

mutation, gene rearrangement, gene amplification, and overexpression of both receptor and ligand has been implicated in the development and progression of human cancers.

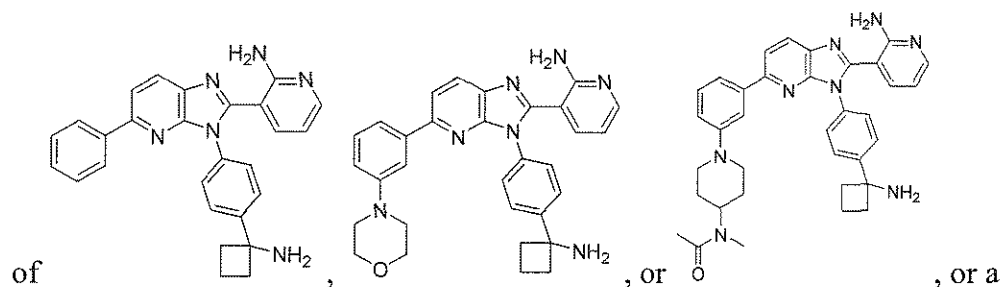
[0005] AKT protein family, which members are also called protein kinases B (PKB) plays an important role in mammalian cellular signaling. In humans, there are three genes in the AKT family: Akt1, Akt2, and Akt3. These genes code for enzymes that are members of the serine/threonine-specific protein kinase family. Akt1 is involved in cellular survival pathways, by inhibiting apoptotic processes. Akt1 is also able to induce protein synthesis pathways, and is therefore a key signaling protein in the cellular pathways that lead to skeletal muscle hypertrophy, and general tissue growth. Akt2 is an important signaling molecule in the Insulin signaling pathway and is required to induce glucose transport. The role of Akt3 is less clear, though it appears to be predominantly expressed in brain.

[0006] The AKT family regulates cellular survival and metabolism by binding and regulating many downstream effectors, e.g. Nuclear Factor- $\kappa$ B, Bcl-2 family proteins and murine double minute 2 (MDM2). Akt1 is known to play a role in the cell cycle. Moreover, activated Akt1 may enable proliferation and survival of cells that have sustained a potentially mutagenic impact and, therefore, may contribute to acquisition of mutations in other genes. Akt1 has also been implicated in angiogenesis and tumor development. Studies have shown that deficiency of Akt1 enhanced pathological angiogenesis and tumor growth associated with matrix abnormalities in skin and blood vessels. Since it can block apoptosis, and thereby promote cell survival, Akt1 is a major factor in many types of cancer.

[0007] Accordingly, there is a need in the art for new compounds and methods for modulating various genes and signaling pathways; and methods for treating proliferation disorders, including cancer. The present invention addresses these needs.

#### SUMMARY OF THE INVENTION

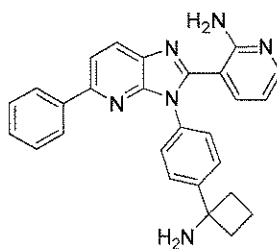
[0007A] In one aspect, there is provided use of a composition comprising at least one



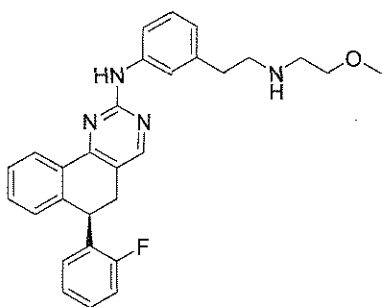
pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof in the manufacture of a

medicament for treating a cell proliferative disorder in a subject in need thereof, wherein said cell proliferative disorder is treated.

