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(71) Applicants: **İSTİNYE ÜNİVERSİTESİ** [TR/TR]; Maltepe İstinye Üniversitesi Topkapı Kampüsü Teyyareci Sami Sk. No:3, 34010 Zeytinburnu/İstanbul (TR). **İSTANBUL ÜNİVERSİTESİ-CERRAHPAŞA REKTÖRLÜĞÜ** [TR/TR]; Avcılar Kampüsü, 34320 Avcılar/İstanbul (TR).

(72) Inventors: **GÖKMEN, Zeliha**; İstanbul Üniversitesi-Cerrahpaşa Avcılar Kampüsü Mühendislik Fakültesi, 34320 Avcılar/İstanbul (TR). **ULUKAYA, Engin**; İstinye Üniversitesi Topkapı Kampüsü Maltepe Mah. Teyyareci Sami Sk. No:3, Zeytinburnu/İstanbul (TR). **AKAR, Remzi Okan**; İstinye Üniversitesi Topkapı Kampüsü Maltepe Mah. Teyyareci Sami Sk. No:3, Zeytinburnu/İstanbul (TR).

(74) Agent: **YALCINER, Ugur G. (YALCINER PATENT & CONSULTING LTD.)**; Remzi Oguz Arik Mah. Tunus Cad. No:85/3-4, 06680 Cankaya/Ankara (TR).

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(54) Title: AN ANTIMETASTATIC AGENT EFFECTIVE ON PROSTATE CANCER CELLS AND SUITABLE FOR USE IN THE TREATMENT OF THESE DISEASES

(57) Abstract: The invention relates to an agent which shows cytotoxic and anticancer properties and also anti-metastatic effects for prostate cancer cells, is suitable for use in the treatment of diseases caused by cancer cells or the prevention or elimination of metastasis caused by these cancer cells, or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent or a mixture thereof.

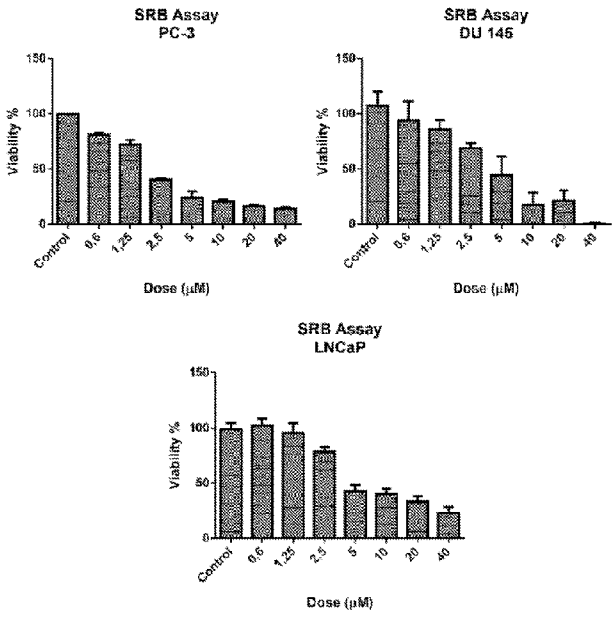


FIGURE 1

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AN ANTIMETASTATIC AGENT EFFECTIVE ON PROSTATE CANCER CELLS AND SUITABLE FOR USE IN THE TREATMENT OF THESE DISEASES

TECHNICAL FIELD

The present invention belongs to the pharmacology technical field and relates to an antimetastatic agent and pharmaceutical compositions comprising these agents, which are effective in prostate cancer cells and can be used to treat diseases associated with these cancer cells or relieve symptoms caused by these diseases.

BACKGROUND

The prostate is the largest accessory gland of the male genital system and constitutes the initial part of the male urethra. The prostate gland, which is made partly of tubuloalveolar glands and partly of intermediate tissue filling between these glands, is 3 cm high, 4 cm wide, and 2 cm thick and has a large walnut size, and weighs about 18-20 grams. The prostate gland is located in the lower part of the small pelvis (pelvis minor), behind the posterior border of the symphysis pubis, in front of the Ampulla Recti, above the Diaphragma Urogenitale and below the bladder. The base (the side facing the bladder) of the prostate gland, which is roughly cone-shaped, is up and the top facing the back is down. The base of the prostate is continuous with the bladder where it is adjacent.

Today, prostate cancer is the most frequently diagnosed cancer among men and the second most common cause of death.

Prostate cancer causes the patient to return to the clinic after a few years by spreading (by metastasizing) to other organs or lymph nodes other than the pelvic region. Therefore, the ability to metastasize is a very important (fatal) feature of prostate cancer. Prostate cancer metastasis usually spreads to the bones or spine. In later stages, it can also metastasize to the lung, liver, distant lymph nodes, or brain. In the art, existing cancer drugs are still insufficient in the treatment of patients with advanced, metastatic prostate cancer. Therefore, it is necessary to investigate strategies for synthesizing and treating stronger and more selective

new drugs with fewer side effects for the treatment of metastatic prostate cancer.

