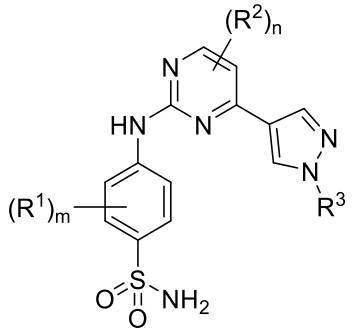
[0005] While these findings indicate CDK2 is a potential target for cancers with deregulated CDK2 activity, no agents targeting CDK2 have been approved to date. Therefore, there is a need to develop new CDK2 inhibitors.

SUMMARY

[0006] The applicant has discovered novel compounds which are effective inhibitors of CDK2 (*see* Synthetic Examples 1-46). In particular, it has been demonstrated that the compounds of the present disclosure effectively inhibit CDK2. Compounds of the disclosure (also referred to herein as the "disclosed compounds") or pharmaceutically acceptable salts thereof effectively inhibit CDK2. (*see* Biological Example 1) and can be used treat various cancers. Importantly, the disclosed compounds are selective CDK2 inhibitors, *i.e.*, the disclosed compounds have no or low activity against CDK1. Advantages associated with such selectivity may include facilitating efficacious dosing and reducing CDK1-mediated on-target toxicities. Some of the disclosed compounds also have the advantage of having high microsomal stability. Compounds of the disclosure also may have favorable toxicity profiles related to other non-kinase targets.

[0006a] In a first aspect of the present disclosure, there is provided a compound of Formula I



(I), or a pharmaceutically acceptable salt thereof, wherein

each R^1 is independently selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 3 halo;

each R^2 is independently selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 3 halo;

R^3 is C_1-C_6alkyl optionally substituted with 1 or 2 groups each independently selected from the group consisting of halo, OH, C_3-C_6cycloalkyl, and 3 to 6-membered heterocyclyl,

wherein the C_3-C_6cycloalkyl is optionally substituted with OH, wherein the 3 to 6-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^a and then is optionally substituted on a ring carbon with OH; or

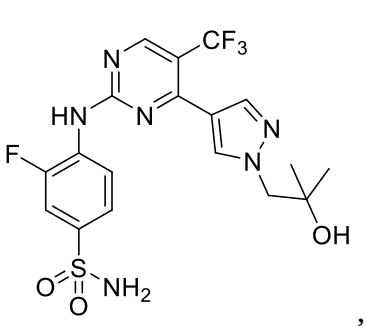
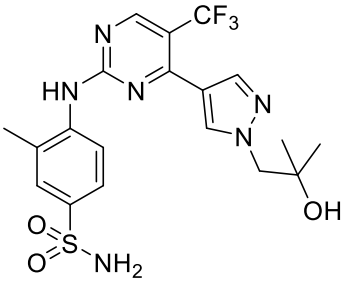
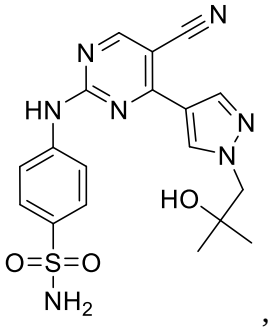
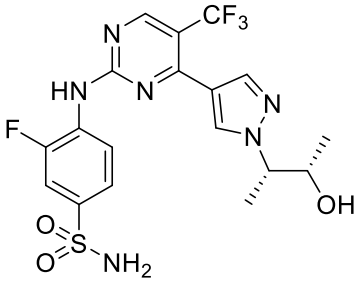
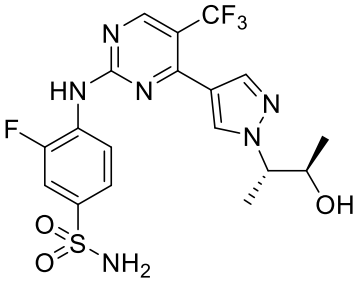
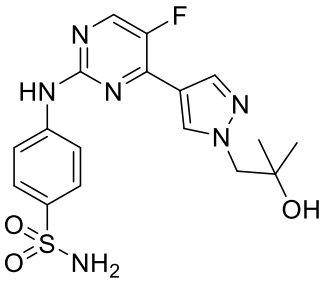
R^3 is C_3-C_6cycloalkyl or 3 to 6-membered heterocyclyl, wherein the C_3-C_6cycloalkyl is optionally substituted with OH or -CH_2OH, wherein the 3 to 6-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^a and then is optionally substituted on a ring carbon with OH or -CH_2OH;

each R^a is independently H or C_1-C_6alkyl;

