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(54) Title: THERAPEUTIC USE

(57) **Abstract:** The present invention relates to the use of arylalkyl-amines and -amides, particularly (S)- α -phenyl-2-pyridineethanamine, or pharmaceutically acceptable salts thereof, in the treatment of cancer in a warm-blooded animal such as man. Further aspects of the invention include a method of treating cancer, and to the use of arylalkyl-amines and -amides, particularly (S)- α -phenyl-2-pyridineethanamine, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in a method of treating cancer.



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THERAPEUTIC USE

The present invention relates to arylalkyl-amines and -amides, particularly (S)- α -phenyl-2-pyridineethanamine, or pharmaceutically acceptable salts thereof, and their use in the treatment of cancer in a warm-blooded animal, such as man. The invention also relates to the use of pharmaceutical compositions containing arylalkyl-amines and -amides, particularly (S)- α -phenyl-2-pyridineethanamine, or pharmaceutically acceptable salts thereof, in a method of treating cancer in a warm blooded animal, such as man, and to the use of arylalkyl-amines and -amides, particularly (S)- α -phenyl-2-pyridineethanamine, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in a method of treating cancer in a warm blooded animal, such as man.

Cancer affects an estimated 10 million people worldwide. This figure includes incidence, prevalence and mortality. More than 4.4 million cancer cases are reported from Asia, including 2.5 million cases from Eastern Asia, which has the highest rate of incidence in the world. By comparison, Europe has 2.8 million cases, North America 1.4 million cases, and Africa 627,000 cases.

In the UK and US, for example, more than one in three people will develop cancer at some point in their life. Cancer mortality in the U.S. is estimated to account for about 600,000 a year, about one in every four deaths, second only to heart disease in percent of all deaths, and second to accidents as a cause of death of children 1-14 years of age. The estimated cancer incidence in the U.S. is now about 1,380,000 new cases annually, exclusive of about 900,000 cases of non-melanotic (basal and squamous cell) skin cancer.

Cancer is also a major cause of morbidity in the UK with nearly 260,000 new cases (excluding non-melanoma skin cancer) registered in 1997. Cancer is a disease that affects mainly older people, with 65% of cases occurring in those over 65. Since the average life expectancy in the UK has almost doubled since the mid nineteenth century, the population at risk of cancer has grown. Death rates from other causes of death, such as heart disease, have fallen in recent years while deaths from cancer have remained relatively stable. The result is that 1 in 3 people will be diagnosed with cancer during their lifetime and 1 in 4 people will die from cancer. In people under the age of 75, deaths from cancer outnumber deaths from diseases of the circulatory system, including ischaemic heart disease and stroke. In 2000, there were 151,200 deaths from cancer. Over one fifth (22 per cent) of

these were from lung cancer, and a quarter (26 per cent) from cancers of the large bowel, breast and prostate.

Worldwide, the incidence and mortality rates of certain types of cancer (of stomach, breast, prostate, skin, and so on) have wide geographical differences which are attributed to racial, cultural, and especially environmental influences. There are over 200 different types of cancer but the four major types, lung, breast, prostate and colorectal, account for over half of all cases diagnosed in the UK and US. Prostate cancer is the fourth most common malignancy among men worldwide, with an estimated 400,000 new cases diagnosed annually, accounting for 3.9 percent of all new cancer cases.

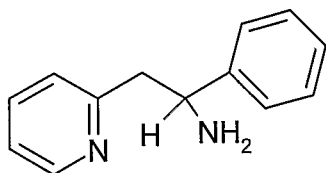
Current options for treating cancers include surgical resection, external beam radiation therapy and / or systemic chemotherapy. These are partially successful in some forms of cancer, but are not successful in others. There is a clear need for new therapeutic treatments.

There are approximately 16, 000 new cases of brain cancer diagnosed each year in the United States, with 13, 000 deaths expected annually (Greenlee, R.T., Murray, T., Bolden, S., and Wingo, P.A. (2000). *Cancer statistics. CA: A cancer Journal for Clinicians*, 50, 7-33). Malignant tumours of the brain are usually debilitating and fatal despite multiple treatments that include surgery, radiation therapy and chemotherapy. Gliomas are the most common brain tumour. A glioma is defined as a tumour of the brain that begins in glial cells (a glial cell is a type of cell that surrounds nerve cells and supports/holds them in place, including astrocytes). Astrocytomas (tumour cells that arise from astrocytes), ependymomas, oligodendrogliomas, and tumours with mixtures of two or more of these cell types are common gliomas, astrocytomas being the most common. Astrocytomas are the second most common type of cancer in children (Osteen, R.T. (Ed.). (1996). *Cancer manual* (9th ed.). Atlanta: American Cancer Society). Since 1960, the five-year survival rate for astrocytomas has increased from 18% to 30%, but in spite of this increase, the average life expectancy following an astrocytoma diagnosis is only 18 months (Silverstein, M.D., Cascino, T.L., & Harmsen, W.S. (1996). High-grade astrocytomas: Resource use, clinical outcomes, and cost of care. *Mayo Clinic Proceedings*, 71, 936-944). Therefore, the incidence of neurological sequelae and the high death rate in patients with malignant gliomas creates a large unmet medical need. For example, the incidence of epilepsy can approach 50% in glioblastoma (a tumour that is part of the astrocytoma cell

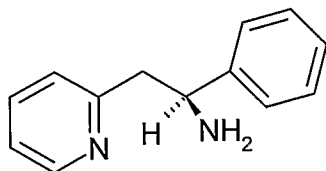
line-it is considered a grade IV astrocytoma) patients. This is especially critical for children. There is thus also a clear need for new treatments for the management and treatment of brain cancer, particularly glioma.

