METHODS OF INHIBITING COLON TUMORS

Background of the Invention

Colon cancer, which includes rectal and colorectal adenocarcinoma, primary or metastatic adenocarcinoma, and the like, is a major health concern today in terms of disease incidence. It has been estimated that one out of twenty-five Americans will develop some form of colon cancer during the course of his lifetime. Sugarbaker, P.H. *et al.*, in *Cancer*, DeVita, V.T., *et al.* (Eds.), Lippincott Publ. Philadelphia, pp. 795-884 (1985).

In terms of treatment, surgery has been widely used with good, mixed or less than favorable results. Particularly among colon cancer patients with locally advanced or metastatic disease, the prognosis is extremely unfavorable with a high rate of morbidity and mortality.

Drug therapies have been tried with less than favorable results. The anti-neoplastic compound, 5-fluorouracil (5-FU), has been the major drug of choice in treating colon cancer, and its use has proven to be only marginally effective. 5-FU may reduce colon tumor size temporarily but there has been little evidence to show that the survival times of patients have been substantially prolonged or that "cures" are obtained (based on five year periods of remission). Chemotherapy with 5-FU has been used in patients with metastases to the liver, but temporary improvement is observed in only 25 percent or less of such cases, and the overall, survival is not significantly affected. LaMont, J.T. and Isselbacher, K., in *Harrison's Principles of Internal Medicine* (10th ed.) McGraw-Hill, New York, p. 1764, (1983). Despite the marginal effectiveness of 5-FU, no other drugs or combination therapy has been convincingly shown to be more effective. Sugarbaker P.H. *et al.*, supra. Woolley, P.V., *et al.*, *New Eng. J. Med.*, 312:1465 (1985).

Drug therapies have also been evaluated with respect to treating human cancer, *e.g.*, human colon cancer xenograft lines, in which human tumors are serially heterotransplanted into immunodeficient, so call "nude" mice, and the mice then tested for their responsiveness to a specific drug. Giovanella, B.C., *et al.*, *Cancer* 5(7):1146 (1983). The data obtained in these studies strongly support the validity of heterotransplanted human tumors, including colon tumors, into immunodeficient mammals, such as "nude" mice, as a predictive model for testing the effectiveness of anticancer agents.

The sodium salt of a naturally occurring alkaloid, camptothecin, was used in a brief clinical trial to evaluate toxic effects on patients with advanced incurable cancers. Gottlieb, G.A., *et al.*, *Cancer Chemotherapy Rep.* 54:461 (1970). Few conclusions could be drawn from this study, although median survival for those patients responding to the treatment increased from about two months to about 3.5+ months.

Camptothecin derivatives or analogs have been synthesized and employed as antileukemic agents in mice (see *e.g.*, Wani, M.C., *et al.*, *J. Med. Chem.* 23:544, 1980; Wani M.C., et al,., *J. Med. Chem.* 30:1774 (1987); and Wani, M.C. *et al.*, *J. Med. Chem.* 30:2317 (1987).

In U.S. Pat. Nos. 4,473,692 and 4,545,880, Miyasaka *et al.* disclose 10-substituted camptothecin derivatives and process for their preparation. The 10-substituted camptothecin derivatives are said to possess anti-tumor activity with reduced or slight toxicity in comparison to the parent camptothecin compound. Miyasaka *et al.* do not disclose specific tumor targets nor do they indicate what level of reduced or slight toxicity is achieved by using their 10-substituted camptothecin compounds.

Recently, the enzyme, human topoisomerase I, has been examined in various human cancers, *e.g.*, leukemia,

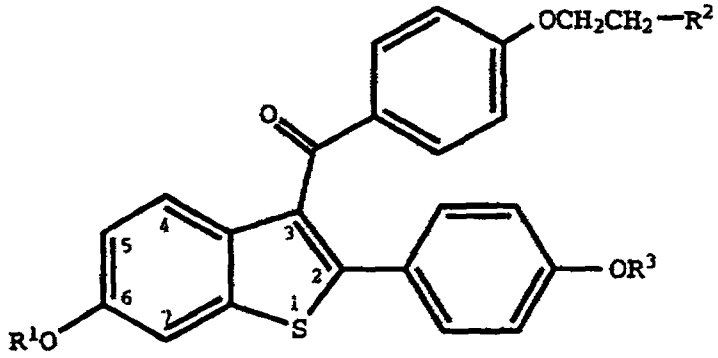
lymphoma. Potmesil M. *et al.*, *Cancer Res.* 48:3537 (1988). Human topoisomerase I is known to be a monomeric protein with an apparent molecular weight of 100,000 daltons. The swivel-like function of the enzyme has been implicated in various DNA transactions (replication, transcription and recombination). Purified mammalian topoisomerase I relaxes positively-supercoiled as well as negatively-supercoiled DNA in a mechanism which involves the transient breakage of one of the two DNA strands and the formation of a covalent topoisomerase I-DNA complex. In this complex, the enzyme is covalently linked to the 3'-phosphoryl end of the broken DNA backbone.

