VEGF Inhibition

Technical Field

In general, the present invention relates to methods for the treatment of conditions associated with abnormal levels of VEGF production and/or secretion.

Background of the Invention

Vascular endothelial growth factor [VEGF; also known as vascular permeability factor (VPF)] is a highly conserved, potent multifunctional cytokine. Abnormal levels of production and or secretion of VEGF have been linked to a number of pathological conditions. For example, high concentrations of biologically active VEGF have been detected in pleural fluids and ascites of cancer patients (Zebrowski *et al.*, 1999a, b).

Ascites, the accumulation of fluid in the abdominal cavity, may result from a number of conditions, including tumours and other disease states such as chronic liver disease. Cirrhosis of the liver is responsible for the majority of cases of ascites and the prognosis is generally poor.

Accumulation of malignant ascites is an important cause of morbidity and mortality in patients with peritoneal carcinomatosis. Causes of malignant ascites formation include colon, gastric, pancreatic, endometrial and ovarian cancer (Smith and Jayson, 2003). For example, the malignant progression of ovarian cancer is predominantly confined to the peritoneal cavity and often evolves to an ascites form (Ozols *et al.*, 1980). Both tumour size and the accumulation of ascites are inversely associated with survival (Hasumi *et al.*, 2002). Current therapeutic treatment of patients with advanced ovarian cancer associates cytoreductive surgery and systemic chemotherapy, the combination of paclitaxel and cisplatin being considered the initial chemotherapy for stage III and IV (Burbridge *et al.*, 1999). However two thirds of patients already have advanced disease when diagnosed, and poor prognoses are associated with rapidly accumulating ascites fluid and highly invasive and pleomorphic cellular phenotypes. There remains a need for an effective method for the treatment of ascites and ascites-associated conditions.

Ascites is linked to peritoneal, as well as tumour microvascular hyperpermeability and several studies have implicated a role for VEGF in ascites formation via increasing vascular permeability. More generally, VEGF exerts a number of important effects on vascular endothelium including inducing new vascular formation. VEGF possesses potent vascular permeability-enhancing activity and abnormal levels of VEGF production or secretion lead to microvascular hyperpermeability. VEGF is now recognized as a key factor required for growth of tumours and is involved in many other disease states such as diabetes, arthritis including rheumatoid arthritis,

psoriasis, endometriosis, cerebral oedema, atheroscelrosis, ischaemic heart disease, and retinopathic diseases such as age related macular degeneration.

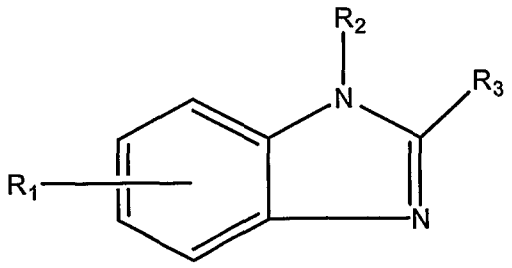
Tumour secretion of VEGF is essential for ascites accumulation. Tumour cells usually represent the main source of VEGF, but tumour-associated stroma is also an important site of VEGF production. Blocking VEGF production or secretion by tumour cells, for example using a VEGF inhibitor, has been shown in animal studies to result in inhibition of ascites formation (Zebrowski *et al.*, 1999a, b; Xu *et al.*, 2000). There is also growing evidence that VEGF production and secretion is not limited to solid tumours, but that VEGF and VEGF receptors are expressed by a variety of leukemias and other haematological malignancies.

Accordingly, VEGF is an attractive target for therapeutic intervention and several strategies to block VEGF activity have been sought, including monoclonal antibodies, VEGF receptor antagonists, tyrosine kinase antagonists and soluble VEGF receptors (VEGF-trap). There remains a need however for an effective method of inhibiting VEGF production and/or secretion and for treatment of conditions associated with VEGF production and/or secretion.

The present invention is predicated on the inventors' surprising finding that the benzimidazole carbamate albendazole has a potent effect on VEGF levels secreted by human ovarian cancer cells *in vitro* and on VEGF levels *in vivo*, and exhibits significant inhibitory effect on a number of conditions associated with abnormal VEGF levels.

Summary of the Invention

According to a first aspect of the present invention there is provided a method for inhibiting VEGF production or secretion in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



I

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted,

straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

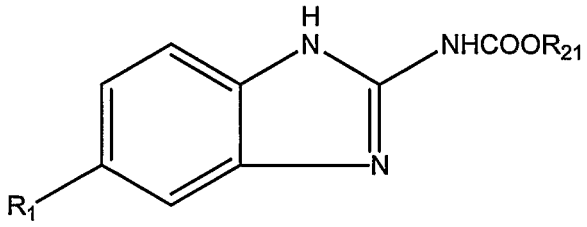
R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, -SR_{14}, -OR_{15}, -SOR_{16}, -SO_2R_{17}, -SCN, -C(O)-R_{18}, -OR_{19}, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

or a metabolite, derivative or analogue thereof.

In one embodiment the R_1 substitution occurs in the 5 or 6 position.

The compound may be a benzimidazole carbamate of Formula II:

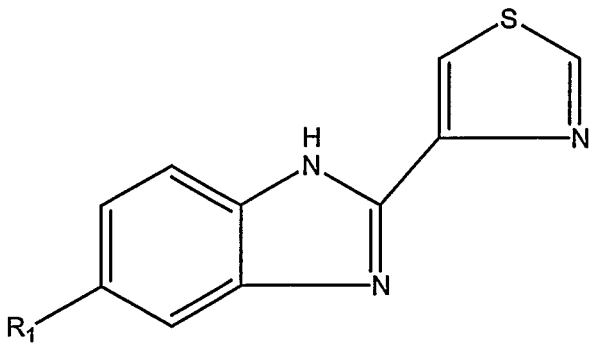


II

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, -SR_7, -SOR_8, -SO_2R_9, -SCN, B'$(CH_2)_nBR_{10}$, -C(O)-R_{11} or –OR_{12}, $COOR_{13}$, -NO_2, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_{21} is H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloakenylalkyl, aryl or arylalkyl.

The compound may be a compound of Formula III:



III

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4.

The compound may be selected from the group consisting of albendazole, albendazole sulphoxide, mebendazole, flubendazole, triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

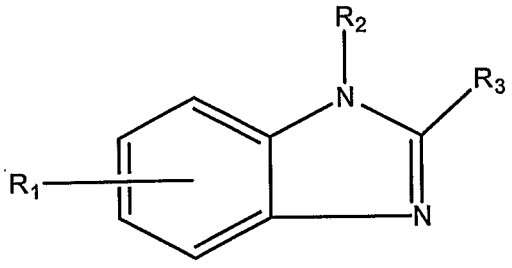
In one embodiment the compound is albendazole, or a metabolite, derivative or analogue thereof.

The VEGF may be produced or secreted by a tumour cell. The tumour cell may be an ovarian, colorectal, liver, pancreatic, gastric, endometrial, renal or other primary or metastatic tumour cell.

The VEGF production or secretion may be associated with an accumulation of fluid in a body cavity, such as ascites or pleural effusion.

