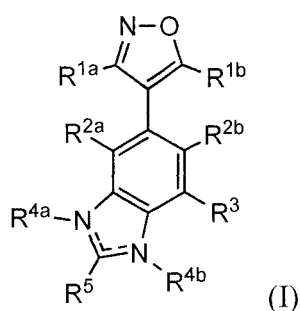


pathological disease states, resulting in the aberrant expression of genes that control cell fate, cell differentiation, cell survival, and inflammatory processes. See, e.g., Cohen, I., *et al.*, *Genes Cancer*, 2: 631-647 (2011); Brooks, W.H., *et al.*, *J. Autoimmun.*, 34: J207-219 (2010); Wierda, R.J., *et al.*, *J. Cell Mol. Med.*, 14: 1225-1240 (2010); Shirodkar, A.V. & Marsden, P.A., *Curr. Opin. Cardiol.*, 26: 209-215 (2011); Villeneuve, L.M., *et al.*, *Clin. Exp. Pharmacol. Physiol.*, 38: 401-409 (2011). BET proteins including BRD4 have been identified as important mediators of altered gene expression profiles found in numerous diseases including cancer, diabetes, obesity, atherosclerosis, cardiovascular and renal disorders, and viral infection. See Muller, S., *et al.*, *Expert Rev. Mol. Med.*, 13: e29 (2011); Zhou, M., *et al.*, *J. Virol.*, 83: 1036-1044 (2009); Chung, C.W., *et al.*, *J. Med. Chem.*, 54: 3827-3838 (2011). For example, MYC has been implicated in the majority of human cancers and BET proteins have been identified as regulatory factors of c-Myc; inhibition of BET proteins, including BRD4, has been shown to downregulate MYC transcription. See Delmore, J.E., *et al.* *Cell*, 146, 904-17 (2011); Lovén, J. *et al.*, *Cell*, 153, 320-34 (2013). Inhibitors and modulators of BET proteins, including BRD4, are therefore needed.

SUMMARY

[0005] Disclosed is a compound of Formula (I)



wherein

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

R^{2a} and R^{2b} are each independently H or halo;

R^3 is

boronic acid or halo; or

$-\text{C}(\text{O})\text{OR}^a$, $-\text{NHC}(\text{O})\text{OR}^a$, $-\text{NHS}(\text{O})_2\text{R}^a$, or $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$; or

selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups, and the other is absent;

R^5 is

$-\text{C}(\text{O})\text{OR}^a$, $-\text{NHC}(\text{O})\text{OR}^a$, $-\text{NHS}(\text{O})_2\text{R}^a$, or $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$; or

selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups;

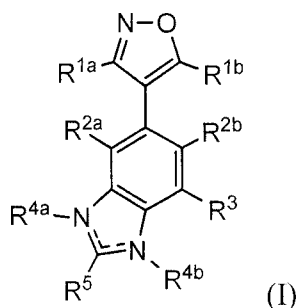
each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione;

wherein the C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl groups are optionally substituted with from 1 to 3 substituents independently selected from C_{1-6} alkyl, C_{5-10} aryl, halo, C_{1-6} haloalkyl, cyano, hydroxy, and C_{1-6} alkoxy;

or a pharmaceutically acceptable salt thereof.

[0005a] One aspect provides a compound of Formula (I)



wherein

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

R^{2a} and R^{2b} are each independently H or halo;

R^3 is

$-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$; or

selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups, and the other is absent;

R^5 is

$-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$; or

selected from the group consisting of H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups;

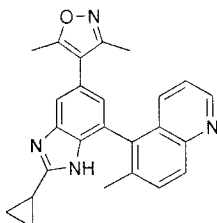
each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, hydroxyl, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione;

wherein the C₁₋₁₀ alkyl, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl groups are optionally substituted with from 1 to 3 substituents independently selected from C₁₋₆ alkyl, C₅₋₁₀ aryl, halo, C₁₋₆ haloalkyl, cyano, hydroxyl, and C₁₋₆ alkoxy;

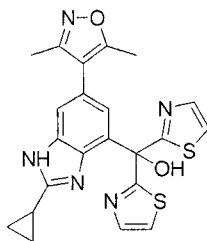
or a pharmaceutically acceptable salt thereof.

[0005b] Another aspect provides for a compound of the following formula



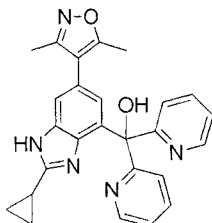
or a pharmaceutically acceptable salt thereof.

[0005c] Another aspect provides for a compound of the following formula



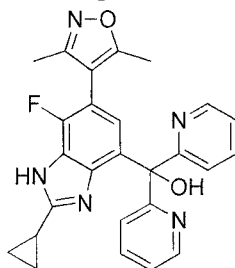
or a pharmaceutically acceptable salt thereof.

[0005d] Another aspect provides for a compound of the following formula



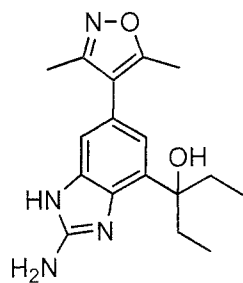
or a pharmaceutically acceptable salt thereof.

[0005e] Another aspect provides for a compound of the following formula

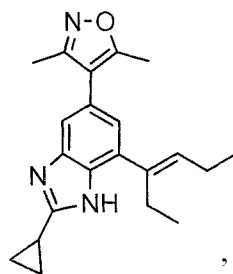


or a pharmaceutically acceptable salt thereof.

