, would not fall within the scope of the current regulation.

This situation, in which a generic version of a drug would not necessarily fall within the schedule for the referenced listed drug, is unique among the CSA schedules in the following respect. The Marinol formulation listed in schedule III is the only listing in the schedules that has the effect of excluding potential generic versions of the brand name formulation.[7] As indicated above, this came about because DEA did not anticipate that other drug products could be approved by FDA that did not fit the description that was included in the schedules. Moreover, Congress structured the CSA so that there would be no distinction—for scheduling purposes—between brand name drug products and their generic equivalents. The rule being proposed here would ensure that this aspect of the CSA holds true for generic drug products approved under 21 U.S.C. 355(j) that reference Marinol as the listed drug.

In addition, 21 U.S.C. 355(j)(2)(C) permits applicants to petition FDA for approval in an ANDA for a drug product that may differ from the listed drug in certain specified ways, if clinical studies are not necessary to establish the safety and effectiveness of the drug product. Among the types of differences permitted is a change in dosage form. This proposed rule would amend the description in Schedule III to include products referencing Marinol that are either capsules or tablets and that otherwise meet the approval requirements in 21 U.S.C. 355(j).

The CSA Scheduling Structure

To understand the legal justification for the rule being proposed here, the scheduling scheme established by Congress under the CSA must first be considered. One court has succinctly summarized this scheme as follows:

> The [CSA] sets forth initial schedules of drugs and controlled substances in 21 U.S.C. 812(c). However, Congress established procedures for adding or removing substances from the schedules (control or decontrol), or to transfer a drug or substance between schedules (reschedule). 21 U.S.C. 811(a). This responsibility is assigned to the Attorney General in consultation with the Secretary of Health and Human Services (''HHS''). *Id.* § 811(b). The Attorney General has delegated his functions to the Administrator of the DEA. 28 CFR 0.100(b). Current schedules are published at 21 CFR 1308.11–1308.15.
>
> There are three methods by which the DEA may initiate rulemaking proceedings to revise the schedules: (1) By the DEA's own motion; (2) at the request of HHS; (3) on the petition of any interested party. 21 U.S.C. 811(a); 21 CFR 1308.43(a). Before initiating rulemaking proceedings, the DEA must request a scientific and medical evaluation from HHS and a recommendation. The statute requires the DEA and HHS to consider eight factors with respect to the drug or controlled substance. 21 U.S.C. 811(b), (c). These factors are:
>
> (1) Its actual or relative potential for abuse.
>
> (2) Scientific evidence of its pharmacological effect, if known.
>
> (3) The state of current scientific knowledge regarding the drug or other substance.
>
> (4) Its history and current pattern of abuse.
>
> (5) The scope, duration, and significance of abuse.
>
> (6) What, if any, risk there is to the public health.
>
> (7) Its psychic or physiological dependence liability.
>
> (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.
>
> 21 U.S.C. 811(c). Although the recommendations of HHS are binding on the DEA as to scientific and medical considerations involved in the eight-factor test, the ultimate decision as to whether to initiate rulemaking proceedings to reschedule a controlled substance is made by the DEA. *See id.* § 811(a), (b).
>
> *Gettman* v. *DEA*, 290 F.3d 430, 432 (DC Cir. 2002).

The FDA plays an important role within HHS in the development of the HHS medical and scientific determinations that bear on eight-factor analyses referred to above (required under section 811(c) for scheduling decisions). Thus, when it comes to newly developed drug products that contain controlled substances, FDA makes medical and scientific determinations for purposes of both the Food Drug and Cosmetic Act (in connection with decisions on whether to approve drugs for marketing) and the CSA (in connection with scheduling decisions). As explained below, the eight-factor analysis can be expected to yield the same conclusions with respect to a brand name drug product and certain generic drugs referencing that product that meet the approval requirements under 21 U.S.C. 355(j).

