COMBINATION THERAPY COMPRISING A DIHYDROPYRAZINO-PYRAZINE COMPOUND AND AN ANDROGEN RECEPTOR ANTAGONIST FOR TREATING PROSTATE CANCER

[0001] This application claims the benefit of U.S. Provisional Application No. 61/813,038, filed April 17, 2013 and U.S. Provisional Application No. 61/815,509, filed April 24, 2013, the entire contents of which are incorporated herein by reference.

1. FIELD

[0002] Provided herein are methods for treating or preventing a cancer, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound and an effective amount of an androgen receptor antagonist to a patient having a cancer.

2. BACKGROUND

[0003] The connection between abnormal protein phosphorylation and the cause or consequence of diseases has been known for over 20 years. Accordingly, protein kinases have become a very important group of drug targets. *See* Cohen, *Nature*, 1:309-315 (2002). Various protein kinase inhibitors have been used clinically in the treatment of a wide variety of diseases, such as cancer and chronic inflammatory diseases, including diabetes and stroke. *See* Cohen, *Eur. J. Biochem.*, 268:5001-5010 (2001), *Protein Kinase Inhibitors for the Treatment of Disease: The Promise and the Problems*, Handbook of Experimental Pharmacology, Springer Berlin Heidelberg, 167 (2005).

[0004] The protein kinases are a large and diverse family of enzymes that catalyze protein phosphorylation and play a critical role in cellular signaling. Protein kinases may exert positive or negative regulatory effects, depending upon their target protein. Protein kinases are involved in specific signaling pathways which regulate cell functions such as, but not limited to, metabolism, cell cycle progression, cell adhesion, vascular function, apoptosis, and angiogenesis. Malfunctions of cellular signaling have been associated with many diseases, the most characterized of which include cancer and diabetes. The regulation of signal transduction by cytokines and the association of signal

molecules with protooncogenes and tumor suppressor genes have been well documented. Similarly, the connection between diabetes and related conditions, and deregulated levels of protein kinases, has been demonstrated. *See e.g.*, Sridhar *et al. Pharmaceutical Research*, 17(11):1345-1353 (2000). Viral infections and the conditions related thereto have also been associated with the regulation of protein kinases. Park *et al. Cell* 101 (7): 777-787 (2000).

[0005] Because protein kinases regulate nearly every cellular process, including metabolism, cell proliferation, cell differentiation, and cell survival, they are attractive targets for therapeutic intervention for various disease states. For example, cell-cycle control and angiogenesis, in which protein kinases play a pivotal role are cellular processes associated with numerous disease conditions such as but not limited to cancer, inflammatory diseases, abnormal angiogenesis and diseases related thereto, atherosclerosis, macular degeneration, diabetes, obesity, and pain.

[0006] Protein kinases have become attractive targets for the treatment of cancers. Fabbro *et al.*, *Pharmacology & Therapeutics* 93:79-98 (2002). It has been proposed that the involvement of protein kinases in the development of human malignancies may occur by: (1) genomic rearrangements (*e.g.*, BCR-ABL in chronic myelogenous leukemia), (2) mutations leading to constitutively active kinase activity, such as acute myelogenous leukemia and gastrointestinal tumors, (3) deregulation of kinase activity by activation of oncogenes or loss of tumor suppressor functions, such as in cancers with oncogenic RAS, (4) deregulation of kinase activity by over-expression, as in the case of EGFR and (5) ectopic expression of growth factors that can contribute to the development and maintenance of the neoplastic phenotype. Fabbro *et al.*, *Pharmacology & Therapeutics* 93:79-98 (2002).

[0007] The elucidation of the intricacy of protein kinase pathways and the complexity of the relationship and interaction among and between the various protein kinases and kinase pathways highlights the importance of developing pharmaceutical agents capable of acting as protein kinase modulators, regulators or inhibitors that have

beneficial activity on multiple kinases or multiple kinase pathways. Accordingly, there remains a need for new kinase modulators.

[0008] The protein named mTOR (mammalian target of rapamycin), which is also called FRAP, RAFTI or RAPT1), is a 2549-amino acid Ser/Thr protein kinase, that has been shown to be one of the most critical proteins in the mTOR/PI3K/Akt pathway that regulates cell growth and proliferation. Georgakis and Younes *Expert Rev. Anticancer Ther.* 6(1):131-140 (2006). mTOR exists within two complexes, mTORC1 and mTORC2. While mTORC1 is sensitive to rapamycin analogs (such as temsirolimus or everolimus), mTORC2 is largely rapamycin-insensitive. Notably, rapamycin is not a TOR kinase inhibitor. Several mTOR inhibitors have been or are being evaluated in clinical trials for the treatment of cancer. Temsirolimus was approved for use in renal cell carcinoma in 2007 and sirolimus was approved in 1999 for the prophylaxis of renal transplant rejection. Everolimus was approved in 2009 for renal cell carcinoma patients that have progressed on vascular endothelial growth factor receptor inhibitors, in 2010 for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who require therapy but are not candidates for surgical resection, and in 2011 for progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. There remains a need for TOR kinase inhibitors that inhibit both mTORC1 and mTORC2 complexes.

[0009] DNA-dependent protein kinase (DNA-PK) is a serine/threonine kinase involved in the repair of DNA double strand breaks (DSBs). DSBs are considered to be the most lethal DNA lesion and occur endogenously or in response to ionizing radiation and chemotherapeutics (for review see Jackson, S. P., Bartek, J. The DNA-damage response in human biology and disease. Nature Rev 2009; 461:1071-1078). If left unrepaired, DSBs will lead to cell cycle arrest and/or cell death (Hoeijmakers, J. H. J. Genome maintenance mechanisms for preventing cancer. Nature 2001; 411: 366-374; van Gent, D. C., Hoeijmakers, J. H., Kanaar, R. Chromosomal stability and the DNA double-stranded break connection. *Nat Rev Genet* 2001; 2: 196-206). In response to the insult, cells have developed complex mechanisms to repair such breaks and these

mechanisms may form the basis of therapeutic resistance. There are two major pathways used to repair DSBs, non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ brings broken ends of the DNA together and rejoins them without reference to a second template (Collis, S. J., DeWeese, T. L., Jeggo P. A., Parker, A.R. The life and death of DNA-PK. Oncogene 2005; 24: 949-961). In contrast, HR is dependent on the proximity of the sister chromatid which provides a template to mediate faithful repair (Takata, M., Sasaki, M. S., Sonoda, E., Morrison, C., Hashimoto, M., Utsumi, H., et al. Homologous recombination and non-homologous end-joining pathways of DNA double-strand break repair have overlapping roles in the maintenance of chromosomal integrity in vertebrate cells. EMBO J 1998; 17: 5497-5508; Haber, J. E. Partners and pathways repairing a double-strand break. Trends Genet 2000; 16: 259-264). NHEJ repairs the majority of DSBs. In NHEJ, DSBs are recognized by the Ku protein that binds and then activates the catalytic subunit of DNA-PK. This leads to recruitment and activation of end-processing enzymes, polymerases and DNA ligase IV (Collis, S. J., DeWeese, T. L., Jeggo P. A., Parker, A.R. The life and death of DNA-PK. Oncogene 2005; 24: 949-961). NHEJ is primarily controlled by DNA-PK and thus inhibition of DNA-PK is an attractive approach to modulating the repair response to exogenously induced DSBs. Cells deficient in components of the NHEJ pathway are defective in DSB repair and highly sensitive to ionizing radiation and topoisomerase poisons (reviewed by Smith, G. C. M., Jackson, S.P. The DNA-dependent protein kinase. *Genes Dev* 1999; 13: 916-934; Jeggo, P.A., Caldecott, K., Pidsley, S., Banks, G.R. Sensitivity of Chinese hamster ovary mutants defective in DNA double strand break repair to topoisomerase II inhibitors. *Cancer Res* 1989; 49: 7057-7063). A DNA-PK inhibitor has been reported to have the same effect of sensitizing cancer cells to therapeutically induced DSBs (Smith, G. C. M., Jackson, S.P. The DNA-dependent protein kinase. *Genes Dev* 1999; 13: 916-934).

[0010] Citation or identification of any reference in Section 2 of this application is not to be construed as an admission that the reference is prior art to the present application.

3. SUMMARY

[0011] Provided herein are methods for treating or preventing a cancer, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound and an effective amount of an androgen receptor antagonist to a patient having a cancer.

[0012] In certain embodiments, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of complete response, partial response or stable disease in a patient having a solid tumor, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist to said patient. In certain embodiments, provided herein are methods for achieving a Prostate Cancer Working Group 2 (PCWG2) Criteria of complete response, partial response or stable disease in a patient having prostate cancer, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist to said patient.

[0013] In certain embodiments, provided herein are methods for increasing survival without tumor progression of a patient having a cancer, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to said patient.

[0014] In certain embodiments, the Dihydropyrazino-Pyrazine Compound is a compound as described herein. In certain embodiments, the androgen receptor antagonist is MDV3100.

[0015] The present embodiments can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 depicts Compound 2 monotherapy and MDV3100 monotherapy in an ETS-positive prostate cancer xenograft model.

[0017] FIG. 2 depicts Compound 2 monotherapy, MDV3100 monotherapy and Compound 2 + MDV3100 combination therapy in an ETS-positive prostate cancer xenograft model.

[0018] FIG. 3 depicts Compound 2 and MDV3100 combination treatment synergy in apoptosis induction. In FIG. 3A Caspase activity of single treatment with Compound 2 or MDV3100 of the LNCaP cell line (ETS+, Androgen dependent) is shown. FIG. 3B, C and D show 3 experiments measuring the caspase activity of combined treatment with Compound 2 and MDV3100: Compound 2 treatment alone (triangles), the expected additive effect of Compound 2 with 30, 10, 3.3 and 1.1 μM MDV3100 (+), and the actual combination effect of Compound 2 and MDV3100 treatment (circles), as measured by caspase induction. FIG. 3E shows an experiment measuring the caspase activity of treatment with Compound 2 and MDV3100 of the VCaP cell line (ETS+, Androgen dependent): Compound 2 treatment alone (triangles), the expected additive effect of Compound 2 with 30, 10, 3.3 and 1.1 μM MDV3100 (+), and the actual combination effect of Compound 2 and MDV3100 treatment (circles), as measured by caspase induction.