The VEGF production or secretion may be associated with retinopathic neovascularisation, such as in proliferative retinopathy or macular degeneration.

According to a second aspect of the present invention there is provided a method for treating or preventing a condition associated with abnormal levels of production or secretion of VEGF in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, -SR_{14}, -OR_{15}, -SOR_{16}, -SO_2R_{17}, -SCN, -C(O)-R_{18}, -OR_{19}, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

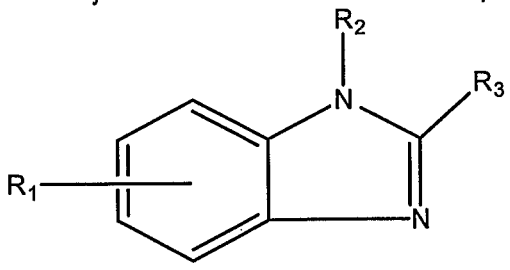
or a metabolite, derivative or analogue thereof.

In one embodiment the compound is albendazole, or a metabolite, derivative or analogue thereof.

The condition may be one associated with increased vascular permeability. The condition may be selected from the group consisting of: ascites, cirrhosis, pleural effusion, cerebral oedema, pulmonary oedema, ischaemic heart disease, macular degeneration, proliferative retinopathy, diabetic retinopathy, retinopathy of prematurity, psoriasis, endometriosis and arthritis, such as rheumatoid arthritis.

Administration of the compound may be systemic or regional depending on the nature of the condition to be treated. Administration may be intracavitary, intravesical, intramuscular, intraarterial, intravenous, subcutaneous, topical or oral. Intracavitary administration may be intraperitoneal or intrapleural.

According to a third aspect of the present invention there is provided a method for the treatment or prevention of ascites or an ascites-associated condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, -SR_7, -SOR_8, -SO_2R_9, -SCN, $B'(CH_2)_nBR_{10}$, -C(O)-R_{11} or –OR_{12}, $COOR_{13}$, -NO_2, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, -SR_{14}, -OR_{15}, -SOR_{16}, -SO_2R_{17}, -SCN, -C(O)-R_{18}, -OR_{19}, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

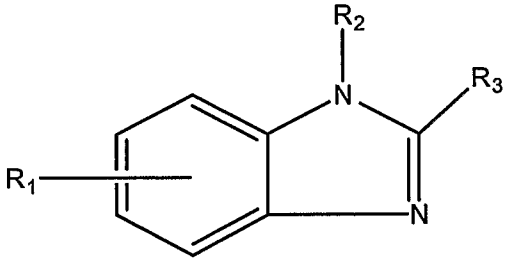
or a metabolite, derivative or analogue thereof.

In one embodiment the compound is albendazole, or a metabolite, derivative or analogue thereof.

The ascites may be malignant ascites. The ascites-associated condition may be cirrhosis.

The compound may be administered systemically or regionally. The compound may be administered intraperitoneally.

According to a fourth aspect of the present invention there is provided a method for the treatment or prevention of a retinopathic disease in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, -SR_7, -SOR_8, -SO_2R_9, -SCN, B'$(CH_2)_n$BR_{10}, -C(O)-R_{11} or –OR_{12}, $COOR_{13}$, -NO_2, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, -SR_{14}, -OR_{15}, -SOR_{16}, -SO_2R_{17}, -SCN, -C(O)-R_{18}, -OR_{19}, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

or a metabolite, derivative or analogue thereof.

In one embodiment the compound is albendazole, or a metabolite, derivative or analogue thereof.

The retinopathic disease may be selected from proliferative retinopathy, diabetic retinopathy, retinopathy of prematurity or macular degeneration.

According to any one of the above aspects and embodiments the compound may be administered in the form of a composition together with one or more pharmaceutically acceptable carriers, adjuvants or diluents.

According to a fifth aspect of the present invention there is provided a composition when used for inhibiting VEGF production or secretion by a cell, wherein the composition comprises a compound of Formula I together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

According to a sixth aspect of the present invention there is provided a composition when used for the treatment or prevention of ascites or an ascites-associated condition, wherein the composition comprises a compound of Formula I together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

According to a seventh aspect of the present invention there is provided a composition when used for the treatment or prevention of a retinopathic disease, wherein the composition comprises a compound of Formula I together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

According to an eighth aspect of the present invention there is provided a composition when used for the treatment or prevention of a condition associated with VEGF production or secretion, wherein the composition comprises a compound of Formula I together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

According to a ninth aspect of the present invention there is provided a method for designing a benzimidazole carbamate treatment regime for a subject, comprising monitoring the serum VEGF concentration in the subject in the presence and absence of one or more candidate benzimidazole carbamates and adjusting the identity and/or dosage of the benzimidazole carbamates so as to achieve a reduction in serum VEGF concentration.

According to a tenth aspect there is provided a method for treating a subject in need of treatment using a benzimidazole carbamate treatment regime designed according to the ninth aspect.

Also contemplated within the above aspects and embodiments are isomers, including stereoisomers and geometric isomers of the compounds of Formula I, II and III, as well as tautomeric forms thereof.

Definitions

In the context of this specification, the term "comprising" means "including principally, but not necessarily solely". Furthermore, variations of the word "comprising", such as "comprise" and "comprises", have correspondingly varied meanings.

The term "inhibiting" as used herein in relation to VEGF levels means preventing, reducing or otherwise ameliorating VEGF production or secretion. For example, depending on the circumstances, including the nature of the condition being treated, it may not be necessary that inhibition should mean completely blocking VEGF production or secretion, but reducing VEGF production to a sufficient degree to enable the desired effect to be achieved.

As used herein the terms "treating" and "treatment" refer to any and all uses which remedy a condition or symptoms, prevent the establishment of a condition or disease, or otherwise prevent, hinder, retard, or reverse the progression of a condition or disease or other undesirable symptoms in any way whatsoever.

The term "ascites-associated condition" as used herein refers to a condition associated with, at least in part, the accumulation of excess fluid in the abdominal cavity. The condition may be characterized by such accumulation, may occur as a result, either directly or indirectly, of such accumulation or itself lead to the accumulation of excess fluid in the abdominal cavity. One exemplary ascites-associated condition is cirrhosis.

As used herein the term "effective amount" includes within its meaning a non-toxic but sufficient amount of an agent or compound to provide the desired effect. The exact amount required will vary from subject to subject depending on factors such as the species being treated, the age and general condition of the subject, the severity of the condition being treated, the particular agent being administered and the mode of administration and so forth. Thus, it is not possible to specify an exact "effective amount". However, for any given case, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

The term "alkyl" as used herein, includes within its meaning monovalent, saturated, straight and branched chain hydrocarbon radicals.

The term "alkenyl" as used herein, includes within its meaning, monovalent, straight and branched chain hydrocarbon radicals having at least one double bond.

The term "aryl" as used herein, includes within its meaning monovalent, single, polynuclear, conjugated and fused aromatic hydrocarbon radicals.