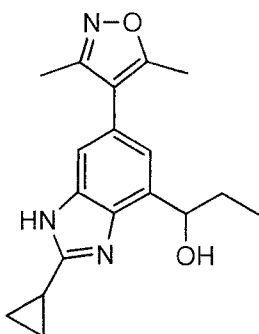
[0006] One embodiment provides for a compound selected from the group consisting of



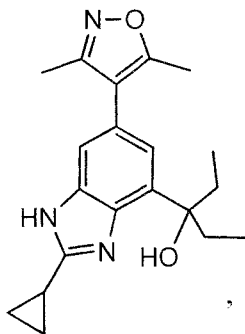
,



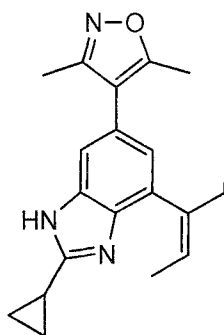
,



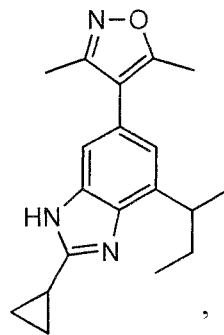
,



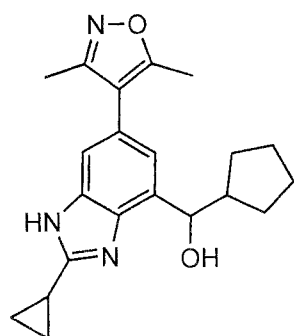
,



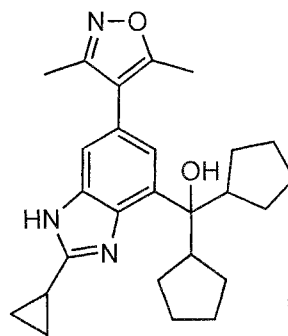
,



,

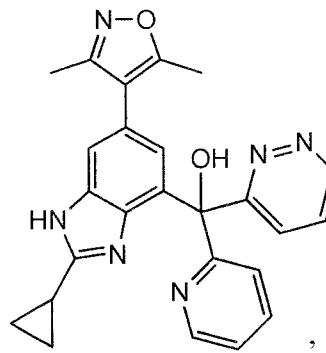
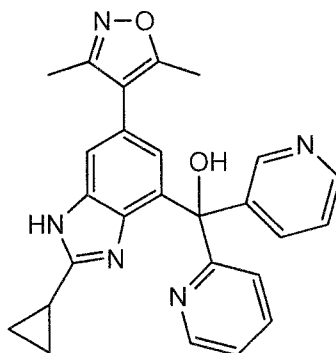
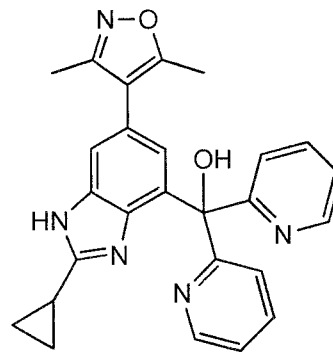
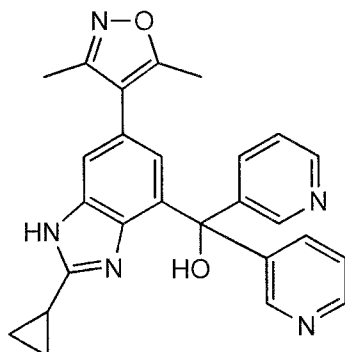
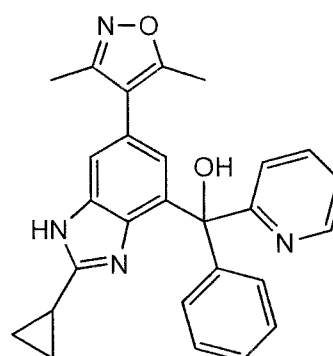
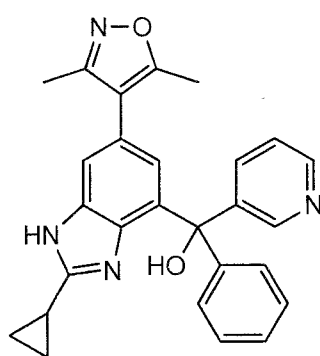
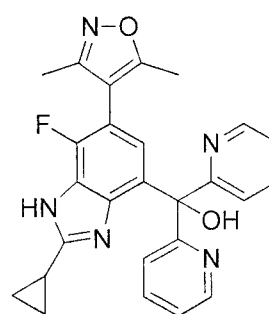
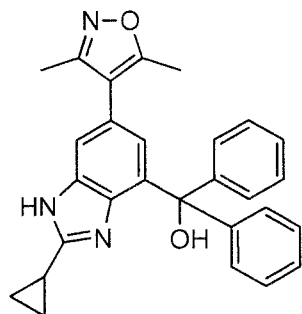


