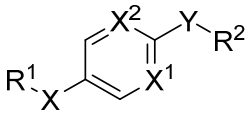
Etemadmoghadam et al., Clin. Cancer Res. (2013) 19: 5960-71; Au-Yeung et al., Clin. Cancer Res. (2017) 23: 1862-1874; Ayhan et al., Modern Pathology (2017) 30: 297-303; Ooi et al., Hum. Pathol. (2017) 61 : 58-67; Noske et al., Oncotarget (2017) 8: 14794-14805. CDK2 in complex with cyclin E phosphorylates the tumor suppressor RB1 during the G1 phase of the cell cycle. Fully phosphorylated RB1 de-represses the E2F transcription factors which regulate transcription of DNA synthesis and repair genes including cyclin A2. CDK2 complexes with cyclin A2 to phosphorylate and regulate DNA-synthesis/repair processes during S-phase progression.

Amplification or overexpression of cyclin A (CCNA2) is known to be involved in several cancer types, including breast, liver, lung, and cervical. *See, e.g.,* Yam et al., Cell Mol. Life Sci. 2002; 59, 1317-1326 and Burkholm et al., Int. J. Cancer, 2001; 93(2) 283-287. Increased activity of cyclin A is also associated with poor clinical prognosis in non-small cell lung cancer. *See* Volm, et al., Br. J. Cancer, 1997; 75(12) 1774-1778. Similarly, Cyclin E2 (CCNE2) overexpression is associated with endocrine resistance in breast cancer cells. *See* Caldon et al., Mol. Cancer Ther. (2012) 11:1488-99; Herrera-Abreu et al., Cancer Res. (2016) 76: 2301-2313. Accordingly, inhibition of CDK2 can provide beneficial effects to cancers associated with aberrations in the cell cycle.

SUMMARY

Some examples provide a compound of Formula (A),



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $–NR^AR^B$, $–C(=O)NR^AR^B$, $–OC(=O)NR^AR^B$, an optionally substituted 5-10 membered heteroaryloxy, or an optionally substituted 5-10 membered heteroaryl;

each R^A and R^B are independently hydrogen, optionally substituted C1-C6 alkyl, C1-C6 haloalkyl, or optionally substituted C3-C10 cycloalkyl;

X is $–(CH_2)_a$C3-C8 cycloalkylene-$(CH_2)_b$- optionally substituted with 1-3 substituents independently selected from halogen, C1-C6 alkyl, and C1-C6 alkoxy; $–(CH_2)_a$C5-C8 cycloalkenylene-$(CH_2)_b$- optionally substituted with 1-2 substituents independently selected from halogen and C1-C6 alkyl; $–(CH_2)_a$phenylene-$(CH_2)_b$-; $–(CH_2)_a$heteroarylene-$(CH_2)_b$-; $–(CH_2)_a$heterocyclylene-$(CH_2)_b$-; and C2-C6 alkylene;

a and b are independently 0, 1, or 2;

X^1 is N or CR^{X1};

X^2 is N or CR^{X2};

CR^{X1} and CR^{X2} are independently selected from hydrogen, halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, C3-C6 cycloalkyl, and C3-C6 cycloalkoxy;

Y is $–NR^C–$, $*–C(=O)NR^C(CR^DR^E)_n–$, $*–NR^CC(=O)(CR^DR^E)_n$ –, or –O–, wherein * indicates the point of connection to the X^1-X^2 ring;

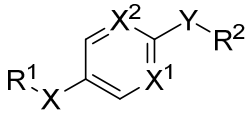
R^C is hydrogen or C1-C6 alkyl;

n is 0, 1, or 2;

each R^D and R^E are independently hydrogen, fluoro, or C1-C6 alkyl; and

R^2 is optionally substituted phenyl, optionally substituted 5-10 membered heteroaryl, or optionally substituted 5-9 membered heterocyclyl.

In one aspect, the present disclosure refers to a compound of Formula (A),



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $–NR^AR^B$, $–C(=O)NR^AR^B$, $–OC(=O)NR^AR^B$, an optionally substituted 5-10 membered heteroaryloxy, or an optionally substituted 5-10 membered heteroaryl;

each R^A and R^B are independently hydrogen, C1-C6 haloalkyl, optionally substituted C1-C6 alkyl, or optionally substituted C3-C10 cycloalkyl;