Quinones are widely distributed in nature, and many clinically important antitumor drugs containing quinine, such as anthracyclines, mitoxantrone, and saintopin, show excellent anticancer activity. These anticancer agents are effective inhibitors of DNA topoisomerase, and it is generally known that the cytotoxicity of quinine analogues results from the inhibition of DNA topoisomerase-II. Quinine analogs can also induce the formation of a semiquinone radical, which can transfer an electron to oxygen to produce superoxide. This process is catalyzed by flavoenzymes such as NADPHcytochrome-P-450 reductase. Naphthoquinones are members of the quinone family and due to their anticancer and antitumor properties, many cancers are the subject of research and development to treat the disease and relieve the symptoms caused by these diseases.

It is thought that pharmaceutical molecules with innovations, technical solutions, and advantages should be obtained in the treatment of prostate cancer, which is one of the most common types of cancer among men, and in the treatment of symptoms of these diseases and the prevention of metastasis.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to an antimetastatic agent in which anticancer, antitumor, and antimetastatic properties against prostate cancer cells are determined by studies on PC-3, DU-145, and LNCaP cell lines, known as the prostate cancer cell line.

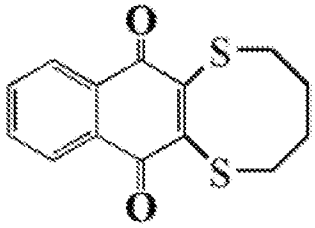
In one aspect, the invention relates to an antimetastatic agent which may exhibit anticancer, antitumor, and antimetastatic properties against prostate cancer cells or which can be used as a drug substance in a pharmaceutical composition to relieve symptoms caused by these diseases.

In one aspect, the invention relates to an antimetastatic agent in which cytotoxic and antimetastatic effects are determined in prostate cancer cell lines for the technical field.

The invention relates in one aspect to an antimetastatic agent which is used to obtain pharmaceutical compositions which are used to relieve prostate cancer diseases or symptoms

caused by these diseases.

In order to achieve all these purposes, the invention is an antimetastatic agent of Formula 2, which has cytotoxic and anticancer properties and anti-metastatic effects for prostate cancer cells, suitable for use in the treatment of diseases caused by cancer cells or in the prevention and elimination of metastasis caused by these cancer cells,



Formula 2

or the pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent, or a mixture thereof.

In another aspect, the invention relates to pharmaceutical compositions comprising Formula 2 or acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers, or a mixture thereof.

A preferred embodiment of the invention is that the pharmaceutical composition comprises an antimetastatic agent shown by Formula 2 or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent or a mixture thereof in the range of 1 μM to 10 μM.

A preferred embodiment of the invention is that the pharmaceutical composition comprises an antimetastatic agent shown by Formula 2 or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent or a mixture thereof in the range of 2.5 μM to 5 μM.

A preferred embodiment of the invention is that the pharmaceutical composition comprises at least one or more excipients.

A preferred embodiment of the invention is that the pharmaceutical composition comprises at least one other active ingredient.

A preferred embodiment of the invention is that the pharmaceutical composition comprises at least one selected from the group consisting of nucleoside analogues, antifloates, other metabolites, topoisomerase I inhibitors, anthracyclines, podophyllotoxins, taxanes, vinca alkaloids, alkylating agents, platinum compounds, antihormones, radiopharmaceuticals, monoclonal antibodies, tyrosine kinase inhibitors, rapamycin mammalian target inhibitors, immune system regulators, histodeacetylase inhibitors as other active ingredients.

In a preferred embodiment of the invention is that the pharmaceutical composition comprises at least one antineoplastic agent and these are selected from a group consisting of cyclophosphamide, ifosfamide, temozolomide, capecitabine, 5-fluoro uracil, methotrexate, gemcitabine, pemetrexed, mitomycin, bleomycin, epirubicin, doxorubicin, etoposide, paclitaxel, irinotecan, docetaxel, vincristine, carboplatin, cisplatin, oxaliplatin, bevacizumab, cetuximab, gefitinib, imatinib, trastuzumab, denosumab, rituximab, sunitinib, zoledronate, abiraterone, anastrozole, bicalutamide, exemestane, goserelin, medroxyprogesterone, octreotide, tamoxifen, bendamustine, carmustine, chlorambucil, lomustine, melphalan, procarbazine, streptozocin, fludarabine, raltitrexed, actinomycin D, dactinomycin, doxorubicin, mitoxantrone, eribulin, topotecan, vinblastine, vinorelbine, afatinib, aflibercept, crizotinib, dabrafenib, interferon, ipilimumab, lapatinib, nivolumab, panitumumab, pembrolizumab, pertuzumab, sorafenib, trastuzumab emtansine, temsirolimus, vemurafenib, ibandronic acid, pamidronate, bexarotene, buserelin, ciproterone, degarelix, folinic acid, fulvestrant, lanreotide, lenalidomide, letrozole, leuprorelin, megestrol, mesna, thalidomide or binary or triple combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the cell viability after 48 hours of administration of the antimetastatic agent at 0.6-40 μM dose range in PC-3, DU 145, and LNCaP cell lines by SRB assay.

Figure 2 shows the detection of apoptosis levels by flow cytometry after 12 and 24 hours of administration of the antimetastatic agent at doses of 2.5 5 and 10 μM in PC-3, DU 145, and

LNCaP cell lines.

Figure 3 shows the EMT-related proteins by western blot method after 12 and 24 hours of administration of the inventive compound at 2.5, 5, and 10 μM doses in PC-3, DU 145, and LNCaP cell lines.