The present invention aims at providing a method and/or medicament which is useful for the treatment of cancer. To this end, the present invention concerns the surprising finding that (S)- α -phenyl-2-pyridineethanamine is a particularly potent anti-cancer agent.

European Patent No. 356035 discloses a large number of compounds for use in the treatment of neurodegenerative disorders, including α -phenyl-2-pyridineethanamine (referred to therein and herein as 1-phenyl-2-(2-pyridinyl)ethylamine),



European patent No. 0633879 discloses the (S)-enantiomer of this compound ((S)- α -phenyl-2-pyridineethanamine), its preparation and its use as a pharmaceutical, in particular in the treatment of neurodegenerative disorders.



There is no hint or suggestion from EP patent No. 356035 or EP patent No. 0633879 that any of the compounds disclosed therein, particularly (S)- α -phenyl-2-pyridineethanamine, would possess the particular beneficial effects that make it such a potent anti-cancer agent.

The potential benefits of the above compounds in the treatment of cancer patients can include:

- slowing the growth of the tumour via a direct effect on tumour cell proliferation and migration (direct cytostatic effect);
- potentiation of the effect of other chemotherapeutic agents and/or radiation therapy.

In addition to those above, the potential benefits of the above compounds in the treatment of glioma patients can include:

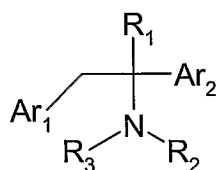
-protection of normal brain tissue from destruction via glutamate-mediated excitotoxicity due to glutamate release from the tumour (this might both decrease neurologic sequelae and slow tumour expansion);

-protection of normal brain tissue from the toxic effects of radiation or chemotherapy;

5 -prevention of tumour-associated seizures (for example, (S)- α -phenyl-2-pyridineethanamine has demonstrated anticonvulsant efficacy); and

-treatment of reactive depression associated with disease, thereby enhancing the quality of life of the patient (for example, (S)- α -phenyl-2-pyridineethanamine has demonstrated antidepressant effect).

10 Therefore according to the present invention, there is provided the use of a compound of formula (I),



(I)

15 wherein

Ar_1 and Ar_2 independently represent phenyl substituted by one or more of amino, nitro, chlorine, bromine, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl or cyano; in addition one of Ar_1 or Ar_2 may represent phenyl;

R_1 represents hydrogen or C_{1-6} alkyl;

20 R_2 represents hydrogen or $COCH_2NH_2$;

R_3 represents hydrogen or C_{1-6} alkyl;

in addition, when R_2 represents hydrogen, then both of Ar_1 and Ar_2 may represent phenyl, one or both of Ar_1 and Ar_2 may represent fluorophenyl or 2-, 3- or 4- pyridinyl, and R_1 may represent C_{1-6} alkoxycarbonyl or trifluoromethyl;

25 provided that:

(a) when R_1 and R_2 each represent H and Ar_1 and Ar_2 each represent phenyl, then R_3 is other than C_{1-6} alkyl;

(b) when Ar_2 represents 2-, 3- or 4-pyridinyl, then R_1 represents C_{1-6} alkyl; and

(c) when R_1 and R_2 each represent H, then Ar_1 does not represent phenyl substituted by amino;
or a pharmaceutically acceptable salt thereof,
in the manufacture of a medicament for use in the treatment of cancer in a warm-blooded
5 animal such as man.

This invention also relates to all stereoisomeric forms, optical enantiomeric forms and pharmaceutically acceptable acid addition salts of the compounds of formula (I).

According to another feature of the present invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the
10 treatment of cancer in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of treating cancer which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

15 According to a further feature of this aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of a compound of
20 formula (I), or a pharmaceutically acceptable salt thereof, in the reduction of proliferation in a cancerous cell or inducing differentiation of a cancerous cell in a warm-blooded animal such as man.

In another aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a
25 medicament for use in the reduction of proliferation in a cancerous cell or inducing differentiation of a cancerous cell in a warm-blooded animal such as man.

In another aspect of the invention there is provided a method for reducing proliferation in a cancerous cell or inducing differentiation of a cancerous cell which comprises administering an effective amount of a compound of formula (I), or a
30 pharmaceutically acceptable salt thereof, in a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a

pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the reduction of proliferation or inducing differentiation of a cancerous cell in a cancerous cell in a warm blooded animal such as man.

In another aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in inducing apoptosis in a cancerous cell in a warm-blooded animal such as man.

