(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 April 2004 (15.04.2004)

PCT

(10) International Publication Number
WO 2004/030627 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2003/031091

(22) International Filing Date: 1 October 2003 (01.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/415,416 2 October 2002 (02.10.2002) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Route 206 and Province Line Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CARBONI, Joan, M.** [US/US]; 311 Michael Road, Yardley, PA 19067 (US). **HURLBURT, Warren, W.** [US/US]; 101 Kettlebrook Drive, Mount Laurel, NJ 08054 (US). **GOTTARDIS, Marco, M.** [US/US]; 9 Harris Road, Princeton, NJ 08540 (US).

(74) Agents: **GIBBONS, Maureen** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

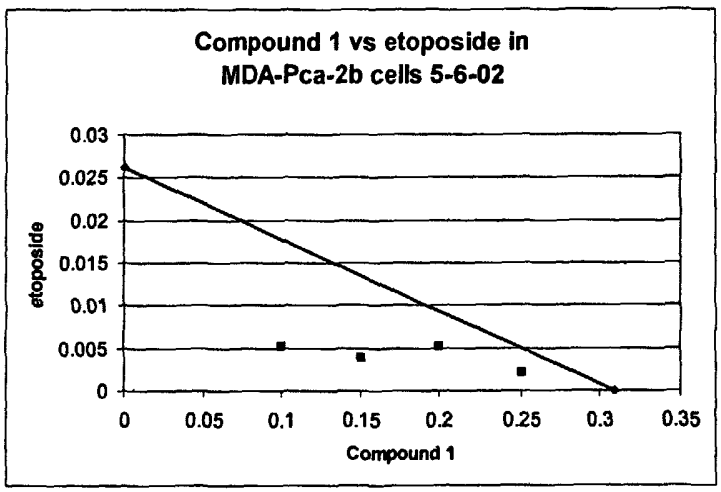
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYNERGISTIC METHODS AND COMPOSITIONS FOR TREATING CANCER



(57) Abstract: Methods of using IGFIR inhibitors in combination with cytotoxic agents are described for the synergistic treatment of cancer.

WO 2004/030627 A2

SYNERGISTIC METHODS AND COMPOSITIONS FOR TREATING CANCER

RELATED APPLICATIONS

This application claims priority benefit under Title 35 § 119(e) of U.S. Provisional Application No. 60/415,416, filed October 2, 2002, entitled "Synergistic Methods and Compositions for Treating Cancer."

FIELD OF THE INVENTION

The present invention relates to therapies for the treatment of cancer, specifically to synergistic methods for treating cancer using IGF1R inhibitors in combination with cytotoxic agents.

BACKGROUND OF THE INVENTION

Chemotherapy, the systemic administration of antineoplastic agents that travel throughout the body via the blood circulatory system, along with and often in conjunction with surgery and/or radiation treatment, has for years been widely utilized in the treatment of a wide variety of cancers.

Today, there are a variety of antineoplastic agents that have successfully been used in the treatment of cancer. However, the search continues for more efficacious and less toxic agents.

Tyrosine kinases are a class of enzymes that have proven to be useful agents for the treatment of cancer. Tyrosine kinases catalyze the transfer of the terminal phosphate of adenosine triphosphate to the phenolic hydroxyl group of a tyrosine residue present in the target protein. Tyrosine kinases play a critical role in signal transduction for several cellular functions including cell proliferation, carcinogenesis, apoptosis, and cell differentiation (Plowman, G. D.; Ullrich, A.; Shawver, L. K.: Receptor Tyrosine Kinases As Targets For Drug Intervention. *DN&P* (1994) 7: 334-339). Inhibitors of these enzymes are actually useful for the treatment or prevention of a variety of proliferative diseases that are dependent on these enzymes. Strong epidemiologic evidence suggests that the overexpression or activation of receptor protein tyrosine kinases leading to constitutive mitogenic signaling is an important factor in a growing number of human malignancies. Tyrosine kinases that have been

implicated in these processes include Abl, CDK's, EGF, EMT, FGF, FAK, Flk-1/KDR, HER-2, IGF-1R, IR, LCK, MET, PDGF, Src, and VEGF (Traxler, P.M. Protein Tyrosine Kinase Inhibitors in Cancer Treatment. *Exp. Opin. Ther. Patents* (1997) **7**: 571-588; incorporated herein by reference).

The IGF1R (insulin-like growth factor-1 receptor) affects cell mitogenesis, survival, transformation, and insulin-like activities by the binding of its ligands, IGF1 and IGF2. This receptor influences post natal growth physiology, and its activity has been associated with malignant disorders such as breast cancer. *See*, Ellis *et al.*, *Breast Cancer Res. Treat.* 1998, 52, 175. The anti-apoptotic effect induced by the IGF1/IGF1R system correlates to the induction of chemoresistance in various tumors. *See*, Grothey *et al.*, *J. Cancer Res. Clin. Oncol.*, 1999, *125*, 166-73. Accordingly, inhibitors of IGF1R are useful in the treatment of cancer, as evidenced in U.S. Patent Application Serial Number 10/105599. IGF1R inhibitors are useful as single agents and also in combination with other anticancer agents.

