USE OF BENZIMIDAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF LEUKEMIA

TECHNICAL FIELD

This invention is a pharmaceutical composition that is useful for the treatment of leukemia, particularly in human and warm blooded animals. The composition contains a benzimidazole derivative.

BACKGROUND OF THE INVENTION

Cancers, including leukemia, are the leading cause of death in animals and humans. The exact cause of leukemia is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of leukemia and tumors has been shown by a number of researchers.

Many types of chemotherapeutic agents have been shown to be effective against leukemia, but not all types of leukemia and tumor cells respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents are not always known.

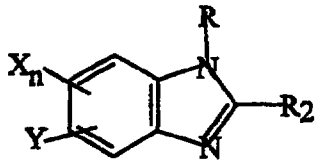
Despite advances in the field of cancer and leukemia treatments the leading therapies to date are radiation and chemotherapy and bone marrow transplants. Chemotherapeutic approaches are said to fight cancers that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for leukemia, cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially rapidly dividing cells (both diseased and normal) have been used.

Clearly, the development of materials that would target leukemia cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to leukemia cells while exerting mild effects on normal cells would be desirable. Therefore, it is an object of this invention to provide a pharmaceutical composition that is effective in treating leukemia with mild or no effects on normal blood cells

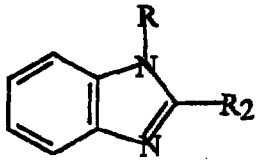
More specifically, it is an object of this invention to provide a composition comprising a pharmaceutical carrier and a benzimidazole derivative as defined herein along with a method for treating leukemia.

SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, which are affected by leukemia comprising a pharmaceutical carrier and an effective amount of a compound selected from the group consisting of:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen, or an alkyl group of from 1 to 8 carbon atoms and R_2 is 4-thiazolyl, $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms, and preferably an alkyl group of less than 7 carbon atoms is claimed. Preferably the compositions are:



wherein R is an alkyl of 1 through 8 carbon atoms and R_2 is selected from the group consisting of 4-thiazolyl, $NHCOOR_1$, wherein R_1 is methyl, ethyl or isopropyl and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids. The most preferred compounds are 2-(4-thiazolyl)benzimidazole, methyl -(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole and those wherein Y is chloro.

These compositions can be used to inhibit the growth of leukemia cells in humans or animals by administration of an effective amount either orally, rectally, topically or parenterally, or intravenously. These compositions do not significantly affect healthy cells.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions:

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical composition of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" is salt of the anti-leukemia compound with an organic or inorganic acid. These preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like.

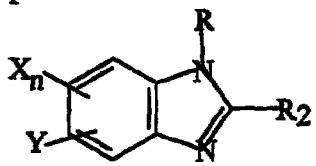
As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-leukemia agent to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

As used herein, "cancer" or "leukemia" refers to all types of cancers or neoplasm or malignant disease which attack normal healthy blood cells or bone marrow which produces blood cells which are found in mammals.

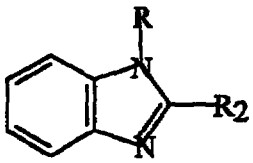
As used herein, the "anti-leukemia compounds" are the benzimidazoles, and their salts. The exact benzimidazoles are described in detail below. The preferred materials are the products sold under the names "thiabendazole®", "benomyl®" and "carbendazim®" by BASF and Hoechst, DuPont and MSD-AgVet.

B. THE ANTI-LEUKEMIA COMPOUNDS

The anti-leukemia compounds are benzimidazole derivatives which are known for their antifungal activities. They are systemic fungicides used to prevent and eradicate fungi. The compounds have the following structure:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen or an alkyl group having from 1 to 8 carbons, and R_2 is 4-thiazolyl, $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms, and preferably and alkyl group of less than 7 carbon atoms. Preferably the compositions are:



wherein R is an alkyl of 1 through 8 carbon atoms and R_2 is selected from the group consisting of 4-thiazolyl, $NHCOOR_1$, wherein R_1 is methyl, ethyl or isopropyl and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids.

The most preferred compounds are 2-(4-thiazolyl)benzimidazole, methyl -(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole and the compounds wherein Y is chloro and X is hydrogen.

These compounds are prepared according to the method described in U.S. 3,738,995 issued to Adams et al, June 12, 1973. The thiazolyl derivatives are prepared according to the method described in Brown et al., J. Am. Chem. Soc., 83, 1764 (1961) and Grenda et al., J. Org. Chem., 30, 259 (1965).

C. DOSAGE

Any suitable dosage may be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and the type of leukemia being treated. Generally a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight and about 400 mg per kg of body weight is suitable. Preferably from 15 mg to about 150 mg/kg of body weight is used. Generally, the

dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds. The dosage unit can also comprise diluents, extenders, carriers and the like. The unit may be in solid or gel form such as pills, tablets, capsules and the like or in liquid form suitable for oral, rectal, topical, intravenous injection or parenteral administration or injection into or around the bone marrow.

D. DOSAGE DELIVERY FORMS

The anti-leukemia compounds are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in US. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

E. METHOD OF TREATMENT

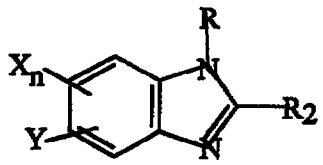
The method of treatment can be any suitable method which is effective in the treatment of the particular leukemia type being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into the bone marrow. The method of applying an effective amount also varies depending on the leukemia being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application of the benzimidazole compounds, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

The following example is illustrative and is not meant to be limiting to the invention.

