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(54) Title: TREATMENT OF CANCER WITH SPECIFIC RXR AGONISTS

(57) Abstract: A method of treating cancer is disclosed comprising administering to a patient in need of such treatment a RXR agonist at a level below the RAR activating threshold and at or above the RXR effective dose.

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TREATMENT OF CANCER WITH SPECIFIC RXR AGONISTS

PRIORITY

[0001] This application claims priority to U.S. Provisional Patent Application No 60/722,264, filed on September 30, 2005, the contents of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to methods of treating cancer.

2. Description of the Related Art

[0003] Compounds which have retinoid-like biological activity are well known in the art and described in numerous United States patents including, but not limited to, U.S. Patent Nos. 5,466,861; 5,675,033 and 5,917,082, all of which are herein incorporated by reference. Preclinical studies with rexinoids suggest that selective activation of retinoid X receptors (RXR), which modulate functions associated with differentiation, inhibition of cell growth, apoptosis and metastasis, may be useful in treating a variety of diseases associated with the biochemical functions modulated by RXR.

[0004] For example, Targretin® (bexarotene), which is a RXR agonist with RAR agonist activity as well, was approved by the U.S. Food and Drug Administration for the treatment, both oral and topical, of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy. Further, recent clinical studies that were conducted using Targretin® (bexarotene) suggest that there is potential for RXR agonists in the treatment of non-small cell lung cancer (NSCLC). Encouraging results were obtained with Targretin® in several Phase II studies in NSCLC. However, the pivotal Phase III clinical study did not show increased survival.

[0005] The following six abstracts relate to Targretin® clinical trials in NSCLC and were disclosed as part of the 2005 American Society of Clinical Oncology (ASCO) Annual Meeting.

[0006] ASCO 2005 Annual Meeting Abstract No. 7116

[0007] Phase II trial of bexarotene capsules in patients with non-small-cell lung cancer (NSCLC) who have failed at least 2 prior systemic therapies for Stage IIIB/IV disease

Author(s): R. Govindan, J. Crowley, L. Schwartzberg, P. Kennedy, B. C. Ekstrand, A. Sandler, D. Jaunakais, R. Ghalie

[0008] The Abstract discloses Phase II studies of bexarotene (Targretin®) plus chemotherapy as a first line therapy for advanced NSCLC and showed a potential improvement in survival. The objectives of this multicenter, single-arm study are to evaluate the effect of bexarotene on survival, quality of life (QOL), and tolerability in patients who have failed more than 2 prior systemic treatments for advanced NSCLC. Methods: To be eligible patients must have NSCLC Stage IV or IIIB (pleural effusion), failed more than 2 prior therapies including a taxane and a platinum compound, ECOG performance status (PS) 0-2, and adequate organ function. Treatment consists of oral bexarotene 400 mg/m² daily plus supplementation with levothyroxine and a lipid-lowering agent. Tumor evaluations are performed every 8 weeks while on treatment. Bexarotene is continued in the absence of disease progression or unacceptable toxicity. Results: To date, 112 of 150 planned patients were enrolled in 31 sites. Patient characteristics: median age = 66 (range, 43-87), 52% are male, 22% have PS 2, 52% have adenocarcinoma, median prior systemic therapies = 3 (range 2-6) and 49% received gefitinib before enrollment. The median duration of bexarotene treatment = 29 days (range 1-211+). For all patients, median survival is 5 months and the estimated 1-year survival is 13%. For patients with PS 0-1, median survival is 6 months and the estimated 1-year survival is 30%. No objective responses are reported. Twelve 12 patients (11%) have stable disease with a median duration of 5.3 months (range 1.3-5.6+). The FACT-G QOL shows that 67% of patients show improvement or no decline in QOL. Eleven patients (10%) discontinued bexarotene due to an adverse event, including hypertriglyceridemia, fatigue, rash, dyspnea, heartburn, limb edema, cognitive disturbance, allergic reaction, and dysphagia. One death due to increased pulmonary infiltrate was considered possibly related to bexarotene. Conclusions: This interim analysis indicates that bexarotene is well tolerated and has encouraging activity in relapsed advanced NSCLC even in heavily pretreated patients. Enrollment continues and results on all 150 patients will be presented.

[0009] (2) ASCO 2005 Annual Meeting Abstract No. 7308.

[0010] Phase II Trial of Gemcitabine (G), Carboplatin (C) and Bexarotene (B) in Patients (patients) with Newly Diagnosed, Locally-Advanced or Metastatic Non-Small Cell Carcinoma of the Lung (NSCLC)

Author(s): F. F. Estephan, N. Hasham-Jiwa, F. Klementich, R. Logrono, M. Eltorky, M. Bhutani, E. Walser, J. Zwischenberger, I. Kessel, D. V. Jones

[0011] The Abstract discloses that the current standard of care for unresectable NSCLC is platinum-based chemotherapy. The Abstract further discloses that there is no benefit to adding together 3 or more cytotoxic agents, but adding a biologic agent may improve response rates and survival. B, a retinoic acid X-receptor agonist, is a differentiating agent with antineoplastic activity. Recent data suggests that the addition of B to platinum-based therapy may increase response rates and survival in NSCLC. Due to the poor outcome in this disease, we are studying a combination of G, C, and B as front-line therapy. Methods: Eligibility criteria includes histologically diagnosed NSCLC stage IIIB/IV; Karnofsky PS 70-100%; age > 18, adequate bone marrow, renal and hepatic function, and written informed consent. Patients receive G, 1 g/m² days 1 and 8 with C, AUC 5 (Calvert formula) on day 8. B, 400 mg/m² PO QD in divided doses is given days 1-28 of each treatment cycle. Patients may receive up to 6 cycles of chemotherapy or 2 cycles after CR achieved. Tumor restaging is performed every 2 cycles of therapy, in the absence of obvious rapid disease progression. Results: 19 patients have been enrolled; 10 males, 9 females; median age is 63.5 years (range 30-85 years). 2 patients had protocol violations (prior chemotherapy (1); small cell cancer on further pathologic evaluation (1)). A median of 2 cycles has been delivered (range 1-6). To date, the overall PR rate is 23.5% (4/17); 2 have had SD (1 progressed by cycle 4), for an overall clinical benefit rate of 35%. One is too early to evaluate. 18 patients to date are evaluable for toxicity. Thus far, the mean TTP is 68 days, and the mean OS is 142 days. The therapy has been well-tolerated with 7 patients experiencing Grade 2-3 myelosuppression (no febrile neutropenia), and 3 patients experiencing Grade 3-4 nausea and emesis. There have been no significant B-related adverse events. Conclusions: The addition of the differentiating agent B to a regimen of G and C is tolerable and active. In contrast to other studies, our early results suggest that the addition of B at this dose and schedule may add little to the

clinical benefit observed with this regimen. Accrual continues in an effort to better define response rate and duration.

[0012] (3) ASCO 2005 Annual Meeting Abstract No. 7270

[0013] Bexarotene Improves TTP in Untreated, Advanced NSCLC, When Given in Combination with Carboplatin/Paclitaxel

Author(s): R. Bordoni, S. Khanwani, M. Saleh, M. Auerbach, F. Steinbaum, J. Cuevas, S. Harris, B. Howell

[0014] The Abstract discloses bexarotene, a specific synthetic retinoid analogue, binds to the α , β , and γ subclass of RXR, providing therapeutic specificity and reduced toxicities in patients with RXR-expressing tumors. Initial phase-I/II clinical trials in NSCLC showed that bexarotene added to chemotherapy prolonged stabilization of disease (TTP) and 1, 2, and 3 yr survival. Methods: Stage IIIB with pleural effusion & Stage IV chemo-naïve patients, ECOG PS 0-2, were enrolled on study and treated with carboplatin IV AUC-6 d1 and paclitaxel IV 100 mg/m² d1, 8, and 15, every 28-d for 4 cycles. Patients were randomized using a 1:1 design to bexarotene PO 400 mg/m²/d either concurrent (C) from Day 1 or sequential (S) at the completion of chemo, for up to a year. Results: From a planned total of 60 patients, 48 have been enrolled thus far; median age 62.3 (range 41-86), 43 Caucasian, 41 TNM Stage IV, 33 males, 34 ECOG PS 1. To date, 44 patients are evaluable for efficacy and toxicity based on ITT (intent to treat); 35 were evaluated for RR: 15 (42.8%) achieved PR (C: 7 and S: 8), 15 (42.8%) exhibited SD (C: 8 and S: 7), and 5 (14.3%) had PD (C: 2 and S: 3), during the first 112 days (C1-4 chemo). TTP analysis was done in 42 patients: 19 patients showed an overall TTP of 152 days (5.06 mo) (C=10: 148.3 days and S=9: 155.5 days); in 23 patients the TTP has not been reached after a median F/U of 79 days (range 10-203). The overall 1yr S was 58.8% with no significant difference between treatment arms (p=0.7). The treatment was well tolerated; overall, AEs were reported in 48% of patients in the S arm vs. 51% in the C arm. The incidence of Gr 3-4 AEs, regardless of the treatment arm, was < 5%. There were no treatment-associated deaths. Conclusions: so far, data suggests a comparable ORR and a potential improvement in TTP, when bexarotene is added to carboplatin/paclitaxel, compared with chemo alone. Toxicity is easily managed.

[0015] (4) ASCO 2005 Annual Meeting Abstract No. 7243

[0016] Weekly paclitaxel (Taxol®), carboplatin (Paraplatin®), and bexarotene (Targretin®) for the treatment of patients with advanced non-small cell lung cancer: Efficacy results from a Phase I/II study.

Author(s): W. J. Petty, K. H. Dragnev, W. C. Black, B. F. Cole, S. Hammond, I. Williams, E. Dmitrovsky, J. R. Rigas

[0017] The Abstract discloses the combination of weekly paclitaxel (Taxol) and every 4 week carboplatin (Paraplatin) as a first-line therapy for advanced non-small cell lung cancer (NSCLC) has been reported. The study noted a median survival time of 8.8 months and a 1-year survival of 39.5%. The current phase I/II study was designed to evaluate the tolerability and activity of the rexinoid, bexarotene (Targretin®) in combination with weekly paclitaxel and every 4 week carboplatin. Methods: Patients with confirmed stage IIIB or IV NSCLC and adequate organ function were enrolled. Prior chemotherapy was allowed for the phase I portion of this study. All patients were scheduled to receive paclitaxel 100 mg/m² weekly for 3 doses every 4 weeks and carboplatin AUC = 6 monthly. Bexarotene oral capsules were administered daily starting on initial day of chemotherapy. Two dose levels of bexarotene were evaluated (300 mg/m²/day and 400 mg/m²/day). The recommended phase II dose of bexarotene was 400 mg/m²/day. Results: As of December 2004, 33 patients were enrolled, 13 patients receiving 300 mg/m²/day and 20 patients at 400 mg/m²/day of bexarotene. Patient characteristics include: age (median 59), gender (female 43%), stage (93% stage IV), Karnofsky performance status (37% with KPS 60-70%), prior chemotherapy (30%), prior radiation (33%), and prior surgery (33%). Hematologic toxicity was mild with grade 3 anemia in 3 patients and grade 3 neutropenia in 4 patients. Non-hematologic toxicities consisted primarily of hyperlipidemia and hypothyroidism which were medically managed. No cases of pancreatitis were observed. With a median follow-up of 15.1 months, the median survival time for all patients is 6.9 months with 1-year survival of 43%. The median survival time for chemotherapy-naïve patients (n = 24) is 8.3 months with a 1-year survival of 47%. Conclusions: The 1-yr survival for chemotherapy-naïve patients treated with bexarotene in combination with weekly paclitaxel and every 4 week carboplatin is encouraging. Ongoing phase III trials will determine whether adding

bexarotene to conventional chemotherapy improves survival as a first line treatment for NSCLC.