Brief Description of the Drawings

The present invention will now be described, by way of example only, with reference to the following drawings:

Figure 1. Effect of intraperitoneal albendazole treatment (150mg/kg x 3 weekly for 4 weeks) on ascites production in nude mice bearing peritoneal OVCAR-3 tumours. Ascites fluid volume (ml) in control and albendazole (ABZ) treated mice. Each value represents the mean ± s.e. of 6 to 8 determinations.

Figure 2. Effect of albendazole on the number of OVCAR-3 cells present in peritoneal ascites fluid aspirated from tumour-bearing nude mice. Each value represents the mean ± s.e. of 6 to 8 determinations.

Figure 3. Effect of albendazole on total weight of peritoneal tumours from nude mice. Each value represents the mean ± s.e. of 6 to 8 determinations.

Figure 4. Effect of albendazole on CA-125 levels in OVCAR-3 tumour-bearing from nude mice. Each value represents the mean ± s.e. of 6 to 8 determinations.

Figure 5. VEGF levels in the peritoneal fluid of nude mice bearing peritoneal OVCAR-3 tumours. Each value represents the mean ± s.e. of 6 to 8 determinations.

Figure 6. Effect of albendazole on plasma VEGF levels in nude mice bearing OVCAR-3 tumours. Each value represents the mean ± s.e. of 6 to 8 determinations.

Figure 7. RT-PCR presenting various VEGF mRNA isoforms extracted from cells aspirated from ascites fluid or peritoneal wash of nude mice bearing peritoneal OVCAR-3 tumours. **A-C** are cells from control animals, while, **D-F** were extracted from albendazole treated intraperitoneally (150 mg/kg x 3 weekly for 4 weeks) animals.

Figure 8. Effect of 6 hour albendazole treatment on VEGF production in SKOV-3 cells *in vitro*. Each value represents the mean ± s.e of 4 determinations. **A.** VEGF levels (pg/10^5 cells) in the presence of varying concentrations (μM) of albendazole. **B.** VEGF levels (pg/10^5 cells) in the presence of varying concentrations (μM) of albendazole following co-treatment with 6 ng/ml MMP-9.

Figure 9. Retinal neovascularisation (blood vessel count) in mice under normoxic and hyperoxic (75% O_2) conditions following treatment with DMSO, PBS or varying concentrations of albendazole (0.1 μg, 1 μg or 10 μg in 2 μl).

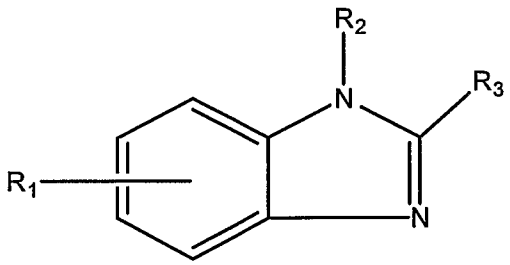
Figure 10. Light micrographs of haematoxylin and eosin stained cross sections (50 μm) of mouse retinas following injection with albendazole in DMSO (**A**) or DMSO alone (**B**).

Best Mode of Performing the Invention

Benzimidazole carbamate compounds are broad-spectrum anthelmintic drugs, widely used for the control of helminth parasites in mammals, including humans. The primary target of benzimidazole carbamates is believed to be tubulin, the compounds acting to inhibit tubulin polymerization and destabilize microtubules. One such benzimidazole carbamate is albendazole (methyl 5-propylthio-IH-benzimidazole-2-yl carbamate). Other benzimidazole carbamates include mebendazole, flubendazole, triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

The present inventors have previously found that albendazole has an anti-proliferative effect on a range of cancer cell lines *in vitro* and on cancers in animal models and clinical studies (WO 02/076454, the disclosure of which is incorporated herein by reference). As disclosed herein, the present inventors have now demonstrated that albendazole has a potent effect on VEGF levels secreted by human ovarian cancer cells *in vitro*, on ascites production, retinal neovascularisation and on VEGF levels *in vivo*.

Accordingly, one aspect of the present invention relates to a method for inhibiting VEGF production or secretion by a cell in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



I

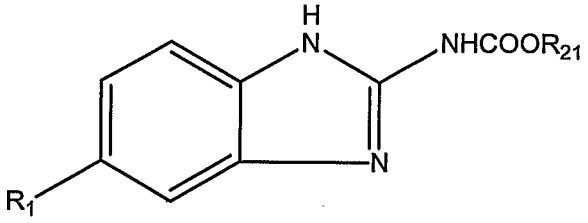
wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, -

SR_{14}, $-OR_{15}$, $-SOR_{16}$, -SCN, $-SO_2R_{17}$, $-C(O)-R_{18}$, $-OR_{19}$, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl; or an analogue, metabolite or derivative thereof.

Typically the compound is a benzimidazole carbamate of formula II

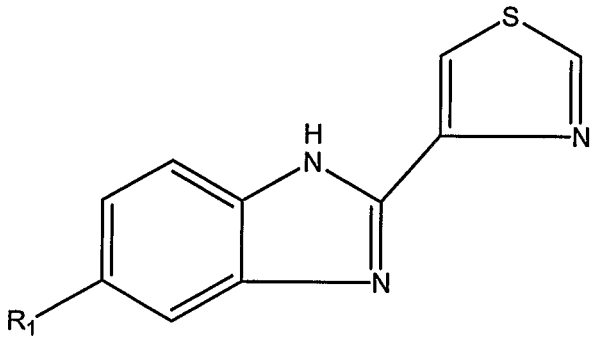


II

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_{21} is H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloakenylalkyl, aryl or arylalkyl,

or of formula III



III

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4.

Those skilled in the art will readily appreciate that isomers, including stereoisomers and geometric isomers, of the above described compounds may exists and the use of such isomers

are included within the scope of the present invention. Further, the use of tautomeric forms of the above compounds is also contemplated. For example the substituted benzimidazole group may exist in a number of tautomeric forms, including where the R_1 substituent is in any one of the 4 to 7 positions.

Albendazole or a metabolite, derivative or analogue thereof (such as albendazole sulphoxide or albendazole sulfone) is one bezimidazole carbamate particularly useful in methods and compositions of the present invention. However it will be readily appreciated by those skilled in the art that other bezimidazole carbamates may also be employed. For example other suitable bezimidazole carbamates include, but are not limited to, mebendazole, flubendazole, triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

Conditions

A compound as described above may act to inhibit the cellular production of VEGF and/or may inhibit secretion of VEGF from cells in the subject undergoing treatment. Accordingly, the present invention provides methods and compositions for the treatment or prevention of conditions associated with abnormal, typically increased, levels of VEGF production or secretion, including conditions associated with increased vascular permeability, using such compounds as described above. Conditions to which methods and compositions of the invention are applicable include, but are not limited to, ascites, cirrhosis and other ascites-associated conditions, pleural effusion, cerebral oedema, pulmonary oedema, ischaemic heart disease, macular degeneration such as age-related macular degeneration, proliferative retinopathy, diabetic retinopathy, retinopathy of prematurity psoriasis, endometriosis and arthritis, such as rheumatoid arthritis.