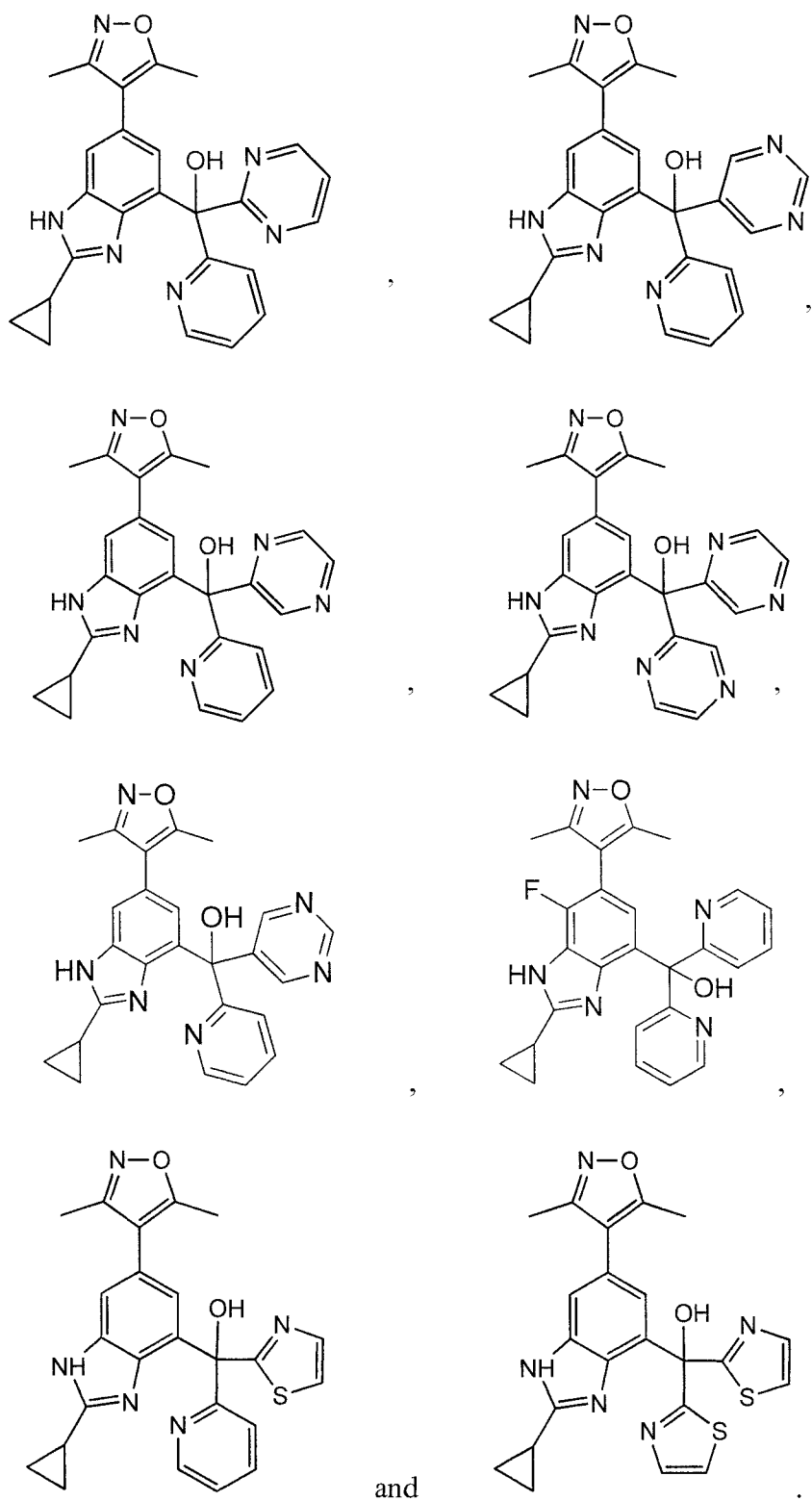
,



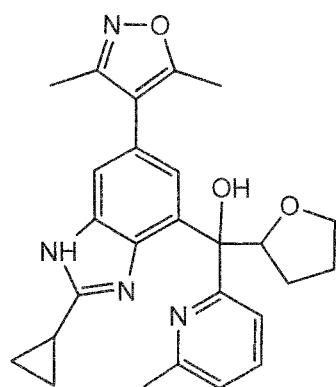
,

[0007] Another embodiment provides for a compound selected from the group consisting of

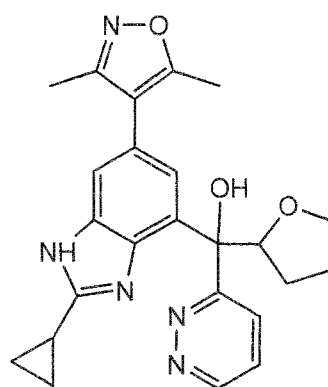




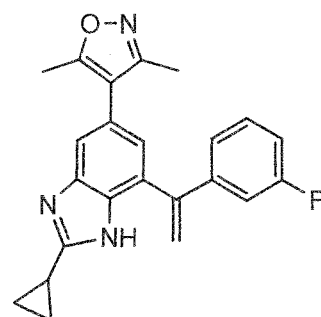
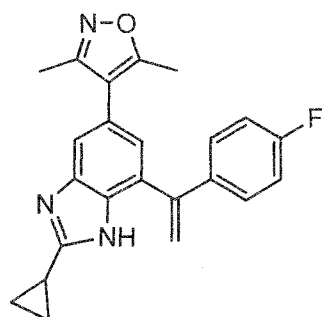
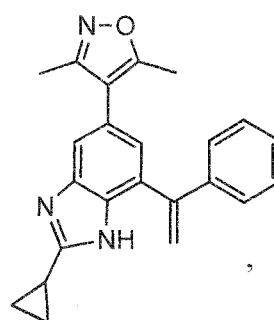
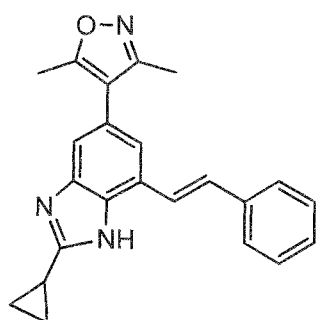
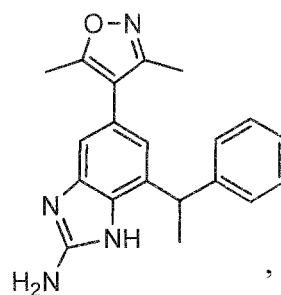
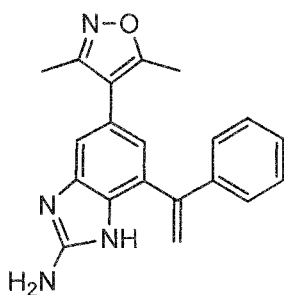
[0008] Another embodiment provides for a compound selected from the group consisting of