However, although combination chemotherapy has improved the response and survival rates of patients with hematological malignancies and some solid tumors, it is well known that anti-cancer drugs often bring on serious side effects that limit the doses physicians can administer. Synergistic combination chemotherapy is especially desirable because the synergy between active ingredients allows for the use of smaller doses of one or both active ingredients, provides greater efficacy at the same doses, and/or prevents or delays the build-up of multi-drug resistance. Accordingly, there is a need in the art for synergistic chemotherapy regimens that are effective for the treatment of cancer with improved toxicity profiles.

SUMMARY OF THE INVENTION

It has now been found, and this forms the subject of the present invention, that the efficacy of both IGF1R inhibitors and cytotoxic anticancer agents are considerably improved when they are administered in combination, resulting in methods for the synergistic treatment of cancer. Thus, the present invention is directed to methods for the synergistic treatment of cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a cytotoxic agent in combination with a therapeutically effective amount of an IGF1R inhibitor in amounts sufficient to achieve synergistic effects, optionally including treatment with an additional anticancer agent.

The present invention also includes pharmaceutical compositions comprising a syntergistically effective amount of an IGF1R inhibitor in combination with a synergistically effective amount of a cytotoxic agent.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is an isobologram demonstrating the synergistic effects observed when an IGF1R inhibitor is administered in combination with etoposide.

Figure 2 is an isobologram demonstrating the synergistic effects observed when an IGF1R inhibitor is administered in combination with cisplatin.

Figure 3 is an isobologram demonstrating the synergistic effects observed when an IGF1R inhibitor is administered in combination with paclitaxel.

DETAILED DESCRIPTION

Advantageously, the present invention provides a method for the synergistic treatment of cancer comprising administering a synergistically, therapeutically effective amount of (1) an IGF1R inhibitor and (2) a cytoxic agent to a mammalian species, preferably a human, in need thereof.

As used herein, the term “synergistic” or "synergistically effective amount" means that the effect achieved with the methods and compositions of this invention is greater than the sum of the effects that results from methods and compositions comprising cytotoxic agents and IGF1R inhibitors separately.

As used herein, "anticancer" agent includes any of the cytotoxic agents in addition hormones and steroids (including synthetic analogs): 17□-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, hlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex, matrix metalloproteinase inhibitors, and other VEGF inhibitors, such as anti-VEGF antibodies and small molecules such as ZD6474 and SU6668 are also included. Anti- Her2 antibodies from Genetech may also be utilized. A suitable EGFR inhibitor is EKB-569 (an irreversible inhibitor). Also included are Imclone antibody C225 immunospecific for the EGFR, and src inhibitors, Casodex® (bicalutamide, Astra Zeneca), Tamoxifen, epidermal growth factor inhibitors, Her-2 inhibitors, MEK-1 kinase inhibitors, MAPK kinase inhibitors, PI3 inhibitors, Src kinase inhibitors, and PDGF inhibitors. Also included are anti-angiogenic and antivascular agents which, by interrupting blood flow to solid tumors, render cancer cells quiescent by depriving them of nutrition. Castration, which also renders androgen dependent carcinomas non-proliferative, may also be utilized. Also included are MET kinase inhibitors, MAP kinase inhibitors, inhibitors of non-receptor and receptor tyrosine kinases, and inhibitors of integrin signaling.

Further advantages over previously disclosed methods include the ability of the instant combination of IGF1R inhibitors and the cytotoxic agent to be individually varied depending on the nature of the cancer cells to be treated. It is also anticipated that the therapeutic effect of the instant compositions may be achieved with smaller amounts of either inhibitor than would be required if such inhibitors were administered alone. This approach minimizes any non-mechanism-based adverse toxicity effects that might result from administration of an amount of an IGF1R inhibitor or a cytotoxic agent alone sufficient to achieve the same therapeutic effect.

The present invention provides methods for the synergistic treatment of a variety of cancers, including, but not limited to, the following:

carcinoma including that of the bladder (including accelerated and metastatic bladder cancer), breast, cervical, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma),

ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, and skin (including squamous cell carcinoma);

hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, and Burketts lymphoma;

hematopoietic tumors of myeloid lineage including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia;

tumors of the central and peripheral nervous system including astrocytoma, neuroblastoma, glioma, and schwannomas;

tumors of mesenchymal origin including fibrosarcoma, liposarcoma, rhabdomyosarcoma, and osteosarcoma; and

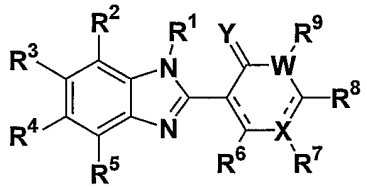
other tumors including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

In a preferred embodiment of this invention, a method is provided for the synergistic treatment of cancerous tumors. The synergistic method of this invention reduces the development of tumors, reduces tumor burden, or produces tumor regression in a mammalian host.

As used herein, the term "IGF1R inhibitor" refers to any biological or small molecule that inhibits the activity of the IGF1 receptor, thereby providing an anti-cancer effect.

IGF1R inhibitors of the present invention and methods for making them are described in U.S. Application Serial No. 10/263,448, the disclosure of which is herein incorporated by reference in its entirety. Additional IGF1R inhibitors that are useful in the present invention include those described by U.S. Patent Application 60/437,926; U.S. Patent Application 60/415066; WO03/048133; WO 01/25220; U.S. Pat. No. 6,337,338 (WO 00/35455); WO 02/102804; WO 02/092599; WO 03/024967; WO 03/ 035619; WO 03/035616; and WO 03/018022, the disclosures of which are herein incorporated by reference in their entirety.