[0018] (5) ASCO 2005 Annual Meeting Abstract No. 7024:

[0019] A randomized phase III trial comparing bexarotene/cisplatin/vinorelbine versus cisplatin/vinorelbine in chemotherapy-naïve patients with advanced or metastatic non-small cell lung cancer (NSCLC)

Author(s): J. Jassem, P. Zatloukal, R. Ramlau, P. Schwarzenberger, S. Orlov, J. Rodrigues-Pereira, G. Temperley, M. Mabry, A. Negro-Vilar, Z. Dziewanowska, SPIRIT I Lung Cancer Study Group

[0020] The Abstract discloses the rexinoid Targretin® (bexarotene) selectively activates RXR receptors which modulate functions associated with differentiation, inhibition of cell growth, apoptosis and metastasis. This trial was performed to determine the survival benefit of adding bexarotene to cisplatin/vinorelbine chemotherapy based upon phase I & II study data. Methods: Patients stratified by stage (IIIb&IV) and gender were randomized to bexarotene (400 mg/m²/d and cisplatin (100 mg/m² Q4 wks) and vinorelbine (25 mg/m² Qwk) iv or cisplatin/vinorelbine alone. Overall survival (primary endpoint) was analyzed by stratified log-rank test, with secondary endpoint by Kaplan-Meier projected two-year survival rates Results: 623 NSCLC patients (13 countries) in equally balanced groups had: median age 61 yrs, 72% male, ECOG 0/1 25%/75%, stage IIIb disease with pleural effusion 18% or Stage IV 82%, adenocarcinoma 40%, squamous 37%. 523 patients had expired at the 18 mo data cutoff. Overall survivals were not different (p=0.29), with medians of 260 days (CI 235-294) and 297 days (CI 263-333); and two-year survival 13.2% and 15.7%, (p=0.40) for the bexarotene and control arms respectively. Study drug related SAE's, ≥ 1% frequency, were generally rare and balanced between treatment groups but neutropenia (3.5% vs 1.0%) was more common in the bexarotene arm while febrile neutropenia (2.6% vs 6.1%) was more common in the control arm. AE's grade 3&4, ≥5% frequency, which were more common in the bexarotene arm included: hypertriglyceridemia (26% vs 0%), dyspnea (10% vs 4%) and hypercholesterolemia (6% vs 0%), with leukopenia (10% vs 16%) more common in the control arm. An initial trend analysis suggesting a relationship between bexarotene dose intensity and biomarker response (triglyceride elevation) with survival is being further

evaluated in parallel with other risk factor analyses to better identify determinants of benefit and risk to bexarotene in a first line setting. Conclusions: This trial demonstrates that bexarotene combined with cisplatin/vinorelbine chemotherapy did not improve overall survival in ITT patients with advanced

[0021] (6) ASCO 2005 Annual Meeting Abstract No. 7001:

[0022] A randomized phase III trial comparing bexarotene/carboplatin/paclitaxel versus carboplatin/paclitaxel in chemotherapy-naïve patients with advanced or metastatic non-small cell lung cancer (NSCLC)

Authors: G. R. Blumenschein, F. Khuri, U. Gatzemeier, W. H. Miller, J. von Pawel, J. R. Rigas, R. S. Herbst, Z. Dziewanowska, A. Negro-Vilar, M. Mabry, SPIRIT II Lung Cancer Study Group

[0023] Abstract: Background: The rexinoid Targretin® (bexarotene) selectively activates RXR receptors which modulate functions associated with differentiation, inhibition of cell growth, apoptosis, and metastasis. A phase III trial was performed to determine the survival benefit of adding bexarotene to carboplatin/paclitaxel chemotherapy based upon phase I & II study data. Methods: NSCLC patients stratified by stage (IIIb&IV) and gender were randomized to bexarotene (400 mg/m²/day) and carboplatin AUC 6 and paclitaxel 200 mg/m² IV every 3 weeks or carboplatin/paclitaxel alone. Overall survival (primary endpoint) difference was analyzed by stratified log-rank test. The secondary endpoint compared Kaplan-Meier projected two-year survival rates. Results: 612 NSCLC patients from six countries (171sites) in equally balanced groups had: median age 63 yrs, 66% male, ECOG 0 34%, ECOG 1 65%, Stage IIIb disease with pleural effusion 13% and Stage IV 87%, adenocarcinoma 52%, squamous 21%. 494 patients had expired at the 18 mo data cutoff. Overall survivals were not different (p=0.19) with medians of 254 days (CI 230-280) and 277 days (CI 249-316), and projected two-year survivals of 12.4% and 16.3% (p=0.24) for the bexarotene plus chemotherapy treatment arm and chemotherapy alone arm respectively. Study drug related SAE's, ≥1% frequency, were generally rare and balanced between treatment groups. AE's of moderately severe and severe grade, ≥5% frequency, which were more common in the bexarotene arm included: neutropenia (28% vs 13%), hypertriglyceridemia (25% vs 0%), asthenia (7% vs 2%), leukopenia (6% vs 1%) and dehydration (5% vs 1%). An initial

trend analysis suggesting a relationship between bexarotene dose intensity and biomarker response (triglyceride elevation) with survival is being further evaluated in parallel with other risk factor analyses to better identify determinants of benefit and risk to bexarotene in a first line setting. Conclusions: This trial demonstrates that bexarotene combined with carboplatin/paclitaxel chemotherapy did not improve overall survival in ITT patients with advanced NSCLC. Additional data analyses will be presented at the meeting.

[0024] A retrospective analysis of the pivotal Targretin[®] trials was also presented at the 2005 ASCO Annual Meeting. More specifically, in the SPIRIT II trial, a subgroup of patients (approximately 40%) had very high elevation of serum triglycerides (Grade 3-4) within 2-3 weeks of initiation of Targretin[®] therapy. These patients who were continued on a reduced Targretin[®] dose (from a mean of 400 mg/m²/d to a mean of 225 mg/m²/d) had a significantly better treatment outcome than the control group (median survival of 12.4 months versus 9.2 months). In striking contrast, the subgroup of patients who had a more modest elevation of serum triglycerides (and, consequently, were maintained at a median dose of 375 mg/m²/d) had a significantly worse treatment outcome (median survival of 6.6 months). These data led to the hypothesis that significant triglyceride elevation identifies (i.e., is a biomarker for) a subgroup of patients sensitive to RXR activation and these patients have a survival benefit from Targretin[®] treatment. Correspondingly, it was hypothesized that those patients with low triglyceride elevation were not responsive to RXR and therefore did not derive a survival benefit from Targretin[®] treatment.

[0025] While this hypothesis seems on its surface to have merit, it fails to explain why the non-responsive group (those with low triglyceride elevation) had decreased survival. Without an explanation of this data, a successful approach to treating cancer patients with Targretin[®], or other RXR agonists, will be hampered.

SUMMARY OF THE INVENTION

[0026] The present invention provides a method of treating cancer comprising administering to a patient in need of such treatment a RXR agonist at a level below the RXR activating threshold and at or above the RXR effective dose.

[0027] In another embodiment, the present invention provides a method of treating cancer comprising dosing a patient in need of such treatment with increasing concentrations of a RXR agonist to determine the RAR activating threshold and the RXR effective dose for the patient; and administering to the patient the RXR agonist at a level below the RAR activating threshold and at or above the RXR effective dose.

[0028] In yet another embodiment, the present invention provides a method for treating cancer comprising the step of administering to a patient in need of such treatment an effective amount of a RXR agonist having a therapeutically beneficial RXR EC₅₀:RAR EC₁₀ ratio range.

[0028A] In another embodiment, the present invention provides a method of treating cancer comprising the steps of (a) selecting a dose of a retinoid X receptor (RXR) agonist which results in a C_{max} below the Retinoic Acid Receptor (RAR) activating threshold and at or above the RXR effective dose; and (b) administering to a patient in need of such treatment the dose selected in step (a); wherein the cancer is effectively treated as a result of the administration.

[0028B] In a further embodiment, the present invention provides a use of a retinoid X receptor (RXR) agonist in the manufacture of a medicament for the treatment of cancer, wherein it is intended that the medicament is administered at a dosage which is selected to result in a C_{max} which is below the Retinoid Acid Receptor (RAR) activity threshold and at or above the RXR effective dose.

BRIEF DESCRIPTION OF THE DRAWING

[0029] FIGS. 1A-1D illustrate the effects of VTP 194204 on nude mice xenografted with human H292 NSCLC tumors. Nude mice were randomized into 4 groups of 10 animals each based on body weight and xenografted subcutaneously in the right flank with H292 cells (2x10⁶ cells). Drug treatment was started immediately after xenografting and continued for 35 days (5 animals of each group) or 55 days (remaining 5 animals). The animals were treated with vehicle (VEH), Taxol 5 mg/kg/week, once a week, i.p., VTP 194204 10 mg/kg/day, 5 days a week, by oral gavage, or VTP 194204 + Taxol. Tumor sizes were measured periodically for 35 days (Panel A). Animals #1-5 of each group were sacrificed after 35 days of treatment and gastrocnemius muscles were determined (Panel C). The body weights and overall appearance of animals #6 through #10 from each group were followed for an extended period (Panels B and D). To appropriately show the overall health of these animals, pictures were taken from their tumor-free left flank on day 55 (Panel D).

DETAILED DESCRIPTION

[0030] Definitions:

[0031] CYP26 means Cytochrome P450 Type 26.

[0032] CRBPI means Cellular Retinol Binding Protein.

Anti-cancer agents include cytotoxic drugs, including, but not limited to, Taxol[®] (paclitaxel), Taxotere[®] (docetaxel), and the like and mixtures thereof. Additional anti-

cancer agents include Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropiramine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedopa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin;

sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazaforin; tirapazamine; toremifene citrate; trestolone acetate; tricyribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinylicinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[0033] Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydridemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox;

diethylnorspermine; dihydro-5-azacytidine; 9- dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocil; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone;

oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrigan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor

antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Preferred additional anti-cancer drugs are 5-fluorouracil and leucovorin.

[0034] Platinum based drugs include, but are not limited to, carboplatin, cisplatin, and the like and mixtures thereof.

[0035] RAR means one or more of RAR α , β and γ .

[0036] RXR means one or more of RXR α , β and γ .

[0037] A RAR biomarker is a distinctive biological, biochemical or biologically derived indicator that signifies patient RAR activity. RAR biomarkers include, but are not limited to, CYP26 levels, CRBPI levels and the like and combinations thereof.

[0038] RAR activation threshold means one or more of the following: a CYP26 level of a 2-fold increase over baseline, and a CRBPI level of a 2-fold increase over baseline.

[0039] RXR EC₉₀:RAR EC₁₀ ratio is calculated by taking the inverse of the RXR EC₉₀ α , β and γ values (nM) divided by the corresponding inverse of the RAR EC₁₀ α , β and γ values (nM). For example, the RXR EC₉₀:RAR EC₁₀ ratio is determined by dividing RAR EC₁₀ by RXR EC₉₀ for α , β and γ . Thus, a value is obtained for all three receptors, referred to herein as (RXR EC₉₀:RAR EC₁₀ ratio) _{α} , (RXR EC₉₀:RAR EC₁₀ ratio) _{β} and (RXR EC₉₀:RAR EC₁₀ ratio) _{γ} , for α , β and γ , respectively. For example, (RXR EC₉₀:RAR EC₁₀ ratio) _{α} is determined by dividing RAR EC₁₀ α by RXR α EC₉₀. The mean RXR EC₉₀:RAR EC₁₀ ratio is the average of all three values. An example is provided below in Tables 1A and 1B.

TABLE 1 (A)

Compound	RXR EC ₉₀ (nM)			RAR EC ₁₀ (nM)		
	α	β	γ	α	β	γ
VTP 194204	0.1	1	0.1	300	200	200
Targretin®	15	100	15	1000	200	300

TABLE 1 (B)

Compound	RXR EC ₉₀ :RAR EC ₁₀ ratio			Mean
	α	β	γ	
VTP 194204	3000	200	2000	1730
Targretin®	67	2	20	30

Table 1 Comparison of safety margins of VTP 194204 and Targretin®

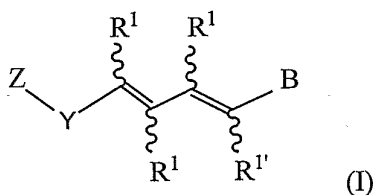
(A) RXR EC₉₀ and RAR EC₁₀ values of VTP 194204 and Targretin®.

(B) Ratio of RXR EC₉₀ to RAR EC₁₀ for VTP 194204 and Targretin®.

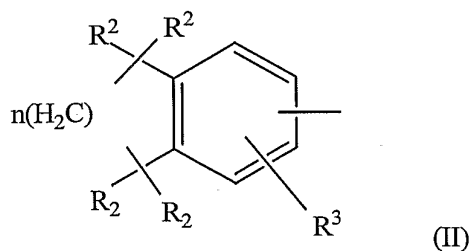
[0040] RXR effective dose means the dose needed to fully activate RXRs as ascertained by pharmacodynamic markers (RXR biomarkers) such as reductions in TSH levels.

[0041] Representative examples of RXR agonists for use herein and processes for their preparation are well known in the art, e.g., in U.S. Patent Nos. 5,663,367; 5,675,033; 5,780,647; 5,817,836; 5,917,082; 6,034,242; 6,048,873; 6,114,533; 6,147,224; 6,313,163; 6,403,638 and 6,720,423, the contents of each of which are incorporated by reference herein in their entirety. Many of the following compounds are included in one or more of these applications.