Figure 4 shows the qRT-PCR of the EMT-associated genes after 24 hours of administration of 2.5μM dose of the inventive compound to PC-3, DU 145, and LNCaP cells.

DETAILED DESCRIPTION OF THE INVENTION

In this detailed description, the subject of the invention belongs to the pharmacology technical field and it relates to an antimetastatic agent which is effective in prostate cancer cells and is suitable for use in the treatment of diseases caused by these cancer cells or the relief of the symptoms caused by these diseases, pharmaceutical compositions comprising these molecules and obtaining these molecules, and it is explained with examples that do not have any limiting effect only for a better understanding of the subject.

In the invention, "prostate cancer" is defined as malignant tumoral formations that occur as a result of abnormal and uncontrolled proliferation of prostate gland cells, which are part of the male reproductive system. The symptoms of the disease are not characteristic and usually, one of the complaints of difficulty in urinating, frequent urination, blood in the urine or semen, erection problems, pain during ejaculation, and involuntary weight loss can be experienced. In the invention, the stage of prostate cancer is not important and may be in the first, second, third, or fourth stages.

In the invention, the "PC-3 cell line" is male human prostate cancer cells. First, the PC3 cell line was formed in 1979 from Grade IV bone metastasis of prostate cancer in a 62-year-old white male. These cells do not respond to androgens, glucocorticoids, or fibroblast growth factors, but the results are influenced by the epidermal growth factors of the cells. The PC-3 cell line is considered to be the standard prostate cancer cell line used in therapeutic research for prostate cancer.

In the invention, the "DU 145 cell line" is a human prostate cancer cell line. The DU-145 cell

line was first isolated from the brain of a 69-year-old male patient with prostate disease. This cell line is suitable as a transfection host. The DU145 cell line is considered to be the standard prostate cancer cell line used in therapeutic research for prostate cancer.

In the invention, the "LNCaP cell line" is a cell line of human cells commonly used in the field of oncology. LNCaP cells are androgen-sensitive human prostate adenocarcinoma cells derived from the left supraclavicular lymph node metastasis of a 50-year-old white male in 1977. The LNCaP cell line is considered to be the standard prostate cancer cell line used in therapeutic research for prostate cancer.

In order to determine the antimetastatic activity of the antimetastatic agent of the invention, studies are carried out especially on cell lines with high metastatic activity. The tests performed on these cell lines are essential to have predictions about the antimetastatic activity of the agent of the present invention to provide technical teachings to the relevant technical field. In terms of use in this way, the antimetastatic agent of the present invention will preferably be administered in the form of a pharmaceutical composition. Preferably, the antimetastatic agent of the invention may be included in the pharmaceutical composition as the drug substance or excipient.

In the invention, "treatment or treating" means preventing, alleviation, improving or blocking at least one disorder that characterizes a pathological disorder in a subject threatened by or has a disorder.

In the invention, "relief of symptoms" refers to all kinds of applications aimed at eliminating at least the symptoms and symptoms, that is, the etiology of diseases, even if the disease is not fully treated.

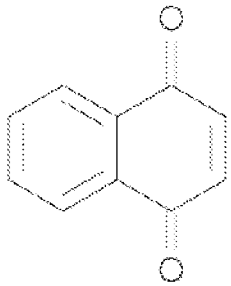
In the invention, the "antimetastatic effect" is the activity of each of the therapeutic products that prevent the spread of cancer cells that have the characteristic of metastasis. Many deaths in cancer diseases are caused by cancer cells with metastatic activity, and reducing the metastatic activity of these cancer cells will allow the recovery rate of cancer diseases to increase and the development of symptoms caused by cancer diseases to be prevented.

The mesenchymal type cell markers mentioned in the invention and scientifically accepted

are vimentin and N-cadherin, where the migration and invasion capacity of the cells is higher, apoptosis-resistant, and extracellular matrix production is increased.

The scientifically accepted epithelial cell marker mentioned in the invention, which is a polarized cell type and is connected to the basal membrane, is E-cadherin.

"Naphthoquinone" is the class of organic compounds structurally associated with naphthalene as known in the art. The naphthoquinone compound class has two isomers, mainly 1,2-naphthoquinone and 1,4-naphthoquinone compounds. The antimetastatic agent of the invention contains the 1,4-naphthoquinone compound as a skeleton. The 1,4-naphthoquinone compound is expressed as Formula 1 for greater clarity.



Formula 1.

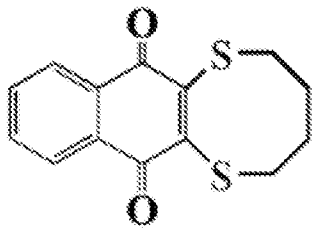
The antimetastatic agent of the invention may contain the compound naphthoquinone as a skeleton, but it has a structure that can cause a cytotoxic effect by reacting with the said cancer cells that can form a treatment for prostate cancer.

The antimetastatic agent of the invention may contain the compound naphthoquinone as a skeleton, but it has a structure that can cause a cytotoxic effect by reacting with the said cancer cells that can form a treatment for prostate cancer. This part, which ensures that the antimetastatic agent has a cytotoxic effect, is .