In some embodiments of the present invention, the IGF1R inhibitor has the formula I:



I

and includes its enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof;

wherein

X is N, C or a direct bond;

Y is O or S;

W is N, C, O, or S; provided that if W is O or S, R^9 is absent;

R^1 is H, alkyl, or alkoxy;

R^2 and R^9 are independently H or alkyl;

R^3 is H, C_{1-6} alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, $-OR^{60}$, $-NO_2$, -OH, $-SR^{60}$, $-NR^{60}R^{61}$, -CN,$-C(O)R^{60}$, $-CO_2R^{60}$, $-CONR^{60}R^{61}$, $OCONR^{60}R^{61}$, $-NR^{62}CONR^{60}R^{61}$, $-NR^{60}SO_2R^{61}$, $-SO_2NR^{60}R^{61}$, $-SO_2R^{63}$, $-C(NR^{62})NR^{60}R^{61}$, $-C(NH^{62})$-morpholine, aryl, heteroaryl, $-(CH_2)_nC(O)_2-R^{60}$, $-NR^{60}R^{61}$ $-(CH_2)_nOR^{60}$, $-(CH_2)_nNR^{60}R^{61}$, $-(CH_2)_nSR^{60}$, $-(CH_2)_n$ aryl, $-(CH_2)_n$ heteroaryl, or $-(CH_2)_n$ heterocycloalkyl, wherein n is 1 to 3:

R^4 is H, halo, alkyl or haloalkyl;

R^5 is H, alkyl, halo, or aryl;

R^6, R^7, and R^8 are each independently -NH-Z-aryl or -NH-Z-heteroaryl wherein Z is $C_1 - C_4$ alkyl, alkenyl, or alkynyl; Z optionally having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, $NR^{60}SO_2R^{61}$ groups; Z optionally incorporating one or more groups selected from the group consisting of CO, CNOH, $CNOR^{60}$, $CNNR^{60}$, $CNNCOR^{60}$ and $CNNSO_2R^{60}$;

R^{60}, R^{61}, R^{62}, and R^{63} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl, heteroarylalkyl, and alkyl-R^{25};

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, -$NR^{30}COOR^{31}$, -$NR^{30}C(O)R^{31}$, -$NR^{30}SO_2R^{31}$, -$C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, or cycloalkyl.

In some embodiments of the present invention, $R^1$is H, alkyl or alkoxy, R^2 is H; R^3 is H, alkyl, -CN, halo, -$C(O)R^{60}$ -$C(O)NR^{60}R^{61}$, -$S(O)_2R^{63}$, piperazine, piperidine, morpholine, triazole, imidazole, wherein the piperazine, piperidine, morpholine, triazole, or imidazole is substituted with H, alkyl, -NHC(O)alkyl, -$NHC(O)_2$alkyl, -NHC(O)alkoxy, -O-$(CH_2)_nR^{64}$ wherein R^{64} is hydroxy, alkoxy, morpholine, or tetrahydropyrimidine; and R^6 is –NH-Z-phenyl; -NH-Z-imidazole; or -NH-Z-pyrazole wherein Z is C1 to C2 alkyl.

In some embodiments of the present invention, the IGF1R inhibitor is selected from the group consisting of:

(*S*)-4-(2-Hydroxy-1-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-Hydroxy-2-(3-iodo-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(2-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(3-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(4-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(2-Bromo-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(*S*)-4-[2-(3-Bromo-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(±)-4-(1-Hydroxymethyl-2-pentafluorophenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(*S*)-4-(1-Hydroxymethyl-2-pyridin-4-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(*S*)-4-[1-Hydroxymethyl-2-(2-naphthalenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
3-(6-Imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-4-(pyridin-2-ylmethoxy)-1H-pyridin-2-one;
(±)-4-[2-(3-Bromo-phenyl)-2-fluoro-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(*S*)-2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
(±)-2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile;
(*S*)-2-{4-[2-(3-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile;
(±)-2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile;
(±)-2-{4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile;
(±)-2-{4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazole-5-carbonitrile;
(*S*)-2-[4-(2-Hydroxy-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazole-5-carbonitrile;
(±)-3-(1H-Benzimidazol-2-yl)-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
(*S*)-3-(1H-Benzimidazol-2-yl)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one;

(±)-3-(1H-Benzimidazol-2-yl)-4-[2-(3-bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;

(*S*)-4-{2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid *iso*propylamide;

(*S*)-4-{2-[4-(1-hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid ethylamide;

(*S*)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-{4-methyl-6-[4-(1-phenyl-methanoyl)-piperazin-1-yl]-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

(*S*)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[6-(4-*iso*propyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(*S*)-3-[6-(4-Benzyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one;

(±)-3-[6-(4-Acetyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl) -1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-*iso*propyl-piperazine-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(*S*)-6-(1-Hydroxymethyl-2-phenyl-ethylamino)-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one;

(*S*)-2-[6-Chloro-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-pyrimidin-4-ylamino]-3-phenyl-propan-1-ol;