[0042] A class of compounds for use herein is represented by Formula I:

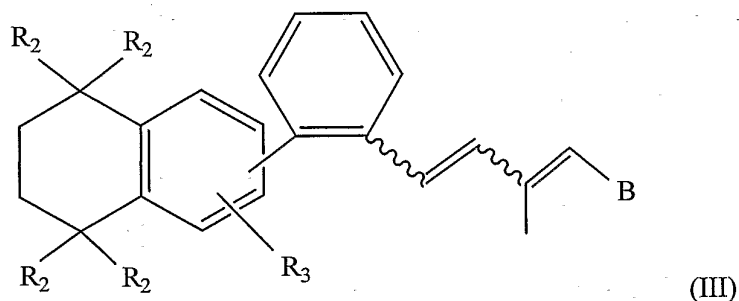


wherein Z is a radical shown in Formula II,



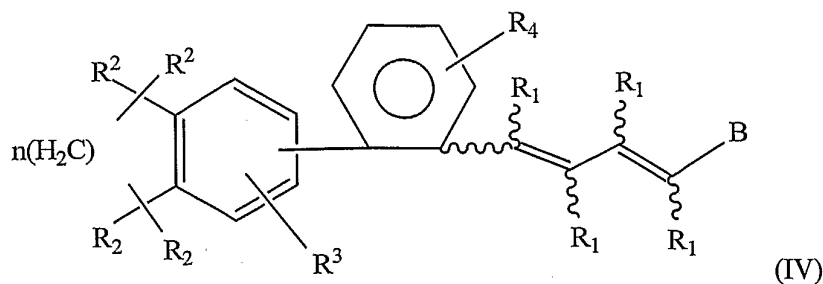
Y is selected from thienyl and furyl, the groups being optionally with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-(CR_1=CR_1-CR_1=CR_1)-$ groups on adjacent carbons; n is 1 or 2; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl, fluoroalkyl or halogen, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $OCOR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group, containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} carbons, or a cycloalkyl groups of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

[0043] Another class of compounds for use herein is represented by Formula III:



wherein R_2 is hydrogen or lower alkyl; R_3 is hydrogen or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

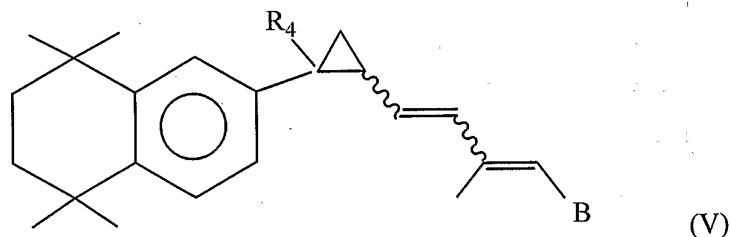
[0044] Another class of compounds for use herein is represented by Formula IV:



wherein n is 1 or 2; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is H, lower alkyl, fluoroalkyl or halogen, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂O COR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or triloar alkylsilyl where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

[0045]

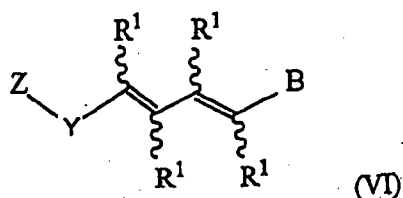
Another class of compounds for use herein is represented by Formula V:



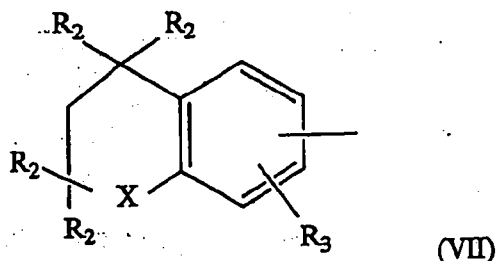
where R_4 is lower alkyl of 1 to 6 carbons; B is COOH or COOR₈ where R_8 is lower alkyl of 1 to 6 carbons, and the configuration about the cyclopropane ring is cis, and the configuration about the double bonds in the pentadienoic acid or ester chain attached to the cyclopropane ring is trans in each of the double bonds, or a pharmaceutically acceptable salt of the compound.

[0046]

Another class of compounds for use herein is represented by Formula VI:

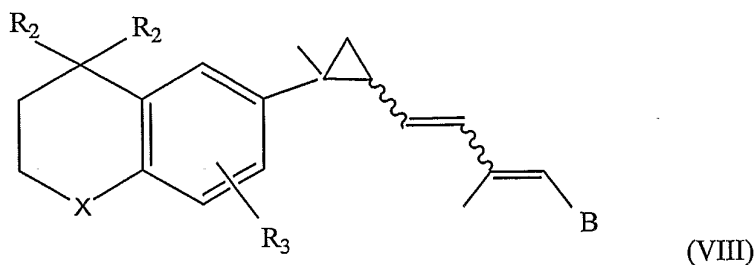


wherein Z is a radical shown in Formula VII:



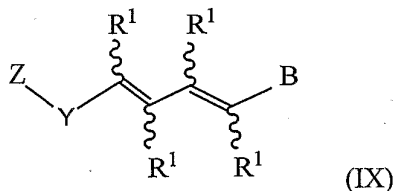
Y is cycloalkyl or cycloalkenyl of 3 to 8 carbons optionally substituted with one or two R_4 groups, or Y is selected from phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-(CR_1=CR_1-CR_1=CR_1)-$ groups on adjacent carbons; X is S or O; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl fluoroalkyl or halogen, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

[0047] Another class of compounds for use herein is represented by Formula VIII:

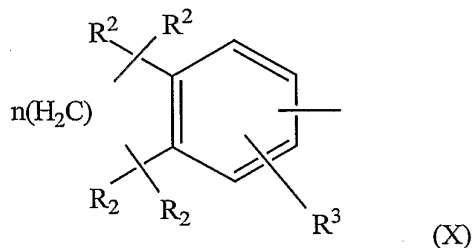


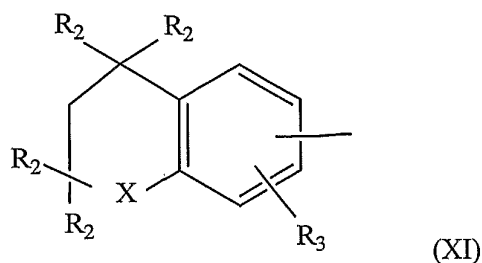
wherein X is S or O; R₂ is hydrogen or lower alkyl; R₃ is hydrogen or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or trilower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons.

[0048] Another class of compounds for use herein is represented by Formula IX:



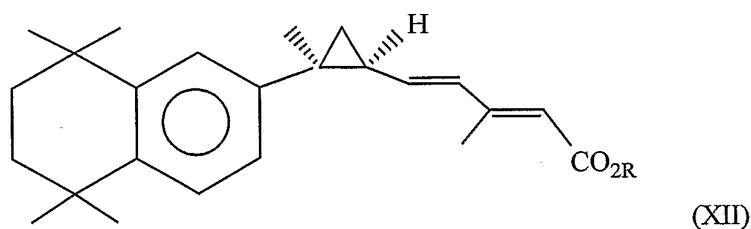
wherein Z is selected from the group consisting of the radicals a radical shown in Formulae X and XI:





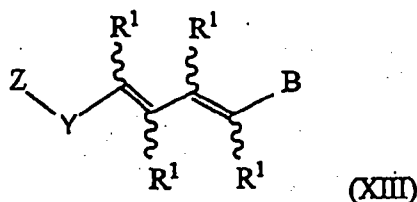
Y is selected from pyridyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, the groups being optionally substituted with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-\text{CR}_1=\text{CR}_1-\text{CR}_1=\text{CR}_1-$ groups on adjacent carbons; X is NR_5 ; n is 1 or 2; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl, fluoroalkyl or halogen; R_5 is H or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR_8 , $\text{CONR}_9\text{R}_{10}$, $-\text{CH}_2\text{OH}$, $\text{CH}_2\text{OR}_{11}$, $\text{CH}_2\text{OCOR}_{11}$, CHO, $\text{CH}(\text{OR}_{12})_2$, CHOR_{13}O , $-\text{COR}_7$, $\text{CR}_7(\text{OR}_{12})_2$, $\text{CR}_7\text{OR}_{13}\text{O}$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 to 5 carbons.

[0049] Another compound for use herein is enantiomerically substantially pure compound of Formula XII:

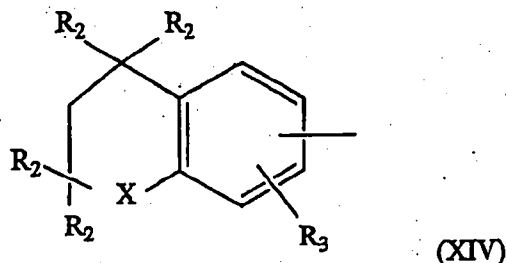


wherein R is H, lower alkyl or 1 to 6 carbons, or a pharmaceutically acceptable salt of the compound.

[0050] Another class of compounds for use herein is represented by Formula XIII:

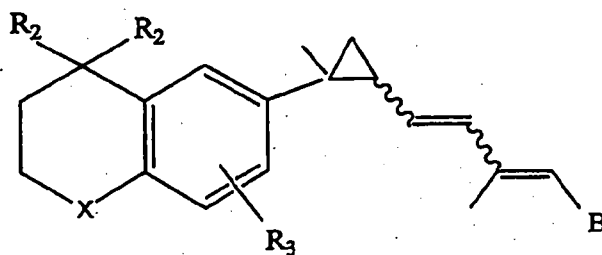


wherein Z is the group shown in Formula XIV:



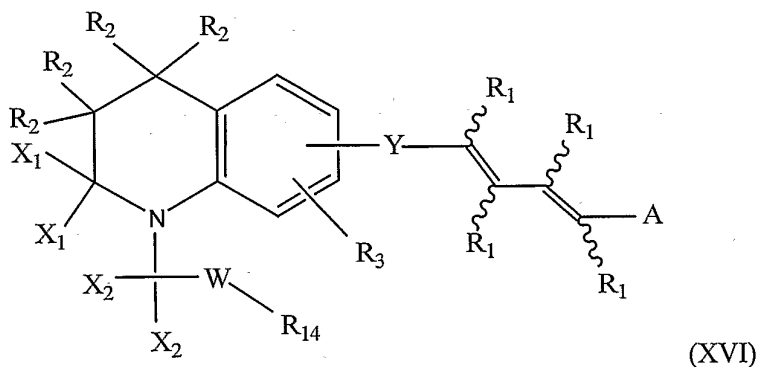
Y is cyclopropyl, the Y group being optionally substituted with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-(CR_1=CR_1-CR_1=CR_1)-$ groups on adjacent carbons; X is NR_5 ; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl, fluoroalkyl or hydrogen; R_5 is H or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 to 5 carbons.

[0051] Another class of compounds for use herein is represented by Formula XV:

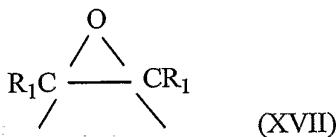


wherein X is NR_5 ; R_5 is H or lower alkyl; R_2 is H or lower alkyl; R_3 is H or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR_8 , $\text{CONR}_9\text{R}_{10}$, $-\text{CH}_2\text{OH}$, $\text{CH}_2\text{OR}_{11}$, $\text{CH}_2\text{OCOR}_{11}$, CHO , $\text{CH}(\text{OR}_{12})_2$, CHOR_{13}O , $-\text{COR}_7$, $\text{CR}_7(\text{OR}_{12})_2$, $\text{CR}_7\text{OR}_{13}\text{O}$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2 to 5 carbons.

[0052] Another class of compounds for use herein is represented by Formula XVI:



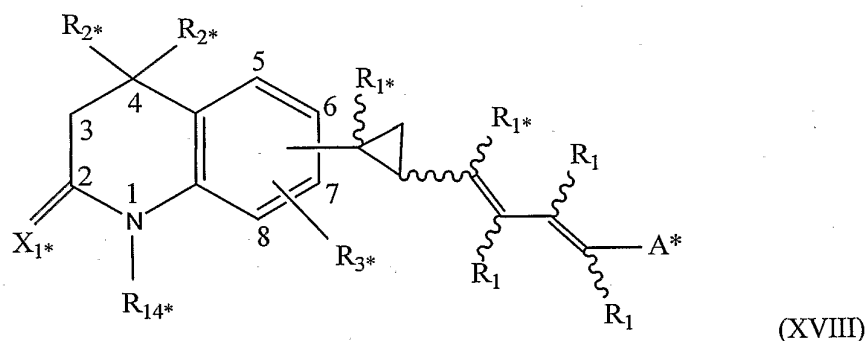
where Y is a bivalent radical having Formula XVII



the two X_1 groups jointly represent an oxo ($=\text{O}$) or thione ($=\text{S}$) function, or X_1 is independently selected from H or alkyl of 1 to 6 carbons; the two X_2 groups jointly represent an oxo ($=\text{O}$) or a thione ($=\text{S}$) function, or X_2 independently selected from H or alkyl of 1 to 6 carbons, with the proviso that one of the joint X_1 grouping or of the joint X_2 grouping represents an oxo ($=\text{O}$) or thione ($=\text{S}$) function; W is O, $\text{C}(\text{R}_1)_2$, or W does not exist; R_1 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R_2 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R_3 is hydrogen, lower alkyl of 1 to 6 carbons, OR_1 , fluoro substituted lower

alkyl of 1 to 6 carbons or halogen, NO₂, NH₂, NHCO(C₁-C₆ alkyl, or NHCO(C₁-C₆) alkenyl; A is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CH(OR₁₃O), -COR₇, CR₇(OR₁₂)₂, CR₇(OR₁₃O), or Si(C₁₋₆alkyl)₃, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2 to 5 carbons, and R₁₄ is H, alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds.