[0007B] In another aspect, there is provided a pharmaceutical composition comprising

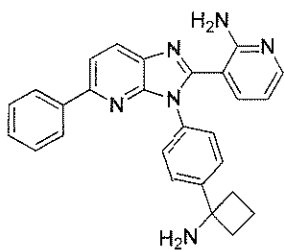


a therapeutically effective amount of a , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a therapeutically effective amount of

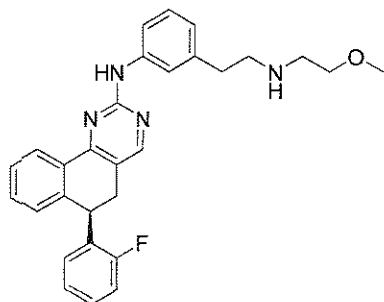


, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and one or more pharmaceutically acceptable carriers or excipients.

[0007C] In yet another aspect, there is provided a kit for the treatment of a cell proliferative disorder in a subject comprising at least two separate vials, a first vial comprising a therapeutically effective amount of a composition comprising

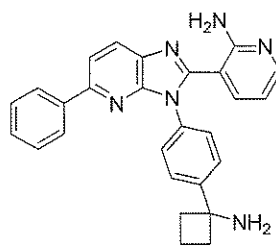


, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a second vial comprising a therapeutically effective amount of a composition

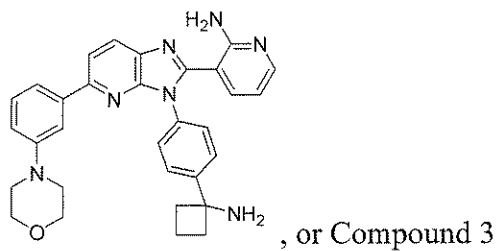


comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, with instructions for administering said composition in said first vial and said composition in said second vial.

[0008] Also disclosed is a method of treating a cell proliferative disorder, said method comprising administering, to a subject in need thereof, a therapeutically effective amount of a

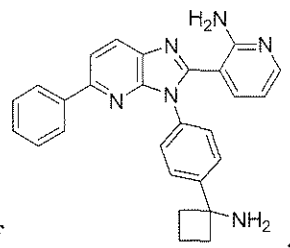


composition comprising at least one of Compound 1

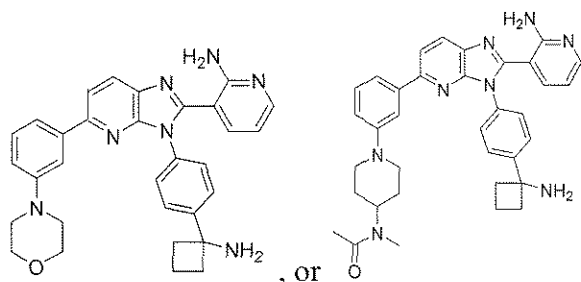


, or Compound 3

We claim:



1. Use of a composition comprising at least one of



, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof in the manufacture of a medicament for treating a cell proliferative disorder in a subject in need thereof, wherein said cell proliferative disorder is treated.

2. The use of claim 1, wherein said cell proliferative disorder is a precancerous condition.
3. The use of claim 1, wherein said cell proliferative disorder is a hematologic tumor or malignancy.
4. The use of claim 1, wherein said cell proliferative disorder is a solid tumor.
5. The use of claim 1, wherein said cell proliferative disorder is a cancer.
6. The use of claim 5, wherein said cancer is lung cancer, small cell lung cancer, non-small cell lung cancer, colon cancer, breast cancer, pancreatic cancer, prostate cancer, anal cancer, renal cancer, cervical cancer, brain, gastric/stomach cancer, head and neck cancer, thyroid cancer, bladder cancer, endometrial cancer, uterine cancer, intestinal cancer, hepatic cancer, leukemia, lymphoma, T-cell lymphoblastic leukemia, primary effusion lymphoma, chronic myelogenous leukemia, melanoma, Merkel cell cancer, ovarian cancer, alveolar soft

part sarcoma (ASPS), clear cell sarcoma (CCS), Paget's disease, rhabdomyosarcoma, angiosarcoma, cholangiocarcinoma or hepatocellular carcinoma.