(*S*)-4-(2-Hydroxy-2-phenyl-ethylamino)-3-(6- imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H- pyridin-2-one;

(*R*)-4-(2-Hydroxy-2-phenyl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(1*S*,2*R*)-4-(1-Hydroxy-indan-2-ylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-Hydroxy-2-(3-hydroxy-phenyl)-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-(2-Hydroxy-2-pyridin-2-yl-ethylamino)-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-*N*-(3-{1-Hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-methanesulfonamide;

(±)-4-[2-(3-Fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(3-Fluoro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*R*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-(2-Chloro-4-{1-hydroxy-2-[3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-2-oxo-1,2-dihydro-pyridin-4-ylamino]-ethyl}-phenyl)-carbamic acid methyl ester;

(*S*)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(*S*)-4-(1-Hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(4-n-butyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(*S*)-3-{6-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-4-(1-hydroxymethyl-2-phenyl-ethylamino)-1H-pyridin-2-one;

(*S*)-4-{2-[4-(1-Hydroxymethyl-2-phenyl-ethylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]-7-methyl-3H-benzimidazol-5-yl}-piperazine-1-carboxylic acid amide;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(4-ethyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1Hpyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-;

(±)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)- piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

(±)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

(±)-3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzimidazol-2-yl]-4-[2-(3-bromo-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;

(*S*)-4-(1-hydroxymethyl-2-phenyl-ethylamino)-3-[4-methyl-6-(2-morpholin-4-yl-ethylamino)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(±)-6-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-5-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-3H-pyrimidin-4-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[6-(1-hydroxy-1-methyl-ethyl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(±)-3-(6-Aminomethyl-4-methyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;

(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-hydroxymethyl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-morpholin-4-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one; and

(*S*)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-piperidin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

(*S*)-4-(1-Benzyl-2-hydroxy-ethylamino)-3-(4-methyl-6-piperidin-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;

4-[2-(3-Chloro-4-methylsulfanyl-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;

4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-piperazin-1-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;

3-[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-propionitrile;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

3-[4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-3H-benzoimidazol-5-yl)-7-methyl-piperazin-1-yl]-propionitrile;

4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid 2-fluoro-ethyl ester;

4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid 2-methoxy-ethyl ester;

4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester;

4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid prop-2-ynyl ester;

4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester;

(*S*)-4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carboxylic acid ethyl ester;

4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoro-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(3,3,3-trifluoro-propyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(3,4,4-trifluoro-but-3-enyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(3-fluoro-2-hydroxy-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-2-methyl-propyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

(*S*)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-acetonitrile;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(4-fluoro-butyryl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2,2-difluoro-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfonyl-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
3-[6-(4-Acetyl-piperazin-1-yl)-4-methyl-1H-benzoimidazol-2-yl]-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-{4-[2-(1-oxo-1l4-thiomorpholin-4-yl)-acetyl]-piperazin-1-yl}-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-{4-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-acetyl]-piperazin-1-yl}-4-methyl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-thiomorpholin-4-yl-acetyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methanesulfinyl-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methoxy-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-methylsulfanyl-acetyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
3-{6-[4-(2-Chloro-acetyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
(S)-4-(2-{4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carbaldehyde;
(*S*)-4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzimidazol-5-yl)-piperazine-1-carbaldehyde;
(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1 H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;

4-[2-(7-Bromo-2,3-dihydro-benzofuran-5-yl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-[2(*S*),6(***R***)-dimethyl-morpholine-4-yl]-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-[2(*S*),6(***R***)-dimethyl-morpholine-4-yl]-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;
4-[2-(3-Chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(7-Bromo-2,3-dihydro-benzofuran-4-yl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(7-bromo-2,3-dihydro-benzofuran-4-yl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-fluoromethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro -phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;

4-[2-(3-Chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-hydroxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-hydroxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro -phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-methoxy-methyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-bromo-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(R)*-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one and 4-[2-(3-chloro-4-methoxy-phenyl)-(*S*)-2-hydroxy-ethylamino]-3-{6-[*(S)*-2-methoxymethyl-morpholin-4-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;

4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(acetamido)- piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxyacetamido)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(acetamido)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Bromo -phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxyacetamido)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroacetamido)-piperidin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methoxyethoxycarbamoyl)- piperidin -1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(methoxycarbamoyl)-piperidin -1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-fluoroethoxy carbamoyl)-piperidin -1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one;
(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
(*S*)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-methoxy-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-hydroxy-ethoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
(*S*)-4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-propoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(2-morpholin-4-yl-propoxy)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;