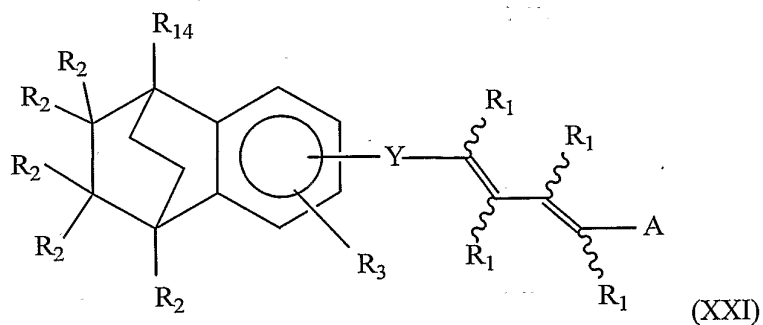
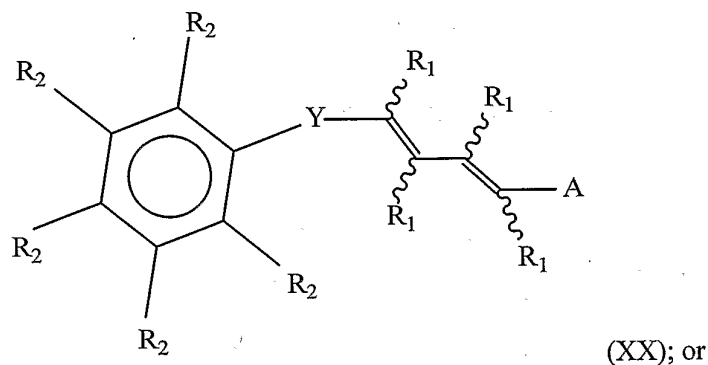
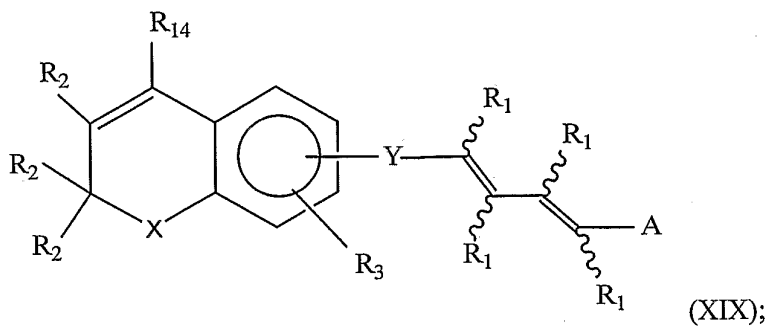
[0053] Another class of compounds for use herein is represented by Formula XVIII:



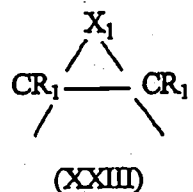
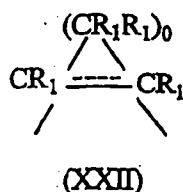
wherein R₁ is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R₁^{*} is hydrogen or C₁₋₆-alkyl; R₂^{*} is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R₃^{*} is hydrogen, lower alkyl of 1 to 6 carbons, fluoro substituted lower alkyl of 1 to 6 carbons or halogen; X₁^{*} is an oxo (=O) or a thione (=S) group; A^{*} is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, where R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, and the cyclopropyl group is attached to the 6 or 7 position of the

tetrahydroquinoline moiety, and R_{14}^* is alkyl of 1 to 10 carbons or fluoro-substituted alkyl of 1 to 10 carbons.

[0054] Another class of compounds for use herein is represented by Formulae XIX, XX or XXI:



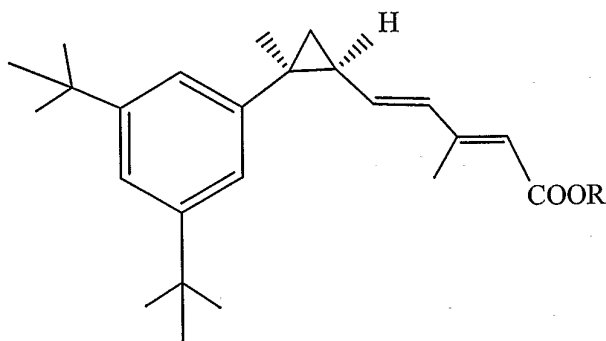
where X is O, S, or $(CR_1R_1)_n$ where n is 0, 1 or 2; Y is a bivalent radical having Formulae XXII or XXIII where o is an integer between 1 through 4



or Y is a bivalent aryl or 5 or 6 membered heteroaryl radical having 1 to 3 heteroatoms selected from N, S and O, the aryl or heteroaryl groups being unsubstituted, or substituted with 1 to 3 C₁₋₆ alkyl or with 1 to 3 C₁₋₆ fluoroalkyl groups with the proviso that when the compound is in accordance with Formula 2 then Y is not a 5 or 6 membered ring; X₁ is S or NH; R₁ is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons, R₂ is independently H, lower alkyl of 1 to 6 carbons, OR₁, adamantyl, or lower fluoroalkyl of 1 to 6 carbons, or the two R₂ groups jointly represent an oxo (=O) group with the proviso that when the compound is in accordance with Formula 2 then at least one of the R₂ substituents is branched-chain alkyl or adamantyl; R₃ is hydrogen, lower alkyl of 1 to 6 carbons, OR₁, fluoro substituted lower alkyl of 1 to 6 carbons or halogen, NO₂, NH₂, NHCO(C₁-C₆) alkyl, or NHCO(C₁-C₆) alkenyl; A is COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CH(OR₁₃O), -COR₇, CR₇(OR₁₂)₂, CR₇(OR₁₃O), or Si(C₁-alkyl)₃, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl) alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, and R₁₄ is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic aryl selected from the group consisting of phenyl, C₁-C₁₀-alkylphenyl, naphthyl, C₁-C₁₀-alkylnaphthyl, phenyl-C₁-C₁₀alkyl, naphthyl-C₁-C₁₀alkyl, C₁-C₁₀-alkenylphenyl having 1 to 3 double bonds, C₁-C₁₀-alkynylphenyl having 1 to 3 triple bonds, phenyl-C₁-C₁₀alkenyl having 1 to 3 double bonds, phenyl-C₁-C₁₀alkenyl having 1 to 3 triple bonds, hydroxyl alkyl of 1 to 10 carbons, hydroxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, hydroxyalkynyl having 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons,

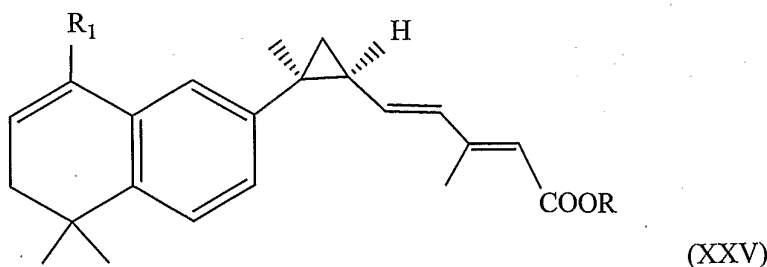
acyloxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons, acyloxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds where the acyl group is represented by COR_8 , or R_{14} is a 5 or 6 membered heteroaryl group having 1 to 3 heteroatoms, the heteroatoms being selected from a group consisting of O, S, and N, the heteroaryl group being unsubstituted or substituted with a C_1 to C_{10} alkyl group, with a C_1 to C_{10} fluoroalkyl group, or with halogen, and the dashed line in Formula XXII represents a bond or absence of a bond.

[0055] Another class of compounds for use herein is represented by Formulae XXIV:



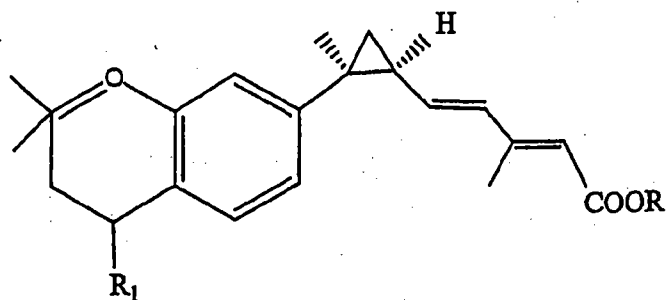
wherein R is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of the compound.

[0056] Another class of compounds for use herein is represented by Formulae XXV:



wherein R is H, lower alkyl of 1 to 6 carbons, and R_1 is iso-propyl or tertiary-butyl, or a pharmaceutically acceptable salt of the compound.

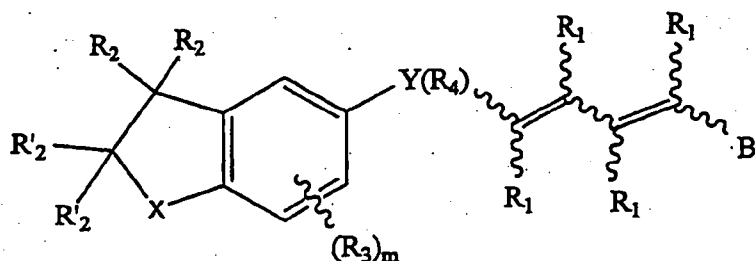
[0057] Another class of compounds for use herein is represented by Formulae XXVI:



(XXVI)

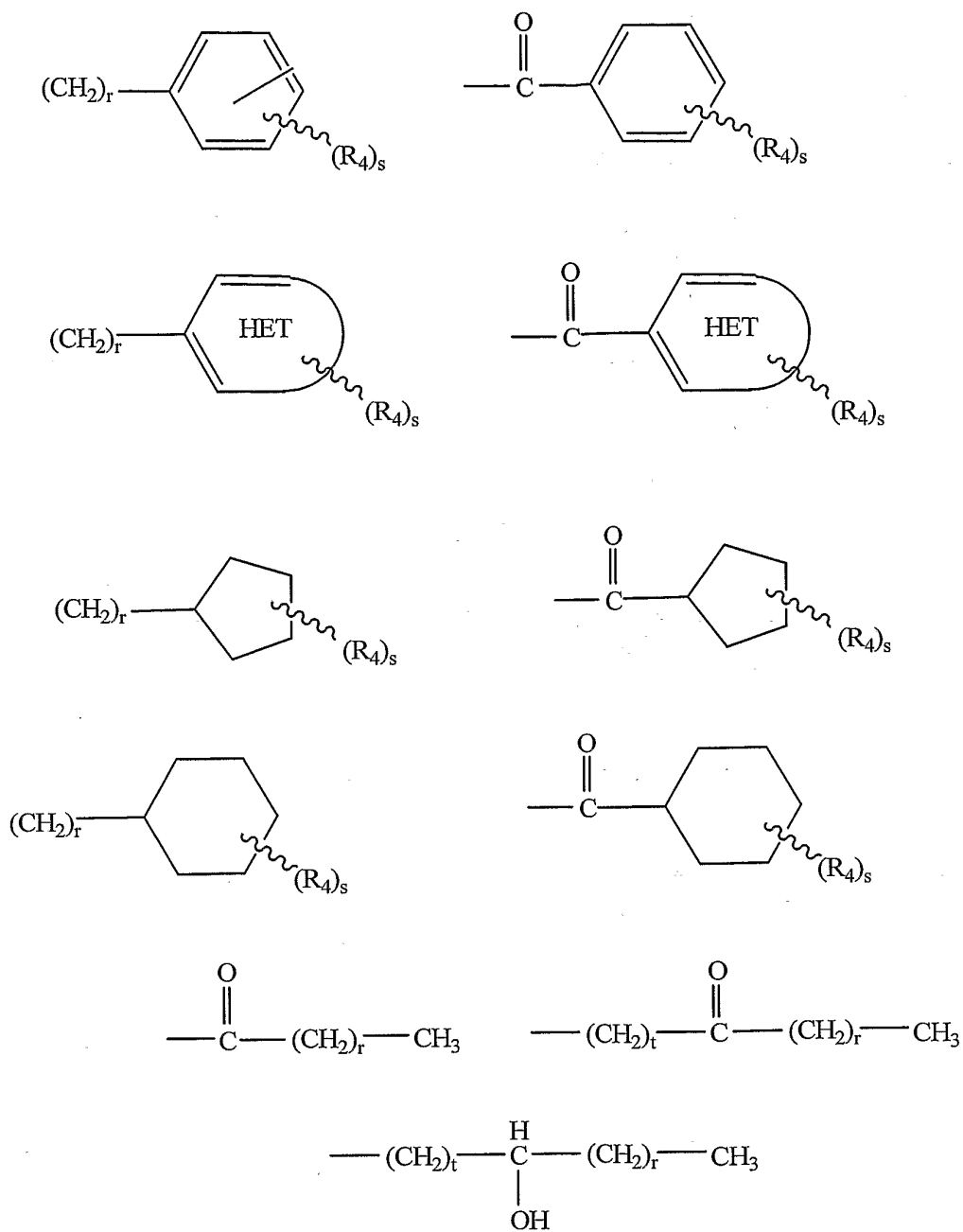
wherein R is H, lower alkyl of 1 to 6 carbons, and R_1 is iso-propyl, n-butyl or tertiary-butyl, or a pharmaceutically acceptable salt of the compound.