X is $–(CH_2)_a$C3-C8 cycloalkylene-$(CH_2)_b$- optionally substituted with 1-3 substituents independently selected from halogen, C1-C6 alkyl, and C1-C6 alkoxy; $–(CH_2)_a$C5-C8 cycloalkenylene-$(CH_2)_b$- optionally substituted with 1-2 substituents independently selected from halogen and C1-C6 alkyl; $–(CH_2)_a$phenylene-$(CH_2)_b$-; $–(CH_2)_a$heteroarylene-$(CH_2)_b$-; $–(CH_2)_a$heterocyclylene-$(CH_2)_b$-; and C2-C6 alkylene;

a and b are independently 0, 1, or 2;

X^1 is N or CR^{X1};

X^2 is N or CR^{X2};

R^{X1} and R^{X2} are independently selected from hydrogen, halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, C3-C6 cycloalkyl, and C3-C6 cycloalkoxy;

Y is $–NR^C–$, $*–C(=O)NR^C(CR^DR^E)_n–$, $*–NR^CC(=O)(CR^DR^E)_n$ –, or –O–, wherein * indicates the point of connection to the X^1-X^2 ring;

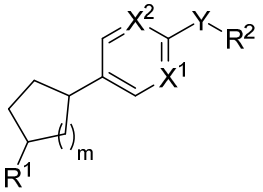
R^C is hydrogen or C1-C6 alkyl;

n is 0, 1, or 2;

each R^D and R^E are independently hydrogen, fluoro, or C1-C6 alkyl; and

R^2 is optionally substituted phenyl, optionally substituted 5-10 membered heteroaryl, or optionally substituted 5-9 membered heterocyclyl.

Some examples provide a compound of Formula (A-I),



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $–NR^AR^B$, $–C(=O)NR^AR^B$, $–OC(=O)NR^AR^B$, or an optionally substituted 5-10 membered heteroaryl;

each R^A and R^B are independently hydrogen, optionally substituted C1-C6 alkyl, C1-C6 haloalkyl, or optionally substituted C3-C10 cycloalkyl;

X^1 is N or CR^{X1};

X^2 is N or CR^{X2};

CR^{X1} and CR^{X2} are independently selected from hydrogen, halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, C3-C6 cycloalkyl, and C3-C6 cycloalkoxy;

Y is $–NR^C–$, $*–C(=O)NR^C(CR^DR^E)_n–$, $*–NR^CC(=O)(CR^DR^E)_n$ –, or –O–, wherein * indicates the point of connection to the X^1-X^2 ring;

R^C is hydrogen or C1-C6 alkyl;

m is 0, 1, or 2;

n is 0, 1, or 2;

each R^D and R^E are independently hydrogen, fluoro, or C1-C6 alkyl; and

R^2 is optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, or optionally substituted 5-6 membered heterocyclyl.

Some examples provide a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Some examples provide a method for treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Some examples provide a method for treating a cancer in a subject in need thereof, comprising: (a) identifying the cancer as being a CDK2-associated cancer; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Some examples provide a method for treating a cancer in a subject in need thereof, comprising: administering to the subject a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, wherein the subject has been identified as having a CDK2-associated cancer.

Some examples provide a method of treating a CDK2-associated cancer, comprising administering a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, to a subject identified or diagnosed as having a CDK2-associated cancer. In one aspect, the present disclosure refers to use of a therapeutically effective amount 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 the treatment of a CDK2-associated cancer in a subject identified or diagnosed as having a CDK2-associated cancer.

Some examples provide a method for treating cancer in a subject in need thereof, comprising: (a) determining that the cancer is associated with a dysregulation of a CDK2 gene, a CDK2 protein, or expression or activity or level of any of the same; and (b) administering to the

subject a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to use of a therapeutically effective amount 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 the treatment of cancer in a subject in need thereof, comprising: determining that the cancer is associated with a dysregulation of a CDK2 gene, a CDK2 protein, or expression or activity or level of any of the same; wherein a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein is to be administered to the subject.

Some examples provide a method for inhibiting metastasis of a cancer in a subject having a cancer in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Some examples provide a method for inhibiting cancer cell invasiveness in a subject having a cancer in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Some examples provide a method for inhibiting mammalian cell proliferation, comprising contacting the mammalian cell with a compound of Formula (A), or a pharmaceutically acceptable salt thereof.

Some examples provide a method for inhibiting CDK2 activity in a mammalian cell, comprising contacting the mammalian cell with a compound of Formula (A), or a pharmaceutically acceptable salt thereof.

Some examples provide a method for inducing apoptosis in mammalian cancer cells, comprising contacting the mammalian cell with a compound of Formula (A), or a pharmaceutically acceptable salt thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entireties. In case of conflict, the present specification, including definitions, will control.