The inventors' findings as disclosed herein demonstrate that intra-peritoneal administration of albendazole rapidly reduces serum VEGF levels. Thus, the monitoring of serum VEGF levels will enable the design and implementation of appropriate benzimidazole carbamate therapy for patients in need of such therapy. Accordingly, an embodiment of the present invention provides a method for designing a benzimidazole carbamate treatment therapy for a subject, comprising monitoring the serum VEGF concentration in the subject in the presence and absence of one or more candidate benzimidazole carbamates and adjusting the identity and/or dosage of the benzimidazole carbamates so as to achieve a reduction in tumour or serum VEGF concentration.

Compositions and routes of administration

Embodiments of the present invention contemplate compositions for inhibiting VEGF production or secretion in a subject and for treating or preventing a condition associated with abnormal levels of production or secretion of VEGF.

According to the methods of present invention compounds and compositions may be administered by any suitable route, either systemically, regionally or locally. The particular route of administration to be used in any given circumstance will depend on a number of factors, including the nature of the condition to be treated, the severity and extent of the condition, the required dosage of the particular compound to be delivered and the potential side-effects of the compound.

For example, in circumstances where it is required that appropriate concentrations of the desired compound are delivered directly to the site in the body to be treated, administration may be regional rather than systemic. Regional administration provides the capability of delivering very high local concentrations of the desired compound to the required site and thus is suitable for achieving the desired therapeutic or preventative effect whilst avoiding exposure of other organs of the body to the compound and thereby potentially reducing side effects.

By way of example, administration according to embodiments of the invention may be achieved by any standard routes, including intracavitary, intravesical, intramuscular, intraarterial, intravenous, intraocular, subcutaneous, topical or oral. Intracavitary administration may be intraperitoneal or intrapleural. For example, in the treatment of ascites the desired compound may be administered intra-peritoneally and for the treatment of pleural effusion administration may be intra-pleural.

In general, suitable compositions may be prepared according to methods which are known to those of ordinary skill in the art and may include a pharmaceutically acceptable diluent, adjuvant and/or excipient. The diluents, adjuvants and excipients must be "acceptable" in terms of being compatible with the other ingredients of the composition, and not deleterious to the recipient thereof.

Examples of pharmaceutically acceptable diluents are demineralised or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oil, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysolpoxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; lower alkanols, for example ethanol or iso-propanol; lower aralkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol, ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrridone; agar; carrageenan; gum tragacanth or gum acacia, and petroleum jelly. Typically, the carrier or carriers will form from 1% to 99.9% by weight of the compositions.

For administration as an injectable solution or suspension, non-toxic parenterally acceptable diluents or carriers can include, Ringer's solution, medium chain triglyceride (MCT), isotonic saline, phosphate buffered saline, ethanol and 1,2 propylene glycol.

Some examples of suitable carriers, diluents, excipients and adjuvants for oral use include peanut oil, liquid paraffin, sodium carboxymethylcellulose, methylcellulose, sodium alginate, gum acacia, gum tragacanth, dextrose, sucrose, sorbitol, mannitol, gelatine and lecithin. In addition these oral formulations may contain suitable flavouring and colourings agents. When used in capsule form the capsules may be coated with compounds such as glyceryl monostearate or glyceryl distearate which delay disintegration.

Adjuvants typically include emollients, emulsifiers, thickening agents, preservatives, bactericides and buffering agents.

Solid forms for oral administration may contain binders acceptable in human and veterinary pharmaceutical practice, sweeteners, disintegrating agents, diluents, flavourings, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatine, corn starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, guar gum, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

Liquid forms for oral administration may contain, in addition to the above agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

Suspensions for oral administration may further comprise dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or acetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as

stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

Emulsions for oral administration may further comprise one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as guar gum, gum acacia or gum tragacanth.

Methods for preparing parenterally administrable compositions are apparent to those skilled in the art, and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa., hereby incorporated by reference herein.

The composition may incorporate any suitable surfactant such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The compositions may also be administered in the form of liposomes. Liposomes are generally derived from phospholipids or other lipid substances, and are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The compositions in liposome form may contain stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art, and in relation to this specific reference is made to: Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, the contents of which is incorporated herein by reference.

Compounds and compositions disclosed herein may be administered either therapeutically or preventively. In a therapeutic application, compounds and compositions are administered to a patient already suffering from a condition, in an amount sufficient to cure or at least partially arrest the condition and its symptoms and/or complications. The compound or composition should provide a quantity of the active compound sufficient to effectively treat the patient.

The effective dose level of the administered compound for any particular subject will depend upon a variety of factors including: the type of condition being treated and the stage of the condition; the activity of the compound employed; the composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of sequestration of compounds; the duration of the treatment; drugs used in combination or coincidental with the treatment, together with other related factors well known in medicine.

One skilled in the art would be able, by routine experimentation, to determine an effective, non-toxic dosage which would be required to treat applicable conditions. These will most often be determined on a case-by-case basis.

Generally, an effective dosage is expected to be in the range of about 0.0001mg to about 1000mg per kg body weight per 24 hours; typically, about 0.001mg to about 750mg per kg body weight per 24 hours; about 0.01mg to about 500mg per kg body weight per 24 hours; about 0.1mg to about 500mg per kg body weight per 24 hours; about 0.1mg to about 250mg per kg body weight per 24 hours; or about 1.0mg to about 250mg per kg body weight per 24 hours. More typically, an effective dose range is expected to be in the range of about 10mg to about 200mg per kg body weight per 24 hours.

Alternatively, an effective dosage may be up to about 5000mg/m^2. Generally, an effective dosage is expected to be in the range of about 10 to about 5000mg/m^2, typically about 10 to about 2500mg/m^2, about 25 to about 2000mg/m^2, about 50 to about 1500mg/m^2, about 50 to about 1000mg/m^2, or about 75 to about 600mg/m^2.

Further, it will be apparent to one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the nature of the particular individual being treated. Also, such optimum conditions can be determined by conventional techniques.

It will also be apparent to one of ordinary skill in the art that the optimal course of treatment, such as, the number of doses of the composition given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The present invention will now be further described in greater detail by reference to the following specific examples, which should not be construed as in any way limiting the scope of the invention.

Examples

Example 1- Albendazole treatment of OVCAR-3 peritoneal tumour bearing nude mice

Cells of the cell line NIH:OVCAR-3 (ATCC Accession No. HTB 161) have the capacity to grow intra-peritoneally in female nude athymic mice. After intra-peritoneal injection, animals develop metastatic spread similar to that of clinical ovarian cancer. Disease progression is characterized by development of massive ascites production, extensive intra-peritoneal tumours and pulmonary metastases. The malignant ascites cells express the ovarian cancer associated antigen CA-125. The mouse model exhibits histopathological and embryological features consistent with human ovarian cancer, a reproducible pattern of metastases which parallels the

human disease, suitable markers for following response to treatment, and drug sensitivity profiles similar to those of human ovarian cancer (Hamilton *et al.,* 1984).