Recently, it was disclosed that topoisomerase I enzyme levels were on average higher in cancerous tissue, *e.g.*, surgical specimens of colorectal carcinoma, in comparison to the enzyme level in normal mucosa (Hsiang, Y.-H., *et al.*, *Proc Ann Meet of the Amer. Assoc. Cancer Res.* 29:172 (1988) Abstract. Although it was stated that topoisomerase I could be considered as an alternative target in chemotherapy of this (colorectal carcinoma) disease, no disclosure or suggestion at all was made as to any specific topoisomerase I interacting drugs.

In view of very poor 5-year survival rates (approximately 50 percent or less) for patients undergoing conventional treatment for colonic cancer, *e.g.*, surgical resection, or chemotherapy with 5-FU, it would be extremely useful to discover a new way to effectively treat human malignant colon tumors using drugs or compounds, following surgery, for example, which helps to establish the diagnosis and removes the bulk of cancer. The drug treatment could also be helpful for patients with advanced disease which has metastasized or spread to various organs, so that surgery is not feasible to remove all the cancerous tissues.

SUMMARY OF THE INVENTION

The invention provides methods for inhibiting colon cancer in mammals by administering to the mammal in need thereof of an effective amount of a compound of formula I.



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$, $-C-(C_1-C_6\ alkyl)$, or $-C-Ar$, wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

DETAILED DESCRIPTION OF THE INVENTION

The current invention concerns the discovery that a select group of 2-phenyl-3-aroylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting colon cancer.

The methods of use provided by this invention are practiced by administering to a human in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit colon cancer. The term "inhibit" includes its

generally accepted meaning which includes prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or a resultant symptom or effect.

Raloxifene, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R^1 and R^3 are hydrogen and R^2 is 1-piperidinyl, is a nuclear regulatory molecule. Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other cell types, raloxifene activates the same genes as estrogen does and displays the same pharmacology, *e.g.*, osteoporosis, hyperlipidemia. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although raloxifene and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Optionally substituted phenyl includes phenyl and phenyl substituted once or twice with C_1-C_6 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, ß-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate,

nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents,

and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit colon cancer, or any other use disclosed herein, and according to this invention will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need thereof from once to about three times each day, or more often as needed to effectively inhibit colon cancer.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route. For such purposes the following oral dosage forms are available.

Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of raloxifene that have been made include those shown below:

Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

Formulation 8: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Desmoid tumors are rare non metastatic tumors of fibrous origin. Clinical correlates suggest that steroid hormones may have a role in the natural history of these tumors: it is predominantly seen in female patients of child-bearing age and regression of these tumors have been associated with menopause or with antiestrogen therapy.

The aim of this work was to identify estrogen receptors in desmoid tumor primary cells, and to evaluate the effect of a compound of formula I on desmoid cells in primary culture.

Because sometimes desmoid tumors develop in patients with Familial Adenomatous Polyposis (FAP), that can degenerate in colon or rectal cancer, we have tested the inhibitory effect of Compound Ia on cellular growth of an adenocarcinoma cell line, (HCT8), and fibroblasts from colon cancer bioptic specimens.

Compound Ia is a compound of formula I wherein R^2 is pyrrolidino, and R^1 and R^3 are hydrogen.