There are studies and inventions in the relevant technical field that naphthoquinone compounds have a cytotoxic effect on various cancer cells. In the present invention, naphthoquinone compounds, which are already known to have a cytotoxic effect on cancer

cells, can easily enter into communication with prostate cancer cells, and to ensure that they have a high cytotoxic effect for these cells, a thio-crown-ether portion has been added and naphthoquinone compounds have been specifically configured for prostate cancer cells. The innovative aspect of the invention is mainly related to the fact that the agent of the invention, which is known to have anticancer and antitumor effects, has antimetastatic activity. As known in the art, while the anticancer and/or antitumor properties of an antimetastatic agent, therapeutic molecule, or composition are known, whether an anticancer and/or antitumor agent, therapeutic and/or composition has antimetastatic activity or not arises as a result of research and development activities. The present inventors have determined the antimetastatic efficacy of the structure shown in Formula 2 to provide a technical contribution in this direction for the related technical field. The present inventors also share the results of testing and laboratory tests while providing these technical teachings for the related technical field.

The antimetastatic agent of the present invention is configured as Formula 2 to have an antimetastatic and cytotoxic effect on prostate cancer cells.



Formula 2.

PC-3, DU-145, and LNCaP cell lines obtained by the procedures known in the art are used to determine the efficacy of the antimetastatic agent of the present invention for prostate cancer cells.

The antimetastatic agent of the invention was subjected to SRB viability testing for PC-3, DU 145, and LNCaP cell lines at doses of 0.6-40 micromoles (to be abbreviated to μM). The SRB viability test is an indirect test that demonstrates viability based on total protein concentration in cells. The results of the said test are shared in Figure 1. According to the results of this test, the dose suppressing half of the viability (IC50) was 2.5 μM in the PC-3 cell line and 5 μM in DU 145 and LNCaP cell line. Viability was found to decrease in a dose-dependent manner.

Apoptosis activity and stages of the antimetastatic agent of the invention were tested in flow cytometry using "Annexin V". "Annexin V" is a phospholipid-binding protein that binds to phosphatidyl serine (PS) with high affinity and selectivity in the presence of calcium, as known in the art. PS is predominantly located on the inner surface of the cell membrane facing the cytosol. When the cell dies of apoptosis, it emerges from the outer surface facing the cytosol and binds with Annexin V. The attached Annexin V is detected by flow cytometry, so that the apoptotic cell ratio is determined. The results obtained here are shared in Figure 2. According to the results of this test, the antimetastatic agent was found to induce apoptosis in prostate cancer cell lines depending on dose and time. The said molecule was found to increase the rate of late apoptotic cells to 93.61% in the PC-3 cell line; 24.38% in the DU 145 cell line; to 41.84% in the LNCaP cell line after 24 hours at a dose of 10 μM.

To determine their effect on the said cell lines, the present inventors subjected the cells to western blot and QRT-PCR applications to examine changes in target protein and mRNA expression in the cells after applying the antimetastatic agent of formula 2. The target protein and mRNAs selected in the tests were selected to be associated with metastasis and the EMT process. The results of these tests are shared in the description and the figures.

According to the information obtained in the invention, the antimetastatic agent was subjected to a western blot test for PC-3, LNCaP, and DU-145 cell lines. The results of this test are shared in Figure 3. According to the results of this test, especially in PC-3 and DU145 cells with metastatic profiles, mesenchymal markers decrease at the protein level after formula 2 administration, while epithelial markers increase.

Expression levels of metastasis-related genes were examined by QRT-PCR after the antimetastatic agent was applied to PC-3, LNCaP, and DU-145 cell lines according to the information obtained in the invention. The results of this test are shared in Figure 4. According to the results of this test, a dramatic decrease was found in Zeb1 mRNA expression, which was associated with metastasis and poor prognosis in prostate cancer in the clinic after the application of Formula 2.

In all of the tests, it was found that the antimetastatic agent increased the markers of epithelial character and reduced mesenchymal markers in human prostate cancer cell lines PC-3, DU 145, and LNCaP. This indicates that the antimetastatic agent of Formula 2 induces

Mesenchymal-Epithelial Transformation (MET) in these cell lines, thus preventing the metastasis of prostate cancer cells. It is anticipated that the antimetastatic agent of Formula 2 carries out the naphthoquinone skeletal structure with the thio-crown-ether part.

As a result of their research and development activities, the present inventors have determined the doses required for the antimetastatic agent of the invention to show metastatic activity for prostate cancer. Accordingly, the antimetastatic agent of the invention should be used in a range of 1 μM to 10 μM for prostate cancer. As seen in Figure 3, it is seen that the antimetastatic E-cadherin protein is increased in PC-3 and DU145 cell lines by the agent of the invention. In Figure 4, it is seen that the metastatic ZEB-1 gene is suppressed as a result of the administration of the 2.5 μM dose of the agent of the invention for 24 hours.

The antimetastatic e-cadherin protein was increased by the agent of the invention, while the metastatic ZEB-1 gene was suppressed by the agent of the invention, as can be seen in the tests performed on the agent obtained in the invention. Therefore, it has been determined that the agent according to the invention has antimetastatic properties.

In a preferred embodiment of the invention, the drug substance in the pharmaceutical composition is in the range of 1 μM to 10 μM as Formula 2. In the most preferred embodiment, the drug substance in the pharmaceutical composition is in the range of 2.5 μM to 5 μM as Formula 2.