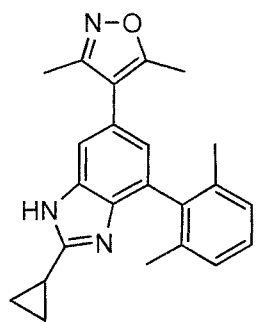
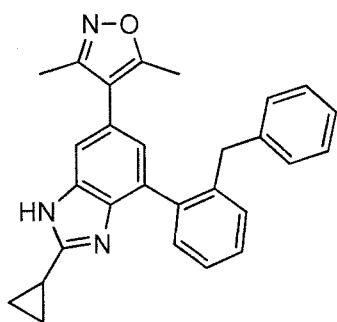
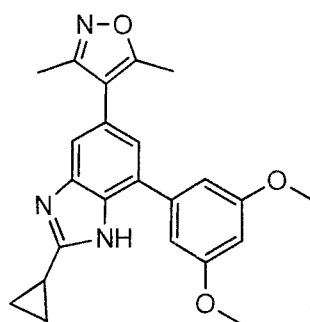
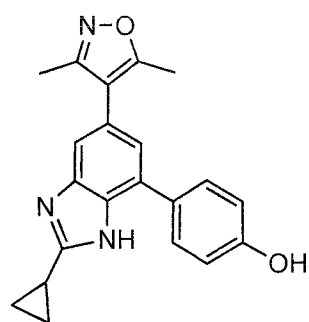
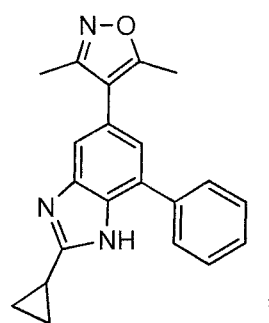
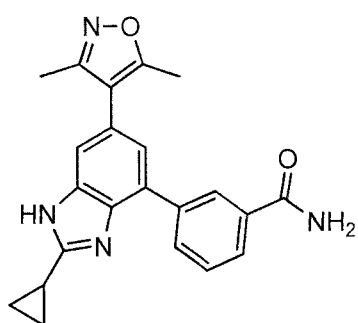
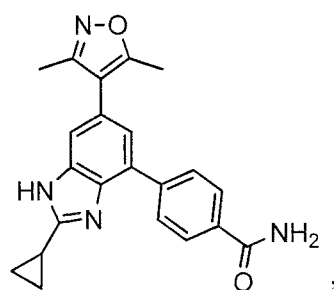
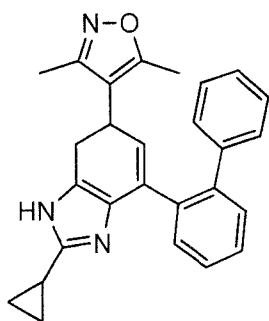
and

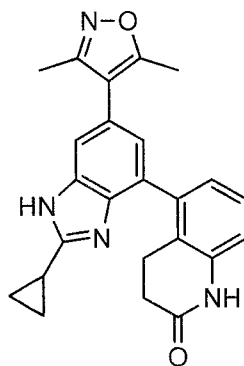
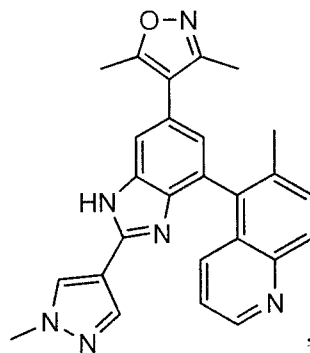
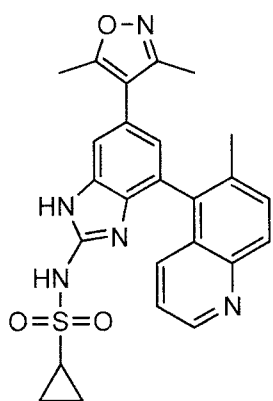
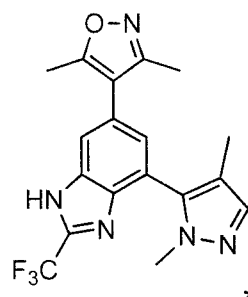
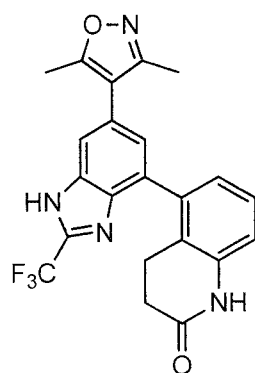


[0009] Another embodiment provides for a compound selected from the group consisting of