[0019] FIG. 4 depicts Compound 2 monotherapy, MDV3100 monotherapy and Compound 2 + MDV3100 combination therapy in a LNCap-HR prostate cancer xenograft model.

5. DETAILED DESCRIPTION

5.1 DEFINITIONS

[0020] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl

and the like. Examples of unsaturared alkyl groups include, but are not limited to, vinyl, allyl, -CH=CH(CH_3), -CH=C(CH_3)$_2$, -C(CH_3)=CH_2, -C(CH_3)=CH(CH_3), -C(CH_2CH_3)=CH_2, -C≡CH, -C≡C(CH_3), -C≡C(CH_2CH_3), -CH_2C≡CH, -CH_2C≡C(CH_3) and -CH_2C≡C(CH_2CH_3), among others. An alkyl group can be substituted or unsubstituted. In certain embodiments, when the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; B(OH)$_2$, or O(alkyl)aminocarbonyl.

[0021] An "alkenyl" group is a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms, typically from 2 to 8 carbon atoms, and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_8)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl and the like. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. An alkenyl group can be unsubstituted or substituted.

[0022] A "cycloalkyl" group is a saturated, or partially saturated cyclic alkyl group of from 3 to 10 carbon atoms having a single cyclic ring or multiple condensed or bridged rings which can be optionally substituted with from 1 to 3 alkyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms ranges from 3 to 5, 3 to 6, or 3 to 7. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1-methylcyclopropyl,

2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple or bridged ring structures such as adamantyl and the like. Examples of unsaturared cycloalkyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, hexadienyl, among others. A cycloalkyl group can be substituted or unsubstituted. Such substituted cycloalkyl groups include, by way of example, cyclohexanone and the like.

[0023] An "aryl" group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl). In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the ring portions of the groups. Particular aryls include phenyl, biphenyl, naphthyl and the like. An aryl group can be substituted or unsubstituted. The phrase "aryl groups" also includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like).

[0024] A "heteroaryl" group is an aryl ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. In some embodiments, heteroaryl groups contain 5 to 6 ring atoms, and in others from 6 to 9 or even 6 to 10 atoms in the ring portions of the groups. Suitable heteroatoms include oxygen, sulfur and nitrogen. In certain embodiments, the heteroaryl ring system is monocyclic or bicyclic. Non-limiting examples include but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl (for example, isobenzofuran-1,3-diimine), indolyl, azaindolyl (for example, pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, benzimidazolyl (for example, 1H-benzo[d]imidazolyl), imidazopyridyl (for example, azabenzimidazolyl, 3H-imidazo[4,5-b]pyridyl or 1H-imidazo[4,5-b]pyridyl), pyrazolopyridyl, triazolopyridyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

[0025] A "heterocyclyl" is an aromatic (also referred to as heteroaryl) or non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. In some embodiments, heterocyclyl groups include 3 to10 ring members, whereas other such groups have 3 to 5, 3 to 6, or 3 to 8 ring members. Heterocyclyls can also be bonded to other groups at any ring atom (*i.e.*, at any carbon atom or heteroatom of the heterocyclic ring). A heterocyclylalkyl group can be substituted or unsubstituted. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl groups. The phrase heterocyclyl includes fused ring species, including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[l,4]dioxinyl, and benzo[l,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Representative examples of a heterocyclyl group include, but are not limited to, aziridinyl, azetidinyl, pyrrolidyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl (for example, tetrahydro-2H-pyranyl), tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, homopiperazinyl, quinuclidyl, indolyl, indolinyl, isoindolyl, azaindolyl (pyrrolopyridyl), indazolyl, indolizinyl, benzotriazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiinyl, benzoxathiinyl, benzothiazinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[l,3]dioxolyl, pyrazolopyridyl, imidazopyridyl (azabenzimidazolyl; for example, 1H-imidazo[4,5-b]pyridyl, or 1H-imidazo[4,5-b]pyridin-2(3H)-onyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl,

thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups. Representative substituted heterocyclyl groups may be mono- substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed below.

[0026] A "cycloalkylalkyl" group is a radical of the formula: -alkyl-cycloalkyl, wherein alkyl and cycloalkyl are defined above. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl, or both the alkyl and the cycloalkyl portions of the group. Representative cycloalkylalkyl groups include but are not limited to cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, and cyclohexylpropyl. Representative substituted cycloalkylalkyl groups may be mono-substituted or substituted more than once.

[0027] An "aralkyl" group is a radical of the formula: -alkyl-aryl, wherein alkyl and aryl are defined above. Substituted aralkyl groups may be substituted at the alkyl, the aryl, or both the alkyl and the aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl.

[0028] A "heterocyclylalkyl" group is a radical of the formula: -alkyl-heterocyclyl, wherein alkyl and heterocyclyl are defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl, or both the alkyl and the heterocyclyl portions of the group. Representative heterocylylalkyl groups include but are not limited to 4-ethyl-morpholinyl, 4-propylmorpholinyl, furan-2-yl methyl, furan-3-yl methyl, pyrdine-3-yl methyl, (tetrahydro-2H-pyran-4-yl)methyl, (tetrahydro-2H-pyran-4-yl)ethyl, tetrahydrofuran-2-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

[0029] A "halogen" is chloro, iodo, bromo, or fluoro.

[0030] A "hydroxyalkyl" group is an alkyl group as described above substituted with one or more hydroxy groups.

[0031] An "alkoxy" group is -O-(alkyl), wherein alkyl is defined above.

[0032] An "alkoxyalkyl" group is -(alkyl)-O-(alkyl), wherein alkyl is defined above.

[0033] An "amine" group is a radical of the formula: $-NH_2$.

[0034] A "hydroxyl amine" group is a radical of the formula: $-N(R^{\#})OH$ or -NHOH, wherein $R^{\#}$ is a substituted or unsubstituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

[0035] An "alkoxyamine" group is a radical of the formula: $-N(R^{\#})O$-alkyl or -NHO-alkyl, wherein $R^{\#}$ is as defined above.

[0036] An "aralkoxyamine" group is a radical of the formula: $-N(R^{\#})O$-aryl or -NHO-aryl, wherein $R^{\#}$ is as defined above.

[0037] An "alkylamine" group is a radical of the formula: -NH-alkyl or $-N(alkyl)_2$, wherein each alkyl is independently as defined above.

[0038] An "aminocarbonyl" group is a radical of the formula: $-C(=O)N(R^{\#})_2$, $-C(=O)NH(R^{\#})$ or $-C(=O)NH_2$, wherein each $R^{\#}$ is as defined above.

[0039] An "acylamino" group is a radical of the formula: $-NHC(=O)(R^{\#})$ or $-N(alkyl)C(=O)(R^{\#})$, wherein each alkyl and $R^{\#}$ are independently as defined above.

[0040] An "O(alkyl)aminocarbonyl" group is a radical of the formula: $-O(alkyl)C(=O)N(R^{\#})_2$, $-O(alkyl)C(=O)NH(R^{\#})$ or $-O(alkyl)C(=O)NH_2$, wherein each $R^{\#}$ is independently as defined above.

[0041] An "N-oxide" group is a radical of the formula: $-N^{+}-O^{-}$.

[0042] A "carboxy" group is a radical of the formula: -C(=O)OH.

[0043] A "ketone" group is a radical of the formula: $-C(=O)(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0044] An "aldehyde" group is a radical of the formula: -CH(=O).

[0045] An "ester" group is a radical of the formula: $-C(=O)O(R^{\#})$ or $-OC(=O)(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0046] A "urea" group is a radical of the formula: -N(alkyl)C(=O)N($R^{\#}$)$_2$, -N(alkyl)C(=O)NH($R^{\#}$), -N(alkyl)C(=O)NH_2, -NHC(=O)N($R^{\#}$)$_2$, -NHC(=O)NH($R^{\#}$), or -NHC(=O)$NH_2^{\#}$, wherein each alkyl and $R^{\#}$ are independently as defined above.

[0047] An "imine" group is a radical of the formula: -N=C($R^{\#}$)$_2$ or -C($R^{\#}$)=N($R^{\#}$), wherein each $R^{\#}$ is independently as defined above.

[0048] An "imide" group is a radical of the formula: -C(=O)N(R#)C(=O)($R^{\#}$) or -N((C=O)($R^{\#}$))$_2$, wherein each $R^{\#}$ is independently as defined above.

[0049] A "urethane" group is a radical of the formula: -OC(=O)N($R^{\#}$)$_2$, -OC(=O)NH($R^{\#}$), -N($R^{\#}$)C(=O)O($R^{\#}$), or -NHC(=O)O($R^{\#}$), wherein each $R^{\#}$ is independently as defined above.

[0050] An "amidine" group is a radical of the formula: -C(=N($R^{\#}$))N($R^{\#}$)$_2$, -C(=N($R^{\#}$))NH($R^{\#}$), -C(=N($R^{\#}$))NH_2, -C(=NH)N($R^{\#}$)$_2$, -C(=NH)NH($R^{\#}$), -C(=NH)NH_2, -N=C($R^{\#}$)N($R^{\#}$)$_2$, -N=C($R^{\#}$)NH($R^{\#}$), -N=C($R^{\#}$)NH_2, -N($R^{\#}$)C($R^{\#}$)=N($R^{\#}$), -NHC($R^{\#}$)=N($R^{\#}$), -N($R^{\#}$)C($R^{\#}$)=NH, or -NHC($R^{\#}$)=NH, wherein each $R^{\#}$ is independently as defined above.

[0051] A "guanidine" group is a radical of the formula: -N($R^{\#}$)C(=N($R^{\#}$))N($R^{\#}$)$_2$, -NHC(=N($R^{\#}$))N($R^{\#}$)$_2$, -N($R^{\#}$)C(=NH)N($R^{\#}$)$_2$, -N($R^{\#}$)C(=N($R^{\#}$))NH($R^{\#}$), -N($R^{\#}$)C(=N($R^{\#}$))NH_2, -NHC(=NH)N($R^{\#}$)$_2$, -NHC(=N($R^{\#}$))NH($R^{\#}$), -NHC(=N($R^{\#}$))NH_2, -NHC(=NH)NH($R^{\#}$), -NHC(=NH)NH_2, -N=C(N($R^{\#}$)$_2$)$_2$, -N=C(NH($R^{\#}$))$_2$, or -N=C(NH_2)$_2$, wherein each $R^{\#}$ is independently as defined above.

