SUMMARY

One embodiment of this disclosure pertains to compounds and therapeutically acceptable salts, prodrugs, metabolites, or salts of prodrugs thereof, which are useful as inhibitors of anti-apoptotic Bcl-2 proteins. In one aspect, there is provided a compound selected from the group consisting of:

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(5R,8R)-1-oxaspiro[4.5]dec-8-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

Another embodiment pertains to a composition for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of this disclosure.

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a subject in need of treatment, said method comprising administering to the subject a therapeutically effective amount of a compound of this disclosure.

Another embodiment pertains to a method of treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a subject in need of treatment, said method comprising administering to the subject therapeutically effective amount of the compound of this disclosure and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

Another embodiment pertains to a composition for treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome, said composition comprising an excipient and a therapeutically effective amount of a compound of this disclosure.

Another embodiment pertains to a method of treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome in a subject in need of treatment, said method comprising administering to the subject a therapeutically effective amount of a compound of this disclosure.

Another embodiment pertains to a method of treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome in a subject in need of treatment, said method comprising administering to the subject therapeutically effective amount of the compound of this disclosure and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

In another aspect, there is provided a composition for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound as disclosed herein or a therapeutically acceptable salt thereof.

In another aspect, there is provided use of a therapeutically effective amount of a compound as disclosed herein or a therapeutically acceptable salt thereof in the manufacture of a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a subject in need of treatment.

In another aspect, there is provided use of a therapeutically effective amount of the compound as disclosed herein or a therapeutically acceptable salt thereof and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent in the manufacture of a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a subject in need of treatment.

In another aspect, there is provided a composition for use in treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome, said composition comprising an excipient and a therapeutically effective amount of a compound as disclosed herein or a therapeutically acceptable salt thereof.

In another aspect, there is provided use of a therapeutically effective amount of a compound as disclosed herein or a therapeutically acceptable salt thereof in the manufacture of a medicament for treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome in a subject in need of treatment.

In another aspect, there is provided use of a therapeutically effective amount of the compound as disclosed herein or a therapeutically acceptable salt thereof and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent in the manufacture of a medicament for treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome in a subject in need of treatment.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S,5R)-5-methyl-1,4-dioxan-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(5R,8R)-1-oxaspiro[4.5]dec-8-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxytetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxaspiro[4.5]dec-8-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-1,4-dioxan-2-

ylmethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxyoxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provided a compound 4-(4-{[2-(4-chloro-2-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

In another aspect, there is provideda compound 4-[4-({2-[4-(difluoromethyl)phenyl]-4,4-dimethylcyclohex-1-en-1-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. With reference to the use of the words "comprise" or "comprises" or "comprising"

4-[4-({2-[4-(difluoromethyl)phenyl]-4,4-dimethylcyclohex-1-en-1-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide;

and therapeutically acceptable salts thereof.

2. A composition for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of a compound of claim 1 or a therapeutically acceptable salt thereof.

3. Use of a therapeutically effective amount of a compound of claim 1 or a therapeutically acceptable salt thereof in the manufacture of a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a subject in need of treatment.

4. Use of a therapeutically effective amount of the compound of claim 1 or a therapeutically acceptable salt thereof and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent in the manufacture of a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, chronic lymphocytic leukemia, myeloma, prostate cancer, small cell lung cancer or spleen cancer in a subject in need of treatment.

5. A composition for use in treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome, said composition comprising an excipient and a therapeutically effective amount of a compound of claim 1 or a therapeutically acceptable salt thereof.

6. Use of a therapeutically effective amount of a compound of claim 1 or a therapeutically acceptable salt thereof in the manufacture of a medicament for treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome in a subject in need of treatment.

7. Use of a therapeutically effective amount of the compound of claim 1 or a therapeutically acceptable salt thereof and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent in the manufacture of a medicament for treating systemic lupus erythematosus, lupus nephritis, or Sjogren's Syndrome in a subject in need of treatment.

8. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[(2S,5R)-5-methyl-1,4-dioxan-2-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

9. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2R)-1,4-dioxan-2-ylmethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

10. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(3-nitro-4-{[(5R,8R)-1-oxaspiro[4.5]dec-8-ylmethyl]amino}phenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

11. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-hydroxytetrahydro-2H-pyran-4-

yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

12. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({4-[(1,4-dioxaspiro[4.5]dec-8-ylmethyl)amino]-3-nitrophenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

13. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(2S)-1,4-dioxan-2-ylmethyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

14. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-{[4-({[4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl]methyl}amino)-3-nitrophenyl]sulfonyl}-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

15. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(3-hydroxyoxetan-3-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

16. A compound 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-[(4-{[(4-cyanotetrahydro-2H-pyran-4-yl)methyl]amino}-3-nitrophenyl)sulfonyl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

17. A compound 4-(4-{[2-(4-chloro-2-fluorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

18. A compound 4-[4-({2-[4-(difluoromethyl)phenyl]-4,4-dimethylcyclohex-1-en-1-yl}methyl)piperazin-1-yl]-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a therapeutically acceptable salt thereof.

5