[0058] Another class of compounds for use herein is represented by Formulae XXVII:



(XXVII)

where X is O or S; Y is a bivalent cycloalkyl or cycloalkenyl radical optionally substituted with one to four R_4 groups, the cycloalkenyl radical having 5 to 6 carbons and one double bond, or Y is a bivalent aryl or 5 or 6 membered heteroaryl radical having 1 to 3 heteroatoms selected from N, S and O, the aryl or heteroaryl groups optionally substituted with 1 to 4 R_4 groups with the proviso that the cycloalkyl or the cycloalkenyl radical is not substituted on the same carbon with the condensed cyclic moiety and with the diene containing moiety; R_1 is independently H, alkyl of 1 to 6 carbons, or fluoroalkyl of 1 to 6 carbons; R_2 is independently H, alkyl of 1 to 8 carbons, or fluoroalkyl of 1 to 8 carbons; R'_2 is independently H, alkyl of 1 to 8 carbons, or fluoroalkyl of 1 to 8 carbons; R_3 is hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, halogen, alkoxy of 1 to 10 carbons, or alkylthio of 1 to 10 carbons; NO_2 , NH_2 , $\text{NHCO}(\text{C}_1\text{-C}_6)$ alkyl, $\text{NHCO}(\text{C}_1\text{-C}_6)$ alkenyl, NR_1H or $\text{N}(\text{R}_1)_2$, benzyloxy, $\text{C}_1\text{-C}_6$ alkyl-substituted benzyloxy, or R_3 is selected from the groups shown below,



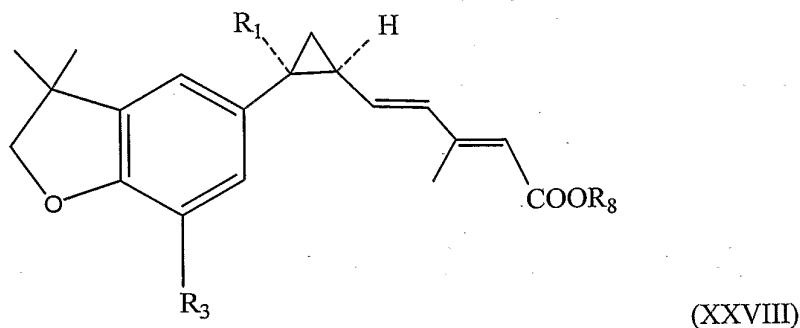
R_4 is H, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 10 carbons, or alkylthio of 1 to 10 carbons; m is an integer having the

values of 0 to 3; r is an integer having the values of 1 to 10; s is an integer having the values 1 to 4; t is an integer having the values 1 to 5;

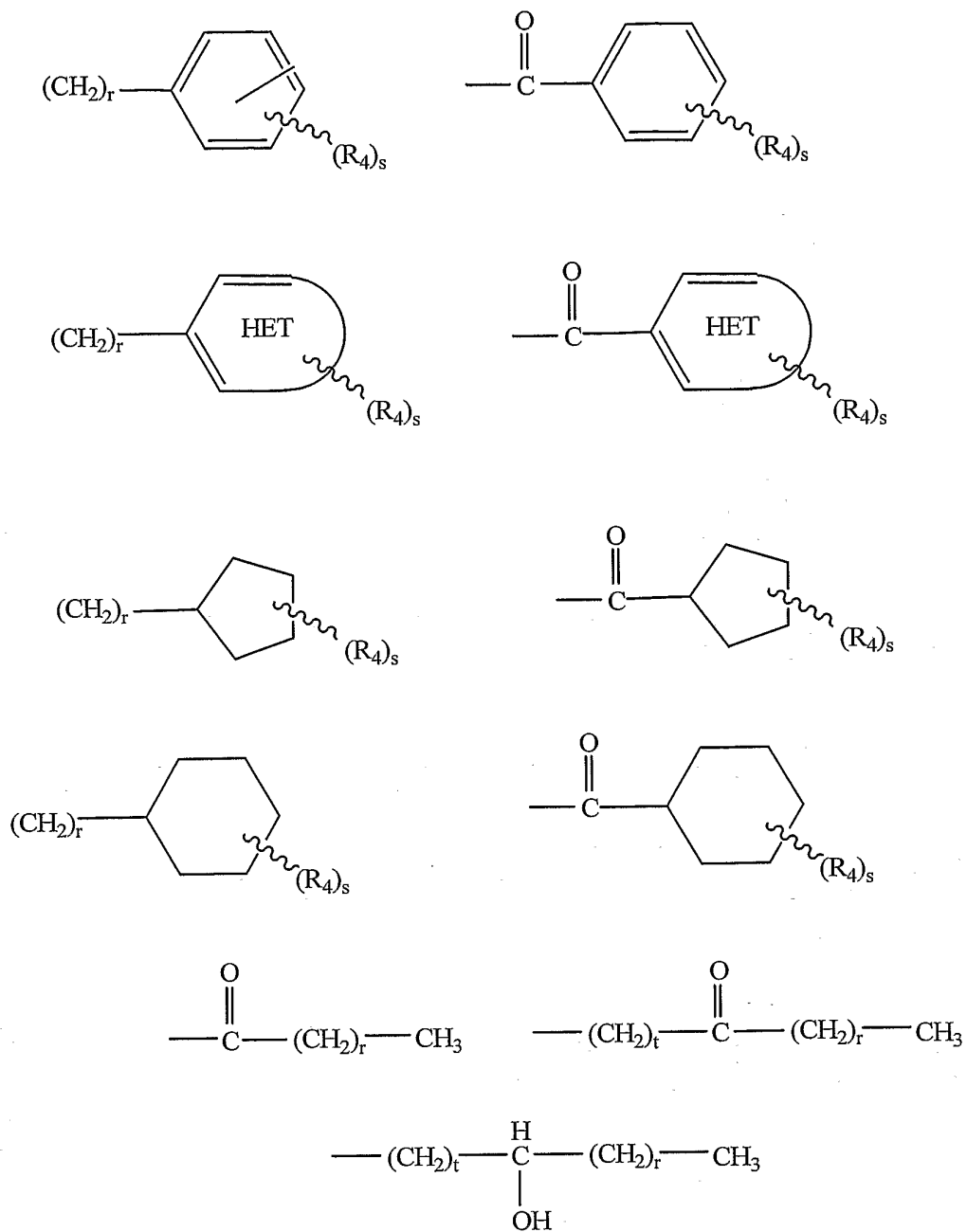


represents a 5 or 6 membered heteroaryl ring having 1 to 3 heteroatoms selected from the group consisting of N, S and O; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or trilower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2 to 5 carbons.

[0059] Another class of compounds for use herein is represented by Formulae XXVIII:



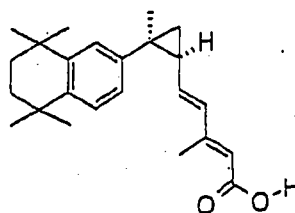
wherein R₁ H or methyl; R₈ is H, alkyl of 1 to 6 carbons, or a pharmaceutically acceptable cation, and R₃ is hydrogen, alkyl of 1 to 10 carbons, halogen, alkoxy of 1 to 10 carbons, or R₃ is selected from the groups shown below





represents a 5 or 6 membered heteroaryl ring having 1 to 3 heteroatoms selected from the group consisting of N, S and O, and t is an integer having the values 1 to 5.

[0060] A preferred compound for use herein is VTP 194204 which means 3,7-dimethyl-6(S),7(S)-methano-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl] 2(E),4(E) heptadienoic acid, and has the following chemical structure:



Pharmaceutically acceptable salts of RXR agonists can also be used in the disclosed method. Compounds disclosed herein which possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly can react with any of a number of organic or inorganic bases, and inorganic and organic acids, to form a salt.

Acids commonly employed to form acid addition salts from RXR agonists with basic groups are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate,

lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

Bases commonly employed to form base addition salts from RXR agonists with acidic groups include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

[0061] TSH means thyroid stimulating hormone.

[0062] TSH modulating agents include, but are not limited to, rexinoids, thyroid hormones and the like and mixtures thereof.

[0063] The instant invention provides a method of treating cancer comprising administering to a patient in need of such treatment a RXR agonist at a level below the RAR activating threshold and at or above the RXR effective dose.

[0064] In another embodiment, the invention provides a method of treating cancer comprising dosing a patient in need of such treatment with increasing concentrations of a RXR agonist to determine the RAR activating threshold and the RXR effective dose for the patient; administering to the patient the RXR agonist at a level below the RAR activating threshold and at or above the RXR effective dose.

[0065] In a preferred embodiment, the cancer is non-small cell lung cancer.

[0066] In another preferred embodiment, the RXR effective dose can be determined by the reduction of the patient's thyroid stimulating hormone (TSH) levels.

[0067] In yet another preferred embodiment, the RAR activating threshold can be determined by measuring at least one RAR biomarkers expressed by the patient.

[0068] In still yet another preferred embodiment, the RAR biomarker is selected from the group consisting of CYP26 level, CRBPI level, and combinations thereof.

[0069] In yet another preferred embodiment, the invention further includes measuring the patient's C_{max} of the RXR agonist and adjusting the dose to maintain the patient's C_{max} at an optimal level.

[0070] In one embodiment, the RXR agonist is Targretin®. In another embodiment, the RXR agonist is 3,7-dimethyl-6(S),7(S)-methano-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl] 2(E),4(E) heptadienoic acid.

[0071] If desired, the methods can further include treating the patient with at least one other anti-cancer agent. Preferred anti-cancer agents include, but are not limited to, a platinum-based compound, a cytotoxic drug and the like and mixtures thereof.

[0072] In a preferred embodiment, the method further includes treating the patient with one or more triglyceride lowering agents.

[0073] In a preferred embodiment, the method further includes treating the patient with one or more TSH modulating agents.

[0074] In another embodiment, the invention provides a method for treating cancer via modulation of RXR including at least the step of administering to a patient in need of such treatment an effective amount of a RXR agonist having a therapeutically beneficial RXR EC_{90} :RAR EC_{10} ratio range. In a preferred embodiment, the mean of the RXR EC_{90} :RAR EC_{10} ratio is at least about 40. In a more preferred embodiment, the mean of the RXR EC_{90} :RAR EC_{10} ratio is at least about 200. Alternatively, the RXR EC_{90} :RAR EC_{10} ratio for one of α , β and γ is at least about 40. More preferably, the RXR EC_{90} :RAR EC_{10} ratio for one of α , β and γ are all at least about 200. Typically, the (RXR EC_{90} :RAR EC_{10} ratio)₀ is at least 40, more typically at least 200. In another alternative, the RXR EC_{90} :RAR EC_{10} ratio for α , β and γ are all at least about 40. More preferably, the RXR EC_{90} :RAR EC_{10} ratio for α , β and γ are all at least about 200.

[0075] A "patient" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

[0076]

[0077] The RXR agonist compounds for use in the methods of the present invention may be used as is or incorporated into a pharmaceutical composition. All modes of administrations are contemplated, e.g., orally, rectally, parenterally, topically, or by intravenous, intramuscular, intrastemal or subcutaneous injection or in a form suitable by inhalation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. The compounds will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, the pharmaceutical composition can be formulated as a liquid, powder, elixir, injectable solution, suspension, suppository, etc.

[0078] Formulations for oral use can be provided as tablets or hard capsules wherein the compounds are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oleaginous medium, e.g., peanut oil, liquid paraffin or olive oil.

[0079] For topical administration in the mouth, the pharmaceutical compositions can take the form of buccal or sublingual tablet, drops or lozenges formulated in conventional manner.

[0080] For topical administration to the epidermis, the compounds can be formulated as creams, gels, ointments or lotions or as transdermal patches. Such compositions can, for example, be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilizing, dispersing, suspending, and/or coloring agents.

[0081] The compounds can also be formulated as depot preparations. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

[0082] The compounds can be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example

by bolus injection or continuous intravenous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0083] The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glyceride.

[0084] For intranasal administration, the compounds can be used, for example, as a liquid spray, as a powder or in the form of drops.

[0085] For administration by inhalation, the compounds can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insulator can be formulated containing a powder mix of the retinoid compound and a suitable powder base such as lactose or starch.

[0086] Aqueous suspensions can include pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g., heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monoleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monoleate. The aqueous suspensions can also contain one or more preservatives,

e.g., ethyl-or-n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

[0087] The compounds will be administered in an amount which is at a level below the RAR activating threshold and at or above the RXR effective dose in accordance with the invention. These amounts can be determined by one skilled in the art.

[0088] The following are non-limiting embodiments of the invention:

EXAMPLE 1 (PROPHETIC EXAMPLE)

[0089] While not intending to be bound by any particular theory, one aspect of the instant invention contemplates that Targretin[®], particularly at high doses, activates RARs in addition to RXRs and this activation of RAR is why the non-responsive group (those with low triglyceride elevation) had decreased survival in the pivotal Targretin[®] clinical trials.

[0090] At a dose of 400 mg/m²/d, Targretin[®] C_{max} values in the blood are estimated to be around 8,000 nM, at which concentration there will be significant activation of RARs by Targretin[®]. Also, since the estimated Targretin[®] C_{max} values are around 2,000 nM at the lower dose (225 mg/m²/d), some detrimental activation of RARs would occur even at this dose.

[0091] Accordingly, it is envisioned that a patient could be dosed with Targretin[®] to determine the RAR activating threshold and the RXR effective dose for the patient; administering to the patient the RXR agonist at a level below the RAR activating threshold and at or above the RXR effective dose.

EXAMPLE 2

[0092] 3,7-dimethyl-6(5),7(S)-methano-[1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl] 2(E),4(E) heptadienoic acid (VTP 194204) is a highly potent (EC₅₀=0.1-0.5 nM) and specific RXR pan-agonist. VTP 194204 is believed to be readily used at purely RXR-activating doses.

PRE-CLINICAL PHARMACOLOGY

[0093] VTP 194204 exhibits tumor growth inhibitory effects in cell lines derived from a variety of tumor types and in animal models of breast and lung cancer. Also in models of cancer-induced cachexia, VTP 194204 maintained body weight, prevented loss of muscle and adipose tissue, improved food consumption, and prolonged survival. The anti-tumor and anti-cachectic properties of VTP 194204 are illustrated in Figure 1. Preliminary studies indicate that the anti-cachectic properties of VTP 194204 are independent of its anti-tumor effects.

