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**Beutler**

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[54] **USE OF SUBSTITUTED ADENINE DERIVATIVES FOR TREATING MULTIPLE SCLEROSIS**

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### Related U.S. Application Data

[63] Continuation of Ser. No. 838,546, Feb. 19, 1992, Pat. No. 5,310,732, which is a continuation-in-part of Ser. No. 460,351, Jan. 3, 1990, Pat. No. 5,106,837, which is a continuation-in-part of Ser. No. 323,350, Mar. 14, 1989, abandoned, which is a continuation-in-part of Ser. No. 169,618, Mar. 16, 1988, abandoned, which is a continuation-in-part of Ser. No. 825,215, Feb. 3, 1986, abandoned.

[51] **Int. Cl.<sup>6</sup>** ..... **A61K 31/70**

[52] **U.S. Cl.** ..... **514/46; 514/45**

[58] **Field of Search** ..... **514/45, 46**

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5,310,732 5/1994 Carson et al. .... 514/46

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### [57] ABSTRACT

Treatment of patients having multiple sclerosis with therapeutic agents containing substituted adenine derivatives such as 2-chloro-2'-deoxyadenosine is shown to markedly ameliorate the disease condition.

**6 Claims, No Drawings**

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## USE OF SUBSTITUTED ADENINE DERIVATIVES FOR TREATING MULTIPLE SCLEROSIS

### STATEMENT OF GOVERNMENT RIGHTS

This invention was made with government support under FDA grant FD-R-000280 and NIH grant numbers NS30218 and RR00833. The government has certain rights in the invention.

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national phase application of copending International Application PCT/US 93/01467 filed Feb. 18, 1993, which is a continuation of copending U.S. application Ser. No. 838,546, now U.S. Pat. No. 5,310,732, filed Feb. 19, 1992, which was a continuation-in-part of copending application Ser. No. 460,351, filed Jan. 3, 1990, now U.S. Pat. No. 5,106,837, that was a continuation-in-part of copending application Ser. No. 323,350 filed Mar. 14, 1989, now abandoned, that was a continuation-in-part of copending application Ser. No. 169,618, filed Mar. 16, 1988, now abandoned, that is a continuation-in-part of copending application Ser. No. 825,215, filed Feb. 3, 1986, now abandoned.

### DESCRIPTION

#### TECHNICAL FIELD

This invention relates to therapeutic methods for treating multiple sclerosis. More particularly, this invention relates to the use of substituted adenine derivatives for treating multiple sclerosis.

#### BACKGROUND OF THE INVENTION

Multiple sclerosis (MS) is the result of demyelination in the brain and spinal cord (central nervous system). Symptoms resulting from this demyelination include weakness, visual impairment, incoordination, and paresthesia (abnormal tingling). The course of the disease is largely unpredictable, but often progresses through a cycle of exacerbation of symptoms followed by remission.

Conventional treatments presently employ therapy with ACTH or corticosteroids such as prednisone. Controlled studies suggest that such treatments induce more rapid clearing of acute symptoms and signs but leave the long-term outcome of the disease unaffected. Long-term maintenance therapy with ACTH or corticosteroids is contraindicated. Evidence indicates that immunosuppressant agents have no long-term benefit. (*Cecil, Textbook of Medicine*, Beeson et al., eds., 15th ed., W. B. Saunders Company, Philadelphia, (1979) page 847)

The etiology of multiple sclerosis is unknown but is linked to a variety of genetic and environmental factors. Both cell-mediated and humoral immune responses, triggered by extraneous or autoantigens may contribute to the pathogenesis of multiple sclerosis. Certain immune response genes may be associated with an increased susceptibility to the disease. The disease may be mediated by T cells that recognize an as yet unidentified autoantigen. For example, experimental allergic encephalomyelitis (EAE), an animal model of demyelinating diseases such as multiple sclerosis, can be induced by immunizing mice with whole myelin or

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In humans with multiple sclerosis, exacerbations are correlated with high levels of neopterin in blood and cerebrospinal fluid. Neopterin is a factor released from monocytes and macrophages in the presence of activated T-cells, thereby implicating these cells as being involved in multiple sclerosis exacerbations. (Fredrickson et al. (1987), *Acta Neurol. Scand.*, 75:352-355; Huber et al. (1984), *J. Exp. Med.*, 160:310-316). At the microscopic level, monocytes, microglial cells (macrophages of the central nervous system), and activated T-cells are found within the demyelinated regions of the nerve cells during multiple sclerosis exacerbations. (*Cecil, Textbook of Medicine* (1979), Beeson et al. (eds.), W. B. Saunders Co., Philadelphia, Pa.).

