METHODS OF TREATING CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 62/599,643, filed December 15, 2017. The entire contents of that application are hereby incorporated by reference herein.

FIELD OF THE INVENTION

[0002] This invention pertains to methods and compositions for the treatment of cancer by administering a bufalin derivative compound.

BACKGROUND OF THE INVENTION

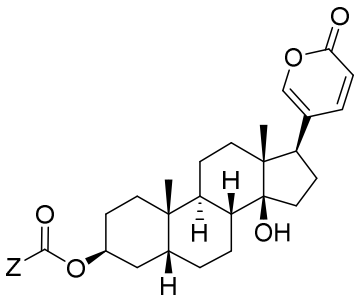
[0003] Despite significant advances in early detection and multi-modal therapies for the treatment of cancer, an unmet medical need exists for the treatment of patients with advanced cancers.

[0004] The traditional Chinese medicine Huachansu (an injectable form of chansu) is used in China for the treatment of a variety of cancers including liver, lung, pancreatic and colorectal cancer. Its anti-cancer activity is attributed to three major steroidal cardiac glycosides: bufalin, resibufogenin and cinobufagin. When tested, bufalin demonstrated strong activity in cancer cell lines and animal models. WO2011/085641 discloses various bufalin derivatives which were shown to be particularly effective in cancer treatment. These compounds find tremendous potential in providing effective therapeutic options for cancer patients.

[0005] The disclosures of all publications, patents, patent applications, and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

SUMMARY

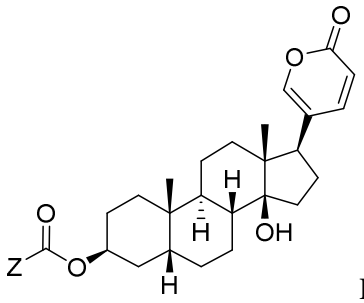
[0006] The present disclosure provides a method of treating cancer in an individual, comprising administering to the individual an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein: Z is $-OR^1$ or $-NR^2R^3$; R^1 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; R^2 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and R^3 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted heterocycloalkyl; and the compound is administered at least once a week for at least two weeks.

[0006a] In one aspect, the present disclosure refers to use of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in an individual, wherein:

Z is $-OR^1$ or $-NR^2R^3$;

R^1 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; R^2 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and R^3 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally

substituted heteroaryl, or R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted heterocycloalkyl;

and the compound is to be administered at least once a week for at least two weeks.

[0007] In some examples, the compound is administered at least two times a week, including for example, at least three times a week. In some examples, the compound is administered three times a week.

[0008] In some examples according to any aforementioned method, the compound is administered for at least three consecutive days during a week, including for example, on days 1, 2, and 3 of each week. In some examples, the compound is administered once every other day during a week, including for example, on days 1, 3, and 5 of each week. In some examples, the compound is administered daily for at least two weeks.

[0009] In some examples, the compound is administered at least once a week for at least two weeks, including for example, at least once a week for two weeks with one week of rest in a 21-day dosage cycle.

[0010] In some examples, the compound is administered at least once a week for at least three weeks, including for example, at least once a week for three weeks with one week of rest in a 28-day dosage cycle.

[0011] In some examples according to any aforementioned method, the compound is administered at the dosage range of about 0.01 mg/m^2 to about 2 mg/m^2.

[0012] In some examples according to any aforementioned method, the compound is administered at the dosage range of about 0.2 mg/m^2 to about 2 mg/m^2.

[0013] In some examples according to any aforementioned method, the total dose of the compound administered to the individual is at least about 0.4 mg/m^2 per week.

[0014] In some examples according to any aforementioned method, the cancer is selected from the group consisting of colorectal cancer, liver cancer, lung cancer, breast cancer, prostate cancer, pancreatic cancer, and oral cancer. In some examples, the cancer is metastatic cancer.

[0015] In some examples according to any aforementioned method, the compound is administered intravenously, including for example, infusion for at least two hours at each administration or continuously by infusion for at least 24 hours at each administration.

[0016] In some examples according to any aforementioned method, the individual expresses (e.g., highly expresses) PI3K and/or pAKT.

[0017] In some examples according to any aforementioned method, the individual has progressed on or failed at least one prior therapy (such as systemic therapy).

[0018] In some examples according to any aforementioned method, the compound is administered at the concentration of about 0.002 mg/mL to about 0.01 mg/mL.

[0019] In some examples according to any aforementioned method, the compound is in a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier. In some examples, the pharmaceutically acceptable carrier comprises an acetate or acetic acid.