[0052] A "enamine" group is a radical of the formula: -N($R^{\#}$)C($R^{\#}$)=C($R^{\#}$)$_2$, -NHC($R^{\#}$)=C($R^{\#}$)$_2$, -C(N($R^{\#}$)$_2$)=C($R^{\#}$)$_2$, -C(NH($R^{\#}$))=C($R^{\#}$)$_2$, -C(NH_2)=C($R^{\#}$)$_2$, -C($R^{\#}$)=C($R^{\#}$)(N($R^{\#}$)$_2$), -C($R^{\#}$)=C($R^{\#}$)(NH($R^{\#}$)) or -C($R^{\#}$)=C($R^{\#}$)(NH_2), wherein each $R^{\#}$ is independently as defined above.

[0053] An "oxime" group is a radical of the formula: -C(=NO($R^{\#}$))($R^{\#}$), -C(=NOH)($R^{\#}$), -CH(=NO($R^{\#}$)), or -CH(=NOH), wherein each $R^{\#}$ is independently as defined above.

[0054] A "hydrazide" group is a radical of the formula: $-C(=O)N(R^{\#})N(R^{\#})_2$, $-C(=O)NHN(R^{\#})_2$, $-C(=O)N(R^{\#})NH(R^{\#})$, $-C(=O)N(R^{\#})NH_2$, $-C(=O)NHNH(R^{\#})_2$, or $-C(=O)NHNH_2$, wherein each $R^{\#}$ is independently as defined above.

[0055] A "hydrazine" group is a radical of the formula: $-N(R^{\#})N(R^{\#})_2$, $-NHN(R^{\#})_2$, $-N(R^{\#})NH(R^{\#})$, $-N(R^{\#})NH_2$, $-NHNH(R^{\#})_2$, or $-NHNH_2$, wherein each $R^{\#}$ is independently as defined above.

[0056] A "hydrazone" group is a radical of the formula: $-C(=N-N(R^{\#})_2)(R^{\#})_2$, $-C(=N-NH(R^{\#}))(R^{\#})_2$, $-C(=N-NH_2)(R^{\#})_2$, $-N(R^{\#})(N=C(R^{\#})_2)$, or $-NH(N=C(R^{\#})_2)$, wherein each $R^{\#}$ is independently as defined above.

[0057] An "azide" group is a radical of the formula: $-N_3$.

[0058] An "isocyanate" group is a radical of the formula: -N=C=O.

[0059] An "isothiocyanate" group is a radical of the formula: -N=C=S.

[0060] A "cyanate" group is a radical of the formula: -OCN.

[0061] A "thiocyanate" group is a radical of the formula: -SCN.

[0062] A "thioether" group is a radical of the formula; $-S(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0063] A "thiocarbonyl" group is a radical of the formula: $-C(=S)(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0064] A "sulfinyl" group is a radical of the formula: $-S(=O)(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0065] A "sulfone" group is a radical of the formula: $-S(=O)_2(R^{\#})$, wherein $R^{\#}$ is as defined above.

[0066] A "sulfonylamino" group is a radical of the formula: $-NHSO_2(R^{\#})$ or $-N(alkyl)SO_2(R^{\#})$, wherein each alkyl and $R^{\#}$ are defined above.

[0067] A "sulfonamide" group is a radical of the formula: $-S(=O)_2N(R^{\#})_2$, or $-S(=O)_2NH(R^{\#})$, or $-S(=O)_2NH_2$, wherein each $R^{\#}$ is independently as defined above.

[0068] A "phosphonate" group is a radical of the formula: $-P(=O)(O(R^{\#}))_2$, $-P(=O)(OH)_2$, $-OP(=O)(O(R^{\#}))(R^{\#})$, or $-OP(=O)(OH)(R^{\#})$, wherein each $R^{\#}$ is independently as defined above.

[0069] A "phosphine" group is a radical of the formula: $-P(R^{\#})_2$, wherein each $R^{\#}$ is independently as defined above.

[0070] When the groups described herein, with the exception of alkyl group are said to be "substituted," they may be substituted with any appropriate substituent or substituents. Illustrative examples of substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyano; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonate; phosphine; thiocarbonyl; sulfinyl; sulfone; sulfonamide; ketone; aldehyde; ester; urea; urethane; oxime; hydroxyl amine; alkoxyamine; aralkoxyamine; N-oxide; hydrazine; hydrazide; hydrazone; azide; isocyanate; isothiocyanate; cyanate; thiocyanate; oxygen (=O); $B(OH)_2$, O(alkyl)aminocarbonyl; cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocyclyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, pyrrolidyl, piperidyl, piperazinyl, morpholinyl, or thiazinyl); monocyclic or fused or non-fused polycyclic aryl or heteroaryl (*e.g.*, phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl) aryloxy; aralkyloxy; heterocyclyloxy; and heterocyclyl alkoxy.

[0071] As used herein, the term "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the Dihydropyrazino-Pyrazine Compounds include, but are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic,

benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995).

[0072] As used herein and unless otherwise indicated, the term "clathrate" means a Dihydropyrazino-Pyrazine Compound, or a salt thereof, in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within or a crystal lattice wherein a Dihydropyrazino-Pyrazine Compound is a guest molecule.

[0073] As used herein and unless otherwise indicated, the term "solvate" means a Dihydropyrazino-Pyrazine Compound, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. In one embodiment, the solvate is a hydrate.

[0074] As used herein and unless otherwise indicated, the term "hydrate" means a Dihydropyrazino-Pyrazine Compound, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[0075] As used herein and unless otherwise indicated, the term "prodrug" means a Dihydropyrazino-Pyrazine Compound derivative that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a Dihydropyrazino-Pyrazine Compound. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a Dihydropyrazino-Pyrazine Compound that include biohydrolyzable moieties such as biohydrolyzable amides,

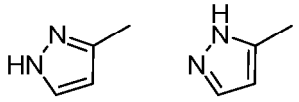
biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. In certain embodiments, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by *Burger's Medicinal Chemistry and Drug Discovery* 6th ed. (Donald J. Abraham *ed.*, 2001, Wiley) and *Design and Application of Prodrugs* (H. Bundgaard *ed.*, 1985, Harwood Academic Publishers Gmfh).

[0076] As used herein and unless otherwise indicated, the term "stereoisomer" or "stereomerically pure" means one stereoisomer of a Dihydropyrazino-Pyrazine Compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The Dihydropyrazino-Pyrazine Compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments disclosed herein, including mixtures thereof. The use of stereomerically pure forms of such Dihydropyrazino-Pyrazine Compounds, as well as the use of mixtures of those forms are encompassed by the embodiments disclosed herein. For example, mixtures comprising equal or unequal

amounts of the enantiomers of a particular Dihydropyrazino-Pyrazine Compound may be used in methods and compositions disclosed herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al., Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al., Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0077] It should also be noted the Dihydropyrazino-Pyrazine Compounds can include E and Z isomers, or a mixture thereof, and cis and trans isomers or a mixture thereof. In certain embodiments, the Dihydropyrazino-Pyrazine Compounds are isolated as either the cis or trans isomer. In other embodiments, the Dihydropyrazino-Pyrazine Compounds are a mixture of the cis and trans isomers.

[0078] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0079] As readily understood by one skilled in the art, a wide variety of functional groups and other stuctures may exhibit tautomerism and all tautomers of the Dihydropyrazino-Pyrazine Compounds are within the scope of the present invention.

[0080] It should also be noted the Dihydropyrazino-Pyrazine Compounds can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), sulfur-35 (^{35}S), or carbon-14 (^{14}C), or may be

isotopically enriched, such as with deuterium (^{2}H), carbon-13 (^{13}C), or nitrogen-15 (^{15}N). As used herein, an "isotopologue" is an isotopically enriched compound. The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term "isotopic composition" refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically encriched compounds are useful as therapeutic agents, e.g., cancer and inflammation therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the Dihydropyrazino-Pyrazine Compounds as described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, there are provided isotopologues of the Dihydropyrazino-Pyrazine Compounds, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched Dihydropyrazino-Pyrazine Compounds.

[0081] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0082] "Treating" as used herein, means an alleviation, in whole or in part, of a cancer or a symptom associated with a cancer, or slowing, or halting of further progression or worsening of those symptoms.

[0083] "Preventing" as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of a cancer, or a symptom thereof.

[0084] The term "effective amount" in connection with an Dihydropyrazino-Pyrazine Compound or an androgen receptor antagonist means an amount alone or in combination capable of alleviating, in whole or in part, a symptom associated with a cancer, or slowing or halting further progression or worsening of those symptoms, or treating or preventing a cancer in a subject having or at risk for having a cancer. The effective amount of the Dihydropyrazino-Pyrazine Compound or an androgen receptor

antagonist, for example in a pharmaceutical composition, may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a subject's body weight to about 100 mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration.

[0085] The term "cancer" refers to any of various malignant neoplasms characterized by the proliferation of cells that can invade surrounding tissue and metastasize to new body sites. Both benign and malignant tumors are classified according to the type of tissue in which they are found. For example, fibromas are neoplasms of fibrous connective tissue, and melanomas are abnormal growths of pigment (melanin) cells. Malignant tumors originating from epithelial tissue, e.g., in skin, bronchi, and stomach, are termed carcinomas. Malignancies of epithelial glandular tissue such as are found in the breast, prostate, and colon, are known as adenocarcinomas. Malignant growths of connective tissue, e.g., muscle, cartilage, lymph tissue, and bone, are called sarcomas. Lymphomas and leukemias are malignancies arising among white blood cells. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance. Bone tissues are one of the most favored sites of metastases of malignant tumors, occurring in about 30% of all cancer cases. Among malignant tumors, cancers of the lung, breast, prostate or the like are particularly known to be likely to metastasize to bone.

[0086] In the context of neoplasm, cancer, tumor growth or tumor cell growth, inhibition may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention

of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia.