Binding studies are performed using intact cells. Desmoid cells are plated on 6-well plates in growth medium (Coon's modified Ham's F12 supplemented with 10% FCS). After 24 hours, the growth medium is substituted with steady state medium without phenol red, and cells are maintained in starvation for 24 hours. Then cells are incubated for one hour with 1 ml of medium without phenol red containing 25 mM HEPES and 0.5% EtOH (binding buffer) and increasing concentrations (0.05- 10 nM) of [^{3}H]17ßE$_2$ with or without a 500-fold excess of unlabeled 17ßE$_2$ and Compound Ia. After incubation, cells are washed two times with 800 µl of binding buffer and lysed with 1N NaOH at 70°C for 30 minutes. Four N HCl is then added to each well for neutralization. Radioactivity is measured by liquid scintillation spectroscopy. ER binding affinity and binding capacity are evaluated by Scatchard analysis.

All subsequent steps are performed at 0-4°C. The pulverized tissue is homogenized with two 10-sec burst in a polytron homogenizer separated by a 30-sec cooling period in the following buffer: 10 mM Tris-HCl, 5 mM EDTA, 10 mM sodium molybdate, 10 mM dithiothreitol, 10% glycerol (v/v), pH 7.4. The homogenate is centrifuged at 7000 g for 20 min and the pellet is discarded, the supernatant was recentrifuged at 105000 g for 60 min to obtain cytosol for estrogen receptor analysis. Cytosol is diluted to 1-2 mg protein/ml. Cytosol protein is determined according to the method of Bradford. For estrogen receptor assessment, cytosol is incubated for 16 hr at 4°C over a concentration range of 0.05-5 nM of [^{3}H]17ßE$_2$ with or without a 500-fold excess of unlabeled 17ßE$_2$ and Compound Ia. ER binding affinity and binding capacity are evaluated by Scatchard analysis.

Cells are plated on 6 well plates at a density of 8x10^4 cell for well in growth medium. After 24 hours, the cells are stimulated in growth medium without phenol

red supplemented with 0.1% DMF, 0.1% EtOH, and different concentrations of Compound Ia ($2x10^{-5}M$, $10^{-5}M$, $5x10^{-6}M$, $10^{-6}M$).

Cells are incubated six days, detached with trypsin/ethylenediamine tetracetic acid solution and then the growth is evaluated by counting to the microscope. The same method is used for colon cancer primary fibroblasts cell line and for HCT8 cell line: this line is cultured in RPMI and incubated 4 days after stimulation.

Collagen type I in culture media and cell layers are measured using an enzyme-linked immunoassay (ELISA). Briefly, cells are incubated for 24 hrs in supplement-free Coon's modified Ham F12 medium containing 50µg/ml ascorbic acid and 100µg/ml ßaminopropionitryl fumarate.

Culture media are harvested and appropriately diluted in 0.1 M carbonate/bicarbonate buffer (pH 9.6) and then used for coating the ELISA plates, overnight at 4°C ELISA plates are incubated 1.5 hrs at 37°C in PBS containing 5% of milk powder (PBS Blotto) to saturate non specific binding sites, 2 hrs at 37°C with PBS Blotto containing the specific polyclonal antibody, and 1.5 hrs at 37°C in PBS Blotto containing goat antirabbit IgG-alkaline phosphatase conjugated complex (Sigma Chemical Co., St. Louis, MO).

Samples are then exposed to 10% diethanolamine (pH 9.8) with 50µg/ml Mg++ and 1 mg/ml paranitrophenyl-phosphate as a substrate of alkaline phosphatase at room temperature. Optical density is read at 405 nM, and concentrations calculated on the basis of the standard curve. Cell monolayers are harvested in 0.5 N NaOH and sonicated to determine cellular Collagen type I. Cell extracts are then diluted in 0.1 M carbonate/bicarbonate buffer (pH 9.6) and used for the coating of the ELISA plates. Standards and samples are assayed in triplicate. Results are expressed as µg protein/µg cellular DNA. DNA content is spectrofluorimetrically measured.

Binding experiments are performed using [^{3}H]17ßE$_2$ as ligand in primary desmoid tumors cells and in frozen specimens of desmoid tumor.

In both experiments, [^{3}H]17ßE$_2$ binding was slightly (approximately 10%) displaced by 500-fold excess of both unlabeled estrogen and Compound Ia. Scatchard analysis of [^{3}H]17ßE$_2$ binding data using the computer binding program LIGAND (Munson P.J., Rodbard D. Anal. Biochem. 1980; 107:220-39.) shows the presence of ER in three different cultures and in two different cytosol preparation from bioptic specimens of desmoid tumors.