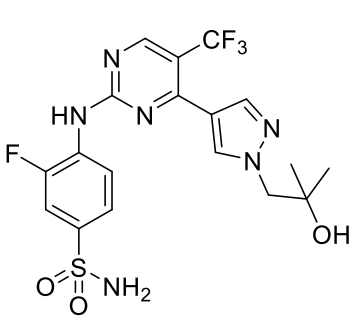
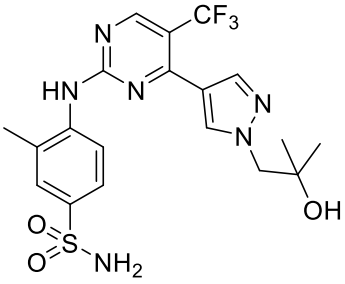
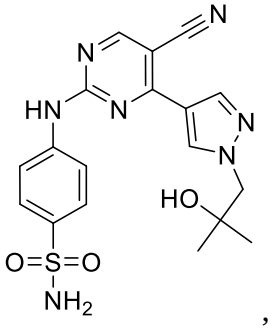
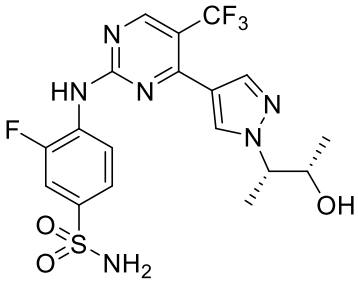
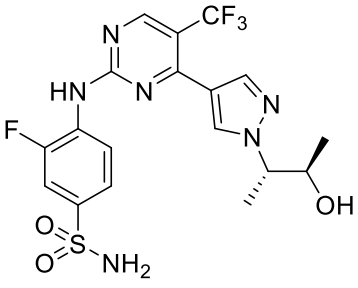
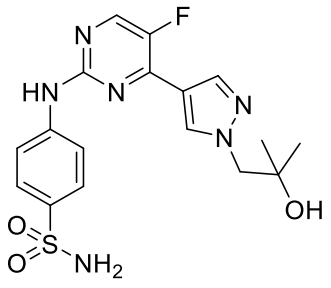
m is selected from the group consisting of 0, 1, 2, 3, and 4, and

n is selected from the group consisting of 0, 1, and 2.

[0006b] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable salt of a compound selected from the group consisting of:


,

,

,

,

, and

.

[0006c] In yet another aspect of the present disclosure, there is provided a compound selected from the group consisting of:


,

,

,

,

, and

.

[0006d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound as disclosed herein, or a pharmaceutically acceptable salt thereof.

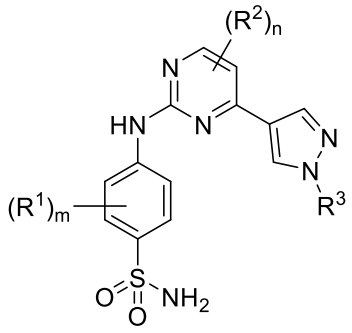
[0006e] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

[0006f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting CDK2.

[0006g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a subject suffering from, or at risk of developing, a solid tumor cancer.

[0006h] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, for use in therapy.

[0007] In one example, the present disclosure provides a compound represented by the following structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, the definition of each variable is provided below.

[0008] In another example, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof (a "pharmaceutical composition of the disclosure").

[0009] The present disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound of the disclosure

(*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the disclosure. In one example, the cancer is uterine cancer (including uterine carcinosarcoma, uterine corpus endometrial carcinoma), endometrial cancer, breast cancer (including breast invasive carcinoma, TNBC (triple negative breast cancer), ER (estrogen receptor)+HER2 (human epidermal growth factor 2)- breast cancer, and HER2+ breast cancer), ovarian cancer (e.g. ovarian serous cystandenocarcinoma), stomach cancer (including stomach adenocarcinoma), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer, kidney cancer, head and neck cancer, liver cancer, prostate cancer, skin cancer, leukemia (including AML (acute myeloid leukemia)), lymphoma (including B-cell lymphoma), sarcoma, esophageal cancer (including esophageal carcinoma), bladder cancer (including bladder urothelial carcinoma), lung cancer (including lung squamous carcinoma and non-small cell lung cancer, e.g., EGFRm (epidermal growth factor receptor mutant)+ non-small cell lung cancer), cholangiocarcinoma, adrenocortical carcinoma, or mesothelioma.