PRE-CLINICAL SAFETY

[0094] IND-enabling safety evaluation and toxicokinetic studies have been completed. No genotoxicity was observed in a battery of tests (Ames, mouse lymphoma TK, and rat micronucleus assays). Repeated oral dose studies for 4 weeks followed by recovery indicated the severe toxic doses of VTP 194204 to be greater than 200 mg/m²/d and 60 mg/m²/d in dogs and rats, respectively. These studies support a starting dose of 6 mg/m²/d for the initial phase I-IIa dose escalation study.

CLINICAL DEVELOPMENT PLAN

[0095] The clinical plan will focus on achieving initial registration approval for treatment of NSCLC patients in a fourth-line setting. The initial Phase I-IIa study in NSCLC patients who have failed other therapies will be a dose-escalation study to determine a pharmacologically effective dose (full activation of RXRs as ascertained by pharmacodynamic markers) for VTP 194204. Preliminary survival data, in comparison to historical controls, will be obtained from the study.

[0096] The Phase II/III registration study in fourth-line NSCLC patients (n~160) will compare VTP 194204 versus best supportive care with crossover upon disease progression. Approval will be based on a primary endpoint of progression-free survival. Subsequent or parallel studies will seek to expand clinical indications for VTP 194204 in NSCLC (e.g., combination with platinum-based therapies or Tarceva®), cancer-associated cachexia and breast cancer.

EXAMPLE 3
(PROPHETIC EXAMPLE)

[0097] A Phase 1-2a Study of the Safety, Pharmacokinetics and Pharmacologically Effective Dose of Oral VTP 194204 in Patients with Advanced, Metastatic Refractory Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION

[0098] VTP 194204, a second-generation rexinoid, is a potent, specific full agonist at all three (α , β and γ) retinoid X receptors (RXRs). VTP 194204 exhibited tumor growth inhibitory effects in cell lines derived from a variety of tumor types and in animal models of breast and lung cancer. Also in models of cancer-induced cachexia, VTP 194204 maintained body weight, prevented loss of muscle and adipose tissue, improved food consumption, and prolonged survival. This Phase I-IIa clinical trial is designed to determine the safety, pharmacokinetics, and pharmacologically effective dose of VTP 194204 for the treatment of NSCLC patients through activation of RXRs.

STUDY DESIGN

STUDY ENDPOINTS

Primary:

[0099] To determine the safety of VTP 194204 administered orally on a daily schedule.

[00100] To determine the pharmacologically effective dose (PED) of VTP 194204 administered orally on a daily schedule.

[00101] To evaluate the pharmacokinetic profile of VTP 194204 in cancer patients.

Secondary:

[00102] To determine the effects of VTP 194204 on survival of NSCLC patients.

[00103] To determine anti-tumor activity of VTP 194204 as manifested by standard response criteria, or by tumor markers.

PATIENT SELECTION:

[00104] Number of Patients: Patients will be entered into the study in cohorts of 1 to 3. The total number of patients entered will be determined by the number of dose escalations

Condition/Disease: Patients will be those with NSCLC refractory to standard therapies.

Inclusion Criteria:

Histologically confirmed NSCLC refractory to conventional therapy.

Male or female, 18 to 75 years of age, inclusive.

ECOG Performance Status 0-2.

Life expectancy > 8 weeks.

Hematology: Hemoglobin ≥ 8.5 g/dl

Platelets $\geq 100,000$ cells/mm³

Neutrophils ≥ 1500 cells/mm³

[00105] PT and PTT within normal limits, except for patients receiving Coumadin® (warfarin sodium, Bristol Myers Squibb) for thromboembolic prophylaxis only, in whom INR of less than 2 will be allowable.

Biochemistry: Total bilirubin ≤ 1.5 x ULN

AST/ALT ≤ 3.0 x ULN

Serum creatinine ≤ 2.0 mg/dl

Serum calcium < 11.5 mg/dl

Fasting serum triglycerides ≤ 2.5 x ULN

[00106] Endocrine: Thyroid stimulating hormone (TSH) WNL (> 0.5 mU/L and < 5.5 mU/L).

[00107] Negative urine pregnancy test for women of child-bearing potential at screening and on Day 0, and agreement to use two reliable forms of contraception during therapy and for 1 month following discontinuation of therapy unless abstinence is the chosen birth control method.

Exclusion Criteria:

[00108] Major surgery within previous 4 weeks; large field radiation therapy (> 25% of the patient's total marrow) or chemotherapy (including investigational agents or participation in another clinical study) within previous 4 weeks; mitomycin C or nitrosoureas within 6 weeks.

[00109] Systemic retinoid therapy, or vitamin A at dosages > 5,000 IU per day, during previous 4 weeks.

[00110] Patients with any prior or current history of thyroid disease, with any history of pituitary disease, or with any history of prior or current treatment with thyroid replacement hormone.

[00111] Primary brain tumors, active brain metastasis including progression from last scan or evidence of cerebral edema, or clinical symptoms of brain metastasis. Patients with prior history of brain metastasis must have brain imaging (e.g., CT, MRI) performed.

[00112] Requirement for steroids or anticonvulsant medication. (Patients taking stable dosages of GnRH analogues or Megace® (megestrol acetate, Bristol Myers Squibb) for at least the previous 3 months will be allowed into the study.)

[00113] Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study.

[00114] Known HIV-positive patients.

[00115] Females who are pregnant, nursing, or planning a pregnancy.

[00116] History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with absorption of study medication.

[00117] Clinically significant abnormalities on screening ECG.

TREATMENT

Definitions:

[00118] PED: defined as the dose at which 90% of all TSH measurements in all patients in a 4-week cycle were 90% below the corresponding basal TSH values provided that at 50% of this dose at least 75% of all TSH measurements in all patients in a 4-week cycle were 80% below the corresponding basal TSH values. It is expected that effective activation of RXRs will occur at a PED.

[00119] DLT: defined as one of the following toxicities (all toxicities graded according to the NCI Common Toxicity Criteria, version 2.0 except the RAR biomarkers):

(1) More than 2-fold increase in levels of at least one RAR biomarker (e.g., CYP 26A, CD38).

(2) Any symptomatic Grade 2 toxicity that requires hold or reduction of study drug administration.

(3) Any Grade 3 or higher symptomatic toxicity (excluding nausea/vomiting in the absence of optimal anti-emetics).

(4) Any Grade 3 asymptomatic biochemical (except SGOT (AST) or SGPT (ALT)) or hematologic toxicity persisting > 7 days.

(5) SGOT (AST)/SGPT (ALT) > 10 x ULN (upper limit of normal range).

(6) Any Grade 4 biochemical or hematologic toxicity.

[00120] MTD: defined as the highest dose level at which less than 2 of a cohort of patients experience a dose-limiting toxicity (DLT) during a minimum period of 4 weeks. This means for a dose to meet the definition of MTD, the study drug will have been administered at that dose to a cohort of at least three patients for at least 4 weeks and only one patient will have experienced only one DLT during that time interval. This will generally be one dose level below that at which DLT occurs in 2 patients. There is no specified minimum duration of study drug exposure required for consideration of a case of DLT for the determination of the MTD.

[00121] The derivation of a recommended dose for future studies will incorporate tolerability of the drug over 8 weeks in at least 3 patients. Thus, if the proposed recommended dose has fewer than 3 patients treated for at least 8 weeks, additional patients will be enrolled at that dose level.

Duration:

[00122] A treatment cycle will be 4 weeks of daily oral study drug administration (Cycle 1) in the absence of dose-limiting toxicity (DLT). After 4 weeks, patients may be allowed to continue on study in 4-week increments of daily oral study drug administration at the same dose level (or reduced dose level) if further treatment is judged to be of possible clinical benefit (Cycles 2-12) to a maximum of 12 cycles.

Dosage/Dose Regimen:

[00123] Three patients will be accrued at each dose level. The initial daily dose of VTP 194204 will be approximately 0.2 mg/m²/day taken as a single, oral dose. Doses will be escalated as described below. In the absence of toxicity greater than Grade 2 on the NCI toxicity scale over a period of 4 weeks, the dose will be escalated by 100% for one to

three patients in each subsequent cohort. No intra-patient dose escalation will be allowed from one cycle to the next. After a given cycle, patients may be allowed to continue on study in further increments of four weeks at the same dose as in the previous cycle, if the investigator determines it to be in the patient's interests to continue in the study. The initial dose and all subsequent dose escalations will be to the nearest capsule size.

[00124] Thyroid hormone and thyroid stimulating hormone (TSH) levels, biomarkers of RXR activation, will be measured weekly in all patients during Cycle 1. In addition, levels of potential biomarkers for retinoic acid receptor (RAR)-specific activity such as retinoic acid-inducible cytochrome P450 enzyme (CYP26A), cellular retinol binding protein-I (CRBPI), CD38, and RAR β 2 will be simultaneously monitored in blood cells at the messenger RNA level by quantitative PCR assays. At a given dose level, if 75% or greater of all TSH measurements in all patients in a 4-week cycle are 80% below the corresponding basal TSH values and no patient exhibits toxicity greater than Grade 2, then a further dose escalation of 100% will be made in a new cohort of 3 additional patients. If 90% of all TSH measurements in all patients in a 4-week cycle at this new dose are 90% below the corresponding basal TSH values, then a pharmacologically effective dose (PED) will be deemed to have been reached. If not, further dose escalations of 100% (or of lesser amounts) will be made in new cohorts of 3 patients each until a PED as defined above is reached unless a dose limiting toxicity (DLT) is reached earlier. The DLT is defined as equal or greater than 2-fold increase in a RAR biomarker level and/or Grade 3 toxicity whichever is reached first. If a PED is reached prior to a DLT, 6 more patients will be enrolled at the PED in order to further validate the PED.

[00125] If a patient develops a DLT, 3 additional patients will be enrolled at that dose level. If none of the 3 additional patients develops a DLT over a period of 4 weeks, the dosage will continue to be escalated 100% for one to three patients in the subsequent cohorts. However, if 1, 2, or all 3 additional patients develop DLT, the dosage will be escalated by 50% in a new cohort of 3 patients. Dose escalation will be carried out until a dose equivalent to PED is reached, unless a dose limiting toxicity (DLT) is reached earlier.

[00126] If one of the patients entered at a dose level experiences DLT, up to 3 additional patients will be entered at that dose level. If none of the 3 additional patients experiences a DLT, dose escalation will proceed with a dose increment of 33% in at least

3 patients per dose level. However, if a second patient in the cohort experiences DLT, then the maximum tolerated dose (MTD) will be deemed to be exceeded. Dose reduction due to DLT or intolerability will be 50% unless a 50% dose reduction will result in dosing at a previously investigated level, then a 33% dose reduction will be investigated.

Visit schedule:

[00127] Patients will be seen for assessment every 7 days (+/- 1 day) for 28 days. Thus, there will be 6 scheduled visits (including screening visit) to the end of the first cycle. Those patients who continue on treatment after 28 days will be seen every 14 days (+/- 2 days), or more frequently if clinically required.

PROPHETIC RESULTS

[00128] The following are predicted, not actual, results:

[00129] PED is 1 mg/m²/d. The blood concentration of VTP 194204 at the PED is 3±1 ng/mL. There was no discernible increase of levels of RAR biomarkers at any of the VTP 194204 dosages including the PED. Thus, dosages of VTP 194204 of approximately 1 mg/m²/d are considered to be purely RXR-activating dosages (i.e., no RAR activation). Such dosages are optimal for treating NSCLC patients. The average median survival for the NSCLC patients in this study was 8.5 months compared to approximately 4 months for historical, matched control patients.

EXAMPLE 4
(PROPHETIC EXAMPLE)

[00130] A Randomized Phase III Trial Comparing VTP 194204/
Carboplatin/Paclitaxel *versus* Carboplatin/Paclitaxel in Chemotherapy-Naïve Patients with
Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

INTRODUCTION

[00131] VTP 194204, a second-generation rexinoid, is a potent, specific full agonist at all three retinoid X receptors. VTP 194204 exhibited tumor growth inhibitory effects in cell lines derived from a variety of tumor types and in animal models of breast and lung

cancer. Also in models of cancer-induced cachexia, VTP 194204 maintained body weight, prevented loss of muscle and adipose tissue, improved food consumption, and prolonged survival. A Phase III trial is designed to demonstrate the survival benefit of the addition of VTP 194204 to carboplatin/paclitaxel chemotherapy.

STUDY DESIGN:

PATIENT SELECTION

[00132] Patients are selected to meet all following conditions
NSCLC at Stage IIIB with pleural effusion or Stage IV;
No prior chemotherapy;
ECOG=0, 1.

TREATMENT:

[00133] Patients stratified by disease stage and gender are randomized to receive VTP 194204 once daily at a pure RXR-activating dose and carboplatin AUC 6 and paclitaxel 200 mg/m², i.e., every 3 weeks or carboplatin/paclitaxel alone. The pure RXR activation dose of VTP 194204 is determined by monitoring induction of hypothyroidism (reduction in TSH levels), a pharmacological biomarker for RXR activation, in the absence of induction of RAR biomarkers in blood.

STUDY ENDPOINTS:

[00134] Primary endpoint: Overall survival

[00135] Secondary endpoint: Kaplan-Meier projected two-year survival rates.