The ANDA Approval Process

The Drug Price Competition and Patent Term Restoration Act of 1984 (known as the ''Hatch-Waxman Amendments''), codified at 21 U.S.C. 355, 360cc, and 35 U.S.C. 156, 271, 282, permits the submission of ANDAs for approval of generic versions of approved drug products. 21 U.S.C. 355(j). The ANDA process shortens the time and effort needed for approval by, among other things, allowing the applicant to demonstrate its product's bioequivalence to a drug already approved under a New Drug Application (NDA) (the ''listed'' drug) rather than having to reproduce the safety and effectiveness data for that drug. If an ANDA applicant establishes that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling, and conditions of use as a listed drug, and that it is bioequivalent to that drug, the applicant can rely on FDA's previous finding that the listed drug is safe and effective. *See id.*[8] Once approved, an ANDA sponsor may manufacture and market the generic drug to provide a safe, effective, and low cost alternative to the American public.

The majority of drugs approved under 21 U.S.C. 355(j) are therapeutically equivalent to the listed drug they reference. This means that the generic drug and the referenced innovator drug are in the same dosage form, contain identical amounts of the active ingredient, and are bioequivalent. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

The key point, for purposes of the rule being proposed here, is that the generic drug can be substituted for the innovator drug with the full expectation that the generic drug will produce the same clinical effect and safety profile as the innovator drug. Consequently, for CSA scheduling purposes, the eight-factor analysis conducted by the FDA and DEA under 21 U.S.C. 811(c) would necessarily result in the same scheduling determination for an approved generic drug product as for the innovator drug to which the generic drug is a therapeutic equivalent. This is because, in conducting the eight-factor analysis, the FDA and DEA would be examining precisely the same medical, scientific, and abuse data for the generic drug product as would be considered for the innovator drug. The same would be true of the innovator drug and a drug product approved pursuant to a petition under 21 U.S.C. 355(j)(2)(C), where the drug approved in the ANDA differs from the listed drug only because it is a tablet and the listed drug is a capsule.

[7] Generally, substances are listed in the CSA schedules based on their chemical classification, rather than any drug product formulation in which they might appear. Because of this, there have been no other situations in which a slight variation between the brand name drug formulation and the generic drug formulation was consequential for scheduling purposes.

[8] See also Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the ''Orange Book''), Intro. at p. vi, (27th ed.).

As noted earlier, these considerations never previously arose for any other controlled substance because the regulation citing the Marinol formulation is the only scheduling regulation that is drug-product-formulation-specific and thereby (inadvertently) excludes potential generic versions.[9] This unintended result is not consistent with the structure and purposes of the CSA, which generally lists categories of substances in the schedules, rather than product formulations.[10] Thus, by ensuring that generic versions of the Marinol formulation which might be approved by the FDA in the future are in the same schedule as Marinol, the rule being proposed here would make the DEA regulations more consistent with the structure and purposes of the CSA. Moreover, because—from a scientific perspective—the eight-factor analysis for such generic products would lead to the same results as with the innovator drug, this proposed rule would eliminate the needless expenditure of agency resources to conduct redundant eight-factor analyses. (HHS and DEA have already conducted the eight-factor analysis for the Marinol formulation.[11]) In a similar vein, this proposed rule will eliminate an unnecessary administrative hurdle that could otherwise stand in the way of allowing generic drugs to reach the American consumer without undue delay.

Finally, for additional clarity, the proposed rule will amend 21 CFR 1308.13(g)(1) to change the phrase ''U.S. Food and Drug Administration approved product'' to ''drug product approved for marketing by the U.S. Food and Drug Administration.''

Note Regarding This Proposed Scheduling Action

In accordance with the provisions of the Controlled Substances Act (21 U.S.C. 811(a)), this action is a formal rulemaking ''on the record after opportunity for a hearing.'' Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (5 U.S.C. 556 and 557). Interested persons are invited to submit their comments, objections or requests for a hearing with regard to this proposal. Persons wishing to request a hearing should note that such requests must be written and manually signed; requests for a hearing will not be accepted via electronic means. Requests for a hearing should be made in accordance with 21 CFR 1308.44 and should state, with particularity, the issues concerning which the person desires to be heard. All correspondence regarding this matter should be submitted to the DEA using the address information provided above.