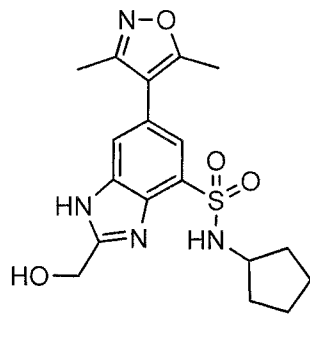
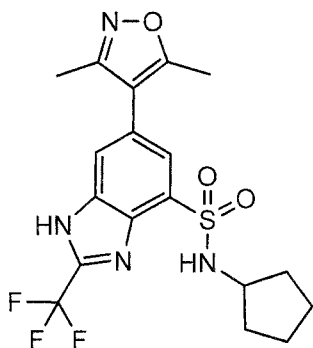
[0010] Another embodiment provides for a compound selected from the group consisting of

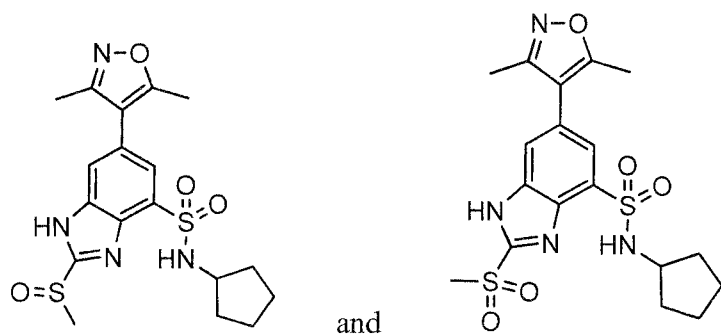




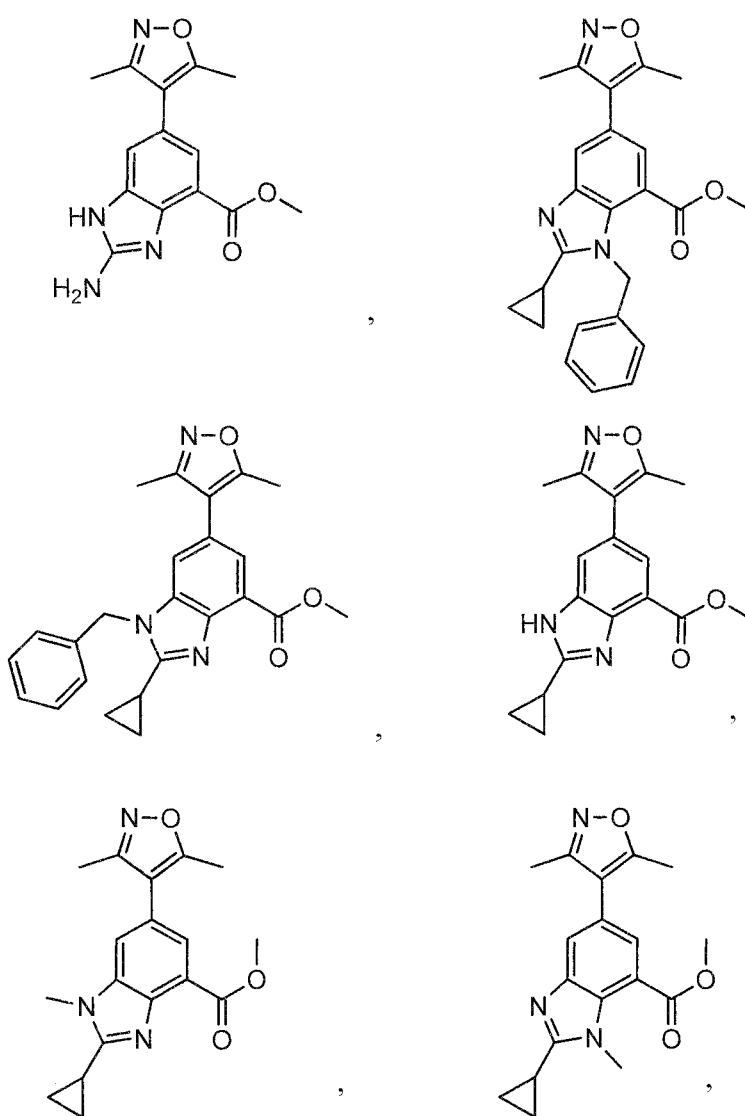
and

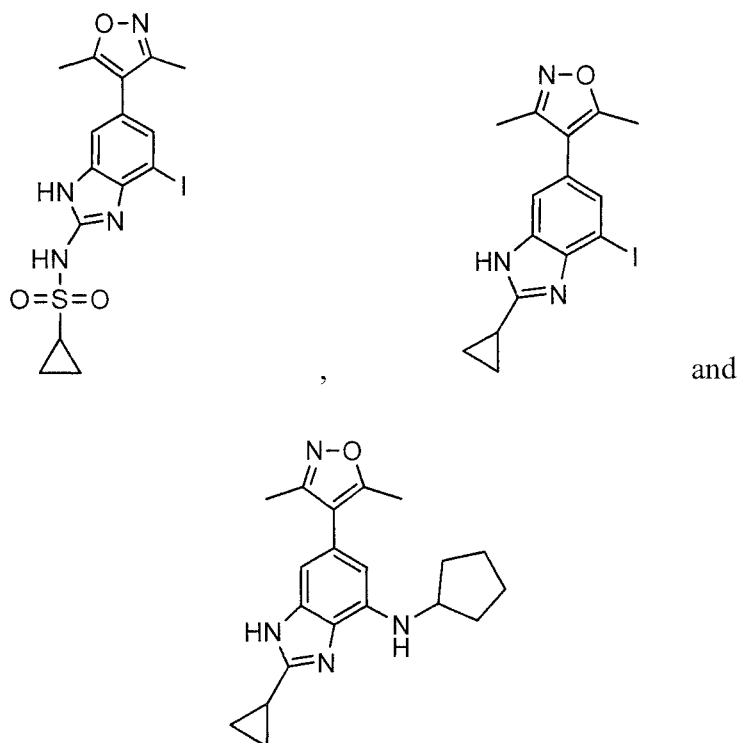
[0011] Another embodiment provides for a compound selected from the group consisting of





[0012] Another embodiment provides for a compound selected from the group consisting of





[0013] Another aspect provides for a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0014] Disclosed is a use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in therapy. Also disclosed is a method of treating a subject having a disease or condition responsive to the inhibition of a bromodomain-containing protein, comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the bromodomain-containing protein is BRD4.