In another aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inducing apoptosis in a cancerous cell in a warm-blooded animal such as man.

In another aspect of the invention there is provided a method of inducing apoptosis in a cancerous cell which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in inducing apoptosis in a cancerous cell in a warm blooded animal such as man.

In the field of medical oncology treatment may comprise known methods of anti-tumour therapy: surgery, radiotherapy or chemotherapy. It is normal practice to use a combination of different forms of treatment to treat each patient with cancer. Examples of such treatment of patients with one or more anti-tumour therapeutic agents are the combined use of irradiation treatment together with chemotherapeutic and/or cytotoxic agents.

Thus, the compounds of formula (I) may be applied as a sole therapy or may involve, in addition, one or more substances and/or treatments. Therefore according to the present invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the conjoint treatment of cancer in a warm-blooded animal such as man.

According to another feature of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for use in the conjoint treatment of cancer in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of conjointly treating cancer which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutical acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for use in the conjoint treatment of cancer in a warm blooded animal such as man.

The anti-cancer activity of such conjoint treatments compared to the use of each component alone can thus be increased, thereby increasing therapeutic efficacy.

By "conjoint treatment" we mean a treatment of an individual with two or more therapeutic agents, a compound of formula (I) being the first therapeutic agent. The second (and optionally third and further) therapeutic agent can be any anti-tumour therapy, e.g. irradiation treatment, treatment with chemotherapeutic drugs, treatment with cytotoxic drugs, hormone therapy, immunotherapy, anti-angiogenic therapy and/or gene therapy. In one embodiment, the conjoint treatment comprises irradiation treatment. In another embodiment, the conjoint treatment comprises treatment with a chemotherapeutic drug.

Such conjoint treatment can be achieved by way of the simultaneous, sequential or separate administration of a Compound of formula (I) and the second (and optionally third or further) therapeutic agent. Sequential administration includes administration of a compound of formula (I) either prior to or after the second therapeutic agent. When the second therapeutic agent is radiation therapy, a compound of formula (I) can be administered pre- or post-radiation. Also, when the second therapeutic agent is a chemotherapeutic drug, a compound of formula (I) can be administered pre- or post-chemotherapy.

In particular embodiments, the compound of formula (I) is a sensitizing agent.

By "sensitizing agent", we mean that a compound of formula (I) is capable of sensitizing cancer cells upon contact to the activity of the second (and optionally third and further) therapeutic agent. This enables reduction of the dosage of the second therapeutic agent

compared to the dosage usually administered in the absence of the sensitizing agent to achieve an anti-cancer effect, increasing the probability of killing the tumour cells. Anti-cancer effects may include reduction in tumour mass, inhibition of proliferation and/or increase in cytotoxicity of standard therapies, increase in survival time, delay in disease progression, thus enhancing/maintaining quality of life. Methods to determine anti-tumour effects are known to those skilled in the art.

According to another aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in sensitizing cancer cells in a warm-blooded animal such as man.

According to another feature of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament to sensitize cancer cells in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of sensitizing cancer cells which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a warm blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier for sensitizing cancer cells in a warm blooded animal such as man.

In one embodiment, the compound of formula (I) is administered throughout the entire course of the treatment, and prior to the administration of the second (and optionally third or further) therapeutic agent. This enables sufficient levels of the compound of formula (I) to be present in the body at the time of administration of the second (and optionally third or further) therapeutic agent e.g. radiation treatment and/ or chemotherapy, thus sensitizing the tumour cells making them more vulnerable to the action of said second (and optionally third or further) therapeutic agent.

Chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) cell cycle inhibitory agents, for example cyclin dependent kinase (CDK) inhibitors, in particular CDK2 inhibitors;

- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example magesrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemetane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, 5 luprolide), inhibitors of testosterone 5 α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example vascular endothelial growth factor, 10 epithelial growth factor, platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);
- (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, 15 fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithamycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulfan, cyclophosphamide, ifosfamide, 20 nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan);
- (iv) antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example receptor tyrosine kinases like Tie-2, inhibitors of integrin α vB3 25 function, angiostatin, razoxin, thalidomide), and including vascular targeting agents; and
- (v) differentiation agents (for example retinoic acid and vitamin D).

Compounds of formula I include:

- 1,2-diphenylethylamine;
1,2-diphenyl-2-propylamine;
30 1,2-bis(4-fluorophenyl)-2-propylamine;
1,2-diphenyl-2-butylamine;
(-)-1,2-diphenyl-2-propylamine;