PROPHETIC RESULTS:

[00136] The predicted, not actual, clinical results are presented in TABLE 2:

TABLE 2
PROPHETIC, NOT ACTUAL, RESULTS

Treatment Group	Median Survival (Months)	Two-Year Survival Rates (%)

Carboplatin/Paclitaxel	9.2	16
VTP 194204/Carboplatin/Paclitaxel	15	30

[00137] While the above description contains many specifics, these specifics should not be construed as limitations of the invention, but merely as exemplifications of preferred embodiments thereof. Those skilled in the art will envision many other embodiments within the scope and spirit of the invention as defined by the claims appended hereto. All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually designated as having been incorporated by reference.

[00138] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

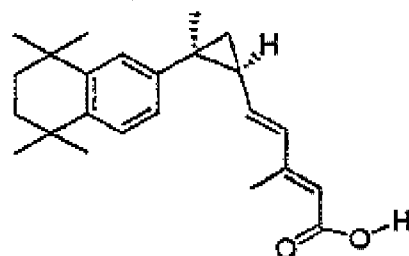
[00139] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating cancer comprising the steps of:
 - (a) selecting a dose of a retinoid X receptor (RXR) agonist which results in a C_{max} below the Retinoic Acid Receptor (RAR) activating threshold and at or above the RXR effective dose; and
 - (b) administering to a patient in need of such treatment the dose selected in step (a);wherein the cancer is effectively treated as a result of the administration.
2. The method according to claim 1, wherein the RAR activating threshold and the RXR effective dose for the patient is determined by dosing the patient with increasing concentrations of a RXR agonist to until the RXR effective dose and the RAR activating threshold are reached.
3. The method according to claim 1, wherein the RXR effective dose is determined by measuring the reduction of the patient's TSH levels.
4. The method according to claim 1, wherein the RAR activating threshold is determined by measuring at least one RAR biomarker expressed by the patient.
5. The method according to claim 4, wherein the RAR biomarker is selected from the group consisting of CYP26 level, CRBPI level and combinations thereof.
6. The method according to any one of claims 1 to 5, further comprising the steps of measuring the patient's C_{max} of the RXR agonist, and adjusting the dose to maintain the patient's C_{max} at an optimal level.
7. The method according to any one of claims 1 to 6, further comprising treating the patient with at least one other anti-cancer agent.
8. The method according to claim 7, wherein the anti-cancer agent is selected from the group consisting of a platinum-based compound, cytotoxic drug and mixtures thereof.
9. The method according to any one of claims 1 to 6, further comprising treating the patient with one or more triglyceride lowering agents.
10. The method according to any one of claims 1 to 6, further comprising treating the patient with one or more TSH modulating agents.

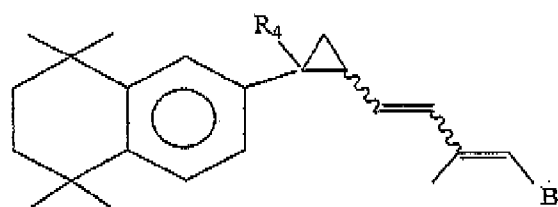
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11. The method according to any one of claims 1 to 10, wherein the cancer is non-small cell lung cancer.
12. The method according to any one of claims 1 to 10, wherein the cancer is breast cancer.
13. The method according to any one of claims 1 to 12, wherein the RXR agonist is administered in an amount from about 0.1 to about 10 mg/m²/day.
14. The method according to any one of claims 1 to 12, wherein the RXR agonist is administered in an amount from about 0.5 to about 2 mg/m²/day.
15. The method according to any one of claims 1 to 14, wherein the RXR agonist is bexarotene.
16. The method according to any one of claims 1 to 14, wherein the RXR agonist is:



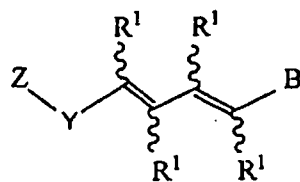
or a pharmaceutically acceptable salt thereof.

17. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure

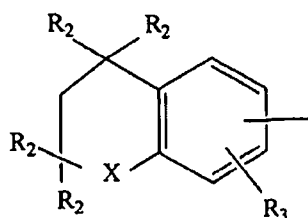


where R₄ is lower alkyl of 1 to 6 carbons; B is COOH or COOR₈ where R₈ is lower alkyl of 1 to 6 carbons, and the configuration about the cyclopropane ring is cis, and the configuration about the double bonds in the pentadienoic acid or ester chain attached to the cyclopropane ring is trans in each of said double bonds, or a pharmaceutically acceptable salt of said compound.

18. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure



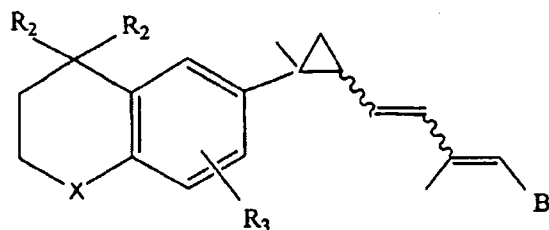
wherein Z is a radical shown in Formula 3,



Formula 3

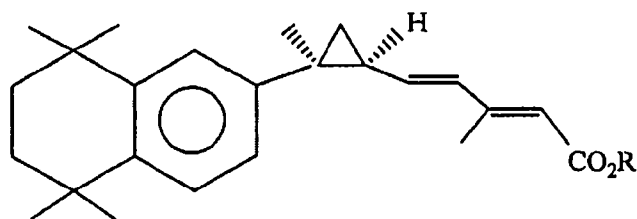
Y is cycloalkyl or cycloalkenyl of 3 to 8 carbons optionally substituted with one or two R_4 groups, or Y is selected from phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, and imidazolyl, said groups being optionally substituted with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-(CR_1=CR_1-CR_1=CR_1)-$ groups on adjacent carbons; X is S or O; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl, fluoroalkyl or halogen, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2 to 5 carbons.

19. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure



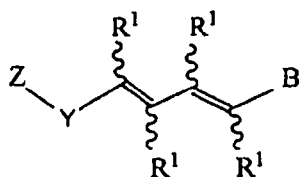
wherein X is S or O; R_2 is hydrogen or lower alkyl; R_3 is hydrogen or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR_8 , $\text{CONR}_9\text{R}_{10}$, $-\text{CH}_2\text{OH}$, $\text{CH}_2\text{OR}_{11}$, $\text{CH}_2\text{OCOR}_{11}$, CHO, $\text{CH}(\text{OR}_{12})_2$, CHOR_{13}O , $-\text{COR}_7$, $\text{CR}_7(\text{OR}_{12})_2$, $\text{CR}_7\text{OR}_{13}\text{O}$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2 to 5 carbons.

20. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure

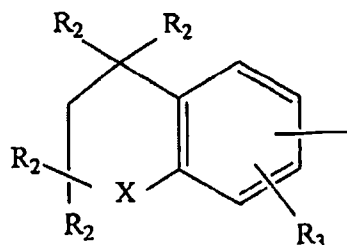


where R is H, lower alkyl or 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

21. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure



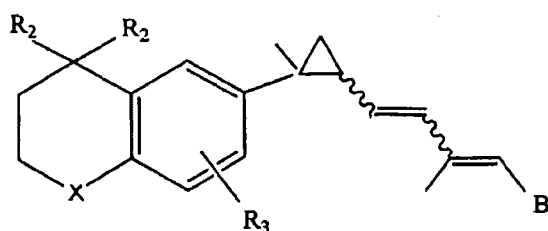
wherein Z is the group shown in Formula 3:



Formula 3

Y is cyclopropyl, said Y group being optionally substituted with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-(CR_1=CR_1-CR_1=CR_1)-$ groups on adjacent carbons; X is NR_5 ; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl, fluoroalkyl or hydrogen; R_5 is H or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2 to 5 carbons.

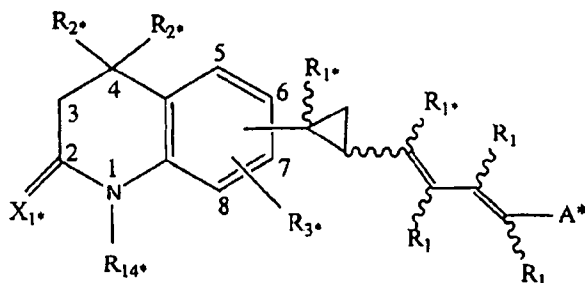
22. The method according to claim 1, wherein the RXR agonist has the chemical structure



wherein X is NR_5 ; R_5 is H or lower alkyl; R_2 is H or lower alkyl; R_3 is H or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10}

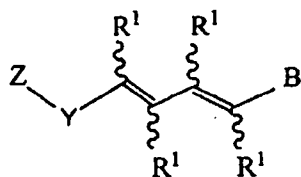
independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2 to 5 carbons.

23. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure

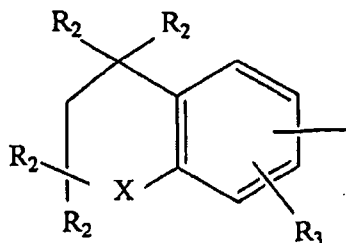


wherein R_1 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R_1^* is hydrogen or C_{1-6} -alkyl; R_2^* is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R_3^* is hydrogen, lower alkyl of 1 to 6 carbons, fluoro substituted lower alkyl of 1 to 6 carbons or halogen; X_1^* is an oxo ($=O$) or a thione ($=S$) group; A^* is hydrogen, $COOH$ or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, where R_8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, and the cyclopropyl group is attached to the 6 or 7 position of the tetrahydroquinoline moiety, and R_{14}^* is alkyl of 1 to 10 carbons or fluoro-substituted alkyl of 1 to 10 carbons.

24. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure



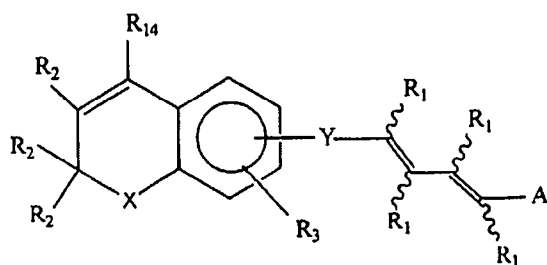
wherein Z is the group shown in Formula 3,



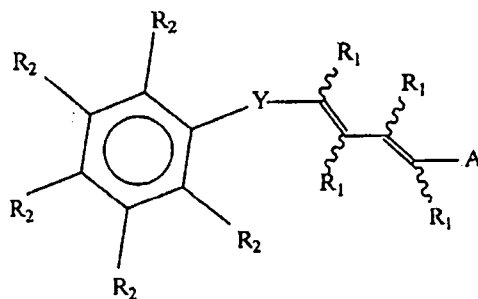
Formula 3

Y is cycloalkyl or cycloalkenyl of 3 to 8 carbons optionally substituted with one or two R_4 groups, or Y is phenyl, said groups being optionally substituted with one or two R_4 groups, the divalent Y radical being substituted by the Z and $-(CR_1=CR_1-CR_1=CR_1)-$ groups on adjacent carbons; X is NR; R_1 and R_2 independently are H, lower alkyl or fluoroalkyl; R_3 is hydrogen, lower alkyl, Cl or Br; R_4 is lower alkyl, fluoroalkyl or halogen; R_5 is H or lower alkyl, and B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or trilower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is a divalent alkyl radical of 2 to 5 carbons.