OVCAR-3 cells (13 x 10 ^{6}) cultured in vitro were injected subcutaneously into nude mice. Eight weeks later tumours were dissected, minced and washed x 3 in PBS. The cultured cells were suspended in 0.3% of Bacto agar in RPMI supplemented with 20% horse serum, penicillin (100 u/ml) streptomycin (2mg/ml) and insulin 3 u/ml, EGF 100 ng/ml, asparagine (0.1mg/ml) and DEAE dextran 0.5mg/ml to yield a cell density of 5 x 10 ^{6} cells per ml. 2-mercaptoethanol was added at a concentration of 50 μM just before cells were plated. A portion (1 ml) of the resultant mixture was added onto a feeder layer which combined 0.2 ml of medium conditioned by adherent spleen cells of mineral oil-primed BALB/c mice in 0.5% Bactoagar. Cultures were incubated at 37° C in 5% CO_2. At 5 day intervals, 0.8 ml of growth medium with EGF (10 ng/ml) was layered onto the agarose surface. After 3 weeks, colonies of cells were harvested in mass and plated in 75 cm2 flasks. These cells were then injected subcutaneously into mice. 50 x 10^{6} tumour cells harvested from these subcutaneously tumours were suspended in 1 ml of medium and injected intra-peritoneally into each carrier nude mouse. Ascites fluid was collected, washed with sterile saline, and centrifuged at 300g and 4°C for 5 minutes.

10 x 10 ^{6} viable tumour cells collected from the ascites fluid and suspended in 1.0 ml of medium (RPMI 1640) were injected intra-peritoneally into each test animal. For all experiments, 6-8 weeks old nude female athymic Balb c nu/nu mice (Animal Resources Centre, Perth, Western Australia) were used as test animals. These animals were housed in pathogen-free isolated conditions in the Biological Resources Centre of the University of New South Wales and were fed autoclaved pellets and water ad libitum. The general health of the animals was checked daily. All protocols used were approved by the University of New South Wales Animal Ethics Committee.

Mice inoculated intra-peritoneally as described above were randomly distributed into either the albendazole treated or control groups. Drug treatment was initiated (x 3 weekly for 4 weeks). Albendazole suspended in 0.5% carboxymethylcellulose was administered at a dose of 150 mg/kg to all treated animals. For oral administration, a suspension of 15 mg/ml was prepared (0.1 ml/10 g body weight) while for intra-peritoneal treatments a suspension of 3mg/ml was used (3mg/1 ml/20 g mice).

Immediately prior to euthanasia, animals were anaesthetised with pentobarbitone, and blood samples were collected through cardiac puncture. Animals were then euthanized by an overdose of the anaesthetic drug. For collection of the ascites fluid, 2 ml of physiological saline was injected intra-peritoneally and the contents of the peritoneal cavity were mixed by kneading. Peritoneal fluid was then recovered, its volume recorded (Figure 1) and the number of viable tumour cells

present counted (Figure 2). Plasma and cell-free ascites fluid were stored at –80° C for subsequent analysis.

Tumours present in the peritoneal cavity were dissected, weighed (Figure 3) and stored for subsequent analysis. Animals were also checked for the presence of metastasis in lung, liver, spleen, stomach and pancreas (data not shown). Tumour marker (CA-125) levels (Figure 4) were analyzed by St George Hospital Biochemistry laboratories. VEGF concentrations in ascites fluid (Figure 5) and plasma (Figure 6) were determined using Elisa kits (Quantikine R& D systems).

The results obtained demonstrate that in OVCAR-3 tumour bearing mice intra-peritoneal albendazole treatment leads to dramatic reductions in ascites volume and VEGF levels.

VEGF isoforms

OVCAR-3 cells isolated from ascites fluid of nude mice bearing tumours (as described above) were examined for the expression of mRNA for various VEGF isoforms ($VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, $VEGF_{206}$) by RT-PCR. Cells were separated through centrifugation (5min at 1500 rpm) and total RNA was isolated from the remaining cell-pellet by using the High Pure RNA Isolation Kit (Roche Diagnostics Corporation) according to the manufacturer's protocol. The RNA concentration was measured in a spectrophotometer at the wavelength of 260 nm using a Quartz Spectrophotometer Cell (BioRad).

Primers for amplification of VEGF were constructed on the basis of the sequences presented in Pellizzaro *et. al* 2002; VEGF sense: 5'-CAC ATA GGA GAG ATG AGC TTC-3' (SEQ ID NO:1); VEGF antisense: 5'-CCG CCT CGG CTT GTC ACA T-3' (SEQ ID NO:2). These primers amplify the following products: 100 bp for $VEGF_{121}$, 230 bp for $VEGF_{165}$, 300 bp for $VEGF_{189}$ and 320 bp for $VEGF_{206}$. The β-Actin gene was used as an internal control (202bp) using primers as follows: β-Actin sense: 5'-CTT CCT GGG CAT GGA GTC CT-3' (SEQ ID NO:3); β-Actin antisense: 5'-GGA GCA ATG ATC TTG ATC TT-3' (SEQ ID NO:4) (Marchini *et. al.* 1996).

250ng/50ng of total RNA was used to amplify VEGF/β-Actin using the SuperScript™One Step RT-PCR with Platinum®*Taq* (Invitrogen). RNA was diluted with DEPC treated water to a final volume of 11 µl for one RT-PCR reaction. 12.5µl 2xReaction Mix (final concentration 1x), 1 µl Primer Mix (40µl DEPC-water, 5µl 100 µM Sense Primer, 5 µl 100 µM Antisense Primer; final Primer-concentration 0.2µM) and 0.5µl RT/Platinum®*Taq* were added to the RNA dilution (total volume of one reaction = 25 µl). To keep the enzymes (RNAse & Taq) inactive all pipette-steps were performed on ice. The amplification was carried out in a Palm Cycler (Corbett Research) after an initial cDNA synthesis at 54°C for 30min and 5min at 94°C for denaturation. This was followed by 27 cycles (denaturation at 94°C for 1min, primer annealing at 60°C for 1min, primer extension at 72°C for 45 s) and a final extension of 72°C for 10min.

The RT-PCR products were visualized by electrophoresis (25min at 120V) on 2% agarose gel in 1xTAE buffer containing ethidium bromide. To quantify the size of the products a 100bp DNA ladder (Invitrogen) was run with the samples. The results are shown in Figure 7 which demonstrates that intra-peritoneal albendazole administration led to a significant reduction in the expression of VEGF mRNA.

Example 2- Effect of albendazole on *in vitro* VEGF secretion

SKOV-3 human cystadenocarcinoma cell line, obtained from the American Type Culture Collection (ATCC Accession No. HTB 77) were grown in McCoy's 5a medium with 1.5 mM L-glutamine, 100 units/ml penicillin, and 100 µg/ml streptomycin, supplemented with 10% FCS. Cells were grown to confluence and harvested by trypsinization with 0.25 mg/ml trypsin/EDTA and suspended in the medium before plating. These were then seeded (2×10^5) on plastic 6-well Corning culture plates. Cultures were maintained in a 37°C incubator in a humidified atmosphere of 95% O2/5% CO_2. Twenty-four hours later, the medium was removed. Subconfluent cultures were washed three times with phosphate buffer followed by incubation for 6 hours with culture medium containing various concentrations of albendazole (0, 0.1, 0.25 and 1.0 µM) dissolved in 1% ethanol. After completion of the treatment period, medium from the wells were individually collected and analysed for the VEGF concentration using an enzyme-linked immunosorbant assay (ELISA) that detects soluble $VEGF_{121}$ and $VEGF_{165}$ isoforms (Quantikine R& D systems, Minneapolis, USA).

