Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
EP 1 575 579 B1

Description

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compositions comprising an apoptosis inducing anti-cancer agent and an IMPDH inhibitor according to claim 1. This invention also relates to the use of these compositions for inducing apoptosis and for treating tumors and cancers.

BACKGROUND OF THE INVENTION

[0002] The synthesis of nucleotides in organisms is required for the cells in those organisms to divide and replicate. Nucleotide synthesis in mammals may be achieved through one of two pathways: the de novo synthesis pathway or the salvage pathway. Different cell types use these pathways to a different extent.

[0003] Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the de novo synthesis of guanine nucleotides. IMPDH catalyzes the NAD-dependent oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) [Jackson R.C. et al., Nature, 256, pp. 331-333, (1975)].


[0005] The de novo synthesis of guanosine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the de novo, rather than salvage pathway to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen [A.C. Allison et al., Lancet II, 1179, (1975) and A.C. Allison et al., Ciba Found. Symp., 48, 207, (1977)]. Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

[0006] Inhibitors of IMPDH are also known. United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 describe mycophenolic acid (MPA) and some of its derivatives as potent, uncompetitive, reversible inhibitors of human IMPDH type I (Ki=33 nM) and type II (Ki=9 nM). MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen [A.C. Allison et al., Ann. N.Y. Acad. Sci., 696, 63, (1993)]. IMPDH inhibitors of different classes have been described in PCT publications WO 97/40028 and WO 98/40381.

[0007] It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumor cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy [M. Nagai et al., Cancer Res., 51, pp. 3886-3890, (1991)].

[0008] WO 00/56331 discloses IMPDH inhibitors and compositions thereof for treating inter alia tumors and cancers, including compositions comprising an IMPDH inhibitor and an additional anti-cancer agent.

[0009] Thus, there remains a need for potent compositions comprising an IMPDH inhibitor with improved pharmacological properties. Such inhibitors would have therapeutic potential as anti-cancer agents.

SUMMARY OF THE INVENTION

[0010] The present invention provides pharmaceutical compositions comprising an apoptosis inducing anti-cancer agent, an IMPDH inhibitor, and a pharmaceutically acceptable carrier according to claim 1. The present invention also provides the use of the compositions of the present invention for inducing apoptosis in a mammal and for treating tumors and cancers in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

[0011] In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

<table>
<thead>
<tr>
<th>Designation</th>
<th>Reagent or Fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
</tbody>
</table>

2
The following terms are employed herein:

Unless expressly stated to the contrary, the terms "-SO₂-" and "-S(O)₂-" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

The terms "halo" or "halogen" refer to a radical of fluorine, chlorine, bromine or iodine.

IMPDH-mediated disease refers to any disease state in which the IMPDH enzyme plays a regulatory role in the metabolic pathway of that disease.

The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. As used herein, the term "patient" refers to a mammal, including a human.

Disclosed are compositions comprising:

1) an apoptosis inducing anti-cancer agent selected from cytarabine, fludarabine, 5-fluoro-2'-deoxyuridine or gemcitabine;
2) an IMPDH inhibitor; and
3) a pharmaceutically acceptable carrier.

[0012] The following terms are employed herein:

[0013] Unless expressly stated to the contrary, the terms "-SO₂-" and "-S(O)₂-" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

[0014] The terms "halo" or "halogen" refer to a radical of fluorine, chlorine, bromine or iodine.

[0015] IMPDH-mediated disease refers to any disease state in which the IMPDH enzyme plays a regulatory role in the metabolic pathway of that disease.

[0016] The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. As used herein, the term "patient" refers to a mammal, including a human.

[0017] Disclosed are compositions comprising:

1) an apoptosis inducing anti-cancer agent selected from cytarabine, fludarabine, 5-fluoro-2'-deoxyuridine or gemcitabine;
2) an IMPDH inhibitor; and
3) a pharmaceutically acceptable carrier.


[0019] According to another embodiment, the invention provides compositions comprising:

1) an apoptosis inducing anti-cancer agent selected from cytarabine, fludarabine, 5-fluoro-2'-deoxyuridine or gemcitabine;
2) a compound of formula A:
wherein:

one of R1 or R2 is selected from hydrogen, ethyl or phenyl; and the other of R1 or R2 is selected from -CH2OH, -CH2CN, -CH2CH2CN or CH2N(CH2CH3)2; or R1 and R2 are taken together to form a 3-tetrahydrofuranyl moiety.