Regulatory Certifications

Regulatory Flexibility Act

The Deputy Administrator hereby certifies that this rulemaking has been drafted in accordance with the Regulatory Flexibility Act (5 U.S.C. 601–612), has reviewed this regulation, and by approving it certifies that this regulation will not have a significant economic impact on a substantial number of small entities. DEA is hereby proposing to modify the listing of the Marinol formulation in schedule III so that certain generic drug products are also included in that listing. Further, this proposed rule will eliminate an unnecessary administrative hurdle that could otherwise stand in the way of allowing generic drugs to reach the American consumer without undue delay.

Executive Order 12866

In accordance with the provisions of the CSA (21 U.S.C. 811(a)), this action is a formal rulemaking ''on the record after opportunity for a hearing.'' Such proceedings are conducted pursuant to the provisions of 5 U.S.C. 556 and 557 and, as such, are exempt from review by the Office of Management and Budget pursuant to Executive Order 12866, 3(d)(1).

Executive Order 12988

This regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform.

Executive Order 13132

This rulemaking does not preempt or modify any provision of state law; nor does it impose enforcement responsibilities on any state; nor does it diminish the power of any state to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

Unfunded Mandates Reform Act of 1995

This rule will not result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $120,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under the provisions of the Unfunded Mandates Reform Act of 1995.

Congressional Review Act

This rule is not a major rule as defined by Section 804 of the Small Business Regulatory Enforcement Fairness Act (Congressional Review Act). This rule will not result in an annual effect on the economy of $100,000,000 or more; a major increase in costs or prices; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Narcotics, Prescription drugs.

Pursuant to the authority vested in the Attorney General under sections 201, 202, and 501(b) of the CSA (21 U.S.C. 811, 812, and 871(b)), delegated to the Administrator and Deputy Administrator pursuant to section 501(a) (21 U.S.C. 871(a)) and as specified in 28 CFR 0.100 and 0.104, and Appendix to Subpart R, sec. 12, the Deputy Administrator hereby orders that Title 21 of the Code of Federal Regulations, Part 1308, is proposed to be amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), unless otherwise noted.

2. Section 1308.13 is proposed to be amended by revising paragraph (g) to read as follows:

§ 1308.13 Schedule III.

* * * * *

(g) *Hallucinogenic substances.*

(1)(i) Dronabinol in sesame oil and encapsulated in a soft gelatin capsule in a drug product approved for marketing by the U.S. Food and Drug Administration (FDA)—7369

(ii) Any drug product in tablet or capsule form containing natural dronabinol (derived from the cannabis

[9] When Congress enacted the CSA in 1970, it scheduled codeine and certain other opiates in three different schedules depending on their respective concentrations. See 21 U.S.C. 812(c), schedule II(a)(1), schedule III(d), and schedule V. However, this differential scheduling for opiates does not specify drug product formulation in a manner that would result in a generic version of an opiate drug product being scheduled separately from the innovator drug.

[10] See note 9.

[11] The last eight-factor analysis for Marinol was completed in 1998, as part of the process of transferring it from schedule II to schedule III. 64 FR 35928 (July 2, 1999).

plant) or synthetic dronabinol (produced from synthetic materials) for which an abbreviated new drug application (ANDA) has been approved by the FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act which references as its listed drug the drug product referred to in the preceding paragraph (g)(1)(i) of this section.—7369

[Some other names for Dronabinol: (6a R-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6 H-dibenzo [b,d]pyran-1-ol] or (-)-delta-9-(trans)-tetrahydrocannabinol]

(2) [Reserved]

Dated: September 17, 2007.

Michele M. Leonhart,

Deputy Administrator.

[FR Doc. E7–18714 Filed 9–21–07; 8:45 am]

BILLING CODE 4410–09–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 300

[EPA–HQ–SFUND–2005–0011; FRL–8471–4]

National Oil and Hazardous Substances Pollution Contingency Plan; National Priorities List

AGENCY: Environmental Protection Agency.

ACTION: Notice of intent to delete the Tabernacle Drum Dump Superfund Site from the National Priorities List.