In another set of experiments, while keeping all other conditions constant, the matrix metalloproteinase MMP-9 (6 ng/ml) was used to stimulate cells to increase VEGF production prior to treatment with albendazole. There is evidence that MMP-9 induces the release of biologically active VEGF in the culture medium of ovarian tumour cells and in ascites of ovarian tumour-bearing mice (Belotti *et al.*, 2003). SKOV-3 cells were exposed to the recombinant activated form of MMP-9, which was directly added to the cell culture medium containing various concentrations of albendazole.

Results obtained for both sets of experiments are presented in Figure 8. It is clear from these results that treatment of SKOV-3 cells (which constitutively release VEGF) with various concentrations of albendazole leads to dose-dependent reduction in VEGF secretion. Using a haemocytometer and Trypan blue exclusion method, viability of cells present in each well was checked (at the end of the treatment period) and the VEGF concentration calculated as picograms per 10^5 cells. Although due to the antiproliferative action of albendazole, cells could not be incubated for longer than 6 hours, a dose -dependent reduction in VEGF concentration was observed. In the absence of MMP-9, at the highest albendazole concentration used (1.0 µM), VEGF concentration were reduced by 64% (Figure 8A). Stimulation of cells with MMP-9 led to a

44.8% increase in VEGF concentration in 6 hours (Figure 8B). Albendazole treatment of MMP-9 stimulated cells led to profound reduction in VEGF concentrations; VEGF concentrations in the 1 μM albendazole treated cells were reduced by 65%. In these cells and under the described conditions, 0.1 μM albendazole blocked the excess VEGF secretion induced by MMP-9 stimulation.

These results clearly show that albendazole profoundly reduces VEGF secretion from SKOV-3 human ovarian cancer cells *in vitro*.

Example 3- Inhibition of neovascularisation in a murine model of proliferative retinopathy

The ability of albendazole to serve as a potential inhibitor of age-related macular degeneration (AMD) was evaluated in a well-established murine model of retinal neovascularisation, ROP (retinopathy of prematurity), relevant to AMD.

The experiments described below were approved by the UNSW Animal Care and Ethics Committee.

Postnatal day 6 (P6) C57BL/6 mice were exposed to hyperoxic (75% oxygen) for 4 days in Quantum-Air Maxi-Sealed cages (Hereford, UK). P10 mice were returned to normoxia, anaesthetized (17 mg/kg ketamine and 2.5 mg/kg xylazine) and bolus intravitreal injections of volume 2μl, containing 0.1, 1 or 10μg albendazole in DMSO; DMSO alone or 1x PBS alone were administered using a 26 gauge beveled needle attached to a micro syringe (SGE International, Melbourne, Australia). Mice remained at room oxygen for a further 7 days then eyes were removed and fixed in 10% formalin/PBS. Serial cross sections (50 microns) were stained with haematoxylin and eosin. Blood vessels from each group were counted under light microscopy (400x) and expressed as the mean ± SEM.

As shown in Figure 9, hyperoxia-normoxia produced a 2-3-fold increase in retinal neovascularisation. Albendazole significantly inhibited hyperoxia-induced retinal angiogenesis following single intravitreal injection of the drug. Inhibition was dose-dependent and observed with amounts as little as 1ug. DMSO alone (the albendazole vehicle) did not affect blood vessel formation in hyperoxia-exposed mice, with blood vessel counts not different from those in the PBS group.

Statistical analysis of the results shown graphically in Figure 9 was performed using a 2-tailed Student's t-test with unequal variance (Table 1).

Table 1: Statistical significance of albendazole treatment

DMSO v 10ug albendazole	P=0.000651889
DMSO v 1ug albendazole	P=0.000117785
DMSO v 0.1ug albendazole	P=0.305488779
1ug v 10ug albendazole	P=0.654672771
1ug v 0.1ug albendazole	P=0.0000853701

Haematoxylin and eosin stained sections (Figure 10) revealed that there was no detectable morphological difference between the DMSO alone injected group (Figure 10B) and the albendazole + DMSO injected group (Figure 10A), other than neovascularisation, suggesting that, within the confines of this study, no adverse or toxic reaction towards albendazole and/or its vehicle, DMSO.

Example 4- Compositions for treatment

In accordance with the best mode of performing the invention provided herein, specific compositions are outlined below. The following are to be construed as merely illustrative examples of compositions and not as a limitation of the scope of the present invention in any way.

Example 4(A)- Composition for parenteral administration

A composition for parenteral injection could be prepared to contain 0.05 mg to 5 g of a compound of formula I (such as albendazole) in 10 mls to 2 litres of 1% carboxymethylcellulose.

Similarly, a composition for intravenous infusion may comprise 250 ml of sterile Ringer's solution, and 0.05 mg to 5 g of a compound of formula I.

A composition suitable for administration by injection may also be prepared by mixing 1% by weight of the compound in 10% by volume propylene glycol and water. The solution can be sterilised by filtration.

Example 4(B)- Composition for oral administration

A composition of a compound of formula I in the form of a capsule may be prepared by filling a standard two-piece hard gelatin capsule with 500 mg of the compound, in powdered form, 100 mg of lactose, 35 mg of talc and 10 mg of magnesium stearate.

Example 4(C)- Composition for topical administration

A typical composition for delivery as a topical ointment includes 1.0 g of a compound of formula I, together with white soft paraffin to 100.0 g, dispersed to produce a smooth, homogeneous product.

Example 4(D) - Eye Drop Composition

A typical composition for delivery as an eye drop is outlined below:

Suitbale compound	0.3 g
Methyl Hydroxybenzoate	0.005 g
Propyl Hydroxybenzoate	0.06 g
Purified Water about to	100.00 ml.

The methyl and propyl hydroxybenzoates are dissolved in 70 ml purified water at 75°C, and the resulting solution is allowed to cool. The compound is then added, and the solution sterilised by filtration through a membrane filter (0.22 μm pore size), and aseptically packed into sterile containers.

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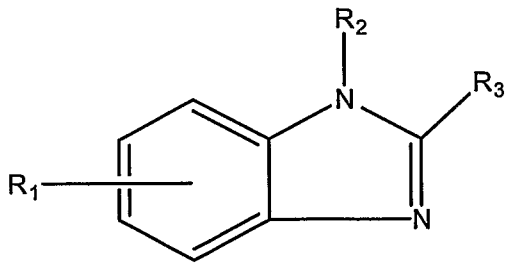
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Claims

1. A method for inhibiting VEGF production or secretion in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



I

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

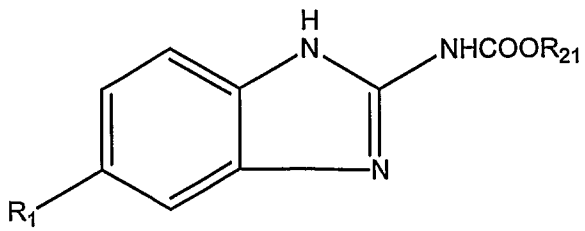
R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, $-SR_{14}$, $-OR_{15}$, $-SOR_{16}$, $-SO_2R_{17}$, -SCN, $-C(O)-R_{18}$, $-OR_{19}$, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

or an isomer, metabolite, derivative or analogue thereof.

