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(54) **METHOD OF TREATMENT FOR CANCER OR VIRAL INFECTIONS**

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(60) Provisional application No. 60/001,888, filed on Aug. 4, 1995.

(51) **Int. Cl.**[7] **A61K 31/27**

(52) **U.S. Cl.** **514/485**; 514/488

(58) **Field of Search** 514/485, 488

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(57) **ABSTRACT**

Methods for the treatment of cancers or viral infections in mammals are disclosed that include administration of an N-chlorophenylcarbamate, or an N-chlorophenylthiocarbamate, or a salt thereof. Such compounds may be used in combination with a chemotherapeutic agent and/or a potentiator.

20 Claims, No Drawings

METHOD OF TREATMENT FOR CANCER OR VIRAL INFECTIONS

The present application is a continuation-in-part of U.S. Ser. No. 09/364,021, filed Jul. 30, 1999 which is a divisional of 08/876,705 filed Jun. 16, 1997, now U.S. 5,932,609 which is a divisional of U.S. Ser. No. 08/680,468 filed on Jul. 15, 1996 now U.S. Pat. No. 5,932,604. U.S. Ser. No. 08/680,468 is a continuation-in-part application of U.S. Ser. No. 08/420,913 filed Apr. 12, 1995, now U.S. Pat. No. 5,629,341. U.S. Ser. No. 08/680,468 also claims priority to U.S. Ser. No. 60/001,888 filed Aug. 4, 1995. The patent and patent applications are incorporated by reference herein.

TECHNICAL FIELD

The present invention relates to methods for the treatment of cancer or a viral infection in mammals, particularly in human and warm blooded animals, using a composition containing N-chlorophenylcarbamate, N-chlorophenylthiocarbamate or salt thereof. The methods may use such a compound in combination with a potentiator or a chemotherapeutic agent.

BACKGROUND OF THE INVENTION

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

Many types of chemotherapeutic agents have been shown to be effective against cancers and tumor cells, but not all types of cancers and tumors 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 treatment the leading therapies to date are surgery, radiation and chemotherapy. Chemotherapeutic approaches are said to fight cancers that are metastasized or ones 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 antimetabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents that target especially rapidly dividing cells (both tumor and normal) have been used.

Clearly, the development of materials that would target cancer cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to cancer cells while exerting mild effects on normal cells would be desirable.

Human Immunodeficiency Virus (HIV), the etiological agent for AIDS (acquired immune deficiency syndrome), is a member of the lentiviruses, a subfamily of retroviruses. HIV integrates its genetic information into the genome of the host. Most importantly, HIV infects and invades cells of the immune system; it breaks down the body's immune system and renders the patient susceptible to opportunistic infections and neoplasms. HIV-1 is cytopathic for T4 lymphocytes, cells of the immune system that express the cell surface differentiation antigen CD4. In addition to CD4+ T cells, the host range of HIV includes cells of the mononuclear phagocytic lineage, including blood monocytes, tissue macrophages, Langerhans cells of the skin and dendritic reticulum cells within lymph nodes.

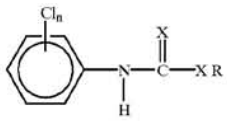
Precursor cells in the bone marrow are released into the blood in an immature circulating form known as monocytes. Monocytes use the blood strictly as a transport medium. Once they arrive where they're going to be used, they leave the blood and complete differentiation into macrophages. Cells of the monocyte/macrophage lineage are a major target population for infection with HIV in the body and are thought to provide reservoirs of virus for disseminating infection throughout the body. HIV is also neurotropic, capable of infecting monocytes and macrophages in the central nervous system causing severe neurologic damage. They can interact and fuse with CD4-bearing T cells, causing T cell depletion and thus contributing to the pathogenesis of AIDS.