Various conventional treatment methodologies have been employed to ameliorate the symptoms of multiple sclerosis. Many of these are directed to use of palliative, anti-inflammatory agents. No treatment to date has had any consistent positive effect on the course of the disease.

Recently, the art has described the use of specific deoxyribosides as anti-inflammatory agents. For instance, U.S. Pat. No. 4,481,197 (Rideout et al.) relates to the use of unsubstituted 3-deaza-2'-deoxyadenosine derivatives in the treatment of inflammation. U.S. Pat. No. 4,381,344 (Rideout et al.) relates to a process for the synthesis of deoxyribosides that utilizes a bacterial phosphorylase.

A deoxyriboside derivative, 2-chloro-2'-deoxyadenosine (CdA), has been found to be an effective agent for the treatment of chronic lymphocytic leukemia and some T cell malignancies. (Carson et al. (1984) *Proc. Natl. Acad. Sci. U.S.A.*, 81:2232-2236; Piro et al. (1988), *Blood* 72:1069-1073) The pharmacokinetics of orally and subcutaneously administered 2-chloro-2'-deoxyadenosine in the treatment of chronic lymphocytic leukemia have been described and compared. (Liliemark et al. (1992) *Journal of Clinical Oncology*, 10, (10): 1514-1518; Juliusson et al. (1992) *Blood*, 80 (Suppl. 1): 1427) Chronic lymphocytic leukemia is a malignancy of B lymphocytes that bear the Leu-1 surface antigen.

The Leu-1 B cells represent a minor proportion of the normal pool of B lymphocytes, usually less than 20 percent. The Leu-1 B cells express surface markers that are typically found on monocytes (Mac-I antigen) and T-lymphocytes (Leu-1 antigen). Approximately 10 percent of patients with chronic lymphocytic leukemia exhibit accompanying autoimmunity, and recently, Leu-1 B cells have been implicated in the pathogenesis of autoimmune diseases.

Phase I clinical trials on human patients with chronic lymphocytic leukemia indicate that infusion of increasing doses of 2-chloro-2'-deoxyadenosine [0.1-0.5 milligrams per kilogram of body weight per day (mg/kg/day)] yielded increasing plasma concentrations of the drug [10-50 nanomolar (nM)]. Those infusions indicated that the drug was well tolerated and did not induce nausea, vomiting or fever. The dose-limiting toxicity was bone marrow suppression, which usually occurred at doses greater than about 0.2 mg/kg/day or at plasma levels of greater than about 20 nM.

Other studies, Montgomery et al. (1959) *J. Am. Chem. Soc.*, 82:463-468, indicated that 2-fluoroadenosine exhibits a relatively high degree of cytotoxicity. Those workers reported that C57 black mice implanted with Adenocarcinoma 755 (Ad755) could tolerate only about 1 milligram per kilogram of body weight. 2-Fluoroadenosine was found to be inactive at that level against Ad755 as well as leukemia L1210 and the Erlich ascites tumor.

U.S. Pat. No. 4,751,221 and its division No. 4,918,179 to

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2-substituted-2'-deoxy-2'-fluoroarabino-furanosyl nucleosides including adenine derivatives. Those compounds were said to have anti-tumor and antitrypanosomal biological activities. Cytotoxicity data showing anti-tumor activity of 2-amino-6-thiopurine, guanine and thiopurine derivatives against murine and human cell lines were reported.