[0015] In some embodiments, the disease or condition is chosen from an autoimmune disease, an inflammatory disease, a neurodegenerative disease, a cardiovascular disorder, a renal disorder, a viral infection, and obesity. In some embodiments, the disease or condition is chosen from rheumatoid arthritis, osteoarthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, asthma, chronic obstructive airways disease, pneumonitis, dermatitis, alopecia, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, hepatitis, primary biliary cirrhosis, sclerosing cholangitis, diabetes (including type I diabetes), and acute rejection of transplanted organs. In some embodiments the disease or condition is cancer, including hematological

cancers, lymphoma, multiple myelomas, leukemias, a neoplasm or a tumor (for example a solid tumor). In some embodiments the disease or condition is a neoplasm or cancer of the colon, rectum, prostate (for example castrate resistant prostate cancer), lung (for example non-small cell lung cancer, and small-cell lung cancer), pancreas, liver, kidney, cervix, uterus, stomach, ovary, breast (for example basal or basal-like breast cancer, and triple-negative breast cancer), skin (for example melanoma), the nervous system (including the brain, meninges, and central nervous system, including a neuroblastoma, a glioblastoma, a meningioma, and a medulloblastoma). In some embodiments the disease or condition is a carcinoma. In some embodiments, the disease or condition is hepatocellular carcinoma. In some embodiments, the disease or condition is a lymphoma. In some embodiments, the disease or condition is a B-cell lymphoma. In some embodiments, the disease or condition is Burkitt's lymphoma. In some embodiments, the disease or condition is diffuse large B-cell lymphoma. In some embodiments, the disease or condition is multiple myeloma. In some embodiments, the disease or condition is chronic lymphocytic leukemia. In some embodiments the disease or condition is NUT midline carcinoma. In some embodiments the subject is a human.

[0016] In some embodiments, the compound is administered intravenously, intramuscularly, parenterally, nasally, or orally. In one embodiment, the compound is administered orally.

[0017] Also provided is a method of inhibiting a bromodomain, comprising contacting the bromodomain with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0018] Also provided is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition responsive to bromodomain inhibition.

[0019] Also provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy. Further provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a subject having a disease or condition responsive to the inhibition of a bromodomain-containing protein. Also provided is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treatment described above. One aspect provides for the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease or condition responsive to the

inhibition of a bromodomain-containing protein. Also provided is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treatment described above.

[0020] Also provided are kits that include a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one embodiment, the kit further includes instructions for use. In one embodiment, a kit includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and instructions for use of the compounds in the treatment of the diseases or conditions described above.

[0021] Also provided are articles of manufacture that include a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one embodiment, the container may be a vial, jar, ampoule, preloaded syringe, or an intravenous bag.

BRIEF DESCRIPTION OF FIGURES

[0022] FIG. 1 shows compound 1020-18 inhibited the viability of 240 cancer cell lines. Relative IC₅₀ values are reported.

[0023] FIG. 2 shows inhibition of tumor growth in an MM.1S xenograft model by compound 1020-18.

[0024] FIG. 3 shows inhibition of tumor growth in a DHL-10 xenograft model by compound 1020-18.

[0025] FIG. 4 shows inhibition by compound 1020-18 of BRD4 binding at the IgH superenhancer.

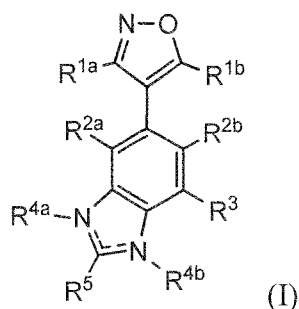
DETAILED DESCRIPTION

[0026] Described herein are compounds of Formula (I), which include compounds of Formulae (Ia), (Ib), (Ic), (Id) and (Ie), compositions and formulations containing such compounds, and methods of using and making such compounds.

[0027] One aspect of the current disclosure relates to compounds of Formula (I)

We claim:

1. A compound of Formula (I)



wherein

R^{1a} and R^{1b} are each independently C₁₋₆ alkyl optionally substituted with from 1 to 5 R²⁰ groups;

R^{2a} and R^{2b} are each independently H or halo;

R³ is

-C(O)OR^a, -NHC(O)OR^a, -NHS(O)₂R^a, or -S(O)₂NR^aR^b; or

selected from the group consisting of C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, amino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C₁₋₆ alkyl optionally substituted with from 1 to 5 R²⁰ groups, and the other is absent;

R⁵ is

-C(O)OR^a, -NHC(O)OR^a, -NHS(O)₂R^a, or -S(O)₂NR^aR^b; or

selected from the group consisting of H, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, amino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups;