2. The method of claim 1 wherein the R_1 substitution occurs in the 5 or 6 position.

3. The method of claim 1 or 2 wherein the compound is a benzimidazole carbamate of Formula II:

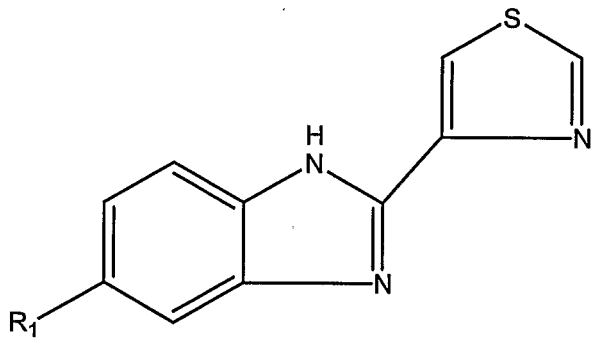


II

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, -SR_7, -SOR_8, -SO_2R_9, -SCN, B'$(CH_2)_nBR_{10}$, -C(O)-R_{11} or –OR_{12}, $COOR_{13}$, -NO_2, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_{21} is H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloakenylalkyl, aryl or arylalkyl.

4. The method of any one of claims 1 to 3 wherein the compound is a compound of Formula III:



III

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, -SR_7, -SOR_8, -SO_2R_9, -SCN, B'$(CH_2)_nBR_{10}$, -C(O)-R_{11} or –OR_{12}, $COOR_{13}$, -NO_2, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4.

5. The method of any one of claims 1 to 4 wherein the compound is selected from the group consisting of albendazole, albendazole sulphoxide, mebendazole, flubendazole, triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

6. The method of claim 5 wherein the compound is albendazole, or a metabolite, derivative or analogue thereof.

7. The method of any one of claims 1 to 6 wherein the VEGF is produced or secreted by a tumour cell.

8. The method of claim 7 wherein the tumour cell is an ovarian, colorectal, liver, pancreatic, gastric, endometrial, renal or other primary or metastatic tumour cell.

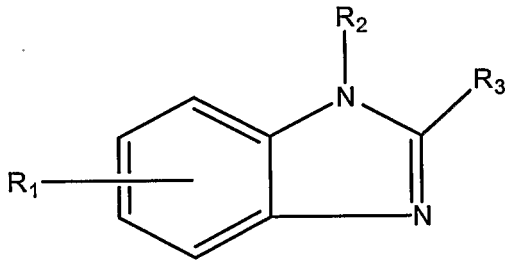
9. The method of any one of claims 1 to 8 wherein the VEGF production or secretion is associated with an accumulation of fluid in a body cavity of the subject.

10. The method of claim 9 wherein the accumulation of fluid in the body cavity is ascites or pleural effusion.

11. The method of any one of claims 1 to 6 wherein the VEGF production or secretion is associated with retinopathic neovascularisation.

12. The method of claim 11 wherein the retinopathic neovascularisation is associated with proliferative retinopathy, diabetic retinopathy, retinopathy of prematurity or macular degeneration.

13. A method for treating or preventing a condition associated with abnormal levels of VEGF production or secretion in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



I

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

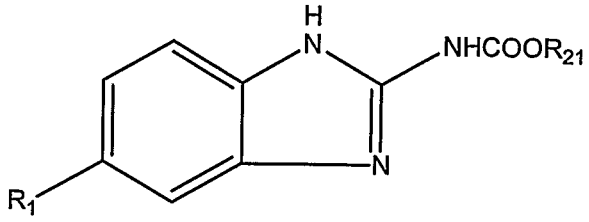
R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, $-SR_{14}$, $-OR_{15}$, $-SOR_{16}$, $-SO_2R_{17}$, -SCN, $-C(O)-R_{18}$, $-OR_{19}$, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

or an isomer, metabolite, derivative or analogue thereof.

14. The method of claim 13 wherein the R_1 substitution occurs in the 5 or 6 position.

15. The method of claim 13 or 14 wherein the compound is a benzimidazole carbamate of Formula II:

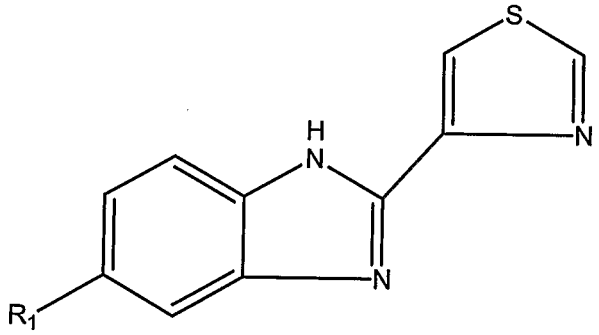


II

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_{21} is H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloakenylalkyl, aryl or arylalkyl.

16. The method of any one of claims 13 to 15 wherein the compound is a compound of Formula III:



III

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4.

17. The method of any one of claims 13 to 16 wherein the compound is selected from the group consisting of albendazole, albendazole sulphoxide, mebendazole, flubendazole, triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

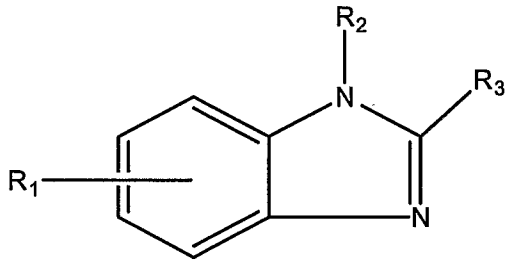
18. The method of claim 17 wherein the compound is albendazole, or a metabolite, derivative or analogue thereof.

19. The method of any one of claims 13 to 18 wherein the condition is associated with increased vascular permeability.

20. The method of any one of claims 13 to 19 wherein the condition is selected from the group consisting of: ascites, cirrhosis, pleural effusion, cerebral oedema, pulmonary oedema, ischaemic heart disease, macular degeneration, proliferative retinopathy, diabetic retinopathy, retinopathy of prematurity, psoriasis, endometriosis and arthritis.

21. The method of claim 20 wherein the arthritis is rheumatoid arthritis.

22. A method for the treatment or prevention of ascites or an ascites-associated condition in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



I

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

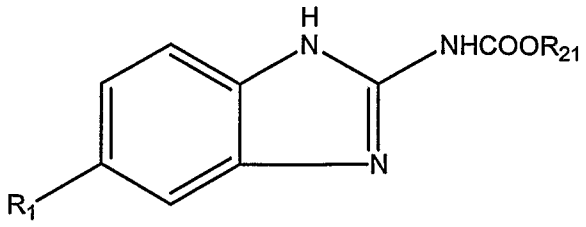
R_2 is selected from H, or substituted or unsubstituted alkyl;

R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, $-SR_{14}$, $-OR_{15}$, $-SOR_{16}$, $-SO_2R_{17}$, -SCN, $-C(O)-R_{18}$, $-OR_{19}$, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

or an isomer, metabolite, derivative or analogue thereof.