U.S. Pat. No. 5,034,518 to Montgomery et al. teaches the synthesis of 2-substituted-2'-deoxy-2'-fluoroaradenosines. Those compounds were said to have anticancer activity, and data for prolongation of life of mice transplanted with P388 leukemia cells were provided.

The biochemical activity of 2-CdA in cells has been reviewed by Ernest Beutler. (*The Lancet* (1992), 340: 952-956—incorporated herein by reference)

The 2',3'-dideoxynucleosides are phosphorylated at the 5'-position in T cells to form the 5'-nucleotide triphosphate derivatives. Those derivatives are well known to be substrates for reverse transcriptase molecules. (Ono et al. (1986) *Biochem. Biophys. Res. Comm.*, 2:498-507)

Those 2',3'-dideoxynucleoside 5'-triphosphates are also utilized by mammalian DNA polymerases beta and gamma. (Waquar et al. (1984) *J. Cell. Physiol.*, 121:402-408) They are, however, poor substrates for DNA polymerase-alpha, the main enzyme responsible for both repair and replicative DNA synthesis in human lymphocytes. In part, these properties may explain the selective anti-HIV activity of the 2',3'-dideoxynucleosides.

Chan et al. (1982) *J. Cell Physiol.*, 111:28-32 studied the pathways of pyrimidine nucleotide metabolism in murine peritoneal macrophages and monocytes, and reported undetectable levels of deoxycytidine kinase or thymidine kinase in these cells. High levels of adenosine kinase were found, however.

Similar high levels of adenosine kinase have been found in human monocytes and human monocyte-derived macrophages (MDM). MDM were found to exhibit about one-tenth to about one-fourth the nucleoside kinase activity of GEM T lymphoblasts (e.g. ATCC CCL 119) toward uridine, deoxycytidine and thymidine, and about two-thirds the adenosine kinase activity of GEM cells. In addition, that adenosine kinase activity of MDM cells was at least about 10-fold higher than any of the other kinase activities. Those studies also indicated relatively low levels of nucleoside phosphorylation using AZT, dideoxycytidine (ddC) and 2',3'-dideoxyadenosine (ddA) in intact GEM T lymphoblasts and still lower levels with the MDM.

Several 2-substituted adenosine derivatives have been reported not to be deaminated by adenosine deaminase. For example, Coddington (1965) *Biochim. Biophys. Acta*, 99:442-451 reported that deoxyadenosine-1-N-oxide, as well as 2-hydroxy-, 2-methyl-, 2-chloro-, 2-acetamido-, and 2-methylthioadenosines were neither substrates nor inhibitors for adenosine deaminase. Montgomery, in *Nucleosides, Nucleotides, and Their Biological Applications*, Rideout et al. eds., Academic Press, New York, page 19 (1983) provides a table of comparative  $K_m$  and  $V_{max}$  data for the deamination of adenosine, 2-haloadenosines 2-halo-deoxyadenosines and 2-fluoroarabinoadenosine that also indicates that those 2-halo adenine derivatives are poor substrates for the enzyme relative to adenine itself. Stoeckler et al. (1982) *Biochem. Pharm.*, 31:1723-1728 reported that the 2'-deoxy-2'-azidoarabosyl and 2'-deoxy-2'-azidoarabosyl-adenine derivatives were substrates for human erythrocytic adenosine deaminase, whereas work of others indicated 2-fluoro-adenosine to have negligible activity with adenosine deami-

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2-Chloro-2'-deoxyadenosine is phosphorylated by non-dividing (normal) human peripheral blood lymphocytes and is converted to the 5'-triphosphate. This adenine derivative is not catabolized significantly by intact human cells or cell extracts, and is phosphorylated efficiently by T lymphocytes. (Carson et al. (1980) *Proc. Natl. Acad. Sci. USA*, 77:6865-6869)

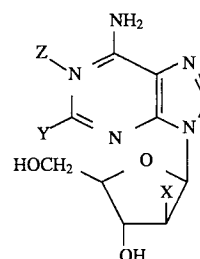
As discussed before, high levels of adenosine kinase have been found in murine peritoneal macrophages and in human monocytes. Adenosine kinase can phosphorylate 2'-deoxyadenosine derivatives, but does so less efficiently than deoxycytidine kinase. (Hershfield et al. (1982) *J. Biol. Chem.*, 257:6380-6386)

Chemotherapeutic agents are described hereinafter that may be employed as therapeutic agents in the treatment of multiple sclerosis.