- (+)-1,2-diphenyl-2-propylamine;
2,3-diphenyl-2-aminopropanoic acid methyl ester;
N-methyl-1,2-diphenyl-2-propylamine;
1-(3-nitrophenyl)-2-phenyl-2-propylamine;
5 1-(3-chlorophenyl)-2-phenyl-2-propylamine;
1-(3-bromophenyl)-2-phenyl-2-propylamine;
1-(3-cyanophenyl)-2-phenyl-2-propylamine;
2-(2-methylphenyl)-1-phenyl-2-propylamine;
1-(4-chlorophenyl)-2-phenyl-2-propylamine;
10 1-phenyl-2-(3,4-dichlorophenyl)-2-propylamine;
1-phenyl-2-(3-methoxyphenyl)-2-propylamine;
1-(4-hydroxyphenyl)-2-phenyl-2-propylamine;
1-(4-hydroxyphenyl)-2-phenylethylamine;
1-phenyl-2-(4-hydroxyphenyl)ethylamine;
15 1,2-bis(4-hydroxyphenyl)ethylamine;
1-phenyl-2-(4-hydroxyphenyl)-2-propylamine;
1,2-bis(4-hydroxyphenyl)-2-propylamine;
1-phenyl-2-(2-pyridinyl)ethylamine;
1-phenyl-2-(3-pyridinyl)ethylamine;
20 1-phenyl-2-(4-pyridinyl)ethylamine;
3,3,3-trifluoro-1,2-diphenyl-2-propylamine;
N-methyl-3,3,3-trifluoro-1,2-diphenyl-2-propylamine;
2-(3-chlorophenyl)-1-phenyl-2-propylamine;
1-(2-chlorophenyl)-2-phenyl-2-propylamine;
25 2-(2-chlorophenyl)-1-phenyl-2-propylamine;
2-(3-nitrophenyl)-1-phenyl-2-propylamine;
2-(4-chlorophenyl)-1-phenyl-2-propylamine;
2-(3,4-dimethoxyphenyl)-1-phenyl-2-propylamine;
2-(4-methylphenyl)-1-phenyl-2-propylamine;
30 2-(4-methoxyphenyl)-1-phenyl-2-propylamine;
1-(3,4-dichlorophenyl)-2-phenyl-2-propylamine;
1-(4-methoxyphenyl)-2-phenyl-2-propylamine;

- 2-amino-N-[1-(3-chlorophenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[2-(2-chlorophenyl)-1-phenyl-1-methylethyl]acetamide;
 2-amino-N-[2-(4-chlorophenyl)-1-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(2-methylphenyl)-2-phenyl-1-methylethyl]acetamide;
 5 2-amino-N-[1-(2-chlorophenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[2-(3-chlorophenyl)-1-phenyl-1-methylethyl]acetamide;
 2-amino-N-[2-(3-aminophenyl)-1-phenyl-1-methyl ethyl]acetamide;
 2-amino-N-[2-(3-bromophenyl)-1-phenyl-1-methylethyl]acetamide;
 2-amino-N-[2-(3-nitrophenyl)-1-phenyl-1-methylethyl]acetamide;
 10 2-amino-N-[1-(3-nitrophenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(3-aminophenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(4-chlorophenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(3,4-dichlorophenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(3,4-dimethoxyphenyl)-2-phenyl-1-methylethyl]acetamide;
 15 2-amino-N-[2-(3-cyanophenyl)-1-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(4-methylphenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(4-hydroxyphenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-N-[1-(4-hydroxyphenyl)-2-phenylethyl]acetamide;
 2-amino-N-[2-(4-hydroxyphenyl)-1-phenyl-1-methylethyl]acetamide;
 20 2-amino-N-[2-(4-hydroxyphenyl)-1-phenylethyl]acetamide;
 2-amino-N-[1,2-bis(4-hydroxyphenyl)-1-methylethyl]acetamide;
 2-amino-N-[1,2-bis(4-hydroxyphenyl)ethyl]acetamide;
 2-amino-N-[1-(3-methoxyphenyl)-2-phenyl-1-methylethyl]acetamide;
 2-amino-W[1-(4-methoxyphenyl)-2-phenyl-1-methylethyl]acetamide;
 25 2-amino-N-[2-(3,4-dichlorophenyl)-1-phenyl-1-methyl-ethyl]acetamide;
 2-amino-N-[2-(4-methoxyphenyl)-1-phenyl-1-methyl-ethyl]acetamide.

In a particular embodiment, the compound of formula (I) is 1-phenyl-2-(2-pyridinyl)ethylamine. In another particular embodiment, the compound of formula (I) is (S)- α -phenyl-2-pyridineethanamine.

- 30 In another particular embodiment, the (S)- α -phenyl-2-pyridineethanamine is substantially free from its (R)-enantiomer. By “substantially free from its (R)-enantiomer”, we mean that a sample of the (S)-enantiomer contains less than 10% by

weight of the (R)-enantiomer (i.e. it is more than 90% enantiopure), in one embodiment the sample contains less than 5% by weight of the (R)-enantiomer, in another embodiment the sample contains less than 2% by weight of the (R)-enantiomer, in another embodiment the sample contains less than 1% by weight of the (R)-enantiomer, and in another embodiment the sample contains pure (S)-enantiomer.

Suitable pharmaceutically-acceptable salts include, for example, salts with alkali metals (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, suitable pharmaceutically-acceptable acid addition salts may be prepared by treatment with various inorganic or organic acids, such as hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, lactic, succinic, fumaric, malic, maleic, tartaric, citric, benzoic, methanesulphonic or carbonic acids.

In one embodiment, the sample contains a compound of formula (I) in the form of an acid-addition salt.

