INHIBITORS OF GLUCOCORTICOID RECEPTOR

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Application Ser. No. 62/405,801 filed October 7, 2016, and U.S. Application Ser. No. 62/526,331 filed June 28, 2017, each of which are hereby incorporated by reference in their entireties.

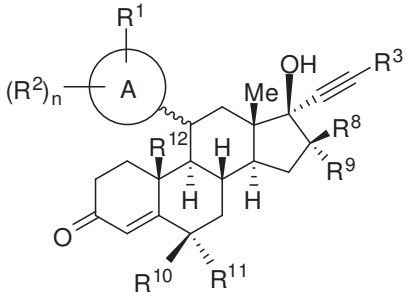
BACKGROUND

[0002] A need exists in the art for an effective treatment of cancer, neoplastic disease, and hypercortisolism.

BRIEF SUMMARY

[0003] Provided herein are substituted steroidal derivative compounds and pharmaceutical compositions comprising said compounds. The subject compounds and compositions are useful as inhibitors of glucocorticoid receptors (GR). Futhermore, the subject compounds and compositions are useful for the treatment of cancer, such as prostate cancer, breast cancer, lung cancer, and ovarian cancer, and hypercortisolism.

[0004] Some examples provided herein describe compounds having the structure of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof:



Formula (III)

wherein

ring A is a heteroaryl, aryl, cycloalkyl, or heterocyclyl;

R^1 is $–NR^{4a}R^{5a}$;

each R^2 is independently $–NR^4R^5$, optionally substituted alkylNR^4R^5, halo, $–OR^6$, –OH, optionally substituted alkyl, haloalkyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heteroalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted hydroxyalkyl, $–C(O)R^6$, $–C(O)OR^6$, $–C(O)NR^4R^5$, $–OC(O)OR^6$, $–OC(O)NR^4R^5$, $–S(O)_2NR^4R^5$, $–S(O)_2R^7$, $–S(O)R^7$, $–SR^7$, $–NR^4S(O)_2NR^4R^5$, –CN, $–CO_2H$, or $–NO_2$;

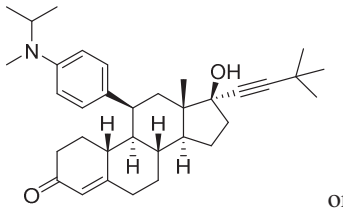
or R^1 and R^2 on adjacent atoms are taken together with the atoms to which they are attached to form an optionally substituted heterocycle;

R^{12} is hydrogen, optionally substituted alkyl, haloalkyl, hydroxy, halo, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, or optionally substituted heteroalkyl;

each R^{13} is independently H, optionally substituted alkyl, haloalkyl, optionally substituted carbocyclyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl; and

n is 0, 1, 2, 3, or 4.

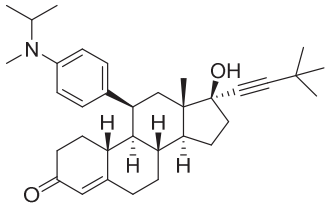
[0004a] In one aspect, the present disclosure refers to a compound that is



or a pharmaceutically acceptable salt or solvate thereof.

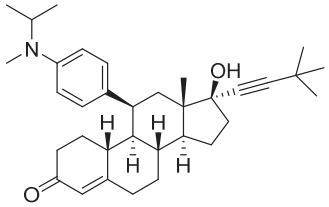
[0004b] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as described herein and at least one pharmaceutically acceptable excipient.

[0004c] In one aspect, the present disclosure refers to use of a compound that is



or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating cancer in a subject in need thereof; wherein the cancer expresses glucocorticoid receptor (GR).

[0004d] In another aspect, the present disclosure refers to use of a compound that is



or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating breast cancer, ovarian cancer, or prostate cancer in a subject in need thereof; wherein the breast cancer, ovarian cancer, or prostate cancer expresses glucocorticoid receptor (GR).