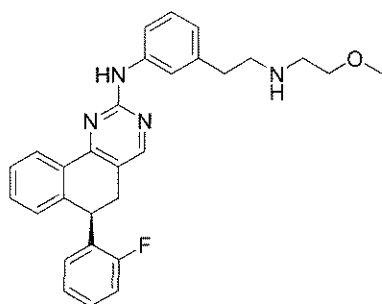
7. The use of claim 5, wherein said cancer is a metastatic cancer.
8. The use of claim 1, wherein said cell proliferative disorder is a non-cancer disorder.
9. The use of claim 8, wherein said non-cancer disorder is pituitary adenoma, leishmaniasis, skin-related hyperproliferative disorders, psoriasis, eczema, hyperpigmentation disorders, *eye-related hyperproliferative disorders*, *age-related macular degeneration*, Herpes simplex virus, Proteus syndrome (Wiedemann syndrome), macrodactyly syndrome, Harlequin ichthyosis, CLOVES syndrome, atopic dermatitis, LEOPARD syndrome, systemic sclerosis, Spinocerebellar ataxia type 1, fibroadipose hyperplasia, hemihyperplasia-multiple lipomatosis syndrome, megalencephaly, rare hypoglycemia, Klippel-Trenaunay syndrome, hamatoma, Cowden syndrome or overgrowth-hyperglycemia.
10. The use of claim 9, wherein said non-cancer disorder is Proteus syndrome.
11. The use of claim 1, wherein said subject is a human.
12. The use of claim 5, wherein said treating cancer comprises a reduction in tumor size, inhibition of metastatic cancer cell invasion or both.
13. The use of claim 1, wherein the composition is to be administered intravenously, orally or intraperitoneally.
14. The use of claim 1, wherein the compositions further comprise one or more pharmaceutically acceptable carriers or excipients.
15. The use of claim 1, wherein the composition is to be administered daily.
16. The use of claim 15, wherein the composition is to be administered at about 50 mg to about 100 mg daily.

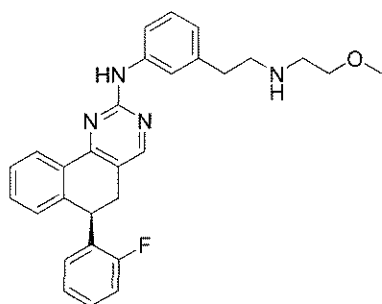
17. The use of claim 16, wherein the composition is to be administered at about 60 mg daily.
18. The use of claim 1, wherein the composition is to be administered in an intermittent dosing regimen, wherein the composition is to be administered at least once in 24 hours, not to be administered for at least six days, and to be administered at least once in 24 hours following the at least six days.
19. The use of claim 18, wherein the composition is to be administered once a week.
20. The use of claim 18, wherein the composition is to be administered once at about 250 mg to about 350 mg.
21. The use of claim 20, wherein the composition is to be administered at about 200 mg daily.
22. The use of claim 20, wherein the composition is to be administered once at about 300 mg.
23. The use of claim 1, wherein the composition is to be administered in an intermittent dosing regimen, wherein the composition is to be administered at least once daily for at least a week, not to be administered for at least a second week, and to be administered daily for at least a third week following the second week.
24. The use of claim 23, wherein the composition is to be administered at about 150 mg to about 250 mg daily.
25. The use of claim 1, wherein the medicament is to be administered with a therapeutically effective amount of an additional anti-proliferative agent, radiation therapy or both.
26. The use of claim 25, wherein the additional anti-proliferative agent is a kinase inhibitor, an alkylating agent, an antibiotic, an anti-metabolite, a detoxifying agent, an interferon, a polyclonal or monoclonal antibody, a HER2 inhibitor, a histone deacetylase

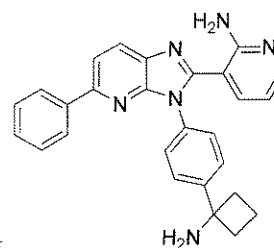
inhibitor, a hormone, a mitotic inhibitor, an MTOR inhibitor, a taxane or taxane derivative, an aromatase inhibitor, an anthracycline, a microtubule targeting drug, a topoisomerase poison drug, or a cytidine analogue drug.