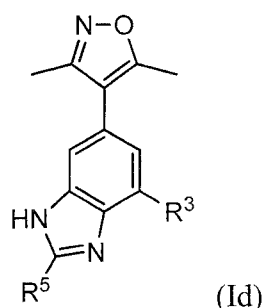
each R^a and R^b is independently selected from the group consisting of H, C₁₋₁₀ alkyl, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; and

each R²⁰ is independently selected from the group consisting of acyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, amino, amido, amidino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C₁₋₁₀ haloalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, C₆₋₂₀ heteroarylalkyl, hydroxy, hydrazino, hydroxyl, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione;

wherein the C₁₋₁₀ alkyl, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl groups are optionally substituted with from 1 to 3 substituents independently selected from C₁₋₆ alkyl, C₅₋₁₀ aryl, halo, C₁₋₆ haloalkyl, cyano, hydroxyl, and C₁₋₆ alkoxy;

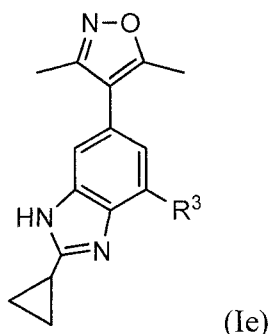
or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 of Formula (Id)



or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1 of Formula (Ie)

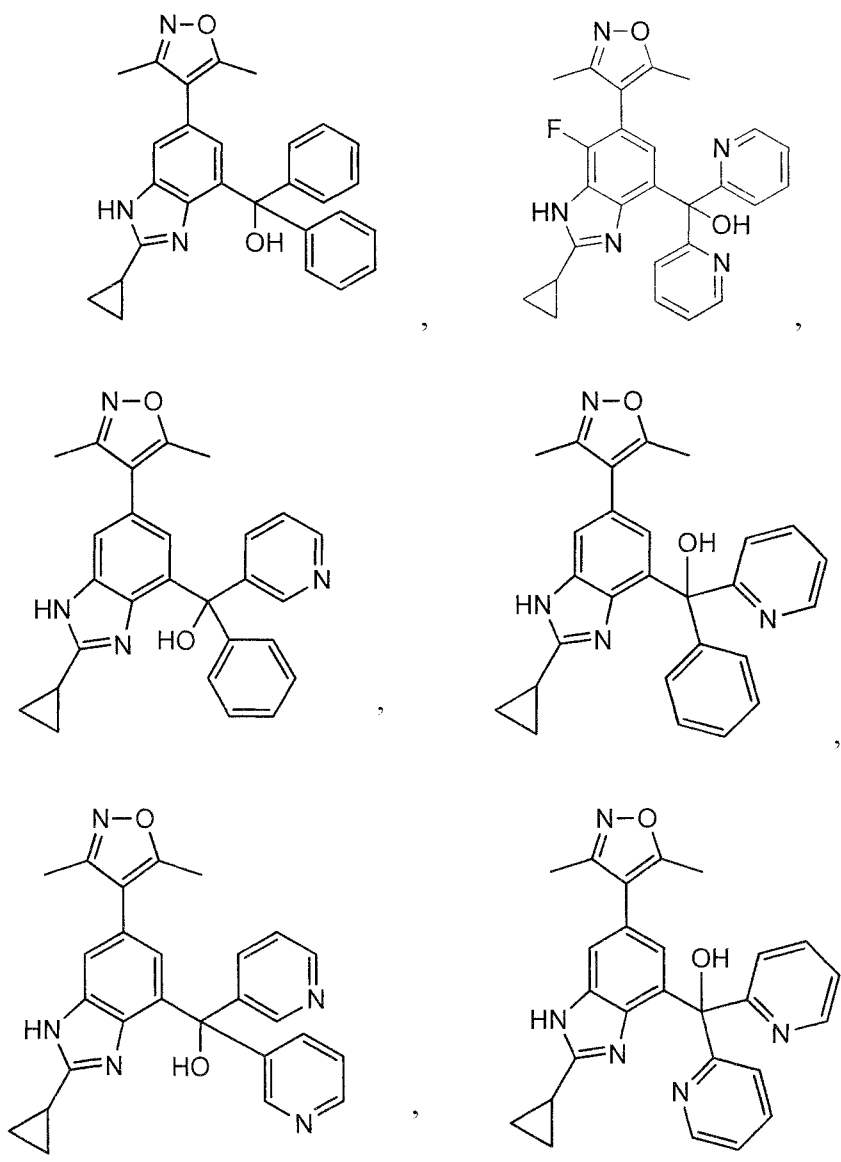


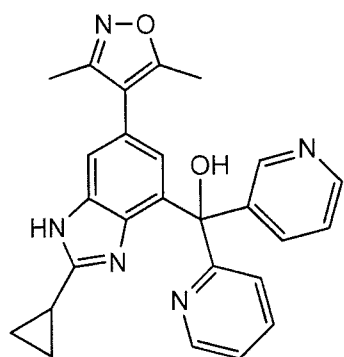
or a pharmaceutically acceptable salt thereof.

4. A compound of any of claims 1-3, wherein R^3 is C_{1-10} alkyl, C_{1-10} alkoxy, or C_{1-10} heteroalkyl, each of which may be optionally substituted with from 1 to 5 R^{20} groups, or a pharmaceutically acceptable salt thereof.