#### SUMMARY OF THE INVENTION

The present invention contemplates a method for treating multiple sclerosis. In this method, a patient having multiple sclerosis is treated with a composition having a pharmacologically acceptable carrier and a substituted adenine derivative dissolved or dispersed therein. The substituted adenine derivative is present in the pharmacologically acceptable carrier in an amount sufficient to provide a therapeutically effective dose over the course of treatment.

Preferred substituted adenine derivatives useful for treating multiple sclerosis may be represented by Formula I having a structural formula corresponding to:



wherein Z is  $O^-$  or absent,

Y is hydrogen or a substituent containing one to about 20 atoms that is free from net ionic charge at physiological pH values, provides a soluble adenine derivative and whose presence on the adenine moiety inhibits deamination of the adenine derivative by adenosine deaminase; and

X is hydrogen or fluoro, with the proviso that Y is hydrogen only when Z is present.

Particularly preferred compounds of Formula I are free of the Z group; i.e. Z is absent, and contain a halo group at the 2-position. The most preferred compounds are 2-chloro-2'-deoxyadenosine and 2-chloro-2'-deoxy-2'-afluoroaradenosine.

Methods for synthesizing all of the above compounds are indicated in U.S. Pat. No. 5,106,837 (Carson et al., Apr. 21, 1992, incorporated herein by reference).

The invention teaches that the disease condition of a patient having multiple sclerosis may be ameliorated by administration of an amount of the above-described composition having a sufficient quantity of the compound of Formula I to provide a therapeutically effective dose. Exemplary dosages range from about 0.04 to about 1.0 mg/kg/day, with dosages of about 0.04 to about 0.2 mg/kg/day being more preferred. Typically, the amount is sufficient to provide

molar (nM) to about 50 nM, more preferably of about 1 nM to about 10 nM.

Preferably, the agent contemplated for use in the present invention is a 2-halo-2'-deoxyadenosine (2-halo-2'-deoxy-9, 1'-beta-ribofuranosyladenine) or a 2-halo-2'-deoxy-2'-

arafluoroadenosine, and most preferably the halo group is chloro.

A further aspect contemplated by the present invention comprises the use of subcutaneous injection for administering an effective amount of the active ingredient (agent) of the invention for treating multiple sclerosis.

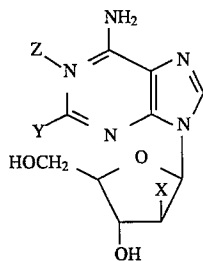
An alternative aspect contemplated by the present invention comprises the peroral administration of an effective amount of the active ingredient (agent) of the invention in a method of treating disease. Preferred compounds of Formula I for oral administration include compounds in which X is fluoro.

In each of the before-described methods, the substituted 2'-deoxyadenosine derivative is administered in a therapeutically effective amount. The effect of a compound of Formula I is dependent upon the route of administration and upon the time and dosage. As a consequence, one can tailor the dosage and duration for which a particular compound is administered to the stage of the disease and the condition of the patient being treated. Where the stage of multiple sclerosis is advanced or life-threatening, treatment may be more aggressive, and a therapeutically effective amount is an amount that is sufficient to kill at least 50 percent of the monocytes present but is less than that which substantially impairs bone marrow function as determined by usual procedures when administration is in vivo. The monocyte killing amount of a compound of Formula I is another measure of a therapeutically effective dose and monocyte death is measured at a time seven days after the initial administration.