R9 is selected from (R)-methyl, (S)-methyl, (R)-ethyl, (S)-ethyl, (R)-hydroxymethyl or (S)-hydroxymethyl; R10 is selected from -CN or 5-oxazolyl; and R11 is selected from halo, -O-(C1-C3) straight alkyl, or -O-(C2-C3) straight alkenyl or alkynyl; and

3) a pharmaceutically acceptable carrier.

According to a preferred embodiment, the apoptosis inducing anti-cancer agent is cytarabine, fludarabine, 5-fluro-2'-deoxyuridine, or gemcitabine. More preferably, it is cytarabine, fludarabine, or 5-fluro-2'-deoxyuridine. Even more preferably, it is fludarabine.

It should be understood that heterocycles may be attached to the rest of the compound by any atom of the heterocycle which results in the creation of a stable structure.

The term "ring atom", as used herein, refers to a backbone atom that makes up the ring. Such ring atoms are selected from C, N, O or S and are bound to 2 or 3 other such ring atoms (3 in the case of certain ring atoms in a bicyclic ring system). The term "ring atom" does not include hydrogen.

The term "-[(C1-C6)-straight or branched alkyl]-X" and "-[(C2-C6)-straight or branched alkenyl or alkynyl]-X" wherein X is anything indicated as being bound to the alkyl, alkenyl or alkynyl, denotes that one or more X groups may be attached to the alkyl, alkenyl or alkynyl chain at any termini.

The present invention is a selection over International PCT Application WO 00/56331 (hereinafter "WO 00/56331"), entitled "Inhibitors of IMPDH Enzyme". Applicants have discovered that when an IMPDH inhibitor, such as those described in WO 00/56331, is combined with an apoptosis inducing anti-cancer agent, such as fludarabine, the resulting composition exhibits strong synergistic effect in inducing apoptosis. This strong synergy renders the compositions of the present invention therapeutically useful in inducing apoptosis and in treating tumors and cancers in mammals.

According to a preferred embodiment, the composition of the present invention comprises a compound of formula (IA):

\[
\text{IA:}
\]

wherein R9 is selected from (R)-methyl, (S)-methyl, (R)-ethyl, (S)-ethyl, (R)-hydroxymethyl or (S)-hydroxymethyl; and R1, R2, R10 and R11 are as defined above.

According to a more preferred embodiment of formula IA, R9 is selected from (S)-methyl, (S)-ethyl or (S)-hydroxymethyl. Most preferably, R9 is (S)-methyl. Compounds wherein R9 is selected from (S)-methyl, (S)-ethyl, or (S)-hydroxymethyl and wherein the portion of the compound represented by -CH(R1)R2 is a C1-C4 straight or branched alkyl, or a C2-C4 straight or branched alkenyl or alkynyl fall within the genus of compounds described in WO 97/40028.

However, applicants have discovered that the presence of an (S) oriented moiety at R9 imparts surprising and unexpectedly increased IMPDH inhibitory activity.

According to another preferred embodiment of formula IA, R11 is selected from O-methyl, O-ethyl or O-isopropyl.

According to an alternate preferred embodiment of formula IA, R1 and R2 are taken together to form a 3-tetrahydrofuranyl moiety that is substituted by -OR6.

According to another preferred embodiment, the compound of formula A is selected from any of those set forth in Table 1, below.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td><img src="image1" alt="Structure 162" /></td>
</tr>
<tr>
<td>163</td>
<td><img src="image2" alt="Structure 163" /></td>
</tr>
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<td>164</td>
<td><img src="image3" alt="Structure 164" /></td>
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<tr>
<td>166</td>
<td><img src="image5" alt="Structure 166" /></td>
</tr>
<tr>
<td>167</td>
<td><img src="image6" alt="Structure 167" /></td>
</tr>
</tbody>
</table>
(continued)

175

Chiral

176

Chiral

177

178

179

Chiral

180

Chiral

181

Chiral
The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds that possess stability sufficient to allow manufacture and maintenance of the integrity for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Pharmaceutically acceptable salts of the compounds within the compositions of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glycoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine.

According to a more preferred embodiment, the present invention provides a composition comprising:

1. fludarabine;
2. compound No. 169; and
3. a pharmaceutically acceptable carrier.

In the above table, certain compounds are shown as salts. It should be understood that the scope of the compounds set forth in any given entry in the table covers all forms of the depicted compound, not just the salt shown.

According to a more preferred embodiment, the present invention provides a composition comprising:

1. fludarabine;
2. compound No. 181; and
3. a pharmaceutically acceptable carrier.
based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-poloxyl-
propylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically
modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other sol-
ubilized derivatives may also be advantageously used to enhance delivery of compounds of this invention.