In another embodiment, the sample contains a compound of formula (I) in the form of the dihydrochloride salt. In another embodiment, a compound of formula (I) is in the form of the benzoate salt. In another embodiment, a compound of formula (I) is in the form of the malate salt.

Where cancer is referred to, particularly it refers to endometrial cancer, liver cancer, stomach cancer, thyroid cancer, rectal cancer, oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, Kaposi sarcoma, ovarian cancer, breast cancer, bladder cancer, colon cancer, melanoma, lung cancer (non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)), gastric cancer, head and neck cancer, brain cancer, glioma, astrocytoma, renal cancer, lymphoma and leukaemia. More particularly it refers to brain cancer, glioma, NSCLC, renal cancer, colon cancer, melanoma, leukaemia, breast cancer and ovarian cancer. In addition, more particularly it refers to brain cancer. In addition, more particularly it refers to glioma. In addition, more particularly it refers to NSCLC. In addition, more particularly it refers to renal cancer. In addition, more particularly it refers to colon cancer. In addition, more particularly it refers to melanoma. In addition, more particularly it refers to leukaemia. In addition, more particularly it refers to breast cancer. In addition, more particularly it refers

to ovarian cancer. In another embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces brain metastases.

It is to be understood that when the cancer is in a metastatic state, that a compound of formula (I) acts at both the primary tumour site and the metastases. A compound of formula (I) both prevents, treats and inhibits metastases. In a further embodiment of the invention, the cancer is in a non-metastatic state.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of the compound will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using the compound for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be

administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight, will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is
5 however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of formula (I).

In order to capitalize upon its cytostatic and/or neuroprotective properties, it may be desirable that a compound of formula (I) is administered throughout the entire course of treatment rather than as an episodic therapy, optionally in combination with radiation
10 therapy and/or chemotherapy, and in a particular embodiment as an oral tablet formulation. In the treatment of malignant glioma, for example, a compound of formula (I), particularly (S)- α -phenyl-2-pyridineethanamine, may be administered orally as a tablet once daily throughout the course of the disease, optionally in combination with radiation therapy and/or chemotherapy. Clinical endpoints may include increase in survival, reduction in
15 seizures and reduction in depression.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, may have the advantages that they are less toxic, more efficacious, are longer lasting, have a broader range of activity, are more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties, than compounds previously
20 indicated in the therapeutic fields mentioned above. For example, (S)- α -phenyl-2-pyridineethanamine has excellent drug-like properties. (S)- α -phenyl-2-pyridineethanamine is water soluble, renally cleared, orally bioavailable, crosses the blood brain barrier, and has low protein binding, simple metabolism and predictable pharmacokinetics. Also, (S)- α -phenyl-2-pyridineethanamine is well tolerated in both
25 young and elderly healthy human volunteers. In humans, (S)- α -phenyl-2-pyridineethanamine has predictable pharmacokinetics, which allows for multiple dosing, and a plasma half-life of 14 hours. Based on human data, its efficacy range will typically be plasma concentrations of about 0.75 to 6.0 μ M. (S)- α -phenyl-2-pyridineethanamine is well tolerated when administered to stroke patients (Lees, K.R., Dyker, A.G., Sharma, A.,
30 Ford, G.A., Ardon, M.E. and Grosset, D.G. *Stroke* 32:466-472, 2001; Diener, H.C., Alkhedr, A., Busse, O., Hacke, W., Zingmark, P.H., Jonsson, N. and Basun, J. *Neurology*, 249:561-568, 2001).

The invention is illustrated by the following non-limiting example.

Example 1.

(S)- α -phenyl-2-pyridineethanamine as an inhibitor of tumour cell growth *in vitro*

In the experiment described below we show the effect of (S)- α -phenyl-2-pyridineethanamine (hereinafter referred to as Compound (A)) on the growth of human tumour cell lines.

Method

Human tumour cell lines were grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. Typically, cells were inoculated into 96 well microtiter plates in 100 μ L at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates were incubated at 37° C, 5 % CO₂, 95 % air and 100 % relative humidity for 24 h prior to addition of Compound (A).

After 24 h (and before the addition of compound (A)), two plates of each cell line were fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of Compound (A) addition (T_z). Compound (A) was solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of Compound (A) addition, an aliquot of frozen concentrate was thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μ g/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions were made to provide a total of five compound (A) concentrations (from 1 x 10⁻⁸ M to 1 x 10⁻⁴ M, or from 1 x 10⁻⁷ M to 1 x 10⁻³ M) plus control. To test the relative potency of compound (A) against the tumour cell lines, aliquots of 100 μ l of these different Compound (A) dilutions were added to the appropriate microtiter wells already containing 100 μ l of medium, resulting in the required final Compound (A) concentrations.