In the growth assay, desmoid tumors primary cells are stimulated when exposed to various concentrations of Compound Ia. The result is a cellular growth inhibition with increasing Compound Ia concentrations (Table 1). Similar results are obtained with the HCT8 cell line (Table 2) and with a colon cancer fibroblastic cell line (Table 3).

Desmoid cells are inhibited in a dose-dependent fashion by Compound Ia at concentrations of 10^{-5}M, $5x10^{-6}$M, 10^{-6}M, with maximal inhibitory effect at 10^{-5}M concentration (Table 4).

Compound Ia is able to displace 17ßE$_2$ binding to desmoid tissue only at very high concentrations (500-fold excess).

Compound Ia is able to significantly inhibit desmoid cell proliferation at micromolar concentrations. In addition, at similar concentrations the compound inhibits the proliferation of epithelial and fibroblastic cells derived from human colon cancer.

Type I collagen production is also significantly reduced in desmoid cell in primary culture by the Compound Ia.

At all the conditions (electroporation, Ca/P precipitation, lyposomes) tested for transfection of desmoid cells with the estrogen responsive elements, the

cells are damaged, resulting not suitable for "in vitro" analysis.

Table 1

Compound Ia (Mol/L)	Cell x 10^{-4}
Control	12.3
2.10^{-5}	0.1
10^{-5}	2.8
5.10^{-6}	7.0
10^{-6}	10.0

Table 2

Compound Ia (Mol/L)	Cell x 10^{-4}
Control	150
2.10^{-5}	3
10^{-5}	71
5.10^{-6}	115

Table 3

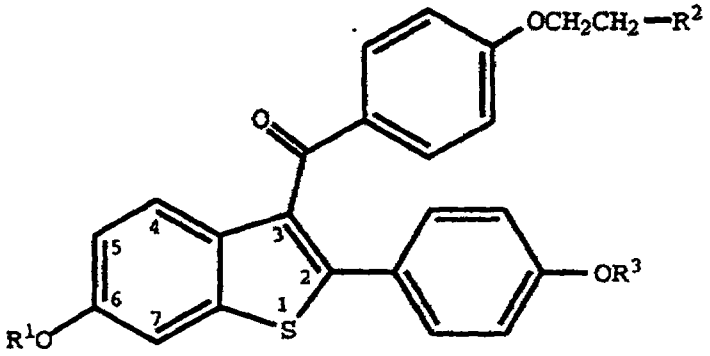
Compound Ia (Mol/L)	Cell x 10^{-4}
Control	7.6
2.10^{-5}	0.1
10^{-5}	5.4
5.10^{-6}	6.3
10^{-6}	7.6

Table 4

	DNA (O.D.)	DNA (µg)	Collagen Type I (pg/well)	Collagen Type I (µg/µg DNA)	Pvalues
Control	4.85±0.32	1.36±0.06	47.82±4.15	35.00±1.41	
Compound Ia 1 µM	8.20±0.23	1.97±0.05	43.78±5.23	22.00±1.46	P<0.005
Compound Ia 5 µM	6.90±0.50	1.85±0.24	38.01±6.24	20.50±0.61	P<0.005
Compound Ia 10 µM	7.90±1.46	1.96±0.29	35.16±2.44	18.00±1.41	P<0.005

We claim:

1. A method of inhibiting colon cancer comprising administering to a mammal in need thereof an effective amount of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$, $-C-(C_1-C_6\ alkyl)$, or $-C-Ar$, wherein Ar is optionally substituted phenyl;

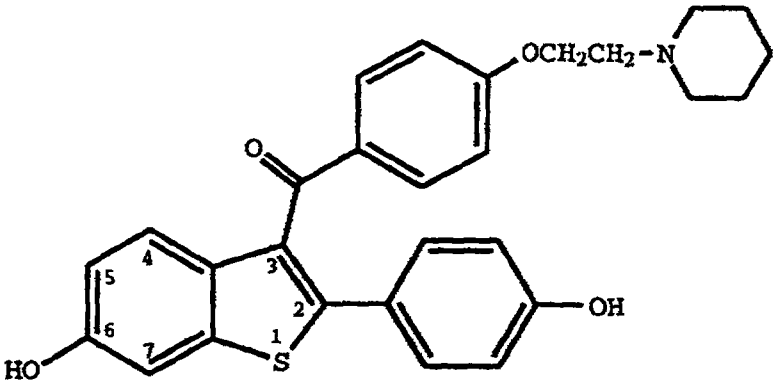
R^2 is selected from the group consisting of pyrrolidine, hexamethyleneimino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