[0041] The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray,
topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration
by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-
acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically
acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term
parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intraarte-
rial, intrasynovial, intraretinal, intrathecal, intraleisional and intracranial injection or infusion techniques.

[0042] The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile
injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in
the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile
injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable
diluent or solvent, for example, as a solution in 1,3-butandiol. Among the acceptable vehicles and solvents that may
be employed are mannitol, water, Ringer’s solution and isotonic sodium chloride solution. In addition, sterile, fixed oils
are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed
including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the
preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in
their poloxymethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or
dispersant such as those described in Pharmacopeia Helvetica, Ph. Helv., or a similar alcohol, or carboxymethyl cellulose
or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms
such as emulsions and/or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar
emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically ac-
ceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0043] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage
form including capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets
for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium
stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried
cornstarch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be sus-
pended or dissolved in an oily phase and combined with emulsifying and/or suspending agents. If desired, certain
sweetening and/or flavoring and/or coloring agents may be added.

[0044] The pharmaceutical compositions of this invention may also be administered in the form of suppositories for
rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-
irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the
rectum to release the active components. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0045] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired
treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the
pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended
or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include mineral oil, liquid
petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water.
Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active
compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include mineral oil,
sorbitan monostearate, polysorbate 60, cetaryl esters wax, cetearyl alcohol, 2-octyldecanol, benzyl alcohol and water.
The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal
suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this
invention.

[0046] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such
compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be
prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to en-
hance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0047] Dosage levels of between 0.01 and 100 mg/kg body weight per day, preferably between 0.5 and 75 mg/kg
body weight per day each of fludarabine and the IMPDH inhibitory compound described herein are useful in a monotherapy
and/or in combination therapy for the prevention and treatment of IMPDH-mediated disease. Typically, the pharmaceu-
tical compositions of this invention will be administered from 1 to 5 times per day or alternatively, as a continuous infusion.
Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined
with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular
mode of administration. A typical preparation will contain from 5% to 95% active compound (w/w). Preferably, such preparations contain from 20% to 80% active compound.

In the compositions of the present invention both, the IMPDH inhibitor and fludarabine, should be present at dosage levels of between 10 to 100%, and more preferably between 10 to 80% of the dosage normally administered in a monotherapy regimen. Fludarabine may be administered separately, as part of a multiple dose regimen, from the IMPDH inhibitory compounds. Alternatively, Fludarabine may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

Upon improvement of a patient’s condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, the patient’s disposition to the disease and the judgment of the treating physician.

Also disclosed is the use of any of the pharmaceutical compositions described above for the manufacture of a medicament for treating an IMPDH-mediated disease in a mammal. Such uses may comprise the additional step of administering to said mammal an agent selected from an anti-inflammatory agent, immunosuppressant, an anti-cancer agent, an anti-viral agent, or an anti-vascular hyperproliferation compound. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of a composition of the present invention.

These uses are useful in suppressing an immune response in a mammal. Such uses are useful in treating or preventing diseases, including, transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allotransplants and heart valve xenografts), graft versus host disease, and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn’s disease, ulcerative colitis), lupus, diabetes, melitits myasthenia gravis, psoriasis, dermatitis, eczema, seborrhea, pulmonary inflammation, eye uveitis, Grave’s disease, Hashimoto’s thyroiditis, Behcet’s or Sjorgen’s syndrome (dry eyes/mouth), pemphigous or immunohaemolytic anaemia, idiopathic adrenal insufficiency, polyglandular autoimmune syndrome, glomerulonephritis, scleroderma, lichen planus, viteligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis.

In a preferred embodiment, these uses are useful for treating tumors and cancer in a mammal. Such uses are useful in treating or preventing diseases, including, liquid and solid tumors and malignancies, such as lymphoma, leukemia and related disorders, myelodysplastic syndrome, metastatic melanoma, and other forms of cancer, such as breast cancer, colon cancer, pancreatic cancer, and prostate cancer.

According to another embodiment, the compounds of the present invention and the compositions of the present invention are useful in treating breast cancer or myelomas, preferably, multiple myeloma. According to a more preferred embodiment, the present invention provides a treatment of multiple myeloma comprising the step of administering to a patient in need thereof compound no. 181 or compound no. 169, combined with fludarabine. More preferably, said treatment of multiple myeloma comprises the step of administering to said patient compound no. 181 combined with fludarabine.

These treatments comprise the step of administering to the mammal a composition of this invention. In a preferred embodiment, this particular treatment comprises the additional step of administering to said mammal a composition of the present invention wherein said composition contains fludarabine.