Determination of cell densities - the sulforhodamine B assay and reading of optical densities

Following Compound (A) addition, the plates were incubated for an additional 48 h at 37°C, 5 % CO₂, 95 % air, and 100 % relative humidity. For adherent cells (e.g. NSCLC, renal and glioma), the assay was terminated by the addition of cold TCA. Cells were fixed

in situ by the gentle addition of 50 µl of cold 50 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant was discarded, and the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4 % (w/v) in 1 % acetic acid was added to each well, and plates were

5 incubated for 10 minutes at room temperature. After staining, unbound dye was removed by washing five times with 1 % acetic acid and the plates were air dried. Bound stain was subsequently solubilized with 10 mM trizma base, and the absorbance was read on an automated plate reader at a wavelength of 515 nm. For suspension cells (e.g. leukaemia), the methodology was the same except that the assay was terminated by fixing settled cells

10 at the bottom of the wells by gently adding 50 µl of 80 % TCA (final concentration, 16 % TCA).

GI50 measurement (50% Growth Inhibition, i.e. Compound (A) inhibited 50% of the growth over 48 hours)

15 The cells will grow at an expected rate over the 48 hours. In this assay, the number of cells at the start of the experiment with no drug added (time zero control) was compared to the number of cells in the control after 48 hours (a certain number of doublings will have occurred during this time). This growth was then compared with the growth that occurred in the wells treated with Compound (A). If the growth in the Compound (A) -

20 treated wells is only half of the rate in the control, it is marked as a "hit".

Using the seven absorbance measurements [(Tz), (C), and test growth in the presence of Compound (A) at the five concentration levels (Ti)], the percentage growth was calculated at each of the Compound (A) concentrations. Growth inhibition of 50% (GI50) was calculated from $[(Ti - Tz)/(C - Tz)] \times 100 = 50$, which was the drug concentration

25 resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the Compound (A) incubation, where

Ti = number of cells in drug-treated wells after 48 hours of growth at the five concentration levels;

Tz = the number of cells in the well just prior to addition of drug; and

30 C = the number of cells, after 48 hours, in the wells that received no treatment, i.e., time 48 hour control.

Results

The criteria established for activity of compound (A) in this screen is greater than 50% growth inhibition of the tumour cells under the conditions of the assay. The results showed (Table 1) that Compound (A) inhibits the cell growth by more than 50% of two human glioma cell lines (SNB-75 and SF-295), a renal cell line (TK-10), a leukaemia cell line (MOLT-4), three non-small cell lung cell lines (NCI H322M, HOP-62 and HOP-92), a colon cell line (HCT-116) and a melanoma cell line (LOX IMVI).

Table 1. Cell growth inhibition of human tumour cell lines by Compound (A).

Each row represents the results from a single experiment. An active "hit" is defined by greater than 50% growth inhibition (see numbers in bold). Activity against a particular cell line is defined as meeting the greater than 50% growth inhibition in at least two separate experiments.

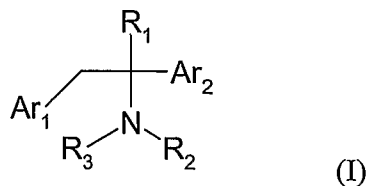
Tumour type	Cell Line	% Growth					
		Log10 conc (M)					
		10 ⁻⁸	10 ⁻⁷	10 ⁻⁶	10 ⁻⁵	10 ⁻⁴	10 ⁻³
Glioma	SNB-75	80	69	57	50	43	ND
Glioma	SNB-75	67	85	59	53	48	ND
Glioma	SF-295	ND	105	107	103	99	31
Glioma	SF-295	100	91	92	73	17	ND
Renal	TK-10	75	75	74	63	17	ND
Renal	TK-10	ND	85	59	53	48	ND
Leukaemia	MOLT-4	ND	105	107	103	99	31
Leukaemia	MOLT-4	100	91	92	73	17	ND
Colon	HCT-116	99	98	98	94	24	ND
Colon	HCT-116	ND	96	101	96	99	44
Melanoma	LOX IMVI	99	100	100	91	33	ND
Melanoma	LOX IMVI	ND	98	101	93	91	34
Lung	HOP-62	72	60	40	47	49	ND
Lung	HOP-62	85	87	84	80	44	ND
Lung	HOP-92	ND	96	97	94	87	49

Lung	HOP-92	103	110	92	76	<u>29</u>	ND
Lung	NCI H322M	ND	98	98	97	87	<u>22</u>
Lung	NCI H322M	96	92	80	75	<u>45</u>	ND
Lung	NCI H322M	83	74	62	58	<u>39</u>	ND

ND, not determined

Claims

1. The use of a compound of formula (I),



5 wherein

Ar₁ and Ar₂ independently represent phenyl substituted by one or more of amino, nitro, chlorine, bromine, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkyl or cyano; in addition one of Ar₁ or Ar₂ may represent phenyl;

R₁ represents hydrogen or C₁₋₆ alkyl;

10 R₂ represents hydrogen or COCH₂NH₂;

R₃ represents hydrogen or C₁₋₆ alkyl;

in addition, when R₂ represents hydrogen, then both of Ar₁ and Ar₂ may represent phenyl, one or both of Ar₁ and Ar₂ may represent fluorophenyl or 2-, 3- or 4- pyridinyl, and R₁ may represent C₁₋₆ alkoxy carbonyl or trifluoromethyl;

15 provided that:

(a) when R₁ and R₂ each represent H and Ar₁ and Ar₂ each represent phenyl, then R₃ is other than C₁₋₆ alkyl;

(b) when Ar₂ represents 2-, 3- or 4-pyridinyl, then R₁ represents C₁₋₆ alkyl; and

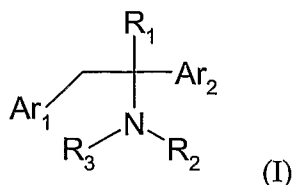
(c) when R₁ and R₂ each represent H, then Ar₁ does not represent phenyl substituted by

20 amino;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for use in the treatment of cancer in a warm-blooded animal such as man.