[0087] As used herein, and unless otherwise specified, the term "in combination with" includes the administration of two or more therapeutic agents simultaneously, concurrently, or sequentially within no specific time limits unless otherwise indicated. In one embodiment, a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist. In one embodiment, the agents are present in the cell or in the subject's body at the same time or exert their biological or therapeutic effect at the same time. In one embodiment, the therapeutic agents are in the same composition or unit dosage form. In other embodiments, the therapeutic agents are in separate compositions or unit dosage forms. In certain embodiments, a first agent can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), essentially concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent, or any combination thereof. For example, in one embodiment, the first agent can be administered prior to the second therapeutic agent, for e.g. 1 week. In another, the first agent can be administered prior to (for example 1 day prior) and then concomitant with the second therapeutic agent.

[0088] The terms "patient" and "subject" as used herein include an animal, including, but not limited to, an animal such as a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig, in one embodiment a mammal, in another embodiment a human. In one embodiment, a "patient" or "subject" is a human having a cancer. In one embodiment, the patient" or "subject" is a human having metastatic castration-resistant prostate cancer who has previously received docetaxel.

[0089] In the context of a cancer, inhibition may be assessed by inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS), among others. OS as used herein means the time from randomization until death from any cause, and is measured in the intent-to-treat population. TTP as used herein means the time from randomization until objective tumor progression; TTP does not include deaths. As used herein, PFS means the time from randomization until objective tumor progression or death. In one embodiment, PFS rates will be computed using the Kaplan-Meier estimates. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident advanced cancer altogether or preventing the onset of a preclinically evident stage of a cancer. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing a cancer.

[0090] In certain embodiments, the treatment of a cancer may be assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*see* Thereasse P., et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J. of the National Cancer Institute; 2000; (92) 205-216 and Eisenhauer E.A., Therasse P., Bogaerts J., et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J. Cancer; 2009; (45) 228–247). Overall responses for all possible combinations of tumor responses in target and non-target lesions with our without the appearance of new lesions are as follows:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

[0091] With respect to the evaluation of target lesions, complete response (CR) is the disappearance of all target lesions, partial response (PR) is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter, progressive disease (PD) is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions and stable disease (SD) is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

[0092] With respect to the evaluation of non-target lesions, complete response (CR) is the disappearance of all non-target lesions and normalization of tumor marker level; incomplete response/stable disease (SD) is the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits, and progressive disease (PD) is the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

[0093] In certain embodiments, treatment of a cancer may be assessed by the inhibition of phosphorylation of S6RP, 4E-BP1, AKT and/or DNA-PK in circulating

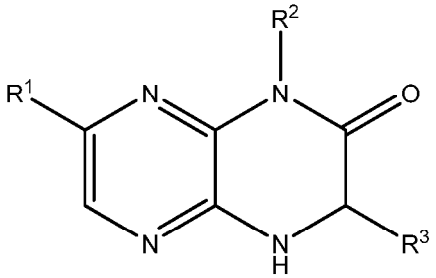
blood and/or tumor cells, and/or skin biopsies or tumor biopsies/aspirates, before, during and/or after treatment with a Dihydropyrazino-Pyrazine Compound. For example, the inhibition of phosphorylation of S6RP, 4E-BP1, AKT and/or DNA-PK is assessed in B-cells, T-cells and/or monocytes. In other embodiments, treatment of a cancer may be assessed by the inhibition of DNA-dependent protein kinase (DNA-PK) activity in skin samples and/or tumor biopsies/aspirates, such as by assessment of the amount of pDNA-PK S2056 as a biomarker for DNA damage pathways, before, during, and/or after Dihydropyrazino-Pyrazine Compound treatment. In one embodiment, the skin sample is irradiated by UV light.

[0094] In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident cancer altogether or preventing the onset of a preclinically evident stage of a cancer. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing a cancer.

5.2 DIHYDROPYRAZINO-PYRAZINE COMPOUNDS

[0095] The compounds provided herein are generally referred to as "Dihydropyrazino-Pyrazine Compound(s)."

[0096] In one embodiment, the Dihydropyrazino-Pyrazine Compounds include compounds having the following formula (I):



(I)

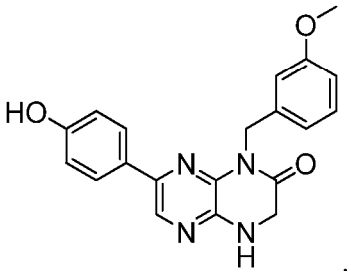
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, metabolites, isotopologues and prodrugs thereof, wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, or substituted or unsubstituted heterocyclylalkyl;

R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted cycloalkylalkyl;

R^3 is H, or a substituted or unsubstituted C_{1-8} alkyl,

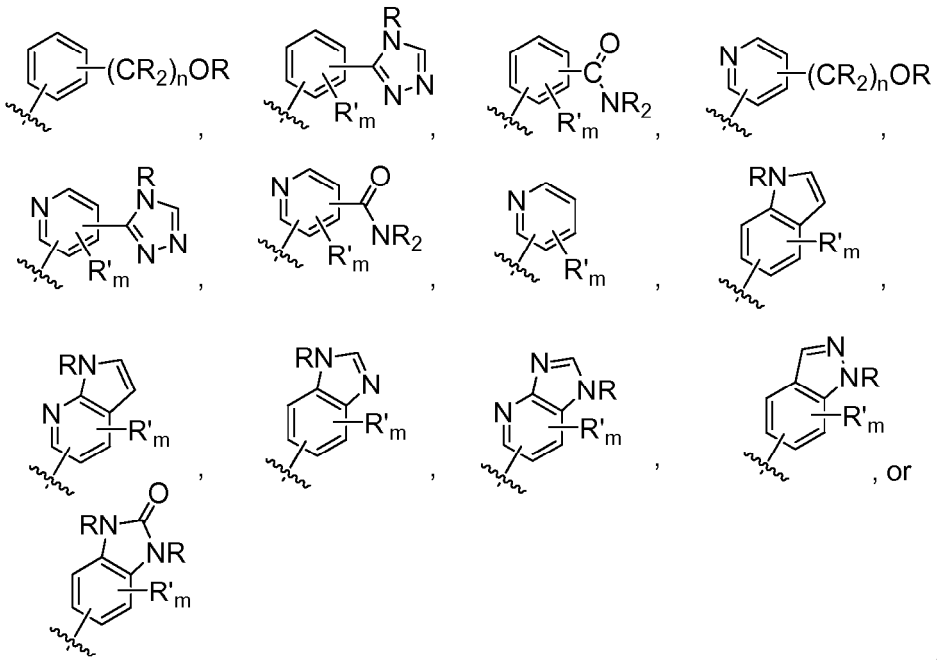
wherein in certain embodiments, the Dihydropyrazino-Pyrazine Compounds do not include 7-(4-hydroxyphenyl)-1-(3-methoxybenzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one, depicted below:



[0097] In some embodiments of compounds of formula (I), R^1 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, 1H-pyrrolo[2,3-b]pyridyl, indazolyl, indolyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some embodiments, R^1 is phenyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl (for example, methyl), substituted or unsubstituted heterocyclyl (for example, a substituted or unsubstituted triazolyl or pyrazolyl), aminocarbonyl, halogen (for example, fluorine), cyano, hydroxyalkyl and hydroxy. In other embodiments, R^1 is pyridyl substituted with

one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl (for example, methyl), substituted or unsubstituted heterocyclyl (for example, a substituted or unsubstituted triazolyl), halogen, aminocarbonyl , cyano, hydroxyalkyl (for example, hydroxypropyl), -OR, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl. In some embodiments, R^1 is 1H-pyrrolo[2,3-b]pyridyl or benzimidazolyl, optionally substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, and $-NR_2$, wherein R is independently H, or a substituted or unsubstituted C_{1-4} alkyl.

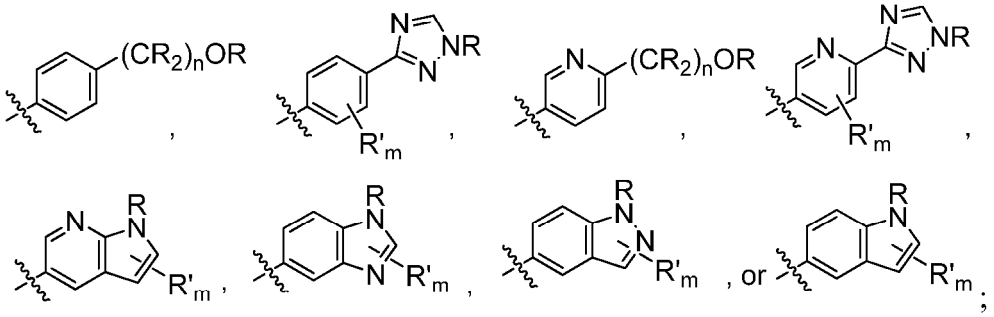
[0098] In some embodiments, R^1 is



;

wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently a substituted or unsubstituted C_{1-4} alkyl (for example, methyl), halogen (for example, fluoro), cyano, -OR, or $-NR_2$; m is 0-3; and n is 0-3. It will be understood by those skilled in the art that any of the subsitutuents R' may be attached to any suitable atom of any of the rings in the fused ring systems.

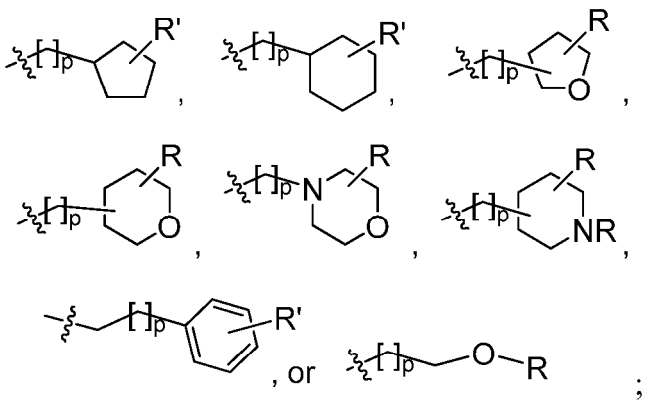
[0099] In some embodiments of compounds of formula (I), R^1 is



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl; R' is at each occurrence independently a substituted or unsubstituted C_{1-4} alkyl, halogen, cyano, -OR or $-NR_2$; m is 0-3; and n is 0-3.