More preferred embodiments of the above treatments are those that employ the preferred compositions as described above.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only.
EXAMPLE 1

Apoptosis Assay

Purpose

[0058] To evaluate apoptosis of cell by measuring AnnexinV positive cells using the Guava Personal Cytometer technology in the presence or absence of compound 181.

Reagents

[0059]

1. Medium: RPMI1640 (JRH #51501-79P) supplemented with 10% FBS (IRVINE Scientific, CA), 50U/ml penicillin + 50ug/ml streptomycin (Gibco), 300 ug/ml L-glutamine (Gibco), 10mM HEPES (Gibco); 4.5 g/L glucose.
2. Nexin Kit (Guava Catalog No. 4700-0010).
4. Daudi cell line (ATCC).
5. 2-Fluoroadenine-9-b-D-arabinofuranoside (F-ara-A Fludarabine des-phosphate), Sigma catalog#F2773.

Procedure

Day 0:

[0060]

1. Dilute cells to 2-2.5x10^5/ml in medium.
2. Plate 100ul cell suspension in media in each well of a 96-well plate, 1 ml in each well of a 24-well plate or 1.2 ml in each well of a 12 well plate.
4. Add 100 μl of test drug solutions to each well of 96-well plate, or 1 ml to each well of 24-well plate. DMSO concentration is 0.1-0.2% for all wells.
5. Incubate plates (37˚C, 5% CO2).

Day 3:

[0061]

1. Follow procedure provided by the manufacturer for staining cells with the Guava Nexin Kit.
2. Analyze samples with the Guava Personal Cytometer following manufacturer’s directions.
3. Analyze results for synergy using Biosoft-CalcuSyn Program.

[0062] A comparison between the % Apoptosis against the concentration of compound 181 alone, fludarabine alone, and a combination of both shows that the combination of compound 181 and fludarabine results in a much greater % apoptosis due to the synergy therebetween.

[0063] The Combination Index Values for Compound No. 181 and Fludarabine (1:1) at ED50, ED 75, and ED90 were 0.21, 0.079, and 0.03, respectively, thus demonstrating strong synergistic effect.

[0064] The scope of this invention is to be defined by the claims appended hereto.

Claims

1. A composition comprising:

(a) an apoptosis inducing anti-cancer agent,
wherein said apoptosis inducing anti-cancer agent is an anti-metabolite, and wherein said anti-metabolite is selected from cytarabine, fludarabine, 5-fluoro-2'-deoxyuridine, or gemcitabine;
(b) a compound of formula (A):
wherein:

one of $R_1$ or $R_2$ is selected from hydrogen, ethyl or phenyl; and the other of $R_1$ or $R_2$ is selected from $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}_2\text{CN}$ or $\text{CH}_2\text{N}$(CH$_2$CH$_3$)$_2$; or wherein $R_1$ and $R_2$ are taken together to form a 3-tetrahydrofuranyl moiety;

$R_9$ is selected from (R)-methyl, (S)-methyl, (R)-ethyl, (S)-ethyl, (R)-hydroxymethyl or (S)-hydroxymethyl;

$R_{10}$ is selected from $-\text{C}=\text{N}$ or 5-oxazolyl; and

$R_{11}$ is selected from halo, $-\text{O}\cdot$(C$_1$-$C_3$) straight alkyl, or $-\text{O}\cdot$(C$_2$-$C_3$) straight alkenyl or alkynyl;

(c) a pharmaceutically acceptable carrier.

2. The composition according to claim 1,
wherein $R_9$ is (S)-methyl, (S)-ethyl, or (S)-hydroxymethyl.

3. The composition according to claim 1,
wherein $R_{11}$ is selected from O-methyl, O-ethyl or O-isopropyl.

4. The composition according to claim 3,
wherein

$R_{10}$ is 5-oxazolyl; and

$R_{11}$ is O-methyl.

5. The composition according to claim 1,
wherein said compound is selected from:
6. The composition according to any one of claims 1-5, wherein said anti-metabolite is fludarabine.

7. The composition according to claim 6, wherein said compound is compound No. 181:

8. A composition according to any one of claims 1-7, for use in inhibiting tumors and cancer in a mammal.

9. A composition according to claim 8, for use in treating or preventing lymphoma, leukemia, myelodysplastic syndrome, metastatic melanoma, breast cancer, colon cancer, pancreatic cancer, and prostate cancer.