[0010] In one example, the cancer to be treated has CCNE1 amplification or overexpression.

[0011] The treatment method disclosed herein further comprises administering to the subject an effective amount of palbociclib (e.g., ibrance®), ribociclib, abemaciclib, tamoxifen, letrozole, olaparib (e.g., lynparza®), niraparib, carboplatin, cisplatin, paclitaxel, gemcitabine, megestrol acetate, medroxyprogesterone acetate, capecitabine (e.g., xeloda®), regorafenib (e.g., stivarga®), afatinib (e.g., gilotrif®), osimertinib (e.g., tagrisso®), gefitinib (e.g., iressa®), erlotinib (e.g., tarceva®), ramucirumab (e.g., cyramza®), an EGFR inhibitor, pralsetinib, ABT-263 (navitoclax), MK-1775 (adavosertib), BAY-1895344, berzosertib, ceralasertib, SRA-737, LY2603618 (rabusertib), or trastuzumab (e.g., herceptin®), or combinations thereof. The EGFR inhibitor may be selected from afatinib, osimertinib, lapatinib, erlotinib, dacomitinib, poziotinib, neratinib, gefitinib JBJ-04-125-02, alflutinib (AST 2818), aumolertinib (formerly almonertinib) (HS10296), BBT-176, BI-4020, BPI-361175, BPI-D0316, CH7233163, gilitertinib, icotinib, JND-3229, lazertinib, nazartinib (EGF 816), avitinib, PCC-0208027, rezivertinib (BPI-7711), TQB3804, zorifertinib (AZ-3759), or DZD9008; an EGFR antibody such as cetuximab, panitumumab, necitumumab, HLX07, JMT101; or a bispecific EGFR and MET antibody (*e.g.*, amivantamab ((JNJ-61186372, JNJ-372)).

[0012] The present disclosure also provides a method of inhibiting CDK2 in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the disclosure (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the disclosure.

[0013] The present disclosure also provides the use of an effective amount of a compound of the disclosure (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure, for the preparation of a medicament for the treatment of cancers.

[0014] In another example, provided herein a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure for use in treating cancers.

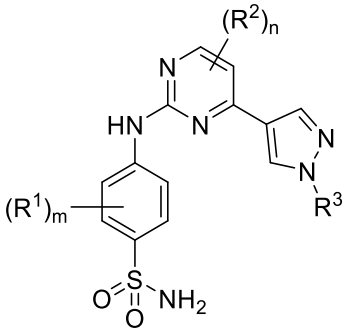
[0015] In one example, the present disclosure provides a method of treating a subject having, or at risk of developing, a disease or disorder associated with CDK2, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, wherein the subject has an amplification of the CCNE1 gene and/or have an expression level of CCNE1 higher than a control expression level of CCNE1. In some examples, the disease or disorder associated with CDK2 is cancer.

[0016] Also provided herein is a method of treating a patient having an amplified expression level of CCNE1 and suffering from, or at risk of developing, a solid tumor cancer, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0017] The contemplated solid tumor cancer may be at least one of: uterine cancer (including uterine carcinosarcoma, uterine corpus endometrial carcinoma), endometrial cancer, breast cancer (including breast invasive carcinoma, TNBC (triple negative breast cancer), ER (estrogen receptor)+HER2 (human epidermal growth factor 2)- breast cancer, and HER2+ breast cancer), ovarian cancer (e.g. ovarian serous cystandenocarcinoma), stomach cancer (including stomach adenocarcinoma), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer, kidney cancer, head and neck cancer, liver cancer, prostate cancer, skin cancer, lymphoma (including B-cell lymphoma), sarcoma, esophageal cancer (including esophageal carcinoma), bladder cancer

CLAIMS

1. A compound of Formula I



(I), or a pharmaceutically acceptable salt thereof, wherein

each R^1 is independently selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 3 halo;

each R^2 is independently selected from the group consisting of halo, OH, CN, C_1-C_4alkyl, and C_1-C_4alkoxy, wherein the C_1-C_4alkyl and C_1-C_4alkoxy are each optionally substituted with 1 to 3 halo;

R^3 is C_1-C_6alkyl optionally substituted with 1 or 2 groups each independently selected from the group consisting of halo, OH, C_3-C_6cycloalkyl, and 3 to 6-membered heterocyclyl, wherein the C_3-C_6cycloalkyl is optionally substituted with OH, wherein the 3 to 6-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^a and then is optionally substituted on a ring carbon with OH; or