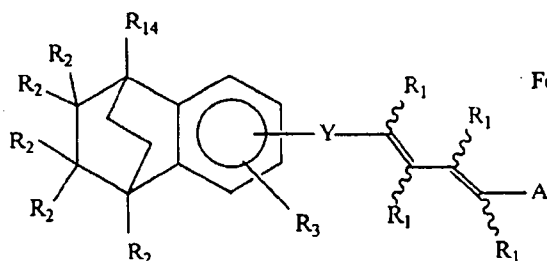
25. The method according to any one of claims 1 to 14, wherein the RXR agonist is a compound of Formula 1, Formula 2 or of Formula 3:



Formula 1

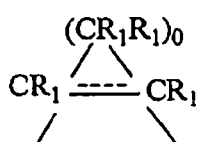


Formula 2

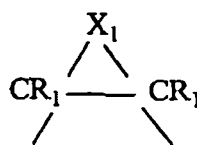


Formula 3

wherein X is O, S, or $(CR_1R_1)_n$ where n is 0, 1 or 2; Y is a bivalent radical having Formula 4 or Formula 5 where o is an integer between 1 through 4



Formula 4

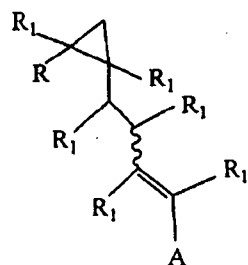


Formula 5

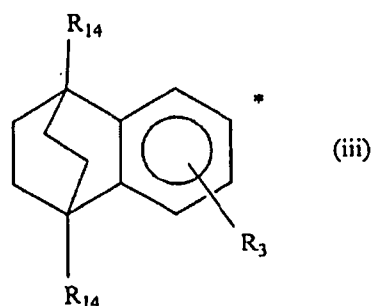
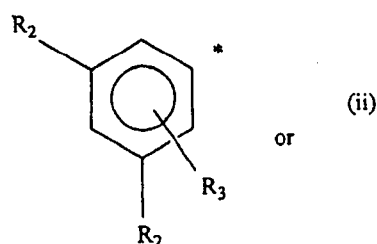
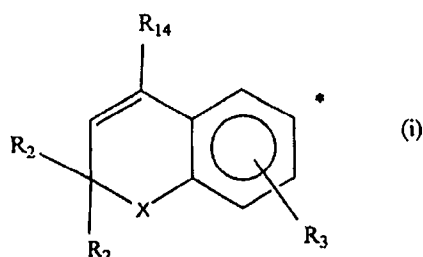
or Y is a bivalent aryl or 5 or 6 membered heteroaryl radical having 1 to 3 heteroatoms selected from N, S and O, said aryl or heteroaryl groups being unsubstituted, or substituted with 1 to 3 C_{1-6} alkyl or with 1 to 3 C_{1-6} fluoroalkyl groups with the proviso that when the compound is in accordance with Formula 2 then Y is not a 5 or 6 membered ring; X_1 is S or NH; R_1 is independently H, lower alkyl of 1 to 6 carbons, or lower fluoroalkyl of 1 to 6 carbons; R_2 is independently H, lower alkyl of 1 to 6 carbons, OR_1 , adamantyl, or lower fluoroalkyl of 1 to 6 carbons, or the two R_2 groups jointly represent an oxo ($=O$) group with the proviso that when the

compound is in accordance with Formula 2 then at least one of the R_2 substituents is branched-chain alkyl or adamantyl; R_3 is hydrogen, lower alkyl of 1 to 6 carbons, OR_1 , fluoro substituted lower alkyl of 1 to 6 carbons or halogen, NO_2 , NH_2 , $NHCO(C_1-C_6)$ alkyl, or $NHCO(C_1-C_6)$ alkenyl; A is $COOH$ or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO , $CH(OR_{12})_2$, $CH(OR_{13}O)$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7(OR_{13}O)$, or $Si(C_{1-6}alkyl)_3$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl) alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, and R_{14} is alkyl of 1 to 10 carbons, fluoro- substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, carbocyclic aryl selected from the group consisting of phenyl, C_1-C_{10} -alkylphenyl, naphthyl, C_1-C_{10} -alkylnaphthyl, phenyl- C_1-C_{10} alkyl, naphthyl- C_1-C_{10} alkyl, C_1-C_{10} - alkenylphenyl having 1 to 3 double bonds, C_1-C_{10} -alkynylphenyl having 1 to 3 triple bonds, phenyl- C_1-C_{10} alkenyl having 1 to 3 double bonds, phenyl- C_1-C_{10} alkenyl having 1 to 3 triple bonds, hydroxyl alkyl of 1 to 10 carbons, hydroxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, hydroxyalkynyl having 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons, acyloxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds, acyloxyalkyl of 1 to 10 carbons, acyloxyalkenyl having 2 to 10 carbons and 1 to 3 double bonds, or acyloxyalkynyl of 2 to 10 carbons and 1 to 3 triple bonds where the acyl group is represented by COR_8 , or R_{14} is a 5 or 6 membered heteroaryl group having 1 to 3 heteroatoms, said heteroatoms being selected from a group consisting of O, S, and N, said heteroaryl group being unsubstituted or substituted with a C_1 to C_{10} alkyl group, with a C_1 to C_{10} fluoroalkyl group, or with halogen, and the dashed line in Formula 4 represents a bond or absence of a bond.

26. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure

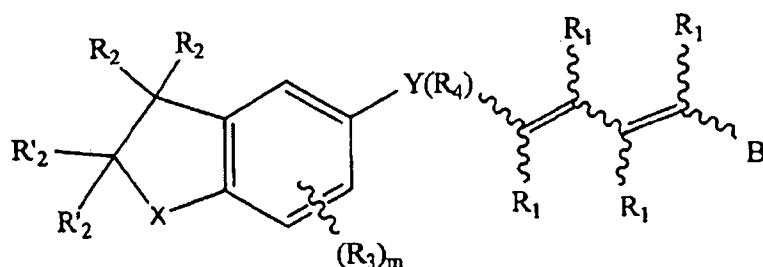


wherein R is a monovalent radical of formulae (i), (ii) or (iii)

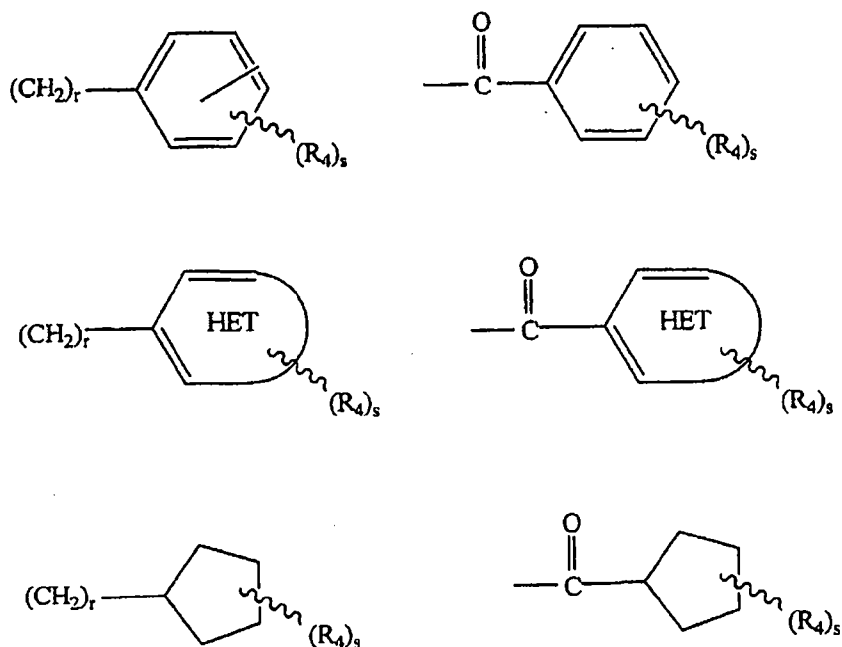


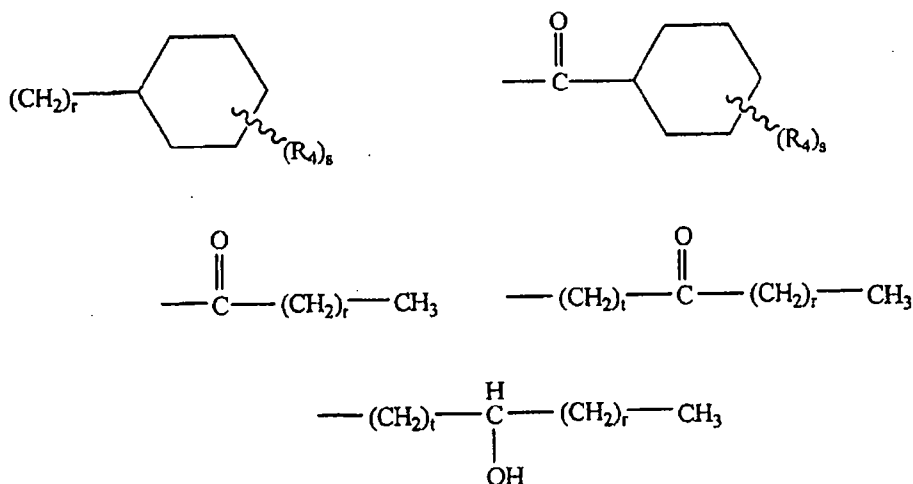
wherein the * shows the aromatic carbon covalently attached to the cyclopropyl ring; X is O, S, or CR₁R₁; R₁, R₂, R₃, and R₁₄ are independently H, lower alkyl of 1 to 6 carbons or adamantyl, with the proviso that when R is in accordance with formula (ii) then at least one of the R₂ substituents is branched-chain alkyl or adamantyl, and A is COOH, a pharmaceutically acceptable salt thereof, COOR₈ or CONR₉R₁₀ where R₈ is lower alkyl of 1 to 6 carbons.

27. The method according to any one of claims 1 to 14, wherein the RXR agonist has the chemical structure



wherein X is O or S; Y is a bivalent cycloalkyl or cycloalkenyl radical optionally substituted with one to four R_4 groups, the cycloalkenyl radical having 5 to 6 carbons and one double bond, or Y is a bivalent aryl or 5 or 6 membered heteroaryl radical having 1 to 3 heteroatoms selected from N, S and O, said aryl or heteroaryl groups optionally substituted with 1 to 4 R_4 groups with the proviso that the cycloalkyl or the cycloalkenyl radical is not substituted on the same carbon with the condensed cyclic moiety and with the diene containing moiety; R_1 is independently H, alkyl of 1 to 6 carbons, or fluoroalkyl of 1 to 6 carbons; R_2 is independently H, alkyl of 1 to 8 carbons, or fluoroalkyl of 1 to 8 carbons; R'_2 is independently H, alkyl of 1 to 8 carbons, or fluoroalkyl of 1 to 8 carbons; R_3 is hydrogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 10 carbons, halogen, alkoxy of 1 to 10 carbons, or alkylthio of 1 to 10 carbons; NO_2 , NH_2 , $\text{NHCO}(\text{C}_1\text{-C}_6)$ alkyl, $\text{NHCO}(\text{C}_1\text{-C}_6)$ alkenyl, NR_1H or $\text{N}(\text{R}_1)_2$, benzyloxy, $\text{C}_1\text{-C}_6$ alkyl-substituted benzyloxy, or R_3 is selected from the groups shown below,





R_4 is H, halogen, alkyl of 1 to 10 carbons, fluoro substituted alkyl of 1 to 6 carbons, alkoxy of 1 to 10 carbons, or alkylthio of 1 to 10 carbons; m is an integer having the values of 0 to 3; r is an integer having the values of 1 to 10; s is an integer having the values 1 to 4; t is an integer having the values 1 to 5;



represents a 5 or 6 membered heteroaryl ring having 1 to 3 heteroatoms selected from the group consisting of N, S and O; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or trilower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons, a cycloalkyl group of 5 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is a divalent alkyl radical of 2 to 5 carbons.

28. The method according to claim 1, wherein the RXR agonist is administered at a dose such that the mean RXR EC₉₀:RAR EC₁₀ ratio is within a therapeutically beneficial range.

29. The method according to claim 28, wherein the mean RXR EC₉₀:RAR EC₁₀ ratio is at least about 40.

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30. The method according to claim 28, wherein the mean RXR EC₉₀:RAR EC₁₀ ratio is at least about 200.
31. The method according to claim 1, wherein the RXR agonist is administered at a dose such that the RXR EC₉₀:RAR EC₁₀ ratio for one of α , β and γ is at least about 40.
32. The method of claim 31, wherein the RXR EC₉₀:RAR EC₁₀ ratio for one of α , β and γ are all at least about 200.
33. Use of a retinoid X receptor (RXR) agonist in the manufacture of a medicament for the treatment of cancer, wherein it is intended that the medicament is administered at a dosage which is selected to result in a C_{max} which is below the Retinoid Acid Receptor (RAR) activity threshold and at or above the RXR effective dose.
34. The use of claim 33, wherein it is intended that the medicament is administered so that the RXR agonist has a mean RXR EC₉₀:RAR EC₁₀ ratio that is within a therapeutically beneficial range.
35. The use of claim 33, wherein it is intended that the medicament is administered so that the RXR agonist has a RXR EC₉₀:RAR EC₁₀ ratio for one of α , β and γ is at least about 40.
36. A method according to any one of claims 1, 28 and 31, substantially as hereinbefore described with reference to any one of the examples.
37. Use according to any one of claims 33 to 35, substantially as hereinbefore described with reference to any one of the examples.

FIG. A

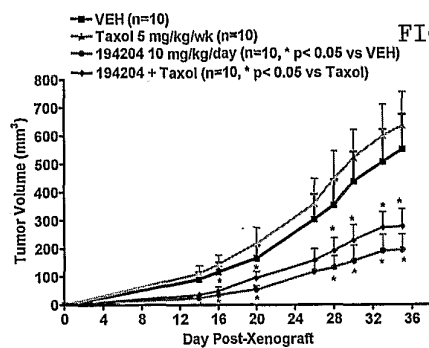


FIG. B

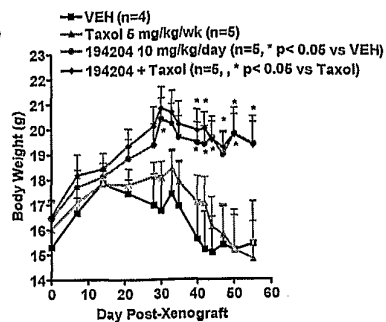


FIG. C

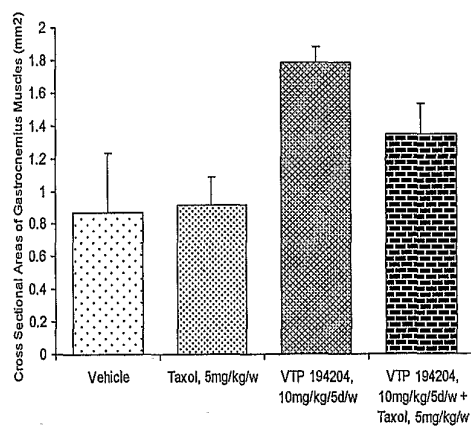


FIG. D