#### DETAILED DESCRIPTION OF THE INVENTION

##### A. Compounds

The present invention contemplates the use of substituted adenine derivatives, i.e. substituted- 2'-deoxy-arabinofuranosyladenine, for treating multiple sclerosis. Preferred substituted adenine derivatives have a structure represented by the following formula, viz. Formula I:



wherein Z is an oxide radical (O<sup>-</sup>) or is absent;

Y is hydrogen or a radical containing one to about twenty atoms that is free from net ionic charge at physiological pH values, provides a soluble adenine derivative, and whose presence on the adenine moiety inhibits deamination of the adenine derivative by adenosine deaminase; and

X is hydrogen or fluorine, with the proviso that Y is hydrogen only when Z is present.

Preferably, Y is chloro. Other Y substituents may be selected from the group consisting of lower alkyl, lower

particularly preferred embodiments, when Y is chloro, X is fluorine.

The preferred compound included in Formula I is 2-chloro-9,1'-beta-D-2'-deoxyribofuranosyladenine, otherwise known as 2-chlorodeoxyadenosine or CdA.

Of the compounds of Formula I, those where X is fluoro are among the preferred compounds for use by oral administration.

Other illustrative compounds included in Formula I are:

2-bromo-9,1'-beta-D-2'-deoxyribofuranosyladenine;  
2-methyl-9,1'-beta-D-2'-deoxyribofuranosyladenine;  
2-fluoro-9,1'-beta-D-2'-deoxyribofuranosyladenine;  
2-acetoamido-9,1'-beta-D-2'-deoxyribofuranosyladenine;  
2-methylthio-9,1'-beta-D-2'-deoxyribofuranosyladenine; ...  
2-chloro-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;  
2-bromo-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;  
2-(N-acetamido)-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;  
2-methylthio-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine.

Further illustrative of compounds of Formula I include the following arabinofuranosyl derivatives of adenine:

2-methyl-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;  
2-isopropyl-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;  
2-hydroxy-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;  
2-chloro-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-fluoro-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-bromo-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-methyl-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-(N-acetamido)-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-hydroxy-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-(2-methylbutyl)-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;  
2-fluoro-9,1'-beta-D-2'-deoxyadenosine-1-oxide; and  
2-chloro-9,1'-beta-D-2'-deoxyadenosine-1-oxide.

It is noted that when X is hydrogen the sugar ring can be named as a 2'-deoxyribofuranosyl or 2'-deoxyarabinofuranosyl radical. Both nomenclatures are utilized herein. When the class of compounds embraced by Formula I is discussed, all of the compounds are considered herein as derivatives of arabinose. However, when specific compounds of the subclass where X=H are discussed, the more familiar deoxyribose nomenclature is used, such as in deoxyadenosine. These compounds are also referred to herein more simply as adenine derivatives.

In the above formulas, and in all other formulas shown herein, hydrogen atoms on the purine and furanosidyl rings that are not needed to show conformation about a particular bond are not shown. Thus, the 8-position adenine hydrogen is not shown.

It is also to be understood that the D isomers of compounds of the formulas are the isomers contemplated. It is further to be noted that the designation "halo" used herein is meant to include fluorine, chlorine and bromine derivatives, and to exclude iodine derivatives, which are unstable and

Where specific halogen derivatives are intended, those compounds are named specifically.

As used herein, "a substituent free from net ionic charge" includes both charged and uncharged radicals, wherein the substituent radical is charged, an internal zwitterionic charge pair is present that results in the absence of a net ionic charge for the molecule at physiologic pH values. N-oxide compounds are exemplary of such substituents.

As used herein, a "soluble adenine derivative" is an adenine derivative which is able to dissolve and remain soluble in a body fluid such as blood at a therapeutically effective dose as is discussed hereinafter.

As used herein, a "substituent whose presence on the adenine moiety inhibits deamination of an adenine derivative by adenosine deaminase" is one that, when 100 microliters of a 1 millimolar solution of the substituted adenine derivative is incubated for three hours at room temperature with 25 units of calf spleen adenosine deaminase (1 unit catalyzes the deamination of 1 micromole of adenosine per minute), produces a single UV-absorbing spot upon cellulose-thin layer chromatography of the reaction mixture whose  $R_f$  value is the same as that of the substituted adenine derivative used.