Mice are randomly selected and divided into groups for treatment. Five groups are infected with leukemia. The diseased animals are dosed for five days, off two days and then dosed for another five days and then three days off, then dosed for five days and off for two days. This dosing on and off in an irregualr pattern was not an ideal regimien, but the results do show a positive benefit for the Carbendazim™. One group of mice was treated with Cytoxan™, 2-[bis(2-chloroethyl)-amino-1-oxo-2-aza-5-oxophosphoridin, a control was dosed with canola oil and three groups were treated with various levels of Carbendazim™, methyl -(butylcarbamoyl)-2-benzimidazole-carbamate. A control with no treatment was also used. The Carbendazim™ was dosed at three levels 4000 mg/kg, 2500 mg/kg and 1000 mg/kg. The Cytoxan™ was dosed at 125 mg/kg. After 8 days, the no treatment group had lost 1 mouse, by day 10, 8 mice were dead and at day 11 all ten mice were dead. The mice in the Cytoxan™ group survived more than 21 days. The higher dose Carbendazim™ group had one mouse die on day 14, two died on days 15,16 and 17 and one each died on days 20, 21, and 22. The mean number of days for this group is 17.3. The intermediate dosage group had 2 mice die on day 14, 4 on day 15, 1 on day 16, 2 on day 19 and 1 on day 21. The mean number of days for this group is 16.50. The lowest dosage group had 2 mice die on day 12, 13, 14, and 15; and 1 died on each of days 16 and 17. The mean number of days for this group is 14.1.

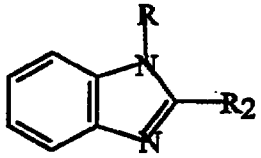
What is Claimed is:

1. A pharmaceutical composition for treating leukemia comprising a safe and effective amount of:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen or an alkyl group having from 1 to 8 carbon atoms, and R_2 is 4-thiazolyl or $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms or the pharmaceutically acceptable inorganic or acid addition salts thereof.

2. A pharmaceutical composition according to Claim 1 comprising a pharmaceutically acceptable carrier and a safe and effective amount of a benzimidazole selected from the group consisting of:



wherein R is hydrogen or an alkyl having from 1 to 8 carbon atoms and R_2 is selected from the group consisting of 4-thiazolyl, $NHCOOR_1$, wherein R_1 is methyl, ethyl or isopropyl and the pharmaceutically acceptable organic or inorganic acid addition salts thereof.

3. A pharmaceutical composition according to Claim 2 wherein said benzimidazole is selected from the group consisting of 2-(4-thiazolyl)benzimidazole, methyl -(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole.

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4. A pharmaceutical composition according to Claim 1, 2 or 3 wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates and mixtures thereof.

5. A method of treating leukemia in warm blooded mammals comprising administering from 2 mg/kg body weight to 400 mg/kg of a pharmaceutical composition comprising a benzimidazole according to Claim 1, 2, 3 or 4.

6. A method according to Claim 5 wherein said benzimidazole is administered orally or enterically, intravenously, peritoneally, or by injection into the bone marrow.

7. A method according to Claim 5 or 6 wherein said benzimidazole is administered in a liquid form and wherein said liquid dosage from is selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

8. A unit dosage composition for treating leukemia infections in animals or humans comprising a benzimidazole according to Claims 1, 2, 3 or 4.

9. A unit dosage composition according to Claim 8 wherein said benzimidazole is administered in a solid form, wherein said solid form includes a carrier selected from the group consisting of lactose, sucrose, gelatin and agar.

10. A unit dosage composition according to Claim 9 wherein said benzimidazole is administered in a liquid form wherein said liquid dosage from is selected from the group consisting of aqueous solutions, emulsions, suspension solutions, and suspensions reconstituted from non-effervescent and effervescent preparations.

4. A pharmaceutical composition according to Claim 1, 2 or 3 wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates and mixtures thereof.

5. The use of a composition comprising a benzimidazole according to any one of claims 1 to 4 in the preparation of a medicament for the treatment of leukaemia in warm blooded mammals.

6. The use of claim 5 wherein the composition is arranged for administration from 2 mg/kg body weight to 400 mg/kg.

7. The use of claim 6 wherein said administration is oral or enteric, intravenous, peritoneal, or by injection into the bone marrow.

8. The use according to any one of Claims 5 to 7 wherein said benzimidazole is in a liquid form selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

9. A unit dosage composition for treating leukemia infections in animals or humans comprising a benzimidazole according to Claims 1, 2, 3 or 4.

10. A unit dosage composition according to Claim 9 wherein said benzimidazole is administered in a solid form, wherein said solid form includes a carrier selected from the group consisting of lactose, sucrose, gelatin and agar.

11. A unit dosage composition according to Claim 10 wherein said benzimidazole is administered in a liquid form wherein said liquid dosage from is selected from the group consisting of aqueous solutions, emulsions, suspension solutions and suspensions reconstituted from non-effervescent and effervescent preparations.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/415 — A1

(11) International Publication Number: **WO 96/40122**

(43) International Publication Date: 19 December 1996 (19.12.96)

(21) International Application Number: PCT/US96/07445

(22) International Filing Date: 22 May 1996 (22.05.96)

(30) Priority Data:
08/473,817 7 June 1995 (07.06.95) US

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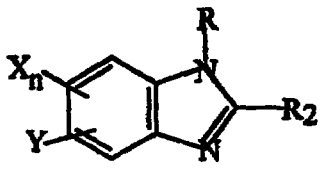
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: USE OF BENZIMIDAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF LEUKEMIA

(57) Abstract

A pharmaceutical composition for the treatment of leukemia in mammals is disclosed. The particular fungicide used is a benzimidazole derivative of formula (I), wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen or an alkyl group having from 1 to 8 carbon atoms, and R_2 is 4-thiazolyl or $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms or the pharmaceutically acceptable inorganic or acid addition salts thereof.



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