Progression from HIV infection to AIDS is primarily determined by the effects of HIV on the cells that it infects, including CD4+ T lymphocytes and macrophages. In turn, cell activation, differentiation and proliferation regulate HIV infection and replication in those cells. HIV and other lentiviruses can proliferate in nonproliferating, terminally differentiated macrophages and growth-arrested T lymphocytes. This ability of lentiviruses, including HIV, to replicate in nonproliferating cells, particularly in macrophages, is believed to be unique among retroviruses.

Due to the above-mentioned problems in the art, the present inventor has sought improvements and provides such improvements herein.

SUMMARY OF THE INVENTION

Methods for treatment of mammals, and in particular, warm blooded animals and humans that are affected by cancer or viral infection comprising administering a therapeutically effective amount of an N-chlorophenylcarbamate, an N-chlorophenylthiocarbamate, or a salt thereof, are provided by the present invention. An N-chlorophenylcarbamate, or an N-chlorophenylthiocarbamate has the formula:



wherein n is from 1 to 3, X is oxygen or sulfur, and R is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, and phenyl.

These compositions are effective in killing or slowing the growth of cancers, yet are safer than adriamycin on normal, healthy cells. The compositions are also particularly effective against cells of monocytic lineage infected with HIV.

DETAILED DESCRIPTION OF THE INVENTION

A. DEFINITIONS:

As used herein, "a therapeutically effective amount," means the concentration or quantity or level of the compound of the present invention that can attain a particular medical end, such as control or destruction of cancer cells, virally-infected cells, or viruses without producing unacceptable toxic symptoms. 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 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 salts.

As used herein, a "subject in need thereof," is a mammal having cancer or having a viral infection. As used herein, "cancer" refers to all types of cancers, or neoplasms or benign or malignant tumors. In one embodiment, those cancers that attack normal healthy blood cells or bone marrow are contemplated by the present invention. Preferred cancers for treatment using methods provided herein include carcinoma. By "carcinoma" is meant a benign or malignant epithelial tumor and includes, but is not limited to, breast carcinoma, prostate carcinoma, non-small cell lung carcinoma, colon carcinoma, CNS carcinoma, melanoma carcinoma, ovarian carcinoma, or renal carcinoma. A preferred host is a human host.

As used herein, "a cell of monocytic lineage" means a cell having a bone marrow precursor cell and that differentiates into a macrophage cell, and includes monocytes and macrophages.

As used herein, "viruses" includes viruses that cause disease in warm blooded animals including retroviruses such as HIV or HTLV, influenza, rhinoviruses, herpes, or the like.

As used herein, an N-chlorophenylcarbamate, or an N-chlorophenylthiocarbamate, or salt thereof are "compounds of the present invention." Such compounds are further set forth in Section B infra.

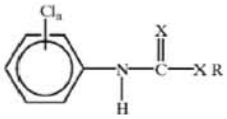
As used herein, "potentiators" are materials that affect the immune system or enhance the effectiveness of the drugs and are further set forth in section E herein.

As used herein, "chemotherapeutic agents" includes DNA-interactive agents, antimetabolites, tubulin-interactive agents, hormonal agents and others, such as asparaginase or hydroxyurea and are as further set forth in Section D infra.

Following long-standing patent law convention, the terms "a" and "an" mean "one or more" when used in this application, including the claims.

B. N-CHLOROPHENYLCARBAMATE OR N-CHLOROPHENYLTHIO CARBAMATE

An N-chlorophenylcarbamate or an N-chlorophenylthiocarbamate has the following structure



wherein n is from 1 to 3, X is oxygen or sulfur, and R is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms and phenyl.

Preferred compounds are those in which R is alkyl with 1 to 4 carbons, preferably, isopropyl; X is oxygen; n is 1; and the chloro group is in the 3 position on the phenyl group. N-3chlorophenylcarbamate is a most preferred compound.

These compounds are prepared according to the method described in U.S. Pat. No. 2,695,225 issued to Witman (1954) and U.S. Pat. No. 2,734,911 issued to Strain (1956), incorporated by reference herein. As used herein, a "a compound of the present invention" is an N-chlorophenylcarbamate, or an N-chlorophenylthiocarbamate, or a salt thereof.