2. The method of Claim 1 wherein said mammal is a human.

3. The method of Claim 2 wherein said compound is the hydrochloride salt thereof.

4. The method of Claim 3 wherein said compound is

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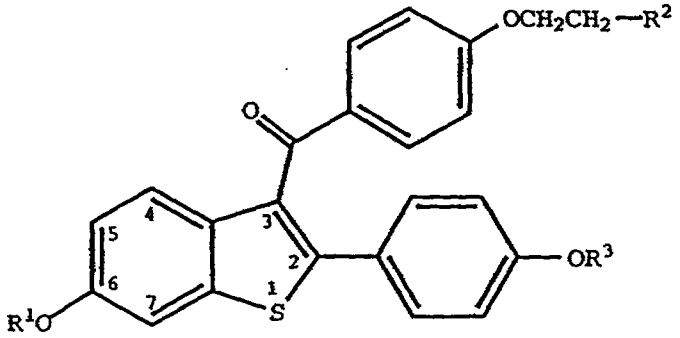
or its hydrochloride salt.

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We claim:

1. A use of an effective amount of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$, $-C-(C_1-C_6\ alkyl)$, or $-C-Ar$, wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidine, hexamethyleneimino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof in a preparation of a medicament for inhibiting colon cancer in a subject in need thereof.

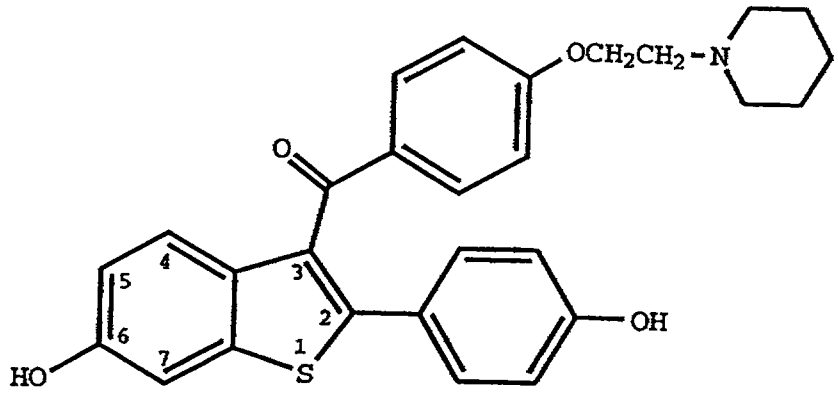
2. The use of Claim 1 wherein said subject is a human.

3. The use of Claim 2 wherein said compound is the hydrochloride salt thereof.

4. The use of Claim 3 wherein said compound is

* C L M S *

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or its hydrochloride salt.

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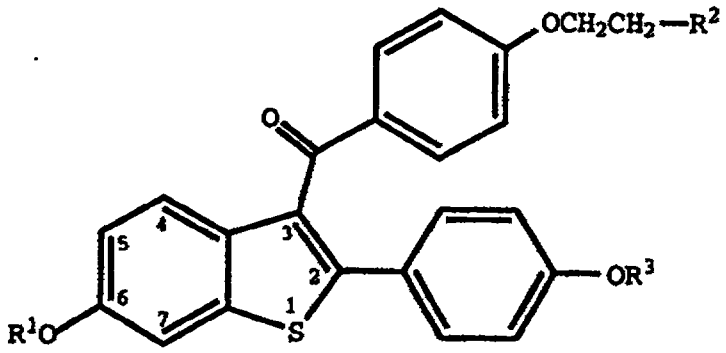
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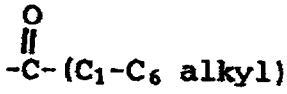
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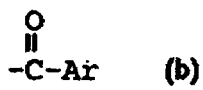
(54) Title: METHODS OF INHIBITING COLON TUMORS



(I)



(a)



(b)

(57) Abstract

A method of inhibiting colon cancer comprising administering to a mammal in need thereof an effective amount of a compound having formula (I), wherein R^1 and R^3 are independently hydrogen, $-CH_3$, (a), or (b), wherein Ar is optionally substituted phenyl; R^2 is selected from the group consisting of pyrrolidine, hexamethyleneimino, and piperidino; or a pharmaceutically acceptable salt or solvate thereof.