SUMMARY: The Environmental Protection Agency (EPA) Region 2 is issuing this notice of intent to delete the Tabernacle Drum Dump Superfund Site (Site), located in Tabernacle Township, Burlington County, New Jersey from the National Priorities List (NPL) and requests public comment on this action. The NPL is Appendix B of the National Oil and Hazardous Substances Pollution Contingency Plan (NCP), 40 CFR part 300, which the EPA promulgated pursuant to section 105 of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), as amended. The EPA and the State of New Jersey, through the New Jersey Department of Environmental Protection, have determined that responsible parties have implemented all appropriate response actions required. No further operation and maintenance activities or five-year reviews are required at this site.

DATES: Comments concerning this site may be submitted on or before October 24, 2007.

ADDRESSES: Submit your comments, identified by Docket ID no. EPA–HQ–SFUND–2005–0011, by one of the following methods:

- *http://www.regulations.gov.* Follow on-line instructions for submitting comments.
- *E-mail: tomchuk.doug@epa.gov.*
- *Fax:* (212) 637–4429.
- *Mail:* Douglas Tomchuk, Remedial Project Manager, U.S. Environmental Protection Agency, Region 2, 290 Broadway, 19th Floor, New York, NY 10007–1866.
- *Hand delivery:* Douglas Tomchuk, U.S. Environmental Protection Agency, Region 2, 290 Broadway, 19th Floor, New York, NY 10007–1866.

Such deliveries are only accepted during the Docket's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to Docket ID no. EPA–HQ–SFUND–2005–0011. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through *http://www.regulations.gov* or e-mail. The *http://www.regulations.gov* Web site is an ''anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going to *http://www.regulations.gov*, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the *http://www.regulations.gov* index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in the hard copy. Publicly available docket materials are available either electronically in *http://www.regulations.gov* or in hard copy at:

EPA Region 2 Superfund Records Center, 290 Broadway, Room 1828, New York, New York 10007–1866, (212) 637–4308, *Hours:* 9 a.m. to 5 p.m., Monday through Friday, excluding holidays, by appointment only.

Information on the Site is also available for viewing at the Site's information repository located at: Tabernacle Municipal Building, 163 Carranza Road, Tabernacle, New Jersey 08088.

FOR FURTHER INFORMATION CONTACT: Douglas Tomchuk, Remedial Project Manager, U.S. Environmental Protection Agency, Region 2, 290 Broadway, 19th Floor, New York, NY 10007–1866, *Telephone:* (212) 637–3956, *Fax:* (212) 637–4429, *E-mail: tomchuk.doug@epa.gov.*

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction

The Environmental Protection Agency (EPA) Region II announces its intent to delete the Tabernacle Drum Dump, located on Carranza Road in Tabernacle Township, Burlington County, New Jersey, from the National Priorities List (NPL) and requests public comment on this action. The NPL constitutes Appendix B of the NCP, 40 CFR part 300, which EPA promulgated pursuant to section 105 of CERCLA, as amended. The EPA identifies sites that appear to present a significant risk to public health, welfare, or the environment and maintains the NPL as the list of those sites. Sites on the NPL may be the subject of remedial actions financed by the Hazardous Substances Superfund Response Trust Fund (Fund). Pursuant to § 300.425(e)(3) of the NCP, any site deleted from the NPL remains eligible for Fund-financed remedial actions if conditions at the site warrant such action.

The EPA will accept comments on the proposal to delete this site for thirty (30) days after publication of this notice in the **Federal Register**.

Section II of this notice explains the criteria for deleting sites from the NPL.

Harold E. Hughes

U. S. SENATE (RET.) 7222 WEST ST. JOHN ROAD GLENDALE ARIZONA 85308

July 17, 1995

Mr. Carl E. Olsen
P. O. Box 4091
Des Moines, Iowa 50333

Dear Mr. Olsen:

Thank you for your recent letter enclosing the most recent status report on legislative and judiciary action relating to the medical use of marijuana.

I now spend most of my time outside the boundaries of Iowa, and actually live in Arizona. I'm simply not available for participation on a local basis. I do support the medical use of marijuana and sincerely hope some relief can be gained from federal restrictions. This probably will require action in the Congress rather than Iowa. I would suggest seeking advice, if you already haven't, from your Congressional offices as to how to proceed.

I wish you well.

Sincerely,

Harold E. Hughes

HEH:hj