An embodiment of the invention relates to pharmaceutical compositions having antimetastatic activity comprising Formula 2 or pharmaceutically acceptable salts thereof. In the said pharmaceutical compositions, Formula 2 or pharmaceutically acceptable salts thereof may be prepared such that they are rich in an enantiomer. The enantiomerically rich mixture is obtained by an enantiomer constituting, for example, at least 60%, or preferably 75%, 90%, 95%, or 99%, as the molar. In one embodiment of the invention, the mixture enriched from one enantiomer may be prepared such that it hardly contains the other enantiomer.

An embodiment of the invention relates to pharmaceutical compositions comprising Formula 2 or pharmaceutically acceptable salts thereof. In the said pharmaceutical compositions, Formula 2 or pharmaceutically acceptable salts thereof may be prepared such that they are rich in a diastereomer. The diastereomer-rich mixture is obtained by at least 60%, or

preferably 75%, 90%, 95%, or 99% of an enantiomer as molar. The mixture enriched from one diastereomer may be prepared such that the other diastereomer comprises virtually no diastereomer in one embodiment of the invention.

In the present invention, pharmaceutically acceptable hydrates, solvates, polymorphs, and optical isomers of the said Formula 2 may also be used.

An embodiment of the invention relates to pharmaceutical compositions suitable for use in the treatment of prostate cancer comprising Formula 2 or pharmaceutically acceptable salts thereof as the drug substance. The said pharmaceutical compounds comprise at least one or more auxiliaries as well as drug substances according to the invention.

In another embodiment of the invention, the pharmaceutical composition comprising Formula 2 or pharmaceutically acceptable salts thereof as the drug substance may comprise at least one other drug substance.

The pharmaceutical composition of the invention may be selected from a subgroup comprising, but not limited to, nucleoside analogues, antifloates, other metabolites, topoisomerase I inhibitors, anthracyclines, podophyllotoxins, taxanes, vinca alkaloids, alkylating agents, platinum compounds, antihormones, radiopharmaceuticals, monoclonal antibodies, tyrosine kinase inhibitors, rapamycin mammalian target inhibitors, immune regulators, histodeacetylase inhibitors, and other substances.

Anticancer agents may be selected from the group consisting of docetaxel, gemcitabine, imatinib, 5-fluorouracil, 9-aminocaptotesine, amine-modified geldanamycin, doxorubicin, paclitaxel, procarbazine, hydroxyurea, mesocyclone, cisplatin, and radionuclides.

The pharmaceutical composition comprising the antimetastatic agent of the invention can be of any form based on the preferred method of administration to a patient. The composition comprising the antimetastatic agent of the invention may be formulated to be administered orally, for example in the form of liquid dispersions or aqueous or fatty suspensions, or the pharmaceutical composition may be formulated for parenteral administration, for example in the form of subcutaneous, intravenous, intramuscular, sternum, intraperitoneal, intradermal, intradermal or other infusion singles. The pharmaceutical composition comprising the

molecules of the invention may also be formulated for administration as a solution for administration by inhalation in the form of a spray tube or for administration by a respirator or nebulizer. The pharmaceutical composition containing the antimetastatic agent of the invention is preferably administered to the patient transdermal, subcutaneous, intranasal, intravenous, intramuscular, intramuscularly, or by inhalation.

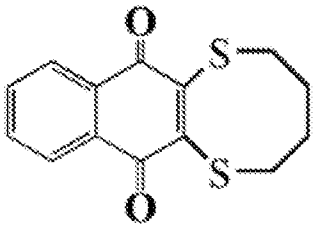
It is intended that the expression "contains" refers to the expression "covers" in the context of this description. Embodiments of the invention may be combined, where technically appropriate.

Embodiments are disclosed herein to include certain features/elements.

The scope of protection of the invention is specified in the attached claims and cannot be limited to those explained for sampling purposes in this detailed description. It is evident that a person skilled in the art may exhibit similar embodiments in light of the above-mentioned facts without drifting apart from the main theme of the invention.

CLAIMS

1. An antimetastatic agent of Formula 2, which has cytotoxic and anticancer properties and anti-metastatic effects for prostate cancer cells, is suitable for use in the treatment of diseases caused by cancer cells or in the prevention and elimination of metastasis caused by these cancer cells,



Formula 2

or the pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent, or a mixture thereof.

2. Pharmaceutical compositions, comprising Formula 2 according to any one of the preceding claims or acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers, or a mixture thereof.

3. A pharmaceutical composition according to claim 2, characterized in that it comprises an antimetastatic agent shown by Formula 2 or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent or a mixture thereof.in the range of 1 µM to 10 µM

4. A pharmaceutical composition according to claim 3, characterized in that it comprises an antimetastatic agent shown by Formula 2 or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, optical isomers, geometric isomers, enantiomers, diastereomers of the said antimetastatic agent or a mixture thereof in the range of 2.5 µM to 5 µM.

5. A pharmaceutical composition according to claim 2, characterized in that it comprises

at least one or more excipients.

6. A pharmaceutical composition according to claims 2 or 3, characterized in that it comprises at least one other active ingredient.