10. Use of a composition according to any one of claims 1-7 in the manufacture of a medicament for treating or preventing lymphoma, leukemia, myelodysplastic syndrome, metastatic melanoma, breast cancer, colon cancer, pancreatic cancer, and prostate cancer.

Patentansprüche

1. Zusammensetzung, welche:

   (a) ein Apoptose herbeiführendes Antikrebsmittel, worin besagtes Apoptose herbeiführendes Antikrebsmittel ein Anti-Metabolit ist und worin besagter Anti-Metabolit ausgewählt ist aus Cytarabin, Fludarabin, 5-Fluor-2'-deoxyuridin oder Gemcitabin;
   (b) eine Verbindung der Formel (A):
worin:

- eines von R₁ oder R₂ ausgewählt ist aus Wasserstoff, Ethyl oder Phenyl; und das andere von R₁ oder R₂ ausgewählt ist aus -CH₂OH, -CH₂CN, -CH₂CH₂CN oder CH₂N(CH₂CH₃)₂; oder worin R₁ und R₂ zusammen genommen sind, um eine 3-Tetrahydrofuranylkomponente zu bilden;
- R₉ ausgewählt ist aus (R)-Methyl, (S)-Methyl, (R)-Ethyl, (S)-Ethyl, (R)-Hydroxymethyl oder (S)-Hydroxymethyl;
- R₁₀ ausgewählt ist aus -C≡N oder 5-Oxazolyl; und
- R₁₁ ausgewählt ist aus Halogen, -O- (C₁-C₃) gerades Alkyl, oder -O-(C₂-C₃) gerades Alkenyl oder Alkinyl;

(c) einen pharmazeutisch annehmbarren Träger

2. Zusammensetzung gemäß Anspruch 1, worin R₉ für (S)-Methyl, (S)-Ethyl oder (S)-Hydroxymethyl steht.


4. Zusammensetzung gemäß Anspruch 3, worin R₁₀ für 5-Oxazolyl steht; und
   R₁₁ für O-Methyl steht.

5. Zusammensetzung gemäß Anspruch 1, worin besagte Verbindung ausgewählt ist aus:


Revendications

1. Article comprenant :

(a) un agent anticancéreux induisant l’apoptose, dans lequel ledit agent anticancéreux induisant l’apoptose est un antimétabolite, et dans lequel ledit antimétabolite est choisi parmi cytarabine, fludarabine, 5-fluoro-2’-déoxyuridine ou gemcitabine ;

(b) un composé de formule (A) :

\[
\text{(A)}
\]

dans laquelle :

un de R\text{1} ou R\text{2} est choisi parmi hydrogène, éthyle ou phényle ; et l’autre de R\text{1} ou R\text{2} est choisi parmi -CH\text{2}OH, -CH\text{2}CN, -CH\text{2}CH\text{2}CN ou CH\text{2}N(CH\text{2}CH\text{3})\text{2} ; ou dans laquelle R\text{1} et R\text{2} sont pris ensemble pour former un groupe caractéristique 3-tétrahydrofuranyle ;

R\text{9} est choisi parmi (R)-méthyle, (S)-méthyle, (R)-éthyle, (S)-éthyle, (R)-hydroxyméthyle ou (S)-hydroxyméthyle ;

R\text{10} est choisi parmi -C=N ou 5-oxazolyle ; et

R\text{11} est choisi parmi halo, alkyle droit -O-(C\text{1}-C\text{3}) ou alcényle ou alcynyle droit -O-(C\text{2}-C\text{3}) ;

(c) un support acceptable pharmaceutiquement.

2. Composition selon la revendication 1, dans laquelle R\text{9} est (S)-méthyle, (S)-éthyle ou (S)-hydroxyméthyle.

3. Composition selon la revendication 1, dans laquelle R\text{11} est choisi parmi O-méthyle, O-éthyle ou O-isopropyle.

4. Composition selon la revendication 3, dans laquelle

R\text{10} est 5-oxazolyle ; et

R\text{11} est O-méthyle.

5. Composition selon la revendication 1, dans laquelle ledit composé est choisi parmi :
6. Composition selon l’une quelconque des revendications 1 à 5, dans laquelle ledit antimétabolite est de la fludarabine.

7. Composition selon la revendication 6, dans laquelle ledit composé est le composé n° 181 :


10. Utilisation d’une composition selon l’une quelconque des revendications 1 à 7 dans la fabrication d’un médicament pour traiter ou prévenir le lymphome, la leucémie, le syndrome myélodysplasique, le mélanome métastatique, le cancer du sein, le cancer du colon, le cancer du pancréas et le cancer de la prostate.
REFERENCES CITED IN THE DESCRIPTION

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