The metabolism of a compound by adenosine deaminase can be investigated by the following procedure. The individual nucleosides, at concentrations from 5–200  $\mu$ M in 10 mM sodium phosphate, pH 7.5, are incubated at 18–20 degrees C. with 0.01 EU/ml calf intestinal adenosine deaminase. The change in the optical density at 265 nm and 250 nm is monitored spectrophotometrically. The  $K_m$  and  $V_{max}$  values are determined by the Lineweaver-Burke method utilizing the  $\Delta E_{265}^M$  between adenosine and inosine.

The ratio  $V_{max}/K_m$  also provides a measure of relative efficiency of deamination by the enzyme. A substituent that provides a  $V_{max}/K_m$  ratio that is about 1 percent or less than that for the ratio obtained using 2'-deoxyadenosine is also a "substituent whose presence on the adenine moiety inhibits deamination of an adenine derivative by adenosine deaminase."

As used herein, lower alkyl radicals include  $C_1$ – $C_6$  straight chain, branched and cyclic alkyl groups, for example, methyl, ethyl, n-butyl, t-butyl, n-hexyl, 1-ethylbutyl, cyclopentyl, cyclohexyl and the like. Lower alkanoylamido radicals include  $C_1$ – $C_6$  radicals, for example, formamido, acetylamido, propionamido, hexamoylamido and the like. Lower alkylthio radicals include  $C_1$ – $C_6$  straight chain, branched and cyclic alkyl groups as discussed above linked to a thio radical.

The pharmacologically acceptable salts of a compound of Formula I are also utilized. The phrase "pharmacologically acceptable salts," as used herein, refers to non-toxic acid addition salts that are generally prepared by reacting a compound with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, phosphate, citrate, acetate, maleate and the like.

#### B. Compositions

A compound of Formula I dissolved or dispersed in or together with a pharmacologically acceptable carrier constitutes a composition of this invention.

A compound of Formula I and its pharmacologically acceptable salts are useful in both short and long term treatment. For instance, a 2-substituted-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine is administered to the patient internally, e.g., subcutaneously by injection, parenterally, orally, or rectally as a suppository, in an effective

Although a compound of Formula I and its pharmacologically acceptable salts can be administered as the pure chemical, it is preferred that it be administered as a pharmaceutical composition. In either event, it is administered in an amount sufficient to provide a therapeutically effective dose as is discussed hereinafter.

Accordingly, the present invention utilizes a pharmaceutical composition comprising a therapeutically effective dose of a compound of Formula I or a pharmacologically acceptable salt thereof, hereinafter referred to as the "active ingredient" or "agent," dissolved or dispersed in a pharmacologically acceptable carrier or diluent.

A pharmaceutical composition is prepared by any of the methods well known in the art of pharmacy all of which involve bringing into association the active compound and the carrier therefor. For therapeutic use, a compound utilized in the present invention can be administered in the form of conventional pharmaceutical compositions. Such compositions can be formulated so as to be suitable for oral, subcutaneous, or parenteral administration, or as suppositories. In these compositions, the agent is typically dissolved or dispersed in a physiologically tolerable carrier.

A carrier or diluent is a material useful for administering the active compound and must be "pharmacologically acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. Thus, as used herein, the phrases "physiologically tolerable" and "pharmacologically acceptable" are used interchangeably and refer to molecular entities and compositions that do not produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a mammal. The physiologically tolerable carrier can take a wide variety of forms depending upon the preparation desired for administration and the intended route of administration.

As an example of a useful composition, a compound of Formula I can be utilized in liquid compositions such as sterile suspensions or solutions, or as isotonic preparations containing suitable preservatives. Particularly well-suited for the present purposes are injectable media constituted by aqueous injectable isotonic and sterile saline or glucose solutions. Additional liquid forms in which these compounds can be incorporated for administration include flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil, and the like, as well as elixirs and similar pharmaceutical vehicles.

The agents can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain stabilizers, preservatives, excipients, and the like in addition to the agent. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

An agent of Formula I can also be used in compositions such as tablets or pills, preferably containing a unit dose of the compound. To this end, the agent (active ingredient) is mixed with conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums, or similar mate-

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