7. A pharmaceutical composition according to claim 4, characterized in that it comprises at least one other active ingredient selected from the group consisting of nucleoside analogues, antifloates, other metabolites, topoisomerase I inhibitors, anthracyclines, podophyllotoxins, taxanes, vinca alkaloids, alkylating agents, platinum compounds, antihormones, radiopharmaceuticals, monoclonal antibodies, tyrosine kinase inhibitors, rapamycin mammalian target inhibitors, immune system regulators, histodeacetylase inhibitors.

8. A pharmaceutical composition according to any one of preceding claims, characterized in that it comprises at least one antineoplastic agent and these are selected from a group consisting of cyclophosphamide, ifosfamide, temozolomide, capecitabine, 5-fluoro uracil, methotrexate, gemcitabine, pemetrexed, mitomycin, bleomycin, epirubicin, doxorubicin, etoposide, paclitaxel, irinotecan, docetaxel, vincristine, carboplatin, cisplatin, oxaliplatin, bevacizumab, cetuximab, gefitinib, imatinib, trastuzumab, denosumab, rituximab, sunitinib, zoledronate, abiraterone, anastrozole, bicalutamide, exemestane, goserelin, medroxyprogesterone, octreotide, tamoxifen, bendamustine, carmustine, chlorambucil, lomustine, melphalan, procarbazine, streptozocin, fludarabine, raltitrexed, actinomycin D, dactinomycin, doxorubicin, mitoxantrone, eribulin, topotecan, vinblastine, vinorelbine, afatinib, aflibercept, crizotinib, dabrafenib, interferon, ipilimumab, lapatinib, nivolumab, panitumumab, pembrolizumab, pertuzumab, sorafenib, trastuzumab emtansine, temsirolimus, vemurafenib, ibandronic acid, pamidronate, bexarotene, buserelin, ciproterone, degarelix, folinic acid, fulvestrant, lanreotide, lenalidomide, letrozole, leuprorelin, megestrol, mesna, thalidomide or binary or triple combinations thereof.

9. The use of an antimetastatic agent shown by Formula 2 for the drug or pharmaceutical composition in the treatment of prostate cancer diseases or the elimination of metastasis caused by these diseases.

