Pharmaceutical Combinations for Treating Cancer

Field of the invention

The present invention relates to pharmaceutical combinations comprising a PPAR agonist and a P38 inhibitor for use in a method for the prevention, delay of progression or treatment of cancer in a subject.

Background of the invention

Despite the ever increasing number of cancer therapies in general, and combination cancer therapies in particular, cancer is still the third most common cause of death worldwide after cardiovascular diseases and infectious/parasitic diseases; in absolute numbers, this corresponds to 7.6 million deaths (ca. 13% of all deaths) in any given year. The WHO estimates deaths due to cancer to increase to 13.1 million by 2030, while the American Cancer Society expects over 1,685,210 new cancer cases diagnosed and 595,690 cancer deaths in the US in 2016. A 2012 survey by McMillan Cancer Support in the UK has revealed that the median survival time of cancer patients overall has increased from 1 year to 6 years since the 1970's. However, for many cancers including esophageal-, stomach-, lung-, brain- and pancreatic cancer, median survival has barely improved, remaining less than one year.

These statistics illustrate the fact that cancer remains a critical health condition and that there is an urgent need for new anticancer drugs.

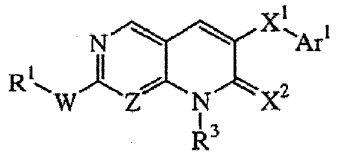
The rationale for combination chemotherapy in cancer is to use drugs that work by different mechanisms, thereby decreasing the likelihood that resistant cancer cells will develop. On the other hand, administration of two or more drugs to treat a given condition, such as cancer, generally raises a number of potential problems due to complex *in vivo* interactions between drugs. The effects of any single drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit, activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug. Thus, when two drugs are administered to treat the same condition, it is unpredictable whether each will complement, have no effect on, or interfere with, the therapeutic activity of the other in a subject. Not only may the interaction between two drugs affect the intended therapeutic activity of each drug, but the interaction

Claims

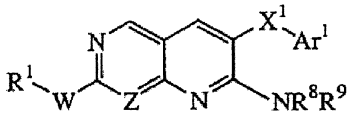
1) A pharmaceutical combination comprising:

(a) a PPAR agonist;

(b) a compound of the formula I or II



Formula I



Formula II

or pharmaceutically acceptable salts thereof, wherein

Z is N or CH;

W is NR^2;

X^1 is O, NR^4 (where R^4 is hydrogen or alkyl), S, or CR^5R^6 (where R^5 and R^6 are independently hydrogen or alkyl) or C=O;

X^2 is O or NR^7;

Ar^1 is aryl or heteroaryl;

R^2 is hydrogen, alkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, heteroalkylcarbonyl, heteroalkyloxycarbonyl or $-R^{21}-R^{22}$ where R^{21} is alkylene or -C(=O)- and R^{22} is alkyl or alkoxy;

R^1 is hydrogen, alkyl, haloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heteroalkylsubstituted cycloalkyl, heterosubstituted cycloalkyl, heteroalkyl, cyanoalkyl, heterocyclyl, heterocyclylalkyl, R^{12}-SO_2-heterocycloamino (where R^{12} is haloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl),-Y^1-C(O)-Y^2-R^{11} (where Y^1 and Y^2 are independently either absent or an alkylene group and R^{11} is hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino), (heterocyclyl)(cycloalkyl)alkyl or (heterocyclyl)(heteroaryl)alkyl;

R^3 is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, alkylene-C(O)-R^{31} (where R^{31} is hydrogen, alkyl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino), amino, monoalkylamino, dialkylamino or NR^{32}-Y^3-R^{33} (where Y^3 is -C(O), -C(O)O-, -C(O)NR^{34}, $S(O)_2$ or $S(O)_2NR^{35}$; R^{32}, R^{34} and R^{35} are

independently hydrogen or alkyl; and R^{33} is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl or optionally substituted phenyl) or acyl;

R^7 is hydrogen or alkyl; and

R^8 and R^9 are independently hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, alkylsulfonyl, arylsulfonyl, -C(O)-R^{81} (where R^{81} is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, alkoxy, aryloxy, amino, mono- or di-alkylamino, arylamino or aryl(alkyl)amino) or R^8 and R^9 together form =$CR^{82}R^{83}$ (where R^{82} and R^{83} are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl or optionally substituted phenyl);

and optionally

(c) one or more pharmaceutically acceptable diluents, excipients or carriers.

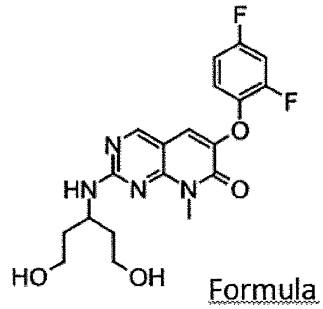
2) A pharmaceutical combination according to claim 1, comprising

(a) a PPAR agonist;

(b) a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof; and optionally

(c) one or more pharmaceutically acceptable diluents, excipients or carriers.

3) A pharmaceutical combination according to claim 2, wherein said compound of formula I is 6-(2,4-Difluorophenoxy)-2-[3-hydroxy-1-(2-hydroxyethyl)-propylamino]-8-methyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (pamapimod, Formula III) or a pharmaceutically acceptable salt thereof.



Formula III

4) A pharmaceutical combination according to any one of claims 1 to 3, wherein said PPAR agonist is pioglitazone or a pharmaceutically acceptable salt thereof.

5) A pharmaceutical combination according to any one of claims 1 to 4, for use as a medicament.

6) A pharmaceutical combination according to any one of claims 1 to 4 for use in a method for the prevention, delay of progression or treatment of cancer in a subject.

7) A pharmaceutical combination for use according to claim 6, wherein the cancer is metastatic cancer.

8) A pharmaceutical combination for use according to claim 6, wherein the cancer is selected from the group consisting of lung cancer, ovarian cancer, prostate cancer, breast cancer, bladder cancer, liver cancer, cancer of the gastrointestinal (GI) tract, hematological cancer and kidney cancer.

9) A pharmaceutical combination for use according to claim 8, wherein
(a) said lung cancer is selected from non-small-cell lung carcinoma and small-cell lung carcinoma;
(b) said breast cancer is selected from ductal carcinoma in situ, invasive ductal carcinoma and invasive lobular carcinoma;
(c) said bladder cancer is selected from transitional cell carcinoma, squamous cell carcinoma, small cell carcinoma, adenocarcinoma and sarcoma;
(d) said liver cancer is selected from hepatocellular carcinoma, hepatoblastoma and cholangiocarcinoma;
(e) said cancer of the GI tract is selected from esophageal cancer, gastric cancer, intestinal cancer, colorectal cancer, and anal cancer;
(f) said hematological cancer is selected from acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, myelodysplastic syndrome (MDS) and multiple myeloma;
(g) said kidney cancer is renal cell adenocarcinoma.

10) A pharmaceutical combination for use according to claim 6, wherein the cancer is cancer of the GI tract, lung cancer or ovarian cancer.

11) A pharmaceutical combination for use according to claim 6, wherein the cancer is lung cancer or ovarian cancer or wherein the cancer is lung cancer or cancer of the GI tract.