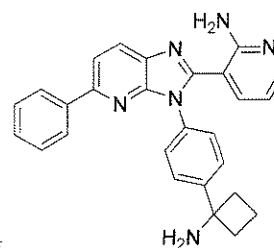
27. The use of claim 25, wherein the additional anti-proliferative agent is a fibroblast growth factor receptor inhibitor.

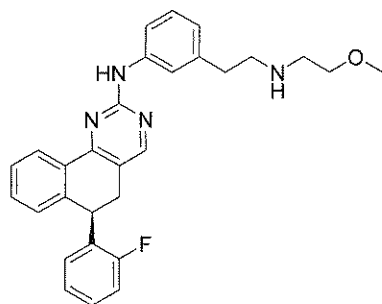
28. The use of claim 25, wherein the additional anti-proliferative agent is a

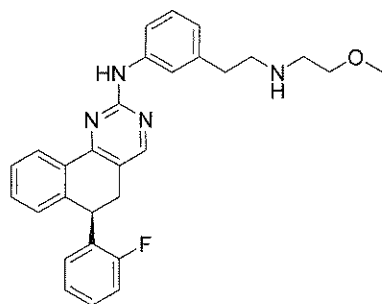


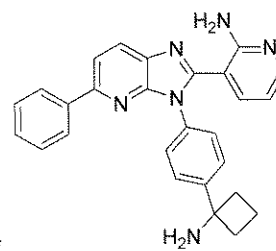
composition comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.



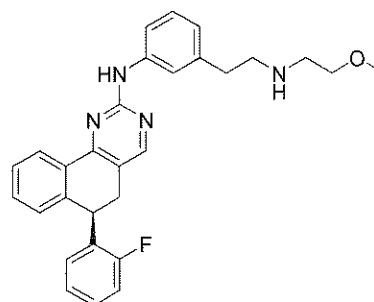
29. The use of claim 28, wherein the composition comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof is administered simultaneously with, preceding administration of, or following administration of the



composition comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

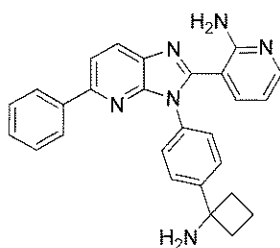


30. The use of claim 28, wherein the composition comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug is to be administered within 24

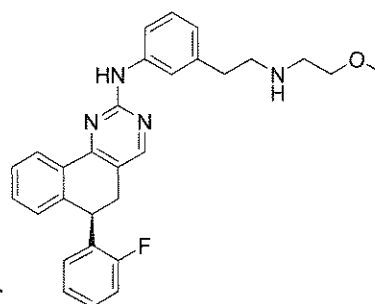


hours of administration of the composition comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

31. A pharmaceutical composition comprising a therapeutically effective amount of a

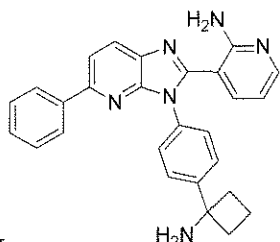


, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug

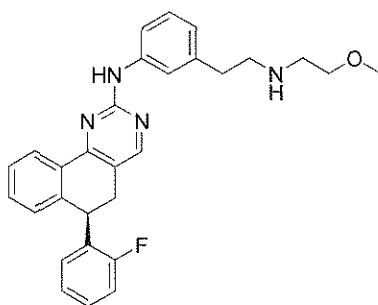


thereof, and a therapeutically effective amount of , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and one or more pharmaceutically acceptable carriers or excipients.

32. A kit for the treatment of a cell proliferative disorder in a subject comprising at least two separate vials, a first vial comprising a therapeutically effective amount of a composition



comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and a second vial comprising a therapeutically effective amount of a



composition comprising , or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, with instructions for administering said composition in said first vial and said composition in said second vial.