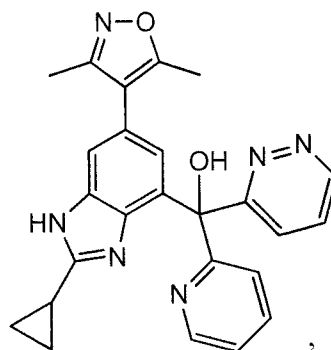
5. A compound of any of claims 1-3, wherein R^3 is an, C_{5-10} aryl, C_{6-20} arylalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl, each of which may be optionally substituted with from 1 to 5 R^{20} groups, or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1 selected from the group consisting of

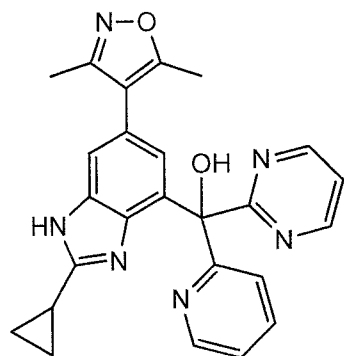




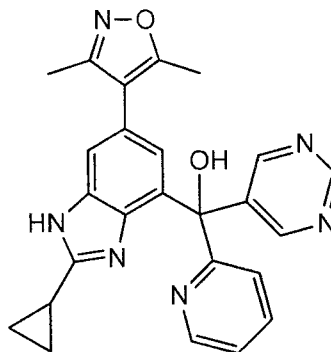
,



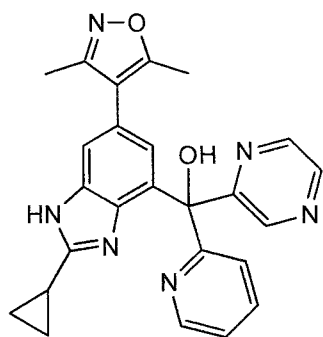
,



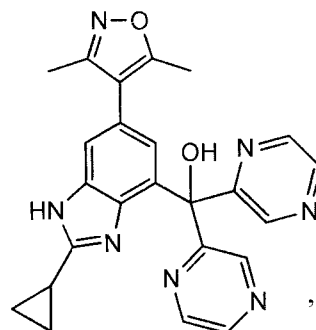
,



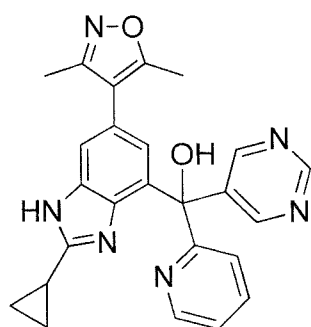
,



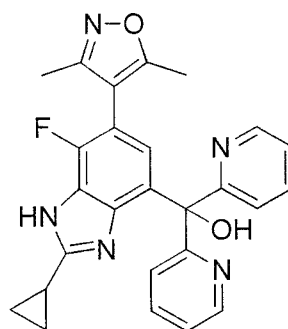
,



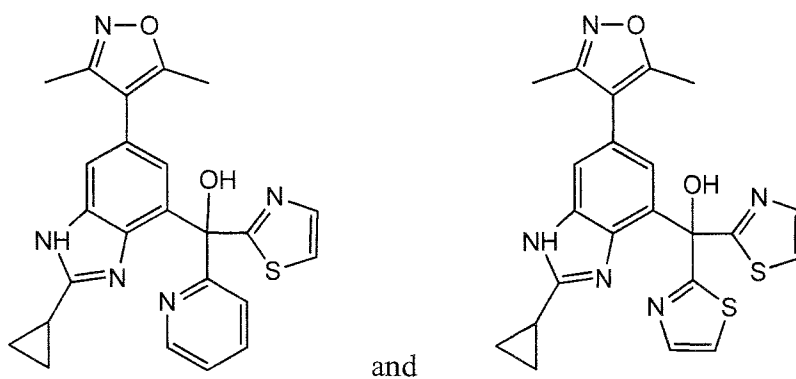
,



,

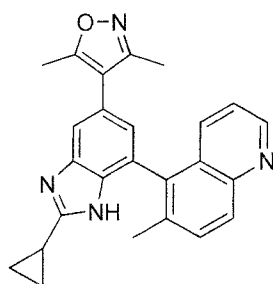


,



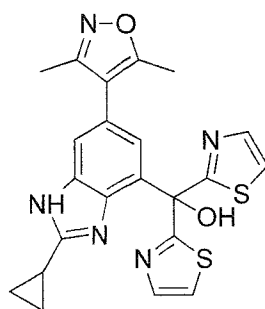
or a pharmaceutically acceptable salt thereof.

7. A compound of the following formula



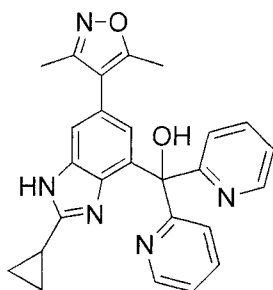
or a pharmaceutically acceptable salt thereof.

8. A compound of the following formula



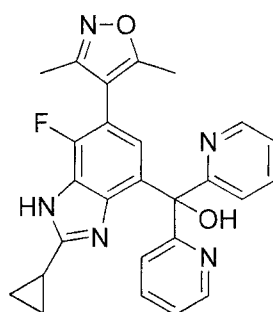
or a pharmaceutically acceptable salt thereof.

9. A compound of the following formula



or a pharmaceutically acceptable salt thereof.

10. A compound of the following formula



or a pharmaceutically acceptable salt thereof.

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

12. The use of a compound of any of claims 1-10, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease or condition responsive to the inhibition of a bromodomain-containing protein.

13. The use of claim 12, wherein the bromodomain-containing protein is BRD4.

14. The use of claim 12, wherein the disease or condition is a neoplasm, cancer or tumor of the colon, rectum, prostate, lung, pancreas, liver, kidney, cervix, uterus, stomach, ovary, breast, skin, or the nervous system.

15. The use of claim 12, wherein the disease or condition is diffuse large B-cell lymphoma or multiple myeloma.