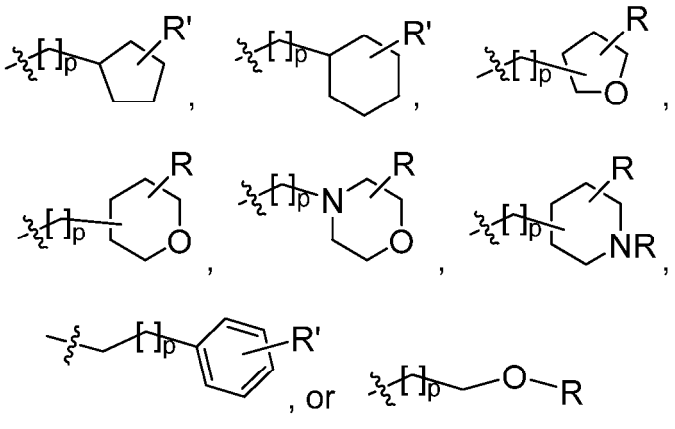
[00100] In some embodiments of compounds of formula (I), R^2 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-heterocyclyl, substituted or unsubstituted C_{1-4} alkyl-aryl, or substituted or unsubstituted C_{1-4} alkyl-cycloalkyl. For example, R^2 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl, *tert*-butyl, n-pentyl, isopentyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, (C_{1-4} alkyl)-phenyl, (C_{1-4} alkyl)-cyclopropyl, (C_{1-4} alkyl)-cyclobutyl, (C_{1-4} alkyl)-cyclopentyl, (C_{1-4} alkyl)-cyclohexyl, (C_{1-4} alkyl)-pyrrolidyl, (C_{1-4} alkyl)-piperidyl, (C_{1-4} alkyl)-piperazinyl, (C_{1-4} alkyl)-morpholinyl, (C_{1-4} alkyl)-tetrahydrofuranyl, or (C_{1-4} alkyl)-tetrahydropyranyl, each optionally substituted.

[00101] In other embodiments, R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); R' is at each occurrence independently H, -OR, cyano,or a substituted or unsubstituted C_{1-4} alkyl (for example, methyl); and p is 0-3.

[00102] In other embodiments of compounds of formula (I), R^2 is H, C_{1-4} alkyl, (C_{1-4}alkyl)(OR),



wherein R is at each occurrence independently H, or a substituted or unsubstituted C_{1-2} alkyl; R' is at each occurrence independently H, -OR, cyano, or a substituted or unsubstituted C_{1-2} alkyl; and p is 0-1.

[00103] In other embodiments of compounds of formula (I), R^3 is H.

[00104] In some such embodiments described herein, R^1 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. For example, R^1 is phenyl, pyridyl, pyrimidyl, benzimidazolyl, 1H-pyrrolo[2,3-b]pyridyl, indazolyl, indolyl, 1H-imidazo[4,5-b]pyridine, pyridyl, 1H-imidazo[4,5-b]pyridin-2(3H)-onyl, 3H-imidazo[4,5-b]pyridyl, or pyrazolyl, each optionally substituted. In some embodiments, R^1 is phenyl substituted with one or more substituents independently selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted heterocyclyl, aminocarbonyl, halogen, cyano, hydroxyalkyl and hydroxy. In others, R^1 is pyridyl substituted with one or more substituents independently selected from the group consisting of C_{1-8} alkyl, substituted or unsubstituted heterocyclyl, halogen, aminocarbonyl, cyano, hydroxyalkyl, -OR, and $-NR_2$, wherein each R is independently H, or a substituted or unsubstituted C_{1-4} alkyl. In still others, R^1 is 1H-pyrrolo[2,3-b]pyridyl or benzimidazolyl, optionally substituted with one or more substituents independently selected from the group consisting of substituted or

unsubstituted C_{1-8} alkyl, and $-NR_2$, wherein R is independently H, or a substituted or unsubstituted C_{1-4} alkyl.

[00105] In certain embodiments, the compounds of formula (I) have an R^1 group set forth herein and an R^2 group set forth herein.

[00106] In some embodiments of compounds of formula (I), the compound inhibits TOR kinase. In other embodiments of compounds of formula (I), the compound inhibits DNA-PK. In certain embodiments of compounds of formula (I), the compound inhibits both TOR kinase and DNA-PK.

[00107] In some embodiments of compounds of formula (I), the compound at a concentration of 10 μM inhibits TOR kinase, DNA-PK, PI3K, or a combination thereof by at least about 50%. Compounds of formula (I) may be shown to be inhibitors of the kinases above in any suitable assay system.

[00108] Representative Dihydropyrazino-Pyrazine Compounds of formula (I) include compounds from Table A.

[00109] **Table A.**

7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*cis*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(1H-pyrrolo[2,3-b]pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

1-ethyl-7-(1H-pyrrolo[3,2-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(1H-benzo[d]imidazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*trans*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*cis*-4-hydroxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(*cis*-4-hydroxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-ethyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*cis*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-((*trans*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((*cis*-4-hydroxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*trans*-4-hydroxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-isopropyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(*trans*-4-hydroxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-isopropyl-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(5-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-hydroxypyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-isopropyl-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
5-(8-isopropyl-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
7-(1H-indazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-aminopyrimidin-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-aminopyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(methylamino)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-hydroxypyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(1H-pyrazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indazol-4-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indazol-6-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(pyrimidin-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-methoxypyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(1H-indazol-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(pyridin-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-aminopyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-methyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
2-(2-hydroxypropan-2-yl)-5-(8-(*trans*-4-methoxycyclohexyl)-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)pyridine 1-oxide;
4-methyl-5-(7-oxo-8-((tetrahydro-2H-pyran-4-yl)methyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)picolinamide;
5-(8-((*cis*-4-methoxycyclohexyl)methyl)-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;

7-(1H-pyrazol-4-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-methoxycyclohexyl)-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3-((7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-2-oxo-3,4-dihydropyrazino[2,3-b]pyrazin-1(2H)-yl)methyl)benzonitrile;
1-((*trans*-4-methoxycyclohexyl)methyl)-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
3-(7-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzamide;
5-(8-((*trans*-4-methoxycyclohexyl)methyl)-7-oxo-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)-4-methylpicolinamide;
3-((7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-2-oxo-3,4-dihydropyrazino[2,3-b]pyrazin-1(2H)-yl)methyl)benzonitrile;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1R,3R)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1S,3R)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1S,3S)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1R,3S)-3-methoxycyclopentyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indazol-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-hydroxycyclohexyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

1-(*cis*-4-hydroxycyclohexyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-morpholinoethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-isopropyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-imidazo[4,5-b]pyridin-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((*cis*-4-methoxycyclohexyl)methyl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*cis*-4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
4-(7-oxo-8-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-5,6,7,8-tetrahydropyrazino[2,3-b]pyrazin-2-yl)benzamide;
7-(1H-indazol-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1S,3R)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1R,3R)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((1R,3S)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

1-((1S,3S)-3-methoxycyclopentyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indol-5-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(1H-indol-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(2-hydroxypropan-2-yl)phenyl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-4-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-((*trans*-4-methoxycyclohexyl)methyl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*cis*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(4-methyl-2-(methylamino)-1H-benzo[d]imidazol-6-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(7-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-benzyl-7-(2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(3-fluoro-4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(*trans*-4-methoxycyclohexyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(5-fluoro-2-methyl-4-(4H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(3-fluoro-2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(2-methoxyethyl)-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*-4-methoxycyclohexyl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(cyclopentylmethyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(2-hydroxypropan-2-yl)phenyl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-7-(6-(1-hydroxyethyl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-7-(6-(1-hydroxyethyl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(2-hydroxypropan-2-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(4-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(3-(trifluoromethyl)benzyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(3-methoxypropyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-methoxyethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-methyl-2-(methylamino)-1H-benzo[d]imidazol-6-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-amino-4-methyl-1H-benzo[d]imidazol-6-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(R)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-methyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
(S)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-methyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,3-dimethyl-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(2-amino-4-methyl-1H-benzo[d]imidazol-6-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;

7-(2-methyl-4-(1H-1,2,4-triazol-3-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
7-(4-(1H-1,2,4-triazol-5-yl)phenyl)-1-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one;
1-(1-hydroxypropan-2-yl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one; and
1-(2-hydroxyethyl)-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one,
and pharmaceutically acceptable salts, clathrates, solvates, stereoisomers, tautomers, metabolites, isotopologues and prodrugs thereof.

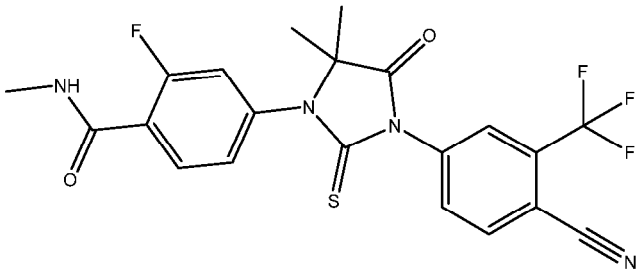
5.3 METHODS FOR MAKING DIHYDROPYRAZINO-PYRAZINE COMPOUNDS

[00110] The Dihydropyrazino-Pyrazine Compounds can be obtained via standard, well-known synthetic methodology, see *e.g.*, March, J. Advanced Organic Chemistry; Reactions Mechanisms, and Structure, 4th ed., 1992. Starting materials useful for preparing compounds of formula (III) and intermediates therefore, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

[00111] Particular methods for preparing compounds of formula (I) are disclosed in U.S. Patent No. 8,110,578, issued February 7, 2012, and U.S. Patent No. 8,569,494, issued October 29, 2013, each incorporated by reference herein in their entirety.

5.4 ANDROGEN RECEPTOR ANTAGONISTS

[00112] In one embodiment, the androgen receptor antagonist is enzalutamide (marketed as Xtandi®, Astellas Pharma US, Inc.), also known as and referred to herein as MDV3100, having the chemical name 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide and the structure:



5.5 METHODS OF USE

[00113] Provided herein are methods for treating or preventing a cancer comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound and an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00114] In certain embodiments, the cancer is prostate cancer.

[00115] In other embodiments, the cancer is a solid tumor. In certain embodiments, the solid tumor is a relapsed or refractory solid tumor. In one embodiment, the cancer is metastatic. In another, the cancer is hormone refractory. In yet another, the cancer is an E-twenty six (ETS) overexpressing cancer.

[00116] In one embodiment, the solid tumor is an advanced solid tumor.

[00117] In another embodiment, the cancer is E-twenty six (ETS) overexpressing castration-resistant prostate cancer.