2. The use of a compound of formula (I),



5 wherein

Ar₁ and Ar₂ independently represent phenyl substituted by one or more of amino, nitro, chlorine, bromine, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkyl or cyano; in addition one of Ar₁ or Ar₂ may represent phenyl;

R₁ represents hydrogen or C₁₋₆ alkyl;

10 R₂ represents hydrogen or COCH₂NH₂;

R₃ represents hydrogen or C₁₋₆ alkyl;

in addition, when R₂ represents hydrogen, then both of Ar₁ and Ar₂ may represent phenyl, one or both of Ar₁ and Ar₂ may represent fluorophenyl or 2-, 3- or 4- pyridinyl, and R₁ may represent C₁₋₆ alkoxy carbonyl or trifluoromethyl;

15 provided that:

(a) when R₁ and R₂ each represent H and Ar₁ and Ar₂ each represent phenyl, then R₃ is other than C₁₋₆ alkyl;

(b) when Ar₂ represents 2-, 3- or 4-pyridinyl, then R₁ represents C₁₋₆ alkyl; and

(c) when R₁ and R₂ each represent H, then Ar₁ does not represent phenyl substituted by

20 amino;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for use in the conjoint treatment of cancer in a warm-blooded animal such as man.

25 3. The use according to claim 1 or claim 2, in which the compound of formula (I) is a sensitizing agent.

4. The use according to claim 2 or claim 3 in which the conjoint treatment comprises irradiation treatment and/or treatment with a chemotherapeutic drug.

5. The use according to any preceding claim, wherein the compound of formula (I) is selected from the group consisting of:

- 1,2-diphenylethylamine;
- 5 1,2-diphenyl-2-propylamine;
- 1,2-bis(4-fluorophenyl)-2-propylamine;
- 1,2-diphenyl-2-butylamine;
- (-)-1,2-diphenyl-2-propylamine;
- (+)-1,2-diphenyl-2-propylamine;
- 10 2,3-diphenyl-2-aminopropanoic acid methyl ester;
- N-methyl-1,2-diphenyl-2-propylamine;
- 1-(3-nitrophenyl)-2-phenyl-2-propylamine;
- 1-(3-chlorophenyl)-2-phenyl-2-propylamine;
- 1-(3-bromophenyl)-2-phenyl-2-propylamine;
- 15 1-(3-cyanophenyl)-2-phenyl-2-propylamine;
- 2-(2-methylphenyl)-1-phenyl-2-propylamine;
- 1-(4-chlorophenyl)-2-phenyl-2-propylamine;
- 1-phenyl-2-(3,4-dichlorophenyl)-2-propylamine;
- 1-phenyl-2-(3-methoxyphenyl)-2-propylamine;
- 20 1-(4-hydroxyphenyl)-2-phenyl-2-propylamine;
- 1-(4-hydroxyphenyl)-2-phenylethylamine;
- 1-phenyl-2-(4-hydroxyphenyl)ethylamine;
- 1,2-bis(4-hydroxyphenyl)ethylamine;
- 1-phenyl-2-(4-hydroxyphenyl)-2-propylamine;
- 25 1,2-bis(4-hydroxyphenyl)-2-propylamine;
- 1-phenyl-2-(2-pyridinyl)ethylamine;
- 1-phenyl-2-(3-pyridinyl)ethylamine;
- 1-phenyl-2-(4-pyridinyl)ethylamine;
- 3,3,3-trifluoro-1,2-diphenyl-2-propylamine;
- 30 N-methyl-3,3,3-trifluoro-1,2-diphenyl-2-propylamine;
- 2-(3-chlorophenyl)-1-phenyl-2-propylamine;
- 1-(2-chlorophenyl)-2-phenyl-2-propylamine;