(*S*)-3-(4-Bromo-6-morpholin-4-ylmethyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
(*S*)-3-[4-Bromo-6-(4-methyl-piperazin-1-ylmethyl-1H-benzimidazol-2-yl)-4-[2-(3-chloro-phenyl)-2-hydroxy-ethylamino]-1H-pyridin-2-one;
(*S*)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-benzimidazol-2-yl]-1H-pyridin-2-one;
4-[2-(3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydropyrimidine-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridine-2-one; and
4-[2-(4-Methoxy-3-Chloro-phenyl)-2(*S*)-hydroxy-ethylamino]-3-[4-methyl-6-(1,4,5,6-tetrahydropyrimidine-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridine-2-one;
4-[2-(3-Chloro-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1,5-dihydro-pyrrol-2-one;
4-[2-(3-Bromo-4-methoxy-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1,5-dihydro-pyrrol-2-one;
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1,5-dihydro-pyrrol-2-one;
(S,S and S,R)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-5-methyl-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1,5-dihydro-pyrrol-2-one;
[1-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperidin-4-yl]-carbamic acid tetrahydro-furan-3-ylmethyl ester;
[1-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperidin-4-yl]-carbamic acid 2-methoxy-propyl ester;
(S)-2-[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-acetamide Bis hydrochloride;
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6[4-(2-methyoxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl1H-pyridin-2-one bis-hydrochloride;
(S)-4-[2-(3-Bromo-phenyl)-2-hydroxy-ethylamino]-3-{6[4-(2-methyoxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl-1H-pyridin-2-one bis hydrochloride;

(S)-4-[2-(3-Cynao-phenyl)-2-hydroxy-ethylamino]-3-{6[4-(2-methyoxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl1H-pyridin-2-one bis hydrochloride;
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperadin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one bis hydrochloride;
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-methylsulfanyl-ethyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one bis hydrochloride;
(S)4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(3R-methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridin-2-one bis hydrochloride; and
(S)4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{6-[4-(2-methoxy-ethyl)-3(R)-methyl-piperazin-1-yl]-4-methyl-1H-benzoimidazol-2-yl}-1H-pyridin-2-one bis hydrochloride.

The IGF1R inhibitors of the present invention are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist, i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients or their pharmaceutically acceptable salts in combination with pharmaceutically acceptable carriers.

In accordance with the present invention, cytotoxic anticancer agents include, but are not limited to, the following:

Alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Natural products and their derivatives (for example, vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ara-C, paclitaxel (paclitaxel is commercially available as Taxol®), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Other anti-proliferative cytotoxic agents are navelbene, CPT-11, anastrazole, letrazole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

Microtubule affecting agents interfere with cellular mitosis and are well known in the art for their anti-proliferative cytotoxic activity. Microtubule affecting agents useful in the invention include, but are not limited to, allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (*e.g.*, NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), Taxol® derivatives (*e.g.*, derivatives (*e.g.*, NSC 608832), thiocolchicine NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), natural and synthetic epothilones including but not limited to epothilone A, epothilone B, and discodermolide *(see* Service, (1996) Science, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in the scientific and patent literature, see, *e.g.,* Bulinski (1997) *J. Cell Sci.* 110:3055 3064; Panda (1997) *Proc.* Natl. Acad. Sci. USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) *Nature* 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem* 271:29807-29812.

The term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in

clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) *Oncology,* 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259).

In some embodiments of the present invention, the cytotoxic agent has paclitaxel-like activity. These include, but are not limited to, paclitaxel and paclitaxel derivatives (paclitaxel-like compounds) and analogues. Paclitaxel and its derivatives are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are well known to those of skill in the art *(see, e.g., U.S.* Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

Thus, anti-proliferative cytotoxic agents which are suitable for use in the methods and compositions of this invention include, but are not limited to, microtubule-stabilizing agents such as paclitaxel (also known as Taxol®), docetaxel (also known as Taxotere®), 7-O-methylthiomethylpaclitaxel (disclosed in U.S. 5,646,176), 4-desacetyl-4-methylcarbonatepaclitaxel, 3'-*tert*-butyl-3'-N-*tert*-butyloxycarbonyl-4-deacetyl-3'-dephenyl-3'-N-debenzoyl-4-O-methoxycarbonyl-paclitaxel (disclosed in USSN 09/712,352 filed on November 14, 2000), C-4 methyl carbonate paclitaxel (disclosed in WO 94/14787), epothilone A, epothilone B, epothilone C, epothilone D, desoxyepothilone A, desoxyepothilone B, [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7-11-dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17 oxabicyclo [14.1.0]heptadecane-5,9-dione (disclosed in WO 99/02514), [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-3-[2-[2-(aminomethyl)-4-thiazolyl]-1-methylethenyl]-7,11-dihydroxy-8,8,10,12,16-pentamethyl-4-17-dioxabicyclo[14.1.0]-heptadecane-5,9-dione (disclosed in USP 6,262,094) and derivatives thereof; and microtubule-disruptor agents.

Also suitable are cytotoxic agents such as CDK inhibitors, an antiproliferative cell cycle inhibitor, epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Additional cytotoxic agents include, melphalan, hexamethyl melamine, thiotepa, cytarabin, idatrexate, trimetrexate, dacarbazine, L-asparaginase, camptothecin, topotecan, bicalutamide, flutamide, leuprolide, pyridobenzoindole derivatives, interferons, and interleukins.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising a therapeutically effective amount of the combinations of this invention and may comprise an additional anti-cancer agent or agents, and a pharmaceutically acceptable carrier. The compositions of the present invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

The IGF1R and cytotoxic agents of the present invention may be administered orally or parenterally including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use, IGF1R inhibitors and the cytotoxic agents and compositions of this invention may be administered, for example, in the form of tablets or capsules, powders, dispersible granules, or cachets, or as aqueous solutions or suspensions. In the case of tablets for oral use, carriers that are commonly used include lactose, corn starch, magnesium carbonate, talc, and sugar, and lubricating agents such as magnesium stearate are commonly added. For oral administration in capsule form, useful carriers include lactose, corn starch, magnesium carbonate, talc, and sugar. When aqueous suspensions are used for oral administration, emulsifying and/or suspending agents are commonly added. In addition, sweetening and/or flavoring agents may be added to the oral compositions. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient(s) are usually employed, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of the solute(s) should be controlled in order to render the preparation isotonic.