Pharmaceutically acceptable addition salts of N-chlorophenylcarbamate, or an N-chlorophenylthiocarbamate, are considered within the scope of compounds of the present invention and are salts with an organic or inorganic acid. Preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, or the like. Such salts may be synthesized from the compound, or derivative thereof, of the present invention that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts may be prepared by reacting a free acid or base form of the compound, or derivative thereof, with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Further suitable salts may be found in *Remington: The Science and Practice of Pharmacy,* 19th ed., Mack Publishing Company, Easton, Pa., 1995, p. 1457.

Pharmaceutically acceptable salts of the compounds of the present invention include conventional non-toxic salts or the quatemary ammonium salts of the compounds or derivatives formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, or the like; and salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, or the like. Preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, or the like.

Further, included within the scope of the compound, or salts thereof, useful for the present invention are prodrugs. As used herein, a "prodrug" is a drug covalently bonded to a carrier wherein release of the drug occurs in vivo when the prodrug is administered to a mammalian subject. Prodrugs of the compounds of the present invention are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to yield the desired compound. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, is cleaved to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, or benzoate derivatives of alcohol or amine functional groups in the compounds of the present invention; phosphate esters, dimethylglycine esters, aminoalkylbenzyl esters, aminoalkyl esters or carboxyalkyl esters of alcohol or phenol functional groups in the compounds of the present invention; or the like.

Compounds of the present invention are known for their herbicidal activities. They are systemic herbicides used to prevent and eradicate certain plants or weeds. Systemic herbicides are differentiated from other herbicides by their ability to be absorbed by the plant and to move through the plant. This systemic ability is not a necessary requirement of the compounds of this invention.

C. SCREENING ASSAYS

Screening assays for determining those cancers susceptible to treatment using compounds of the present invention include incubating cell line models representing specific cancers as set forth, for example, by the National Cancer Institute, in the presence and absence of such compounds. Viability of cells may be determined by the MTT assay (Promega Corp., Madison, Wis. 53711), or the SRB (sulforhodamine B) assay (Skehan, et al., *JNCI*, 82:13,1107, 1990). Susceptibility to said compounds exists when viability in the presence of a compound of the present invention is less than viability in the absence of such compound.

Exemplary cell line models representing specific cancers include, but are not limited to, the following:

- Non-small cell lung cancer NCIH23, NCIH324, NCIH522, A549/ATCC, A549(ASC), CALU1, EKVX, NCIH125M, NCIH226, NCIH520, SKMES1, NCIH322M, NCIH358M, NCIH460, NCIH292, HOP62, HOP18, HOP19, HOP92, LXFL 529, SW1573, LXFS 650L, ML1019, ML1076, ML1045, or UABLG22;
- Small cell lung cancer: NCIH69, NCIH146, NCIH82, NCIH524, DMS 114, DMS 273, HOP27, SHP77, or RHOS;
- Colon cancer: HT29, HCC2998, HCT116, LOVO, SW 1116, SW620, COLO 205, DLD1, WIDR, COLO 320DM, HCT15, CXF 280, KM12, KM20L2, COLO 741, CXF 264L, COLO 746, UABC02, ML1059, CAC02, HT29/PAR, HT29/MDR1, or NB4;
- Breast cancer: MCF7, MCF7/ADRRES, ZR751, ZR7530, MDAMB231/ATCC, HS 578T, UISOBCA1, MCF7/ATCC, SKBR3, MDAMB435, MDAN, BT549, T47D, MDAMB231, MAXF 401, BT474, or MDAMB488;
- Ovarian cancer OVCAR3, OVCAR4, OVCAR5, OVCAR8, A2780, IGROV1, SKOV3, OVXF 899, A1336, or ES2;
- Leukemia: P388, P3888/ADR, CCRFCEM, CCRFSB, K562, MOLT4, L1210, HL60(TB), RPMI8226, SR, or K562/ADR;
- Fibroblast IMR90, or CCD19LU;
- Renal cancer: U031, SN12C, SN12S1, SN12K1, SN12L1, SN12A1, A498, A704, CAKI1, RXF 393, RXF831, 7860, SW156, TK164, 769P, SS78, ACHN, TKI0, RXF 486L, UOK57, or UOK57LN;
- Melanoma: LOX IMVI, MALME3M, RPMI7951, SKMEL2, SKMEL5, SKMEL28, SKMEL31, UCSD 242L, UCSD 354L, M14, M19MEL, UACC82, UACC257, MEXF 514L, or UABMEL3;
- Prostate cancer PC3, PC3M, DU145, LNCAP, 1013L, UMSCP1, WIS, JE, RER, MRM, DHM, AG, RB, RVP, FC, WAE, DB/SMC, JCA1, ND1, WMF, TSUPR1, JECA, GDP, T10, WBW, RVP1, or WLL;
- CNS cancer SNB7, SNB19, SNB4, SNB56, SNB75, SNB78, U251, TE671, SF268, SF295, SF539, XF 498, SW 1088, SW 1783, U87 MG, SF767, SF763, Al 72, or SMSKCNY;.
- Bone/muscle: A204/ATCC, OHS, TE85, A673, CHA59, MHM 25, RH18, RH30, or RD; and
- Lymphoma: AS283, HT, KD488, PA682, SUDHL7, RL, DB, SUDHL1, SUDHL4, SUDHL10, NUDUL1, or HUT 102.

D. CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agents are generally grouped as DNA-interactive agents, antimetabolites, tubulin-interactive agents, hormonal agents, other agents such as asparaginase or hydroxyurea, and agents as set forth in Table 1. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. Chemotherapeutic agents used in combination with an N-chlorophenylcarbamate, or an N-chlorophenylthiocarbamate, or salts thereof of the present invention may be selected from any of these groups but are not limited thereto. For a detailed discussion of the chemotherapeutic agents and their method of administration, see Dorr, et al, *Cancer Chemotherapy Handbook*, 2d edition, pages 15–34, Appleton & Lange (Connecticut, 1994) herein incorporated by reference.

DNA-interactive agents include alkylating agents, e.g. cisplatin, cyclophosphamide, altretamine; DNA strand-breakage agents, such as bleomycin; intercalating topoisomerase II inhibitors, e.g., dactinomycin and doxorubicin); nonintercalating topoisomerase II inhibitors such as, etoposide and teniposide; and the DNA minor groove binder picamycin, for example.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA, or protein molecules, or with smaller amino acids, glutathione, or similar chemicals. Generally, alkylating agents react with a nudeophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, or sulfhydryl group in nucleic acids, proteins, amino acids, or in glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood.

Typical alkylating agents include, but are not limited to, nitrogen mustards, such as chlorambucil, cyclophosphamide, isofamide, mechlorethamine, melphalan, uracil mustard; aziridine such as thiotepa; methanesulphonate esters such as busulfan; nitroso ureas, such as carmustine, lomustine, streptozocin; platinum complexes, such as cisplatin, carboplatin; bioreductive alkylator, such as mitomycin, and procarbazine, dacarbazine and altretamine.

DNA strand breaking agents include bleomycin, for example.

DNA topoisomerase II inhibitors include the following intercalators, such as amsacrine, dactinomycin, daunorubicin, doxorubicin (adriamycin), idarubicin, and mitoxantrone; nonintercalators, such as etoposide and teniposide, for example.

A DNA minor groove binder is plicamycin, for example.

Antimetabolites interfere with the production of nucleic acids by one of two major mechanisms. Certain drugs inhibit production of deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replication. Certain of the compounds are analogues of purines or pyrimidines and are incorporated in anabolic nucleotide pathways. These analogues are then substituted into DNA or RNA instead of their normal counterparts.