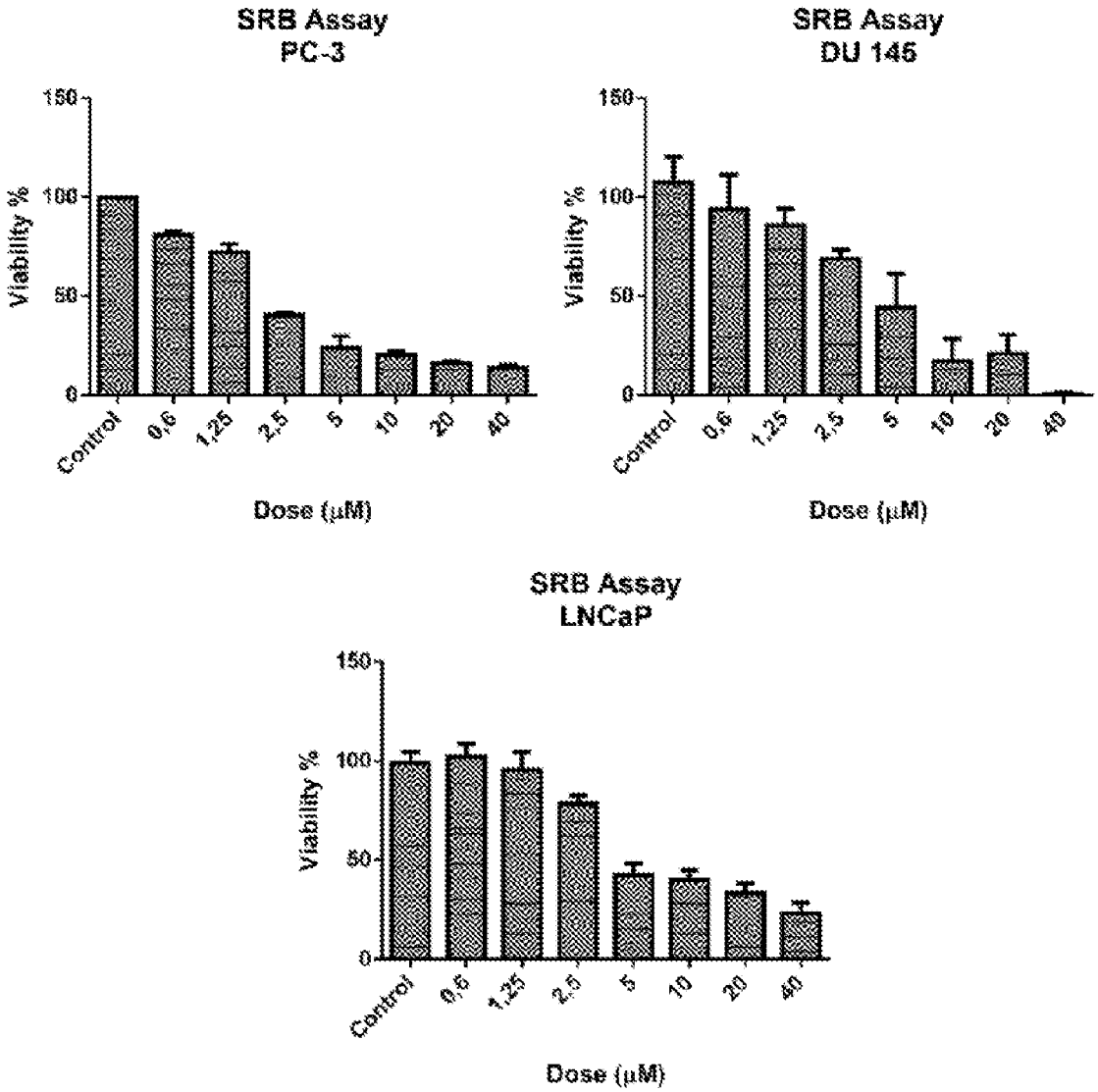

SRB Assay
PC-3
Viability %
150
100
50
0
Control
0,6
1,25
2,5
5
10
20
40
Dose (µM)
SRB Assay
DU 145
Viability %
150
100
50
0
Control
0,6
1,25
2,5
5
10
20
40
Dose (µM)
SRB Assay
LNCaP
Viability %
150
100
50
0
Control
0,6
1,25
2,5
5
10
20
40
Dose (µM)

FIGURE 1

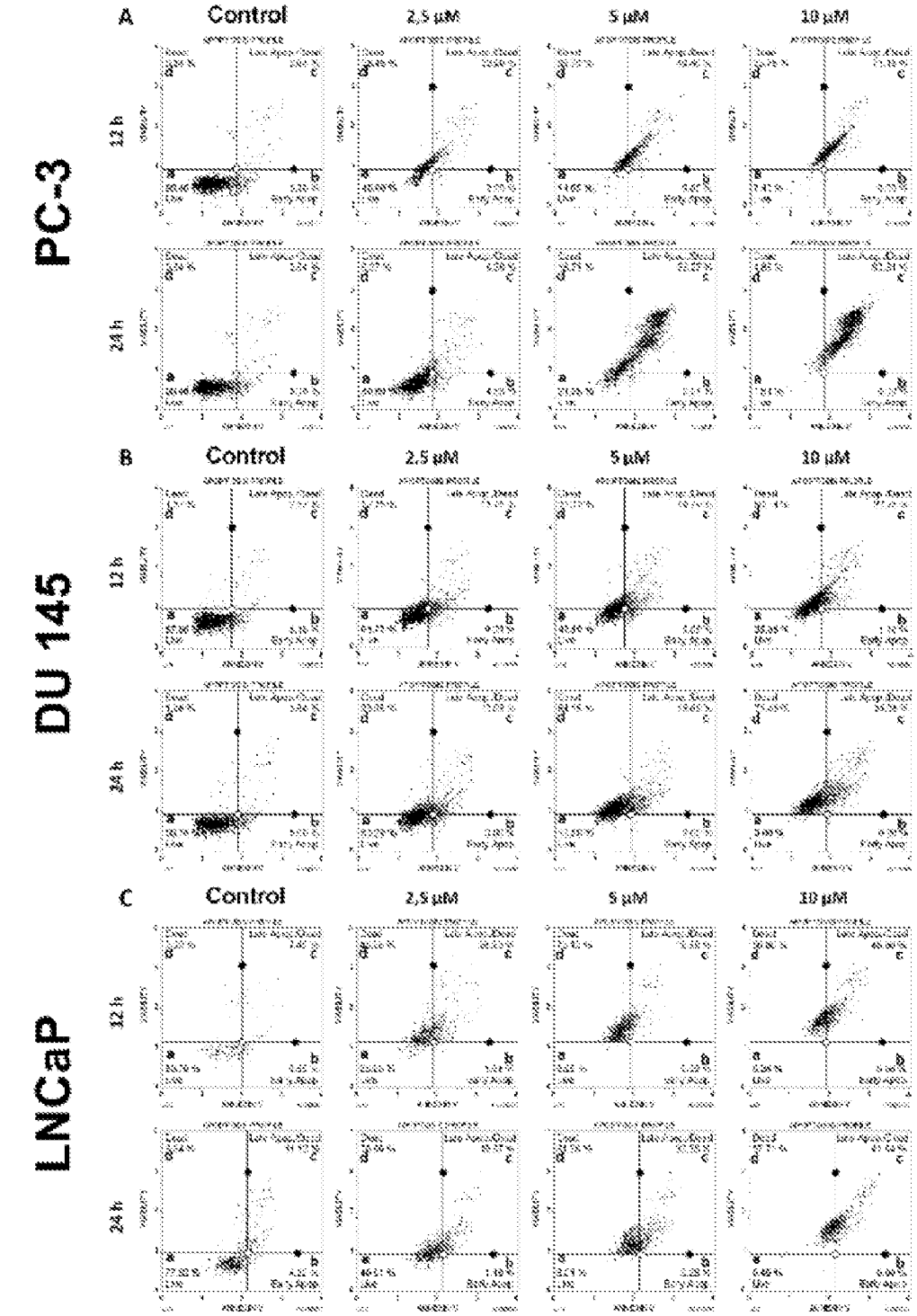

A
Control
2,5 µM
5 µM
10 µM
12 h
24 h
PC-3
B
Control
2,5 µM
5 µM
10 µM
12 h
24 h
DU 145
C
Control
2,5 µM
5 µM
10 µM
12 h
24 h
LNCaP