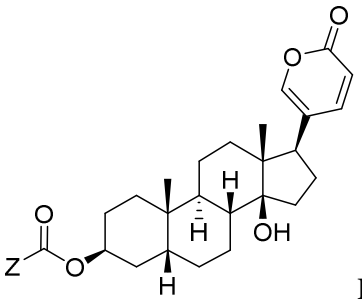
[0020] In some examples according to any aforementioned method, the individual is human.

[0021] In some examples according to any aforementioned method, the compound is of Formula I, or a pharmaceutically acceptable salt thereof, wherein Z is $-OR^1$ or $-NR^2R^3$. In some examples, Z is $-OR^1$, wherein R^1 is optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl. In some examples, Z is $-NR^2R^3$, wherein R^2 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl, and R^3 is optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl or R^2 and R^3 are taken together with the atom to which they are attached to form a 4- to 8-membered heterocycloalkyl. In one example, R^2 is hydrogen and R^3 is optionally substituted alkyl.

[0022] In some examples according to any aforementioned method, the compound is selected from Compound Nos. 1-7, or a pharmaceutically acceptable salt thereof:

What is claimed is:

1. Use of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in an individual, wherein:

Z is $-OR^1$ or $-NR^2R^3$;

R^1 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; R^2 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and R^3 is optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^2 and R^3 are taken together with the atom to which they are attached to form an optionally substituted heterocycloalkyl;

and the compound is to be administered at least once a week for at least two weeks.

2. The use of claim 1, wherein the compound is to be administered at least two times a week.

3. The use of claim 1, wherein the compound is to be administered at least three times a week.

4. The use of claim 3, wherein the compound is to be administered for at least three consecutive days during a week.

5. The use of claim 3, wherein the compound is to be administered once every other day during a week.

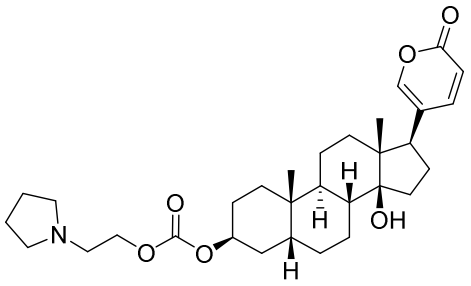
6. The use of claim 3, wherein the compound is to be administered three times a week.

7. The use of claim 4, wherein the compound is to be administered on days 1, 2, and 3 of each week.

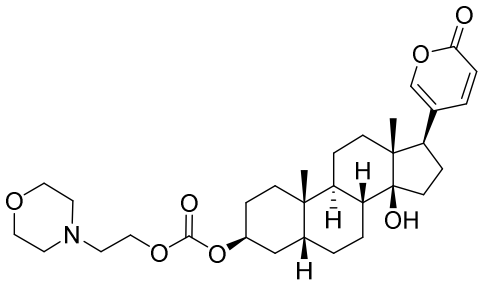
8. The use of claim 5, wherein the compound is to be administered on days 1, 3, and 5 of each week.

9. The use of claim 3, wherein the compound is to be administered daily for at least two weeks.
10. The use of any one of claims 1-8, wherein the compound is to be administered at least once a week for at least two weeks.
11. The use of any one of claims 1-8, wherein the compound is to be administered at least once a week for at least three weeks.
12. The use of claim 10, wherein the compound is to be administered at least once a week for two weeks with one week of rest in a 21-day dosage cycle.
13. The use of claim 11, wherein the compound is to be administered at least once a week for three weeks with one week of rest in a 28-day dosage cycle.
14. The use of any one of claims 1-13, wherein the compound is to be administered at the dosage range of about 0.02 mg/m^2 to about 2 mg/m^2.
15. The use of any one of claims 1-13, wherein the compound is to be administered at the dosage range of about 0.2 mg/m^2 to about 2 mg/m^2.
16. The use of any one of claims 1-15, wherein the total dose of the compound to be administered to the individual is at least about 0.4 mg/m^2 per week.
17. The use of any one of claims 1-16, wherein the cancer is selected from the group consisting of colorectal cancer, liver cancer, lung cancer, breast cancer, prostate cancer, pancreatic cancer, and oral cancer.
18. The use of any one of claims 1-16, wherein the cancer is selected from the group consisting of colorectal cancer, breast cancer, liver cancer, gastric cancer, and non-small cell lung cancer.
19. The use of any one of claims 1-18, wherein the cancer is locally advanced or metastatic cancer.
20. The use of any one of claims 1-19, wherein the compound is to be administered intravenously.
21. The use of claim 20, wherein the compound is to be administered by infusion for at least 30 minutes at each administration.
22. The use of claim 20, wherein the compound is to be administered by infusion for at least 2 hours at each administration.
23. The use of claim 20, wherein the compound is to be administered continuously by infusion for at least 24 hours at each administration.