Antimetabolites useful herein include, but are not limited to, folate antagonists such as methotrexate and trimetrexate; pyrimidine antagonists, such as fluorouracil, fluorodeoxyuridine, CB3717, azacitidine, cytarabine, and floxuridine; purine antagonists include mercaptopurine, 6thioguanine, fludarabine, pentostatin; sugar modified analogs include cyctrabine, fludarabine; and ribonucleotide reductase inhibitors include hydroxyurea.

Tubulin interactive agents act by binding to specific sites on tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind the protein, the cell can not form microtubules. Tubulin interactive agents include vincristine and vinblastine, both alkaloids and paclitaxel, for example.

Hormonal agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. Hormonal agents include, but are not limited to, estrogens, conjugated estrogens and ethinyl estradiol and diethylstilbesterol, chlortrianisen and idenestrol; progestins such as hydroxyprogesterone caproate, medroxyprogesterone, and megestrol; and androgens such as testosterone, testosterone propionate; fluoxymesterone, and methyltestosterone.

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti-inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to haft DNA synthesis. These compounds include, but are not limited to, prednisone, dexamethasone, methylprednisolone, and prednisolone.

Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Antihormonal antigens include, for example, antiestrogenic agents such as tamoxifen, antiandrogen agents such as flutamide; and antiadrenal agents such as mitotane and aminoglutethimide.

Further agents include the following: hydroxyurea appears to act primarily through inhibition of the enzyme ribonucleotide reductase, and asparaginase is an enzyme which converts asparagine to nonfunctional aspartic acid and thus blocks protein synthesis in the tumor.

Taxol (paclitaxel) is a preferred chemotherapeutic agent.

A listing of currently available chemotherapeutic agents according to class, and including diseases for which the agents are indicated, is provided as Table 1.

TABLE 1

Neoplastic Diseases[1] for which Exemplary Chemotherapeutic agents are Indicated

Class	Type of Agent	Name	Disease[2]
Alkylating Agents	Nitrogen Mustards	Mechlorethamine (HN_2)	Hodgkin's disease, non-Hodgkin's lymphomas
		Cyclophosphamide	Acute and chronic lymphocytic leukemias, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma, neuroblastoma, breast, ovary, lung, Wilms' tumor, cervix, testis, soft tissue sarcomas
		Ifosfamide	
		Melphalan	Multiple myeloma, breast, ovary
		Chlorambucil	Chronic lymphocytic leukemia, primary macroglobulinemia, Hodgkin's disease, non-Hodgkin's lymphomas
		Estramustine	Prostate
	Ethylenimines and Methylmelamines	Hexamethylmelamine	Ovary
		Thiotepa	Bladder, breast, ovary
	Alkyl Sulfonates	Busulfan	Chronic granulocytic leukemia
	Nitrosoureas	Carmustine	Hodgkin's disease, non-Hodgkin's lymphomas, primary brain tumors, multiple myeloma, malignant melanoma
		Lomustine	Hodgkin's disease, non-Hodgkin's lymphomas, primary brain tumors, small-cell lung
		Semustine	Primary brain tumors, stomach, colon
		Streptozocin	Malignant pancreatic insulinoma, malignant carcinoid
	Triazenes	Dacarbazine	Malignant melanoma, Hodgkin's disease, soft tissue sarcomas
		Procarbazine	
		Aziridine	
Antimetabolites	Folic Acid Analogs	Methotrexate	Acute lymphocytic leukemia, choriocarcinoma, mycosis fungoides, breast, head and neck, lung, osteogenic sarcoma
		Trimetrexate	
	Pyrimidine Analogs	Fluorouracil	Breast, colon, stomach, pancreas, ovary, head and neck, urinary bladder, premalignant skin lesions (topical)
		Floxuridine	
		Cytarabine Azacitidine	Acute granulocytic and acute lymphocytic leukemias
	Purine Analogs and Related Inhibitors	Mercaptopurine	Acute lymphocytic, acute granulocytic, and chronic granulocytic leukemias

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