FIGURE 2

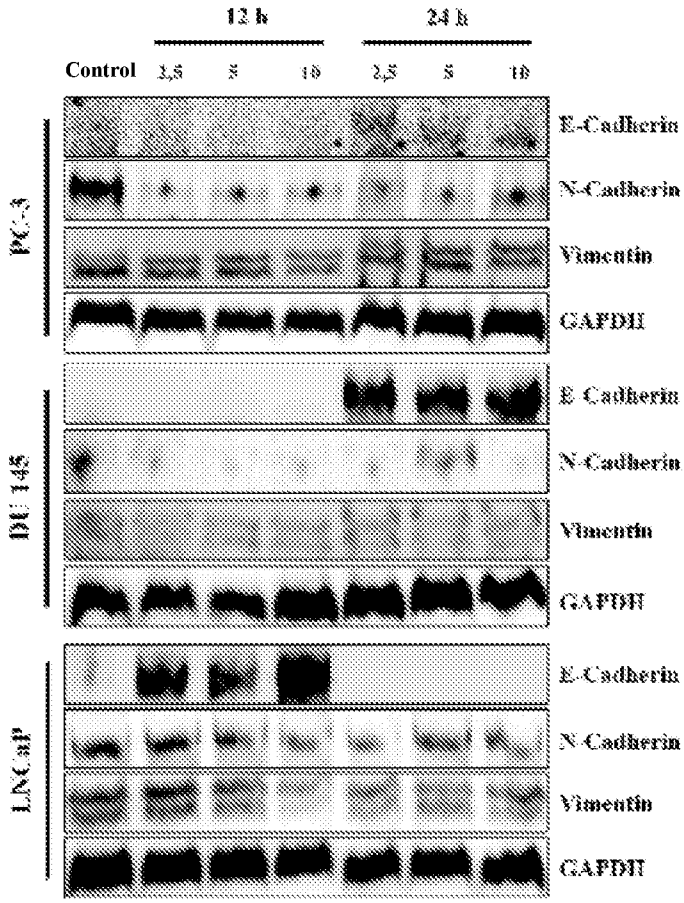


FIGURE 3

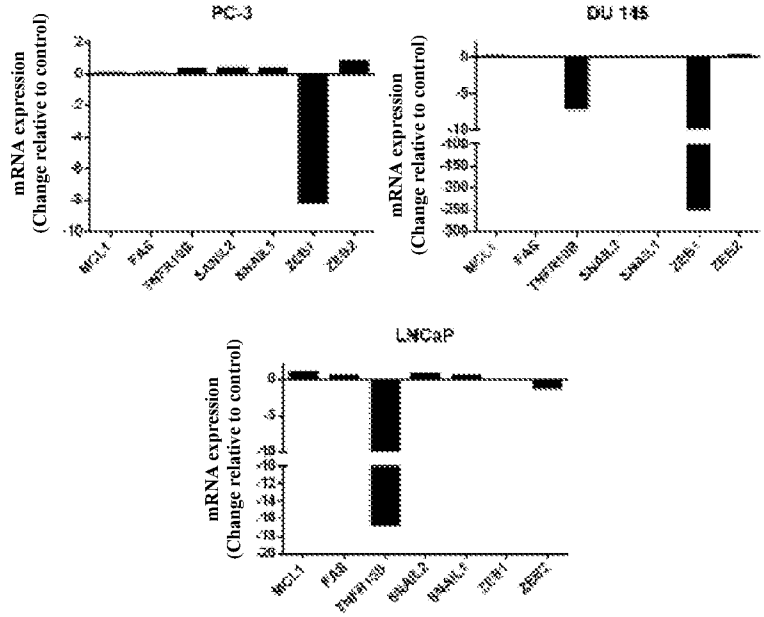


FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2022/051215

A. CLASSIFICATION OF SUBJECT MATTER

A61P 35/00 (2006.01)i; C07C 211/30 (2006.01)i; C07C 211/42 (2006.01)i; C07C 50/12 (2006.01)i; A61K 31/122 (2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P; C07C; A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Epodoc, Patentscope, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 20090247472 A1 (Centre National de la Recherche Scientifique CNRS Universite des Sciences et Tech (Bordeaux 1) Universite de Bordeaux FLUOFARMA) 01 October 2009 (2009-10-01) Abstract, description; paragraph 37, claim 1	1-9
A	JP 5339040 B2 (Mukogawa Gakuin Educational Institution) 04 March 2010 (2010-03-04) Whole document	1-9
A	JP 2689717 C (Summa Health Systems LLC) 21 December 2007 (2007-12-21) Whole document	1-9
A	KR 20000001047 A (KOREA KUMHO PETROCHEM CO LTD [KR]) 15 January 2000 (2000-01-15) Whole document	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2023	**23 June 2023**

Name and mailing address of the ISA/TR
Turkish Patent and Trademark Office (Turkpatent)
Hipodrom Caddesi No. 13
06560 Yenimahalle
Ankara
Türkiye
Telephone No. **+903123031000**
Facsimile No. **+903123031220**

Authorized officer
Hatice ERSÖZ SEÇER
Telephone No. **+903123031655**