[00118] In other embodiments, the cancer is a cancer associated with the pathways involving mTOR, PI3K, or Akt kinases and mutants or isoforms thereof. Other cancers within the scope of the methods provided herein include those associated with the pathways of the following kinases: PI3Kα, PI3Kβ, PI3Kδ, KDR, GSK3α, GSK3β, ATM,

ATX, ATR, cFMS, and/or DNA-PK kinases and mutants or isoforms thereof. In some embodiments, the cancers associated with mTOR/ PI3K/Akt pathways include solid tumors, for example, prostate cancer;.

[00119] In other embodiments, the cancer is metastatic castration-resistant prostate cancer.

[00120] In other embodiments, the cancer is breast cancer.

[00121] In certain embodiments, provided herein are methods for achieving a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of complete response, partial response or stable disease in a patient having a solid tumor, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist to said patientIn certain embodiments, provided herein are methods for achieving a Prostate Cancer Working Group 2 (PCWG2) Criteria of complete response, partial response or stable disease in a patient having prostate cancer, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist to said patient

[00122] In certain embodiments, provided herein are methods for increasing survival without tumor progression of a patient having a cancer, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to said patient.

[00123] In one embodiment, provided herein are methods for preventing or delaying a Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1) of progressive disease in a patient, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer. In one embodiment the prevention or delaying of progressive disease is characterized or achieved by a change in overall size of the target lesions, of for example, between -30% and +20% compared to pre-treatment. In another embodiment, the change in size of the target lesions is a reduction in overall size of more than 30%, for example, more than 50% reduction in target lesion size compared to pre-treatment. In another, the prevention is characterized

or achieved by a reduction in size or a delay in progression of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by a reduction in the number of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by a reduction in the number or quality of non-target lesions compared to pre-treatment. In one embodiment, the prevention is achieved or characterized by the absence or the disappearance of target lesions compared to pre-treatment. In another, the prevention is achieved or characterized by the absence or the disappearance of non-target lesions compared to pre-treatment. In another embodiment, the prevention is achieved or characterized by the prevention of new lesions compared to pre-treatment. In yet another embodiment, the prevention is achieved or characterized by the prevention of clinical signs or symptoms of disease progression compared to pre-treatment, such as cancer-related cachexia or increased pain.

[00124] In certain embodiments, provided herein are methods for decreasing the size of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00125] In certain embodiments, provided herein are methods for decreasing the size of a non-target lesion in a patient compared to pre-treatment, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00126] In certain embodiments, provided herein are methods for achieving a reduction in the number of target lesions in a patient compared to pre-treatment, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00127] In certain embodiments, provided herein are methods for achieving a reduction in the number of non-target lesions in a patient compared to pre-treatment,

comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00128] In certain embodiments, provided herein are methods for achieving an absence of all target lesions in a patient, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00129] In certain embodiments, provided herein are methods for achieving an absence of all non-target lesions in a patient, comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer.

[00130] In certain embodiments, provided herein are methods for treating a cancer, the methods comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer, wherein the treatment results in a complete response, partial response or stable disease, as determined by Response Evaluation Criteria in Solid Tumors (for example, RECIST 1.1).

[00131] In certain embodiments, provided herein are methods for treating a cancer, the methods comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer, wherein the treatment results in a reduction in target lesion size, a reduction in non-target lesion size and/or the absence of new target and/or non-target lesions, compared to pre-treatment.

[00132] In certain embodiments, provided herein are methods for treating a cancer, the methods comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer, wherein the treatment results in prevention or retarding of clinical progression, such as cancer-related cachexia or increased pain.

[00133] In some embodiments, provided herein are methods for treating a cancer, the methods comprising administering an effective amount of a Dihydropyrazino-Pyrazine Compound in combination with an effective amount of an androgen receptor antagonist to a patient having a cancer, wherein the treatment results in one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors (including tumor secreted hormones, such as those that contribute to carcinoid syndrome), delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), and/or increased Overall Survival (OS), among others.

[00134] In some embodiments, the Dihydropyrazino-Pyrazine Compound is a compound as described herein. In one embodiment, the Dihydropyrazino-Pyrazine Compound is a compound of formula (I). In one embodiment, the Dihydropyrazino-Pyrazine Compound is a compound from Table A. In one embodiment, the Dihydropyrazino-Pyrazine Compound is Compound 1 (a Dihydropyrazino-Pyrazine Compound set forth herein having molecular formula $C_{21}H_{27}N_5O_3$). In one embodiment, the Dihydropyrazino-Pyrazine Compound is Compound 2 (a Dihydropyrazino-Pyrazine Compound set forth herein having molecular formula $C_{16}H_{16}N_8O$). In one embodiment, the Dihydropyrazino-Pyrazine Compound is Compound 3 (a Dihydropyrazino-Pyrazine Compound set forth herein having molecular formula $C_{20}H_{25}N_5O_3$). In one embodiment, Compound 1 is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1r,4r)-4-methoxycyclohexyl)-3,4-dihydropyrazino-[2,3-b]pyrazin-2(1H)-one, alternatively named 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one, or 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((1R*,4R*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one. In another embodiment, Compound 2 is 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one, or a tautomer thereof, for

example, 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one, or 1-ethyl-7-(2-methyl-6-(1H-1,2,4-triazol-5-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one. In another embodiment, Compound 3 is 1-((*trans*)-4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one, alternatively named 1-((1r,4r)-4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one. In one embodiment, Compound 3 is a metabolite of Compound 1.

[00135] In one embodiment, the androgen receptor antagonist is MDV-3100.

[00136] A Dihydropyrazino-Pyrazine Compound administered in combination with an androgen receptor antagonist can be further combined with radiation therapy or surgery. In certain embodiments, a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist to patient who is undergoing radiation therapy, has previously undergone radiation therapy or will be undergoing radiation therapy. In certain embodiments, a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist to a patient who has undergone surgery, such as tumor removal surgery.

[00137] Further provided herein are methods for treating patients who have been previously treated for a cancer, as well as those who have not previously been treated. Further provided herein are methods for treating patients who have undergone surgery in an attempt to treat a cancer, as well as those who have not. Because patients with a cancer have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with a cancer.

[00138] In certain embodiments, a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist to a patient in cycles. Cycling therapy involves the administration of an active agent(s) for a period of time,

followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance, avoid or reduce the side effects, and/or improves the efficacy of the treatment.

[00139] In one embodiment, a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist daily in single or divided doses for about 3 days, about 5 days, about one week, about two weeks, about three weeks, about four weeks (e.g., 28 days), about five weeks, about six weeks, about seven weeks, about eight weeks, about ten weeks, about fifteen weeks, or about twenty weeks, followed by a rest period of about 1 day to about ten weeks. In one embodiment, the methods provided herein contemplate cycling treatments of about one week, about two weeks, about three weeks, about four weeks, about five weeks, about six weeks, about eight weeks, about ten weeks, about fifteen weeks, or about twenty weeks. In some embodiments, a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist in single or divided doses for about 3 days, about 5 days, about one week, about two weeks, about three weeks, about four weeks (e.g., 28 days), about five weeks, or about six weeks with a rest period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 29, or 30 days. In some embodiments, the rest period is 1 day. In some embodiments, the rest period is 3 days. In some embodiments, the rest period is 7 days. In some embodiments, the rest period is 14 days. In some embodiments, the rest period is 28 days. The frequency, number and length of dosing cycles can be increased or decreased.

[00140] In one embodiment, the methods provided herein comprise: i) administering to the subject a first daily dose of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist; ii) optionally resting for a period of at least one day where an androgen receptor antagonist is not administered to the subject; iii) administering a second dose of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist to the subject; and iv) repeating steps ii) to iii) a plurality of times.

[00141] In one embodiment, the methods provided herein comprise administering to the subject a dose of an androgen receptor antagonist on day 1, followed by administering a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist to the subject on day 2 and subsequent days.

[00142] In certain embodiments, a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist is administered continuously for between about 1 and about 52 weeks. In certain embodiments, a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist is administered continuously for about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. In certain embodiments, a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist is administered continuously for about 7, about 14, about 21, about 28, about 35, about 42, about 84, or about 112 days.

[00143] [00109] In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist the Dihydropyrazino-Pyrazine Compound is administered at an amount of about 2.5 mg to about 50 mg per day (such as about 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg, 10 mg, 15 mg, 16 mg, 20 mg, 25 mg, 30 mg, 45 mg, 60 mg, 90 mg, 120 mg or 128 mg per day) and an androgen receptor antagonist is administered at an amount of about 50 mg to about 200 mg per day (such as about 80 mg, about 120 mg or about 160 mg per day). In certain embodiments, about 2.5 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 10 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 15 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 16 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg,

about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 20 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 25 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 30 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, about 45 mg per day of a Dihydropyrazino-Pyrazine Compound is administered in combination with about 80 mg, about 120 mg or about 160 mg per day of an androgen receptor antagonist. In certain embodiments, when an androgen receptor antagonist is administered in combination with a Dihydropyrazino-Pyrazine Compound, the androgen receptor antagonist is administered as four discrete capsules. For example, when a dose of 160 mg per day of an androgen receptor antagonist is administered in combination with a Dihydropyrazino-Pyrazine Compound, it can be administered as four 40 mg capsules. A Dihydropyrazino-Pyrazine Compound and an androgen receptor antagonist can each be independently administered once (QD), twice (BD), three times (TID) or four times per day.

[00144] In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist, the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is from about 1:1 to about 1:10. In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist, the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is less than about 1:1, less than about 1:3 or less than about 1:10. In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist, the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is about 1:1, about 1:3 or about 1:10.

[00145] In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist, the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is from about 1:1 to about 1:30. In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist, the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is less than about 1:1, less than about 1:10 or less than about 1:30. In certain embodiments, when a Dihydropyrazino-Pyrazine Compound is administered in combination with an androgen receptor antagonist, the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is about 1:1, about 1:10 or about 1:30.

5.6 PHARMACEUTICAL COMPOSITIONS AND ROUTES OF ADMINISTRATION

[00146] Provided herein are compositions comprising an effective amount of a Dihydropyrazino-Pyrazine Compound and an effective amount of an androgen receptor antagonist and compositions, comprising an effective amount of a Dihydropyrazino-Pyrazine Compound and an androgen receptor antagonist and a pharmaceutically acceptable carrier or vehicle.