For preparing suppositories according to the invention, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously in the wax, for example by stirring. The

molten homogeneous mixture is then poured into conveniently sized molds and allowed to cool and thereby solidify.

Liquid preparations include solutions, suspensions and emulsions. Such preparations are exemplified by water or water/propylene glycol solutions for parenteral injection. Liquid preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid preparations that are intended for conversion, shortly before use, to liquid preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The IGF1R and/or cytotoxic agent may also be delivered transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The IGF1R inhibitor may be administered prior to, simultaneously with, or subsequent to the administration of the cytotoxic agent.

The combinations of the present invention may also be used in conjunction with other well-known anticancer therapies, including radiation, chemotherapy and surgery. Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), *e.g.*, 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Generally, treatment is initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided

and administered in portions during the day if desired. Intermittent therapy (*e.g.*, one week out of three weeks or three out of four weeks) may also be used.

Also, in general, the IGF1R inhibitor and the cytotoxic agent do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the IGF1R inhibitor may be administered orally to generate and maintain good blood levels thereof, while the cytotoxic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of IGF1R inhibitor and cytotoxic agent and/or radiation chemotherapy and/or surgery will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

Administration of either the cytotoxic agent and/or the IGF1R inhibitor may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent--*i.e.*, IGF1R inhibitor, cytotoxic agent, additional anticancer drugs, surgery, or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan,

and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

In order to facilitate a further understanding of the invention, the following example is presented primarily for the purpose of illustrating more specific details thereof. The scope of the invention should not be deemed limited by the examples, but encompasses the entire subject matter defined in the claims.

EXAMPLE 1

^{3}H-Thymidine Uptake Cell Proliferation Assay Utilizing Drug Combinations of IGF1R Inhibitors and cytotoxic agents

Stock drug concentrations were 10mM in 100% DMSO (dimethyl sulfoxide), with subsequent dilutions performed in 70% DMSO.

Serial dilutions (1:4 or 1:5) were used to establish the 50% inhibitory dose of both the test and standard compounds alone. The cells were seeded in a 50ul volume using a 96-well format 24 hrs prior to addition of the drug. The next day, each well received an additional 25ul of the test compound or media (containing DMSO), and 25ul of the standard compound or media (containing DMSO). A dose response curve was established for the standard compound; the test compound was then added as a single dose to the standard compound dose curves. All wells contain a final volume of 100ul and a final concentration of 0.35% DMSO.

After dosing, the cells were allowed to incubate at 37°C in an atmosphere of 5% CO_2 until they were labeled with 0.44uCi/well ^{3}H-thymidine; after a total of 72 hours post dosing, wells were harvested. Wells without cells were used to calculate a background value, and wells with cells but without drug were used to calculate a total control value. At harvest, the cells were trypsized and the amount of ^{3}H-thymidine incorporated was captured by glass filter and counted by scintillation.

Concentrations of each drug alone or combinations of the two drugs administered together that blocked growth by 50% (IC_{50}) were calculated. Assuming zero interaction between the two compounds, these points on the axes can be joined by a straight line (isobole) which indicates combinations of standard and test drugs

that are isoeffective with either drug alone. The isoeffect is the IC_{50}. When drug combinations fall along this straight line they are assumed to be additive. When the drug combinations are more effective than expected, lower concentrations are required to produce the isoeffect (IC_{50}) and are considered synergistic. These points will fall below the zero interaction isobole. When drug combinations require higher concentrations than expected to produce the isoeffect, they are considered antagonistic and the points will fall above the zero interaction isobole. All of the combinations tested fall at or below the zero interaction isobole as depicted in Figures 1 and 2 "Compound 1" represents an IGF1R inhibitors according to Formula I.

The present invention is not limited to the embodiments specifically described above, but is capable of variation and modification without departure from the scope of the appended claims.

WE CLAIM:

1. A method for the synergistic treatment of cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a cytotoxic agent in combination with a therapeutically effective amount of an IGF1R inhibitor in amounts sufficient to achieve synergistic effects.

2. The method according to claim 1 wherein the cytotoxic agent comprises radiation therapy.

3. The method according to claim 1, wherein the cytotoxic agent is administered prior to the IGF1R inhibitor.

4. The method according to claim 1 wherein the cytotoxic agent is administered subsequent to the IGF1R inhibitor.

5. The method according to claim 1 for the synergistic treatment of cancerous solid tumors.

6. The method according to Claim 1 wherein the cytotoxic agent is a microtubule-affecting agent; a natural product or derivative thereof, or a platinum coordination complex.

7. The method according to claim 6 wherein said microtubule-affecting agent is allocolchicine, Halichondrin B, colchicine, colchicine derivatives, dolastatin 10, maytansine, rhizoxin, paclitaxel, a paclitaxel derivative, thiocolchicine, trityl cysteine, vinblastine sulfate, vincristine sulfate, epothilone A, epothilone B, discodermolide, estramustine, nocodazole, or MAP4.