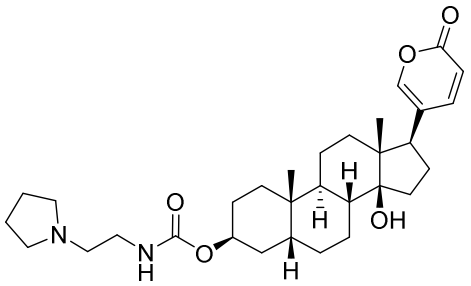
24. The use of any one of claims 1-23, wherein the individual has a high level of PI3K and/or pAKT.
25. The use of any one of claims 1-24, wherein the individual has progressed on or failed at least one prior systemic therapy.
26. The use of any one of claims 1-25, wherein the compound is to be administered at the concentration of about 0.002 mg/mL to about 0.01 mg/mL.
27. The use of any one of claims 1-26, wherein the compound is in a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier.
28. The use of claim 27, wherein the pharmaceutically acceptable carrier comprises an acetate or acetic acid.
29. The use of any one of claims 1-28, wherein the individual is human.
30. The use of any one of claims 1-29, wherein the compound is of Formula I, or a pharmaceutically acceptable salt thereof, wherein Z is $-OR^1$.
31. The use of claim 30, wherein R^1 is optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl.
32. The use of any one of claims 1-29, wherein the compound is of Formula I, or a pharmaceutically acceptable salt thereof, wherein Z is $-NR^2R^3$.
33. The use of claim 32 wherein R^2 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl, and R^3 is optionally substituted alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl.
34. The use of claim 33, wherein R^2 is hydrogen and R^3 is optionally substituted alkyl.
35. The use of claim 32, wherein R^2 and R^3 are taken together with the atom to which they are attached to form a 4- to 8-membered heterocycloalkyl.
36. The use of any one of claims 1-29, wherein the compound is selected from Compound Nos. 1-7, or a pharmaceutically acceptable salt thereof:



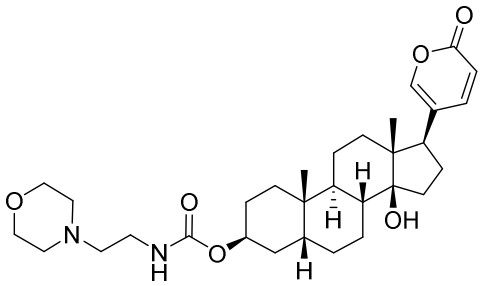
Compound 1



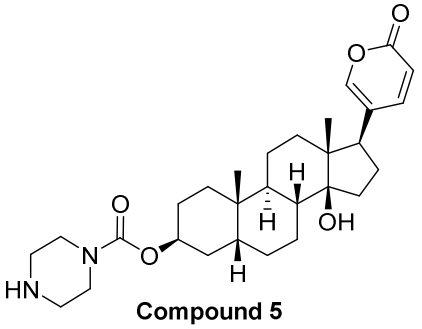
Compound 2



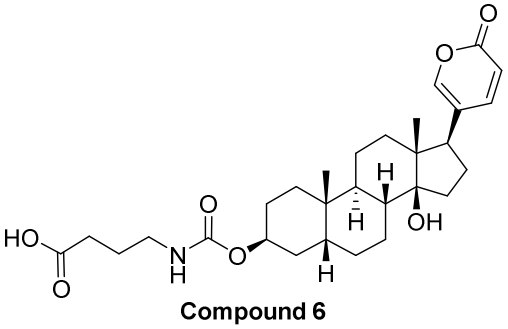
Compound 3



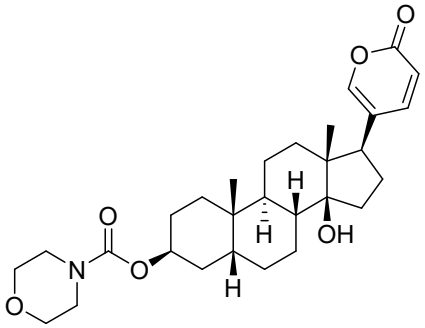
Compound 4



Compound 5



Compound 6



Compound 7

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