[00147] In some embodiments, the pharmaceutical compositions described herein are suitable for oral, parenteral, mucosal, transdermal or topical administration.

[00148] The compositions can be administered to a patient orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions and syrups. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as an excipient *(e.g.,* sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder *(e.g.,* cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator *(e.g.,* starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a

lubricant *(e.g.,* magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent *(e.g.,* citric acid, menthol, glycine or orange powder), a preservative *(e.g,* sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer *(e.g.,* citric acid, sodium citrate or acetic acid), a suspending agent *(e.g.,* methylcellulose, polyvinyl pyrroliclone or aluminum stearate), a dispersing agent *(e.g.,* hydroxypropylmethylcellulose), a diluent *(e.g.,* water), and base wax *(e.g.,* cocoa butter, white petrolatum or polyethylene glycol). The effective amount of the Dihydropyrazino-Pyrazine Compound in the pharmaceutical composition may be at a level that will exercise the desired effect; for example, about 0.005 mg/kg of a patient's body weight to about 10 mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration.

[00149] The dose of a Dihydropyrazino-Pyrazine Compound and the dose of an androgen receptor antagonist to be administered to a patient is rather widely variable and can be subject to the judgment of a health-care practitioner. In general, the Dihydropyrazino-Pyrazine Compounds and an androgen receptor antagonist can be administered one to four times a day in a dose of about 0.005 mg/kg of a patient's body weight to about 10 mg/kg of a patient's body weight in a patient, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration. In one embodiment, the dose is about 0.01 mg/kg of a patient's body weight to about 5 mg/kg of a patient's body weight, about 0.05 mg/kg of a patient's body weight to about 1 mg/kg of a patient's body weight, about 0.1 mg/kg of a patient's body weight to about 0.75 mg/kg of a patient's body weight or about 0.25 mg/kg of a patient's body weight to about 0.5 mg/kg of a patient's body weight. In one embodiment, one dose is given per day. In any given case, the amount of the Dihydropyrazino-Pyrazine Compound administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

[00150] In another embodiment, provided herein are unit dosage formulations that comprise between about 1 mg and about 2000 mg, about 1 mg and about 200 mg, about 35 mg and about 1400 mg, about 125 mg and about 1000 mg, about 250 mg and about

1000 mg, about 500 mg and about 1000 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg or about 2.5 mg to about 20 mg of a Dihydropyrazino-Pyrazine Compound alone or in combination with an androgen receptor antagonist. In another embodiment, provided herein are unit dosage formulations that comprise 1 mg, 2.5 mg, 5 mg, 7.5 mg, 8 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 45 mg, 50 mg, 70 mg, 100 mg, 125 mg, 140 mg, 175 mg, 200 mg, 250 mg, 280 mg, 350 mg, 500 mg, 560 mg, 700 mg, 750 mg, 1000 mg or 1400 mg of a Dihydropyrazino-Pyrazine Compound alone or in combination with an androgen receptor antagonist. In another embodiment, provided herein are unit dosage formulations that comprise about 2.5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg or about 45 mg of a Dihydropyrazino-Pyrazine Compound alone or in combination with an androgen receptor antagonist. In a particular embodiment, provided herein are unit dosage formulations that comprise about 5 mg, about 7.5 mg and about 10 mg of a Dihydropyrazino-Pyrazine Compound alone or in combination with an androgen receptor antagonist.

[00151] In a particular embodiment, provided herein are unit dosage formulations comprising about 10 mg, about 15 mg, about 30 mg, about 45 mg, about 50 mg, about 75 mg, about 100 mg or about 400 mg of a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist.

[00152] In a particular embodiment, provided herein are unit dosage formulations comprising about 20 mg to about 60 mg of an androgen receptor antagonist in combination with a Dihydropyrazino-Pyrazine Compound. In a particular embodiment, provided herein are unit dosage formulations comprising about 40 mg of an androgen receptor antagonist in combination with a Dihydropyrazino-Pyrazine Compound.

[00153] In certain embodiments, provided herein are unit dosage formulations wherein the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is from about 1:1 to about 1:10. In certain embodiments, provided herein are unit dosage formulations wherein the Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is less than about 1:1, less than about 1:3 or less than about 1:10. In certain embodiments, provided herein are unit dosage formulations wherein the

Dihydropyrazino-Pyrazine Compound:androgen receptor antagonist ratio is about 1:1, about 1:3 or about 1:10.

[00154] A Dihydropyrazino-Pyrazine Compound can be administered in combination with an androgen receptor antagonist once, twice, three, four or more times daily.

[00155] A Dihydropyrazino-Pyrazine Compound can be administered in combination with an androgen receptor antagonist orally for reasons of convenience. In one embodiment, when administered orally, a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist is administered with a meal and water. In another embodiment, the Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension. In another embodiment, when administered orally, a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist is administered in a fasted state.

[00156] The Dihydropyrazino-Pyrazine Compound can also be administered in combination with an androgen receptor antagonist intravenously, such as intravenous infusion, or subcutaneously, such as subcutaneous injection. The mode of administration is left to the discretion of the health-care practitioner, and can depend in-part upon the site of the medical condition.

[00157] In one embodiment, provided herein are capsules containing a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist without an additional carrier, excipient or vehicle.

[00158] In another embodiment, provided herein are compositions comprising an effective amount of a Dihydropyrazino-Pyrazine Compound, an effective amount of an androgen receptor antagonist, and a pharmaceutically acceptable carrier or vehicle, wherein a pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In one embodiment, the composition is a pharmaceutical composition.

[00159] The compositions can be in the form of tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions and the like. Compositions can be formulated to contain a daily dose, or a convenient fraction of a daily dose, in a dosage unit, which may be a single tablet or capsule or convenient volume of a liquid. In one embodiment, the solutions are prepared from water-soluble salts, such as the hydrochloride salt. In general, all of the compositions are prepared according to known methods in pharmaceutical chemistry. Capsules can be prepared by mixing a Dihydropyrazino-Pyrazine Compound with a suitable carrier or diluent and filling the proper amount of the mixture in capsules. The usual carriers and diluents include, but are not limited to, inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[00160] Tablets can be prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. In one embodiment, the pharmaceutical composition is lactose-free. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders. Illustrative tablet formulations comprising Compound 2 are provided herein.

[00161] A lubricant might be necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant can be chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils. Tablet disintegrators are substances that swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood

cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethyl cellulose, for example, can be used as well as sodium lauryl sulfate. Tablets can be coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compositions can also be formulated as chewable tablets, for example, by using substances such as mannitol in the formulation.

[00162] When it is desired to administer a Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist as a suppository, typical bases can be used. Cocoa butter is a traditional suppository base, which can be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

[00163] The effect of the Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist can be prepared and incorporated in a tablet or capsule, or as a slow-release implantable device. The technique also includes making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules can be coated with a film that resists dissolution for a predictable period of time. Even the parenteral preparations can be made long-acting, by dissolving or suspending the Dihydropyrazino-Pyrazine Compound in combination with an androgen receptor antagonist in oily or emulsified vehicles that allow it to disperse slowly in the serum.

[00164] In certain embodiments, the Dihydropyrazino-Pyrazine Compound is administered in a formulation set forth in U.S. Patent Application Publication No. 2013-0142873, published June 6, 2013, which is incorporated herein in its entirety (see particularly paragraph [0323] to paragraph [0424], and paragraph [0636] to paragraph [0655]). In other embodiments, the Dihydropyrazino-Pyrazine Compound is administered in a formulation set forth in U.S. Provisional Patent Application No. 61/828,506, filed May 29, 2013, which is incorporated herein in its entirety (see

particularly paragraph [0246] to paragraph [0403], and paragraph [0571] to paragraph [0586]).

[00165] In certain embodiments, the Dihydropyrazino-Pyrazine Compound is administered in a formulation set forth in U.S. Provisional Application No. 61/813,064, filed April 17, 2013, which is incorporated herein in its entirety (see particularly paragraph [0168] to paragraph [0189] and paragraph [0262] to paragraph [0294]). In other embodiments, the Dihydropyrazino-Pyrazine Compound is administered in a formulation set forth in U.S. Provisional Patent Application No. 61/911,201, filed December 3, 2013, which is incorporated herein in its entirety (see particularly paragraph [0170] to paragraph [0190], and paragraph [0264] to paragraph [0296]).

5.7 KITS

[00166] In certain embodiments, provided herein are kits comprising a Dihydropyrazino-Pyrazine Compound and an androgen receptor antagonist.

[00167] In certain embodiments, provided herein are kits comprising one or more unit dosage forms of a Dihydropyrazino-Pyrazine Compound, such as those described herein, and one or more unit dosage forms of an androgen receptor antagonist, such as those described herein.

[00168] In certain embodiments, the kits provided herein further comprise instructions for use, such as for administering a Dihydropyrazino-Pyrazine Compound and an androgen receptor antagonist.

6. EXAMPLES

6.1 BIOCHEMICAL ASSAYS

[00169] **mTOR HTR-FRET Assay**. The following is an example of an assay that can be used to determine the TOR kinase inhibitory activity of a test compound. Dihydropyrazino-Pyrazine Compounds were dissolved in DMSO and prepared as 10 mM stocks and diluted appropriately for the experiments. Reagents were prepared as follows:

[00170] "Simple TOR buffer" (used to dilute high glycerol TOR fraction): 10 mM Tris pH 7.4, 100 mM NaCl, 0.1% Tween-20, 1 mM DTT. Invitrogen mTOR (cat#PV4753) was diluted in this buffer to an assay concentration of 0.200 μg/mL.

[00171] ATP/Substrate solution: 0.075 mM ATP, 12.5 mM $MnCl_2$, 50 mM Hepes, pH 7.4, 50 mM β-GOP, 250 nM Microcystin LR, 0.25 mM EDTA, 5 mM DTT, and 3.5 μg/mL GST-p70S6.

[00172] Detection reagent solution: 50 mM HEPES, pH 7.4, 0.01% Triton X-100, 0.01% BSA, 0.1 mM EDTA, 12.7 μg/mL Cy5-αGST Amersham (Cat#PA92002V), 9 ng/mL α–phospho p70S6 (Thr389) (Cell Signaling Mouse Monoclonal #9206L), 627 ng/mL α–mouse Lance Eu (Perkin Elmer Cat#AD0077).