8. The method according to claim 6 wherein said natural product is a vinca alkaloid, an antitumor antibiotic, an enzyme, lymphokine, epipodophyllotoxin, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ara-C, Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, an Interferon, Etoposide, or Teniposide.

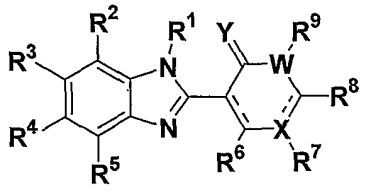
9. The method according to claim 6 wherein said platinum coordination complex is cisplatin or carboplatin.

10. The method according to claim 1 wherein said cytotoxic agent is etoposide.

11. The method according to claim 1 wherein said cytoxic agent is cisplatin or carboplatin.

12. The method according to claim 1 further comprising the administration of an additional anticancer agent.

13. The method according to claim 1 wherein said IGF1R inhibitor has the following formula I



I

its enantiomers, diastereomers, pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof;

wherein

X is N, C_1-C_3 alkyl, or a direct bond;

Y is O or S ;

W is N, C, O, or S; provided that if W is O or S, R^9 is absent;

R^1 is H, alkyl, or alkoxy;

R^2 and R^9 are independently H or alkyl;

R^3 is H, C_{1-6} alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, $-OR^{60}$, $-NO_2$, -OH, $-SR^{60}$, $-NR^{60}R^{61}$, -CN,$-C(O)R^{60}$, $-CO_2R^{60}$, $-CONR^{60}R^{61}$, $OCONR^{60}R^{61}$, $-NR^{62}CONR^{60}R^{61}$, $-NR^{60}SO_2R^{61}$, $-SO_2NR^{60}R^{61}$, $-SO_2R^{63}$, $-C(NR^{62})NR^{60}R^{61}$, $-C(NH^{62})$-morpholine, aryl, heteroaryl, $-(CH_2)_nC(O)_2-R^{60}$, $-NR^{60}R^{61}$ $-(CH_2)_nOR^{60}$, $-(CH_2)_nNR^{60}R^{61}$, $-(CH_2)_nSR^{60}$, $-(CH_2)_n$ aryl, $-(CH_2)_n$ heteroaryl, or $-(CH_2)_n$ heterocycloalkyl, wherein n is 1 to 3:

R^4 is H, halo, alkyl or haloalkyl;

R^5 is H, alkyl, halo, or aryl;

R^6, R^7, and R^8 are each independently -NH-Z-aryl or -NH-Z-heteroaryl wherein Z is $C_1 - C_4$ alkyl, alkenyl, or alkynyl; Z optionally having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, $NR^{60}SO_2R^{61}$ groups; Z optionally incorporating one or more groups selected from the group consisting of CO, CNOH, $CNOR^{60}$, $CNNR^{60}$, $CNNCOR^{60}$ and $CNNSO_2R^{60}$;

R^{60}, R^{61}, R^{62}, and R^{63} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl, heteroarylalkyl, and alkyl-R^{25};

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, or cycloalkyl.

14. The method according to 13 wherein R^3 is an optionally substituted morpholine, thiomorpholine, sulfoxymorpholine, sulfonylmorpholine, or homomorpholine.

15. The method according to claim 13 wherein R^3 is a substituted or unsubstituted piperazine or piperadine.

16. The method according to claim 13 wherein R^6 is -NH-Z-aryl, or -NH-Z-heteroaryl.

17. The method according to claim 16 wherein said aryl is a substituted or unsubstituted phenyl.

18. The method according to claim 16 wherein said heteroaryl is a substituted or unsubstituted pyridinyl, imidazolyl, pyrazolyl, pyrrolyl or triazolyl.

19. The method of claim 1 wherein the cytotoxic agent is paclitaxel, etoposide, or cisplatin and the IGF1R inhibitor is selected from the group consisting of:
(±)-4-[2-(3-Chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(*S*)-4-[2-(3-Fluoro-phenyl)-1-hydroxymethyl-ethylamino]-3-(6-imidazol-1-yl-4-methyl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(±)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(6-imidazol-1-yl-1H-benzimidazol-2-yl)-1H-pyridin-2-one;
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-(4-methyl-6-morpholin-4-yl-1H-benzoimidazol-2-yl)-1 H-pyridin-2-one;
(S)-2-[4-(2-{4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-2-oxo-1,2-dihydro-pyridin-3-yl}-7-methyl-3H-benzoimidazol-5-yl)-piperazin-1-yl]-acetamide Bis hydrochloride;
(S)-4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-{4-methyl-6-[4-(2-methylsulfanyl-ethyl)-piperazin-1-yl]-1H-benzoimidazol-2-yl}-1H-pyridin-2-one bis hydrochloride;
(S)4-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-3-[4-methyl-6-(3R-methyl-piperazin-1-yl)-1H-benzoimidazol-2-yl]-1H-pyridin-2-one bis hydrochloride; and
(S)-4-[2-(3-Chloro-phenyl)-2-methoxy-ethylamino]-3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-4-methyl-1H-benzimidazol-2-yl}-1H-pyridin-2-one.