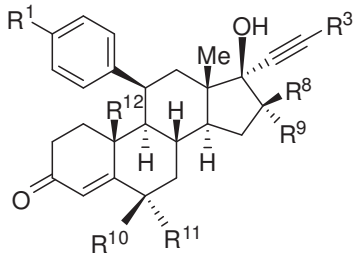
[0005] In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{12} is hydrogen, alkyl, haloalkyl, hydroxy, halo, carbocyclyl, or heteroalkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{12} is C_{1-6} alkyl or hydrogen. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{12} is methyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{12} is H. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, ring A is monocyclic heteroaryl or monocyclic aryl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, ring A is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, ring A is phenyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} is C_{2-8} alkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} is C_{3-6} alkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} is C_{2-4} alkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} is ethyl, i-propyl, or t-butyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{5a} is –H, optionally substituted alkyl, or haloalkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{5a} is –H or alkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{5a} is C_{1-6} alkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} and R^{5a} are taken together with the N atom to which they are attached to form an optionally substituted heterocycle. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{4a} and R^{5a} are taken together with the N atom to which they are attached to form an optionally substituted pyrrolidinyl, an optionally substituted morpholinyl, an optionally substituted thiomorpholinyl, an optionally substituted piperidinyl, or an optionally substituted piperazinyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable

salt, solvate, or prodrug thereof, n is 0, 1, or 2. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, n is 0. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, n is 1.

[0006] In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, each R^2 is independently $–NR^4R^5$, halo, $–OR^6$, alkyl, fluoroalkyl, carbocyclyl, heteroalkyl, heterocyclyl, $–S(O)_2NR^4R^5$, or $–S(O)_2R^7$. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is optionally substituted C_{2-8} alkyl, haloalkyl, or optionally substituted carbocyclyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is C_{4-8} alkyl, haloalkyl, or optionally substituted carbocyclyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is CF_3, t-butyl, or cyclopropyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is C_{4-8} alkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is t-butyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is haloalkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is CF_3. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is optionally substituted carbocyclyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^3 is cyclopropyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^8 and R^9 are each independently –H, alkyl, or carbocyclyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^8 and R^9 are –H. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{10} and R^{11} are each independently –H, C_{1-6} alkyl, halo, C_{1-6} alkoxy, or –OH. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{10} and R^{11} are each –H. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^{10} and R^{11} are taken together with the atom to which they are attached to form a 3-, 4-, 5-, or 6- membered ring. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4 and R^5 are each independently –H, C_{1-6} alkyl, or $–S(O)_2R^7$. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^4 and R^5 attached to the same N atom are taken together with the N atom to which they are attached to form a substituted or unsubstituted 4-, 5-, or 6-membered ring heterocycle additionally containing 0-3 heteroatoms selected from the group consisting of –O–, –NH–, $–NR^6–$, –S–, and $–S(O)_2–$. In some examples

of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^6 is alkyl, carbocyclyl, or fluoroalkyl. In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, R^7 is alkyl, carbocyclyl, optionally substituted aryl, optionally substituted aralkyl, or optionally substituted heterocyclyl.

[0007] In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, the compound has the structure of Formula (IIIa):



Formula (IIIa).

[0008] Some examples provided herein describe a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (III) or (IIIa), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0009] Also provided herein are methods for treating or preventing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (III) or (IIIa), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. Also provided herein are methods for reducing incidences of cancer recurrence, the method comprising administering to a subject in cancer remission a therapeutically effective amount of a compound having the structure of Formula (III) or (IIIa), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. Some examples provided herein describe methods for treating a chemo-resistant cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (III) or (IIIa), or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0010] In some examples, the cancer is triple negative breast cancer, high grade serous ovarian cancer, castration resistant prostate cancer, or doubly resistant prostate cancer. In some examples, the cancer is non-small cell lung cancer. In some examples, the methods further comprise administering a second therapeutic agent to the subject. In some examples, the methods further comprise administering one or more additional therapeutic agents. In some examples, the second or additional therapeutic agent is an androgen receptor signaling inhibitor. In specific examples, the androgen receptor signaling inhibitor is 3,3'-diindolylmethane (DIM), abiraterone acetate, ARN-509, bexlosteride, bicalutamide, dutasteride, epristeride, enzalutamide, finasteride, flutamide, izonsteride, ketoconazole, N-butylbenzene-sulfonamide, nilutamide, megestrol, steroidal antiandrogens, turosteride, or any combinations thereof. In some examples, the second or additional therapeutic agent is a chemotherapeutic agent. In other examples, the

