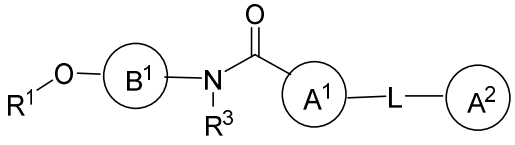
present an opportunity to treat cancers more effectively and/or to treat cancers that have become resistant to currently available medicines.

[0005] The present invention addresses the foregoing needs and provides other related advantages.

SUMMARY

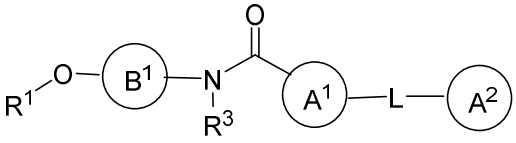
[0006] The disclosure provides heterobifunctional compounds, pharmaceutical compositions, and their use treating disease, such as cancer. In particular, one example of the disclosure provides a collection of heterobifunctional compounds, such as a compound represented by Formula **I**:



(**I**)

or a pharmaceutically acceptable salt thereof, where the variables are as defined in the detailed description. Further description of additional collections of heterobifunctional compounds are described in the detailed description. The compounds may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0006a] In one aspect, the disclosure provides a compound represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is phenyl substituted by (i) cyano and m occurrences of R^4, and (ii) C_{1-4} alkoxyl or C_{1-4} haloalkoxyl;

R^2 represents independently for each occurrence C_{1-4} alkyl;

R^3 is hydrogen or C_{1-4} alkyl;

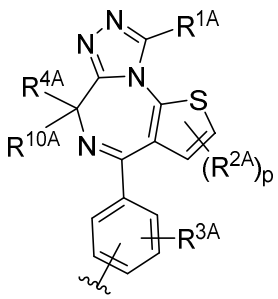
R^4 is C_{1-4} alkyl;

R^5 represents independently for each occurrence C_{1-4} alkyl or halogen;

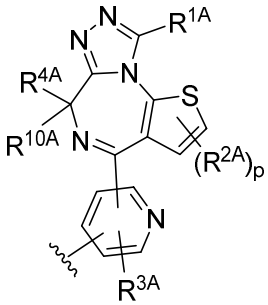
A^1 is a pyrimidinylene, pyridazinylene, pyrazinylene, pyridinylene, or phenylene, each of which is substituted with n occurrences of R^5;

L is a linker; and

A^2 is one of the following:



or



;

B^1 is (i) cyclobutylene substituted by 1, 2, 3, or 4 occurrences of R^2 or (ii) cyclohexylene substituted by 0, 1, or 2 occurrences of R^2;

R^{1A} is C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^{2A} represents independently for each occurrence C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^{3A} is hydrogen, halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxyl;

R^{4A} is -(C_{0-6} alkylene)-(5-6 membered heteroaryl containing 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, and sulfur), -(C_{1-6} alkylene)-$C(O)N(R^{5A})(R^{6A})$, -(C_{1-6} alkylene)-$N(R^{5A})C(O)R^{7A}$, -(C_{1-6} alkylene)-CO_2R^{7A}, -(C_{1-6} alkylene)-$OC(O)R^{7A}$, -(C_{1-6} alkylene)-cyano, -(C_{1-6} alkylene)-O-(C_{1-6} alkyl), C_{1-6} alkyl, C_{3-6} cycloalkyl, or hydrogen; or R^{4A} and R^{10A} taken together with the carbon atom to which they are attached form a C_{3-5} saturated carbocyclic ring;

R^{5A} and R^{6A} are independently hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or R^{5A} and R^{6A} are taken together with the nitrogen atom to which they are attached to form a 3-7 membered ring containing 1 nitrogen atom;

R^{7A} is C_{1-6} alkyl, -(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or C_{3-6} cycloalkyl;

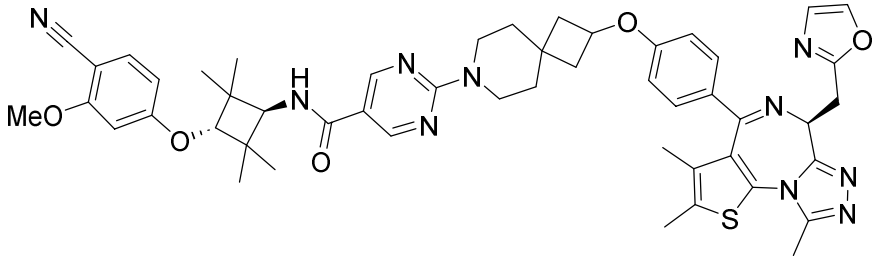
R^{10A} is hydrogen or C_{1-4} alkyl; and

m, n, and p are independently 0, 1, or 2.

[0006b] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable carrier.

[0006c] In one aspect, the disclosure provides use of a compound as disclosed herein in the manufacture of a medicament for treating cancer, wherein the cancer is ovarian cancer, uterine cancer, endometrial cancer, cervical cancer, prostate cancer, testicular cancer, breast cancer, brain cancer, lung cancer, oral cancer, esophageal cancer, head and neck cancer, stomach cancer, colon cancer, rectal cancer, skin cancer, sebaceous gland carcinoma, bile duct cancer, gallbladder cancer, liver cancer, pancreatic cancer, bladder cancer, urinary tract cancer, kidney cancer, eye cancer, thyroid cancer, lymphoma, or leukemia.

[0007] Another example of the disclosure provides a crystalline compound of Formula **II-5**:



(**II-5**).

The compound may be part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

[0008] Another example of the disclosure provides a method of treating cancer. The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula **I**, to treat the cancer.

[0009] Another example of the disclosure provides a method of causing death of a cancer cell. The method comprises contacting a cancer cell with an effective amount of a compound described herein, such as a compound of Formula **I**, to cause death of the cancer cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1** is a graph showing detected ternary complex formation between test compound, androgen receptor, and BRD4 protein, as further described in Example 67.

[0011] **Figure 2** is a graph showing detected ternary complex formation between Compound II-5, androgen receptor, and BRD4 protein, as further described in Example 68.

[0012] **Figure 3** is graph showing cell viability as a function of dose of Compound II-5, as further described in Example 69.

[0013] **Figure 4** is a graph that shows the relative ternary complex formation present with treatment of Compound II-5 at varying doses in samples collected at the end of the PK/PD Castrate VCaP Tumor Xenograft Model study, as further described in Example 70.

[0014] **Figure 5** is a graph that shows the relative total amount of cMYC mRNA present in tumors collected at the end of the PK/PD Ar^{amp}, $V7^{+}$ Castrate VcaP Model, for different dose amounts of Compound II-5, as further described in Example 70.

[0015] **Figure 6** is a graph that shows the relative total amount of HEXIM1 mRNA present in tumors collected at the end of the PK/PD Ar^{amp}, $V7^{+}$ Castrate VcaP Model, for each of the different dose amounts of Compound II-5, as further described in Example 70.

[0016] **Figure 7** is a graph that shows the relative total amount of TXNIP mRNA present in tumors collected at the end of the PK/PD Ar^{amp}, $V7^{+}$ Castrate VcaP Model, for each of the different dose amounts of Compound II-5, as further described in Example 70.

[0017] **Figure 8** is a graph that showing tumor growth in mice treated with either Compound II-5, Compound A, or vehicle, as further described in Example 70.

[0018] **Figure 9** is a waterfall plot that shows change in size of tumors at the end of study relative to baseline in mice treated with either Compound II-5, Compound A, or vehicle, as further described in Example 70.