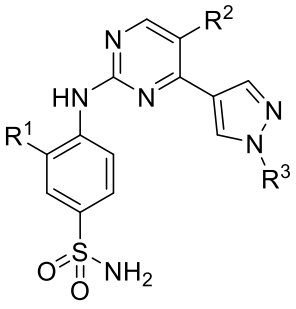
R^3 is C_3-C_6cycloalkyl or 3 to 6-membered heterocyclyl, wherein the C_3-C_6cycloalkyl is optionally substituted with OH or -CH_2OH, wherein the 3 to 6-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^a and then is optionally substituted on a ring carbon with OH or -CH_2OH;

each R^a is independently H or C_1-C_6alkyl;

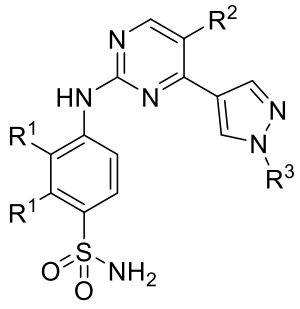
m is selected from the group consisting of 0, 1, 2, 3, and 4, and

n is selected from the group consisting of 0, 1, and 2.

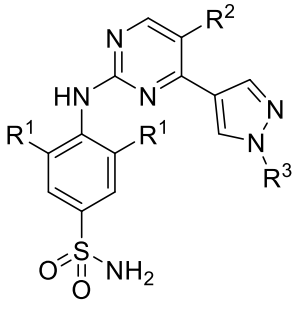
2. The compound of Claim 1, wherein the compound is of Formula IIA, Formula IIB, Formula IIC, or Formula IID



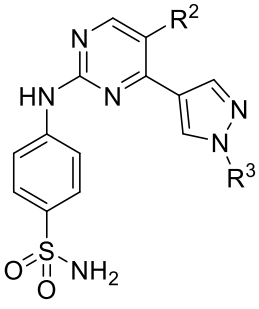
(IIA),



(IIB),



(IIC), or



(IID), or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 or 2, wherein each R^1 is independently selected from the group consisting of halo, methyl, and methoxy.

4. The compound of any one of Claims 1 to 3, wherein each R^2 is independently selected from the group consisting of halo, CN, methyl, and ethyl, wherein the methyl and ethyl are each optionally substituted with 1 to 3 halo.

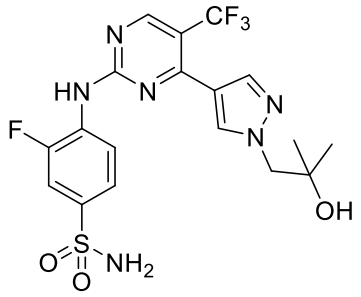
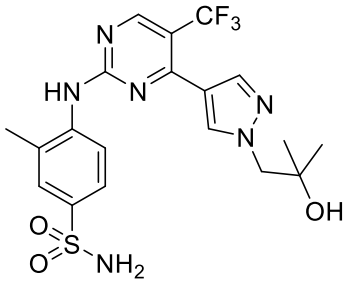
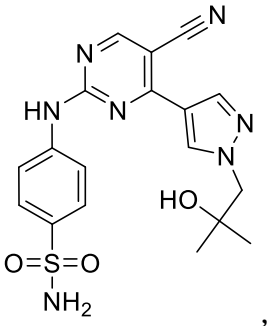
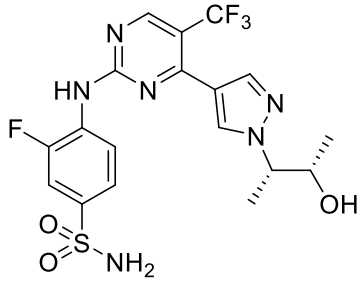
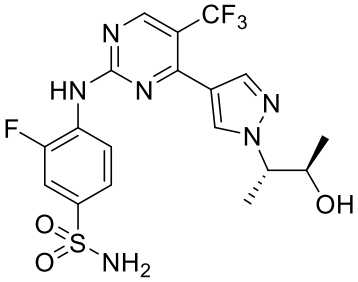
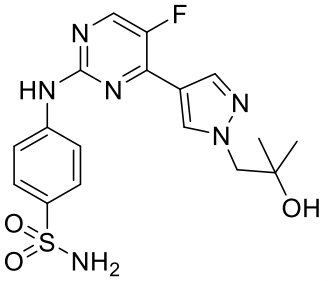
5. The compound of any one of Claims 1 to 4, wherein R^3 is C_1-C_5alkyl optionally substituted with 1 or 2 groups each independently selected from the group consisting of halo, OH, cyclopropyl and oxetanyl, wherein the cyclopropyl and oxetanyl are each optionally substituted with OH.