20. A pharmaceutical composition comprising a synergistically effective amount of an IGF1R inhibitor in combination with a synergistically effective amount of a cytotoxic agent.

FIG. 1

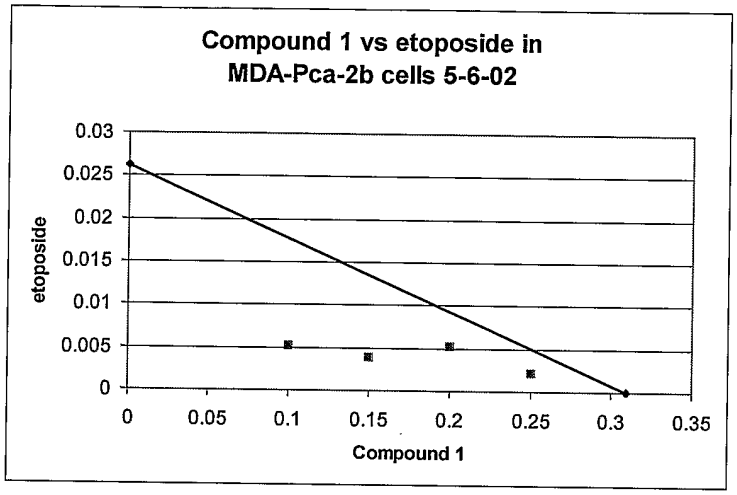

Compound 1 vs etoposide in
MDA-Pca-2b cells 5-6-02
etoposide
0.03
0.025
0.02
0.015
0.01
0.005
0
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
Compound 1

FIG. 2

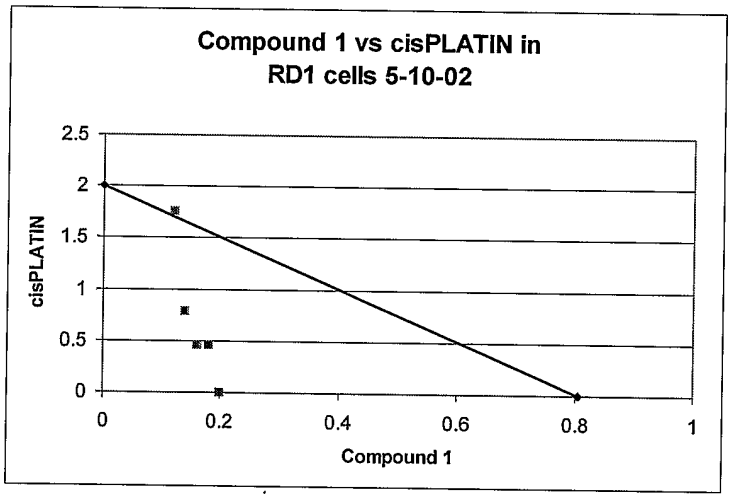
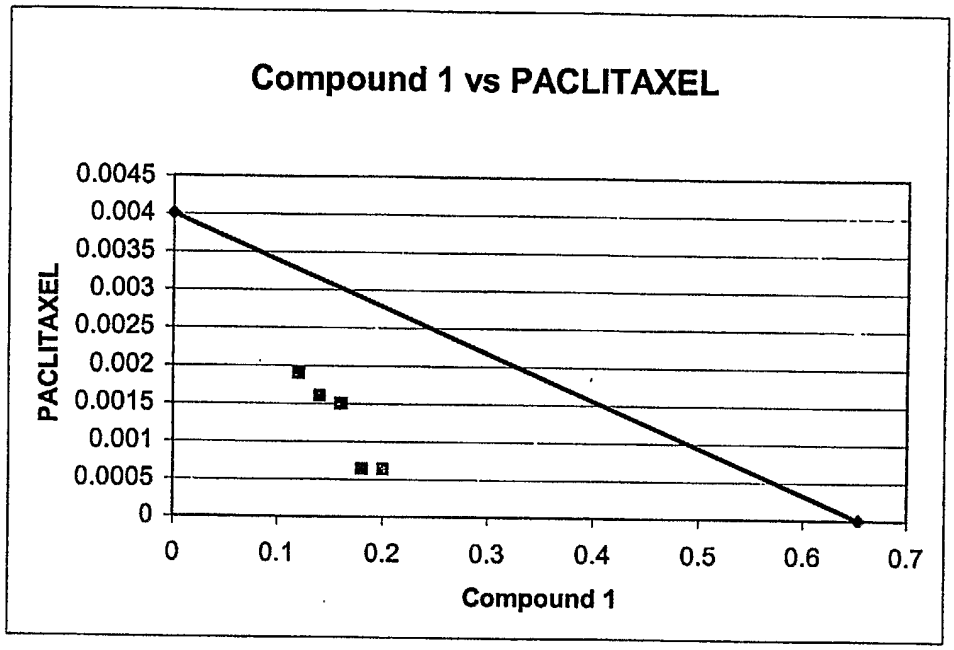

Compound 1 vs cisPLATIN in
RD1 cells 5-10-02
cisPLATIN
2.5
2
1.5
1
0.5
0
0
0.2
0.4
0.6
0.8
1
Compound 1

FIG. 3


Compound 1 vs PACLITAXEL
PACLITAXEL
0.0045
0.004
0.0035
0.003
0.0025
0.002
0.0015
0.001
0.0005
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Compound 1