second or additional therapeutic agent is cisplatin, carboplatin, paclitaxel, gemcitabine, doxorubicin, camptothecin, topotecan, or any combinations thereof. In some examples, the second or additional therapeutic agent is an immunotherapy agent (e.g., an anti-PD-L1 agent or an anti-PD1 agent). In certain examples, the second or additional therapeutic agent is an anti-PD-L1 agent. In certain examples, the second or additional therapeutic agent is an anti-PD1 agent.

[0011] Other examples provided herein describe methods for treating a hypercortisolism disease or disorder in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound having the structure of Formula (III) or (IIIa), or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In certain examples, the hypercortisolism disease or disorder is Cushing's syndrome. In certain examples, the hypercortisolism disease or disorder is refractory Cushing's syndrome.

INCORPORATION BY REFERENCE

[0012] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

DETAILED DESCRIPTION OF THE INVENTION

[0013] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

Definitions

[0014] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0015] "Amino" refers to the $-NH_2$ radical.

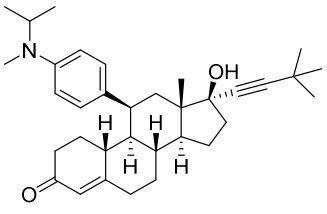
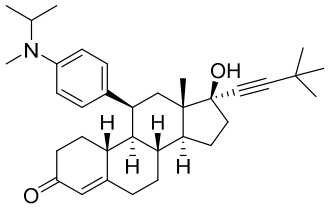
[0016] "Cyano" refers to the -CN radical.

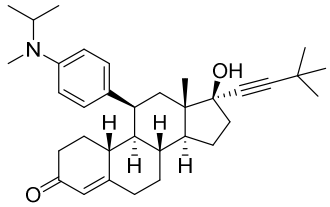
[0017] "Nitro" refers to the $-NO_2$ radical.

[0018] "Oxa" refers to the -O- radical.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound that is  or a pharmaceutically acceptable salt or solvate thereof.
2. A pharmaceutical composition comprising the compound of claim 1 and at least one pharmaceutically acceptable excipient.
3. Use of a compound that is  or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating cancer in a subject in need thereof; wherein the cancer expresses glucocorticoid receptor (GR).
4. The use of claim 3, wherein the cancer is chemo-resistant.
5. The use of claim 3, wherein the cancer is breast cancer.
6. The use of claim 5, wherein the cancer is chemo-resistant.
7. The use of claim 3, wherein the cancer is ovarian cancer.
8. The use of claim 7, wherein the cancer is chemo-resistant.
9. The use of claim 3, wherein the cancer is prostate cancer.
10. The use of claim 9, wherein the cancer is chemo-resistant.
11. The use of claim 9, wherein the cancer is castration resistant prostate cancer.
12. The use of any one of claims 3-11, wherein a therapeutically effective amount of a second therapeutic agent is to be further administered to the subject selected from an androgen receptor inhibitor, cisplatin, carboplatin, paclitaxel, gemcitabine, doxorubicin, camptothecin, topotecan, an anti-PD-L1 agent or an anti-PD1 agent, and any combinations thereof.
13. The use of any one of claims 3-11, wherein a therapeutically effective amount of nab-paclitaxel is to be further administered to the subject.
14. The use of any one of claims 3-11, wherein a therapeutically effective amount of enzalutamide is to be further administered to the subject.

15. Use of a compound that is  or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating breast cancer, ovarian cancer, or prostate cancer in a subject in need thereof; wherein the breast cancer, ovarian cancer, or prostate cancer expresses glucocorticoid receptor (GR).