23. The method of claim 22 wherein the R_1 substitution occurs in the 5 or 6 position.

24. The method of claim 22 or 23 wherein the compound is a benzimidazole carbamate of Formula II:

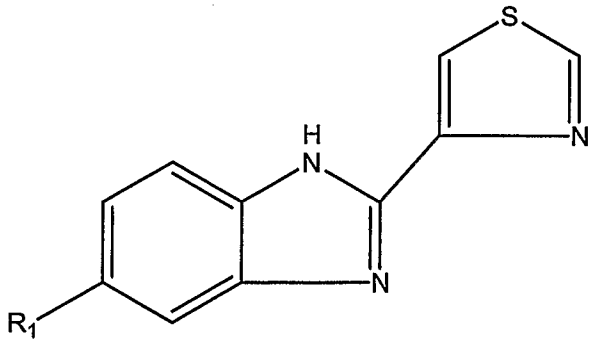


II

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_{21} is H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloakenylalkyl, aryl or arylalkyl.

25. The method of any one of claims 22 to 24 wherein the compound is a compound of Formula III:



III

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4.

26. The method of any one of claims 22 to 25 wherein the compound is selected from the group consisting of albendazole, albendazole sulphoxide, mebendazole, flubendazole,

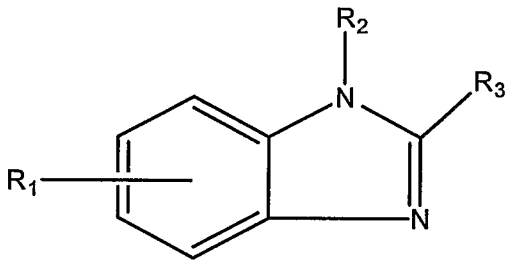
triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

27. The method of claim 26 wherein the compound is albendazole, or a metabolite, derivative or analogue thereof.

28. The method of any one of claims 22 to 27 wherein the ascites is malignant ascites.

29. The method of any one of claims 22 to 27 wherein the ascites-associated condition is cirrhosis.

30. A method for the treatment or prevention of a retinopathic disease in a subject, the method comprising administering to the subject an effective amount of a compound of Formula I:



I

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_2 is selected from H, or substituted or unsubstituted alkyl;

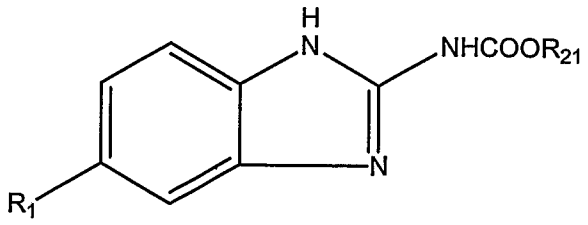
R_3 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, 5- or 6- membered heterocyclic ring the heteroatom(s) of which are selected from one or more of O, S and/or N, $-SR_{14}$, $-OR_{15}$, $-SOR_{16}$, $-SO_2R_{17}$, -SCN, $-C(O)-R_{18}$, $-OR_{19}$, $NR_{20}COOR_{21}$, where R_{15} to R_{21} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl or arylalkyl;

or an isomer, metabolite, derivative or analogue thereof.

31. The method of claim 30 wherein the R_1 substitution occurs in the 5 or 6 position.

32. The method of claim 30 or 31 wherein the compound is a benzimidazole carbamate of Formula II:

31

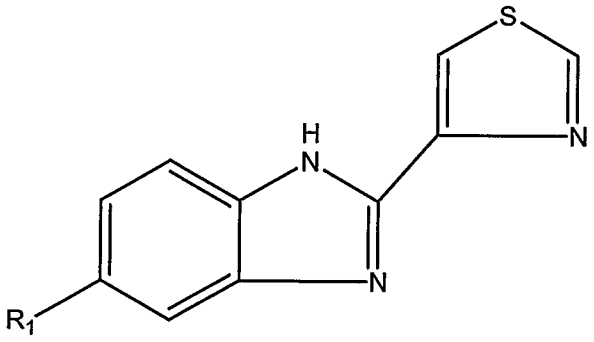


II

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4;

R_{21} is H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloakenylalkyl, aryl or arylalkyl.

33. The method of any one of claims 30 to 32 wherein the compound is a compound of Formula III:



III

wherein R_1 is selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, $-SR_7$, $-SOR_8$, $-SO_2R_9$, -SCN, $B'(CH_2)_nBR_{10}$, $-C(O)-R_{11}$ or $-OR_{12}$, $COOR_{13}$, $-NO_2$, $NR_{13a}COOR_{13b}$, isothiocyanato, or –CN where R_7 to R_{13b} are each independently selected from H, substituted or unsubstituted, straight or branch chain alkyl, alkenyl, alkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenylalkyl, aryl, arylalkyl, B and B' are independently selected from O, S, S(O) or SO_2 and n is 1 to 4.

34. The method of any one of claims 30 to 33 wherein the compound is selected from the group consisting of albendazole, albendazole sulphoxide, mebendazole, flubendazole, triclabendazole, oxfenbendazole, luxabendazole, cambendazole, oxibendazole, parbendazole, thiabendazole, cyclobendazole, dribendazole, etibendazole and fenbendazole.

35. The method of claim 34 wherein the compound is albendazole, or a metabolite, derivative or analogue thereof.

36. The method of any one of claims 30 to 35 wherein the retinopathic disease is selected from proliferative retinopathy, diabetic retinopathy, retinopathy of prematurity and macular degeneration.

37. The method according to any one of the preceding claims wherein the compound is administered systemically or regionally.

38. The method according to any one of the preceding claims wherein administration is intracavitary, intravesical, intramuscular, intraarterial, intravenous, intraocular, subcutaneous, topical or oral.

39. The method of claim 38 wherein intracavitary administration is intraperitoneal or intrapleural.

40. A composition when used for inhibiting VEGF production or secretion by a cell, wherein the composition comprises a compound of Formula I, II or III together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

41. A composition when used for the treatment or prevention of ascites or an ascites-associated condition, wherein the composition comprises a compound of Formula I, II or III together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

42. A composition when used for the treatment or prevention of a retinopathic disease, wherein the composition comprises a compound of Formula I, II or III together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

43. A composition when used for the treatment or prevention of a condition associated with VEGF production or secretion, wherein the composition comprises a compound of Formula I, II or III together with one or more pharmaceutically acceptable carriers, diluents or adjuvants.

44. A method for designing a benzimidazole carbamate treatment regime for a subject, comprising monitoring the serum VEGF concentration in the subject in the presence and absence of one or more candidate benzimidazole carbamates and adjusting the identity and/or dosage of the benzimidazole carbamates so as to achieve a reduction in serum VEGF concentration.

45. A method for treating a subject in need of treatment using a benzimidazole carbamate treatment regime designed according to claim 44.