- 2-(2-chlorophenyl)-1-phenyl-2-propylamine;
2-(3-nitrophenyl)-1-phenyl-2-propylamine;
2-(4-chlorophenyl)-1-phenyl-2-propylamine;
2-(3,4-dimethoxyphenyl)-1-phenyl-2-propylamine;
5 2-(4-methylphenyl)-1-phenyl-2-propylamine;
2-(4-methoxyphenyl)-1-phenyl-2-propylamine;
1-(3,4-dichlorophenyl)-2-phenyl-2-propylamine;
1-(4-methoxyphenyl)-2-phenyl-2-propylamine;
2-amino-N-[1-(3-chlorophenyl)-2-phenyl-1-methylethyl]acetamide;
10 2-amino-N-[2-(2-chlorophenyl)-1-phenyl-1-methylethyl]acetamide;
2-amino-N-[2-(4-chlorophenyl)-1-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(2-methylphenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(2-chlorophenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[2-(3-chlorophenyl)-1-phenyl-1-methylethyl]acetamide;
15 2-amino-N-[2-(3-aminophenyl)-1-phenyl-1-methyl ethyl]acetamide;
2-amino-N-[2-(3-bromophenyl)-1-phenyl-1-methylethyl]acetamide;
2-amino-N-[2-(3-nitrophenyl)-1-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(3-nitrophenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(3-aminophenyl)-2-phenyl-1-methylethyl]acetamide;
20 2-amino-N-[1-(4-chlorophenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(3,4-dichlorophenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(3,4-dimethoxyphenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[2-(3-cyanophenyl)-1-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(4-methylphenyl)-2-phenyl-1-methylethyl]acetamide;
25 2-amino-N-[1-(4-hydroxyphenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-N-[1-(4-hydroxyphenyl)-2-phenylethyl]acetamide;
2-amino-N-[2-(4-hydroxyphenyl)-1-phenyl-1-methylethyl]acetamide;
2-amino-N-[2-(4-hydroxyphenyl)-1-phenylethyl]acetamide;
2-amino-N-[1,2-bis(4-hydroxyphenyl)-1-methylethyl]acetamide;
30 2-amino-N-[1,2-bis(4-hydroxyphenyl)ethyl]acetamide;
2-amino-N-[1-(3-methoxyphenyl)-2-phenyl-1-methylethyl]acetamide;
2-amino-W[1-(4-methoxyphenyl)-2-phenyl-1-methylethyl]acetamide;

2-amino-N-[2-(3,4-dichlorophenyl)-1-phenyl-1-methyl-ethyl]acetamide;
2-amino-N-[2-(4-methoxyphenyl)-1-phenyl-1-methyl-ethyl]acetamide.

6. The use according to any preceding claim, in which the compound of formula (I) is
5 1-phenyl-2-(2-pyridinyl)ethylamine.

7. The use according to any of claims 1 to 4, in which the compound of formula (I) is
(S)- α -phenyl-2-pyridineethanamine.

10 8. The use according to claim 7 in which (S)- α -phenyl-2-pyridineethanamine is
greater than 98% enantiopure.

9. The use according to any preceding claim in which the compound of formula (I) is
in the form of an acid addition salt.

15

10. The use according to any preceding claim in which the cancer is selected from the
group consisting of: endometrial cancer, liver cancer, stomach cancer, thyroid cancer,
rectal cancer, oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer,
ewings tumour, neuroblastoma, Kaposi sarcoma, ovarian cancer, breast cancer, bladder
20 cancer, colon cancer, melanoma, lung cancer (including non small cell lung cancer
(NSCLC) and small cell lung cancer (SCLC)), gastric cancer, head and neck cancer, brain
cancer, glioma, astrocytoma, renal cancer, lymphoma and leukaemia.

11. The use according to any preceding claim in which the cancer is brain cancer.

25

12. The use according to any preceding claim in which the cancer is glioma.

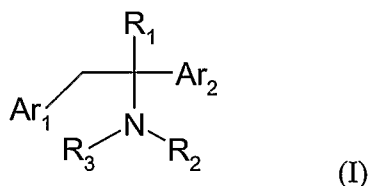
13. The use according to any of claims 1 to 10 in which the cancer is selected from the
group consisting of: NSCLC, renal cancer, colon cancer, melanoma and leukaemia.

30

14. The use according to any of claims 1 to 13 in which the cancer is in a metastatic
state.

15. The use according to any of claims 1 to 13 in which the cancer is in a non-metastatic state.

- 5 16. A method of treating cancer which comprises administering to a warm blooded animal in need of such treatment an effective amount of a compound of formula (I)



wherein

- 10 Ar_1 and Ar_2 independently represent phenyl substituted by one or more of amino, nitro, chlorine, bromine, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl or cyano; in addition one of Ar_1 or Ar_2 may represent phenyl;

R_1 represents hydrogen or C_{1-6} alkyl;

R_2 represents hydrogen or $COCH_2NH_2$;

R_3 represents hydrogen or C_{1-6} alkyl;

- 15 in addition, when R_2 represents hydrogen, then both of Ar_1 and Ar_2 may represent phenyl, one or both of Ar_1 and Ar_2 may represent fluorophenyl or 2-, 3- or 4- pyridinyl, and R_1 may represent C_{1-6} alkoxy carbonyl or trifluoromethyl;

provided that:

- 20 (a) when R_1 and R_2 each represent H and Ar_1 and Ar_2 each represent phenyl, then R_3 is other than C_{1-6} alkyl;
- (b) when Ar_2 represents 2-, 3- or 4-pyridinyl, then R_1 represents C_{1-6} alkyl; and
- (c) when R_1 and R_2 each represent H, then Ar_1 does not represent phenyl substituted by amino, or a pharmaceutically acceptable salt thereof.