6. The compound of any one of Claims 1 to 4, wherein R^3 is C_1-C_5alkyl substituted with OH.

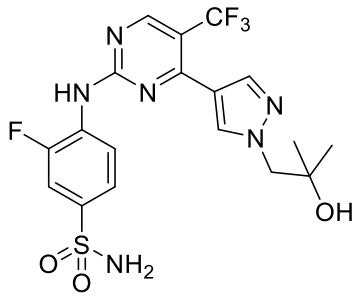
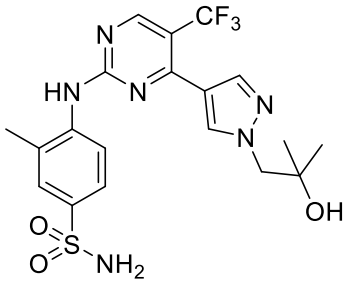
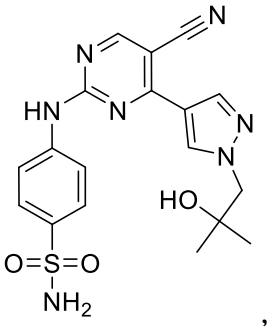
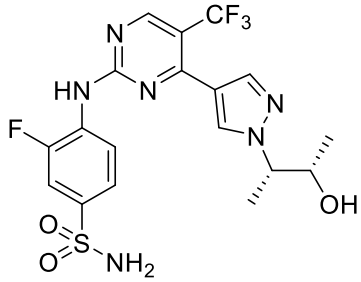
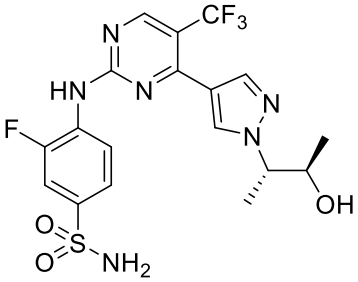
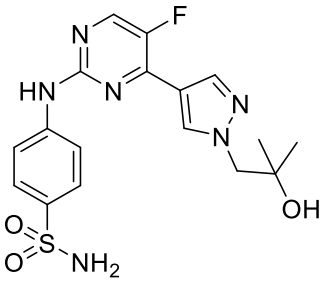
7. The compound of Claim 1 or 2, wherein each R^1 is methyl, each R^2 is independently selected from the group consisting of halo, methyl, and CF_3, and R^3 is C_1-C_6alkyl substituted with OH.

8. The compound of Claim 1 or 2, wherein each R^1 is halo, each R^2 is independently selected from the group consisting of halo, CN, methyl, ethyl, and CF_3, and R^3 is C_1-C_6alkyl substituted with OH.

9. A pharmaceutically acceptable salt of a compound selected from the group consisting of:


,

,

,

,

, and

.

10. A compound selected from the group consisting of:


,

,

,

,

, and

.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof.

12. Use of a compound of any of claims 1-10, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 11, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

13. The use of claim 12, wherein the cancer is breast cancer.

14. Use of a compound of any of claims 1-10, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 11, in the manufacture of a medicament for inhibiting CDK2.

15. Use of a compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 11, in the manufacture of a medicament for treating a subject suffering from, or at risk of developing, a solid tumor cancer.

16. The use of claim 15, wherein the solid tumor cancer is at least one of : uterine cancer (including uterine carcinosarcoma, uterine corpus endometrial carcinoma), endometrial cancer, breast cancer (including breast invasive carcinoma, TNBC (triple negative breast cancer), ER (estrogen receptor)+HER2 (human epidermal growth factor 2)- breast cancer, and HER2+ breast cancer), ovarian cancer (e.g. ovarian serous cystandenocarcinoma), stomach cancer (including stomach adenocarcinoma), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer, kidney cancer, head and neck cancer, liver cancer, prostate cancer, skin cancer, lymphoma (including B-cell lymphoma), sarcoma, esophageal cancer (including esophageal carcinoma), bladder cancer (including bladder urothelial carcinoma), lung cancer (including lung squamous carcinoma and non-small cell lung cancer, e.g., EGFRm (epidermal growth factor receptor mutant)+ non-small cell lung cancer), cholangiocarcinoma, adrenocortical carcinoma, or mesothelioma.

17. A compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 11, for use in therapy.