[00173] To 20 μL of the Simple TOR buffer is added 0.5 μL of test compound in DMSO. To initiate the reaction 5 μL of ATP/Substrate solution was added to 20 μL of the Simple TOR buffer solution (control) and to the compound solution prepared above. The assay was stopped after 60 min by adding 5 μL of a 60 mM EDTA solution; 10 μL of detection reagent solution was then added and the mixture was allowed to sit for at least 2 hours before reading on a Perkin-Elmer Envision Microplate Reader set to detect LANCE Eu TR-FRET (excitation at 320 nm and emission at 495/520 nm).

[00174] Dihydropyrazino-Pyrazine Compounds were tested in the mTOR HTR-FRET assay and were found to have activity therein, with certain compounds having an IC_{50} below 10 μM in the assay, with some compounds having an IC_{50} between and 0.005 nM and 250 nM, others having an IC_{50} between and 250 nM and 500 nM, others having an IC_{50} between 500 nM and 1 μM, and others having an IC_{50} between 1 μM and 10 μM.

[00175] **DNA-PK assay**. DNA-PK assay is performed using the procedures supplied in the Promega DNA-PK assay kit (catalog # V7870). DNA-PK enzyme can be purchased from Promega (Promega cat#V5811).

[00176] Selected Dihydropyrazino-Pyrazine Compounds as described herein have, or are expected to have, an IC_{50} below 10 μM in this assay, with some Dihydropyrazino-

Pyrazine Compounds as described herein having an IC_{50} below 1 μM, and others having an IC_{50} below 0.10 μM.

6.2 CELL BASED ASSAYS

[00177] Apoptosis Induction.

[00178] Increasing concentrations of compound (Compound 2 and/or MDV3100: 30 μM) were spotted via an acoustic dispenser (EDC ATS-100) into an empty 384-well plate in a 10-point serial dilution fashion (3-fold dilution) in duplicate within the plate. Cells (LNCaP, PC3 or VCAP) were then directly seeded at desired densities to the compound-spotted 384-well plates. Cells were cultured for 48 hours at 37 °C/5% CO_2 and were assessed via Caspase 3/7-Glo (Promega) and read for luminescence. Results are shown in FIG. 3B, C and D for LNCAP, and in FIG. 3E for VCAP, wherein Compound 2 and MDV3100 combination treatment synergistically induces apoptosis.

6.3 IN VIVO ASSAYS

[00179] ETS-positive prostate cancer xenograft model. Results are shown in FIGs. 1 and 2.

[00180] LNCap-HR tumor model. A xenograft study was conducted with castration resistant LNCaP (LNCaP-HR) tumor-bearing mice. Castration resistant LNCaP-HR tumors were developed by several cycles of serial transplantation and in vivo passaging of parental LNCaP tumor cells in castrated SCID (severe combined immunodeficiency) mice. For xenograft studies, tumor-bearing animals were generated by injecting precisely determined numbers of cells or precise size of tumor fragments subncutaneously in the flank region above the right hind leg into castrated SCID mice. Following inoculation of animals, the tumors were allowed to grow to a certain size prior to randomization. The mice bearing LNCaP-HR xenograft tumors ranging between 200 and 600 mm^3 were pooled together and randomized into various treatment groups. A typical efficacy study design involved administering one or more compounds at various

dose levels to tumor-bearing mice. Additionally, reference chemotherapeutic agents (positive control) and negative controls were similarly administered and maintained. Routes of administration can include intraperitoneal (IP) or oral (PO). Tumor measurements and body weights were taken over the course of the study and morbidity and mortality were recorded. Necropsy, histopathology, western blots, MesoScale, immunohistochemistry and PCR can also be performed to enhance understanding of disease and drug action. For a typical xenograft study, SCID mice bearing LNCaP-HR tumors were randomized and dosed with compounds ranging from, for example, 100 mg/kg to 0.1 mg/kg with different dose scheduling, including, but not limited to, qd, q2d, q3d, q5d, q7d and bid. In certain studies a combination of two or more agents were dosed simultaneously. The compounds were formulated in various types of formulation. Some of the formulations included CMC-Tween (0.5%CMC/0.25%Tween), NPS (n-methylpyrrolidone, PEG, Saline), DMSO-CMC-Tween (1% CMC, 0.1% Tween 80 and 5% dimethyl sulfoxide in water) and were delivered orally or intraperitonially. The mice were dosed for 2-4 weeks. Tumors were measured twice a week using calipers and tumor volumes were calculated using the formula of $W^2 \times L / 2$. Statistical analysis was performed using a one-way analysis of variance (ANOVA) followed by Dunnett's post-hoc comparison with the vehicle-treated control group.

[00181] The xenograft study was conducted with castration resistant LNCaP-HR tumor-bearing mice. Castrated male SCID mice were inoculated subcutaneously with LNCaP-HR cells in the flank region above the right hind leg. Following inoculation of animals, the tumors were allowed to grow to about 325 mm^3 prior to randomization. On Day 26 following tumor cell inoculation, the mice bearing LNCaP-HR tumors ranging between 98 and 530 mm^3 were pooled together and randomized into various treatment groups. Compound 2 was formulated in 0.5% CMC and 0.25% Tween 80 in water (as a suspension). The animals were orally administered vehicle (CMC-Tween) or Compound 2 once daily (QD) for up to 15 days. Doses of Compound 2 ranged between 1 and 5 mg/kg. The positive control MDV-3100 (50 mg/kg, Q4D) was administered via oral route. MDV-3100 was formulated in 1% CMC , 0.1% Tween 80 and 5% dimethyl

sulfoxide (DMSO) in water (as a suspension). Tumors were measured twice a week using calipers and tumor volumes were calculated using the formula of $W^2 \times L / 2$. Statistical analysis was performed using a one-way analysis of variance (ANOVA) followed by Dunnett's post-hoc comparison with the vehicle-treated control group. Results are shown in FIG. 4.

6.4 COMPOUND FORMULATIONS

[00182] Illustrative formulations of Compound 1 useful in the methods provided herein are set forth in Tables 1-4, below.

[00183] **Table 1**

Ingredients	**Amounts**	
	mg	**% w/w**
Compound 1	20.0	15.38
Lactose monohydrate, NF (Fast Flo 316)	63.98	49.22
Microcrystalline cellulose, NF (Avicel pH 102)	40.30	31.00
Croscarmellose sodium, NF (Ac-Di-Sol)	3.90	3.00
Stearic acid, NF	0.52	0.40
Magnesium Stearate, NF	1.30	1.00
Total	130.0	100
Opadry yellow 03K12429	5.2	4.0

[00184] **Table 2**

Ingredients	**Amounts**	
	mg	**% w/w**
Compound 1	5.0	3.80
Lactose monohydrate, NF (Fast Flo 316)	78.98	60.70
Microcrystalline cellulose, NF (Avicel pH 102)	40.30	31.00
Croscarmellose sodium, NF (Ac-Di-Sol)	3.90	3.00
Stearic acid, NF	0.52	0.40

Ingredients	Amounts	
	mg	% w/w
Magnesium Stearate, NF	1.30	1.00
Total	130.0	100
Opadry II pink 85F94211	5.2	4% weight gain

[00185] Table 3

Ingredients	Amounts			
	mg			% w/w
Compound 1	15.0	20.0	30.0	15.38
Lactose monohydrate, NF (Fast Flo 316)	48.37	64.50	96.75	49.62
Microcrystalline cellulose, NF (Avicel pH 112)	30.23	40.30	60.45	31.00
Croscarmellose sodium, NF (Ac-Di-Sol)	2.925	3.90	5.85	3.00
Magnesium Stearate, NF	0.975	1.30	1.95	1.00
Total	97.50	130.0	195.00	100
Opadry yellow 03K12429	3.9			4.0
Opadry II Pink 85F94211		5.2		4.0
Opadry Pink 03K140004			7.8	4.0

[00186] Table 4

Ingredients	Amounts	
	mg	% w/w
Compound 1	45.00	15.38
Lactose monohydrate, NF (Fast Flo 316)	143.955	49.22

Ingredients	Amounts	
	mg	% w/w
Microcrystalline cellulose, NF (Avicel pH 102)	90.675	31.00
Croscarmellose sodium, NF (Ac-Di-Sol)	8.775	3.00
Stearic acid, NF	1.170	0.40
Magnesium Stearate, NF	2.925	1.00
Total	292.50	100
Opadry pink 03K140004	11.70	4.0

[00187] Illustrative formulations of Compound 2 useful in the methods provided herein are set forth in Table 5, below.

[00188] **Table 5: Exemplary Tablet Formulations**

	% w/w (mg)			
Batch #	**1**	**2**	**3**	**4**
Ingredients				
Compound 2 (active ingredient)	10	10	10	10
Mannitol (Mannogem EZ)	qs	qs	qs	qs
Microcrystalline Cellulose (PH 112)	25	25	25	25
Sodium Starch Glycolate	3	3	3	3
Silicon dioxide	1	1	1	1
Stearic acid	0.5	0.5	0.5	0.5
Disodium EDTA			0.5	0.5
BHT		0.4		0.4
Magnesium Stearate	0.65	0.65	0.65	0.65
Total	100	100	100	100
Color	Yellow	Yellow	Yellow	Yellow

[00189] A number of references have been cited, the disclosures of which are incorporated herein by reference in their entirety. The embodiments disclosed herein are not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the disclosed embodiments and any

embodiments that are functionally equivalent are encompassed by the present disclosure. Indeed, various modifications of the embodiments disclosed herein are in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. Use of a Dihydropyrazino-Pyrazine Compound in combination with MDV3100 in the manufacture of a medicament for treating a prostate cancer, wherein the Dihydropyrazino-Pyrazine Compound is 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one or a pharmaceutically acceptable salt, solvate, stereoisomer, tautomer, or isotopologue thereof.

2. The use of claim 1, wherein the prostate cancer is relapsed or refractory prostate cancer.

3. The use of claim 1, wherein the prostate cancer is castration-resistant prostate cancer.

4. The use of claim 1, wherein the prostate cancer is an E-twenty six (ETS) overexpressing prostate cancer.

5. The use of claim 1, wherein the prostate cancer is metastatic castration-resistant prostate cancer.