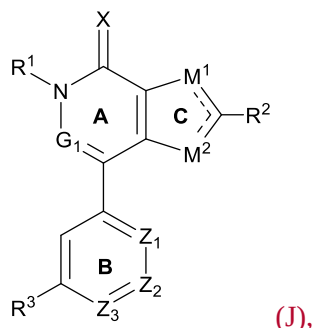


Cell, 19: 523-534 (2005)). BET bromodomain inhibitors have also been shown to reactivate HIV transcription in models of latent T cell infection and latent monocyte infection (Banerjee, et al., J. Leukocyte Biol. doi:10.1189/jlb.0312165). BRDT has an important role in spermatogenesis (Matzuk, et al., Cell 150: 673-684 (2012)).

[0005] Due to this potential as an epigenetic target, a number of small molecule compounds that inhibit the function of BET family proteins have been developed, and many of them have demonstrated promising anti-cancer activities with both solid and hematologic malignancies in preclinical studies. This has led to several early-phase clinical trials. Included among these are RO6870810 (formerly TEN-010), ZEN003694, BMS-986158, CPI-0610, I-BET762, OTX015, FT-1101, INCB054329, PLX51107, GS-5829, and ABBV-075. While these efforts are promising, there is need for better selectivity and improved durability of BET inhibitors that provide enhanced efficacy while reducing toxicity related to off-target effects. The present invention relates to novel BET inhibitors.

SUMMARY OF THE INVENTION

[0005a] In an aspect of the present disclosure, there is provided a compound of Formula (J):



or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each === is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G₁ is CR^a or N, wherein:

R^a is hydrogen, halogen, or C₁-C₄ alkyl;

Z₁ is C-W₁-R^c; wherein:

each W₁ is independently -O- or -NR^{w1}- , wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently C₃-C₆ cycloalkyl, 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z₂ is C-W₂-R^d or N, wherein:

W₂ is -O-, - NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

Z₃ is C-R^e or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

M¹ is S or CR^{1a};

M² is S or CR^{2a}, provided that

(1) when M¹ is S, then the ---- adjacent to M¹ is a single bond and the ---- adjacent to M² is a double bond,

(2) when M² is S, then the ---- adjacent to M² is a single bond and the ---- adjacent to M¹ is a double bond, and

(3) either M¹ or M² is S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy,

C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹ or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R³ is -(CH₂)_mNR¹³S(O)₂R¹⁴ wherein m is 0, 1, 2 or 3; C₃-C₆ cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH; C₁-C₄ alkyl substituted by halogen, oxo, -CN, or -OH; or C₁-C₆ alkynyl;

R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)C₃-C₆ cycloalkyl, -(C₁-C₃ alkylene) 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene) C₆-C₁₄ aryl, -NR¹⁵R¹⁶, or -C(O)R¹², wherein each of R¹⁰ and R¹¹ is independently optionally substituted by halogen, oxo, -CN, -CF₃, -OH, -NR¹³R¹⁴, -C(O)NR¹³R¹⁴, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, -CF₃, or -OH,

or R¹⁰ and R¹¹ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -CF₃, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH;

each R¹² is independently halogen, cyano, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁵, -NR¹⁵R¹⁶, -C(O)NR¹⁵R¹⁶, -NR¹⁵C(O)R¹⁶, -S(O)₂R¹⁵, -NR¹⁵S(O)₂R¹⁶, -S(O)₂NR¹⁵R¹⁶, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl, each of which is independently optionally substituted by halogen, oxo, -CF₃, -CN, -OH, -NR¹³R¹⁴, or -NR¹³C(O)R¹⁴;

R¹³ and R¹⁴ are independently hydrogen, C₁-C₄ alkyl C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R¹³ and R¹⁴ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

each R¹⁵ and R¹⁶ are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered

heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH, or R¹⁵ and R¹⁶ are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier.

[0005c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in therapy.

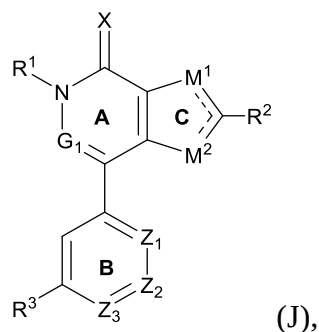
[0005d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treating cancer in an individual in need thereof.

[0005e] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing for inhibiting bromodomain and extraterminal domain (BET) in a cell.

[0005f] In another aspect of the present disclosure, there is provided a use of the compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease mediated by bromodomain and extraterminal domain (BET).

[0005g] In a further aspect of the present disclosure, there is provided a kit comprising the compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0006] In one ~~aspect~~example, provided is a compound of Formula (J):



or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein --- , X, G₁, R¹, R², R³, M¹, M², Z₁, Z₂, and Z₃ are defined herein.

[0007] In some ~~embodiment~~examples, the compounds provided herein are BET inhibitors that selectively target and covalently bind the protein of interest. In some ~~embodiment~~examples, the BET inhibitors comprise a compound of the Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0008] In some embodimentexamples, provided herein is a pharmaceutical composition comprising a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in combination with at least one pharmaceutically acceptable carrier, diluent, or excipient.

[0009] In some embodimentexamples, use of a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for the manufacture of a medicament is provided.

[0010] In some embodimentexamples, provided herein is a method of treating a disease mediated by inhibition of the BET family of proteins in an individual. In some embodimentexamples, such method comprises administering to the subject an effective amount of a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising the same, at a frequency and for duration sufficient to provide a beneficial effect to the subject.

[0011] In some embodimentexamples, provided herein are methods for treating or preventing disorders that are ameliorated by inhibition of BET. In some embodimentexamples, such methods comprise of administering to the subject a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, alone, or in combination with a pharmaceutically acceptable carrier.

[0012] In another aspectexample, the methods are directed to methods of treating or preventing an inflammatory disease or cancer or AIDS. In some embodimentexamples, such methods comprise of administering to the subject a therapeutically effective amount of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof,

or a pharmaceutically acceptable salt of any of the foregoing, alone, or in combination with a pharmaceutically acceptable carrier.

[0013] In another ~~aspect~~example, provided herein is the use of a compound of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, alone or in combination with a second active pharmaceutical agent, in the manufacture of a medicament for treating or preventing conditions and disorders disclosed herein, with or without a pharmaceutically acceptable carrier.

[0014] In another ~~aspect~~example, a method of synthesis is provided for a compound having the structure of Formula (J) or any related formulae where applicable, such as Formula (I), (II), (IIa-1) to (IIa-8), (III), (IIIa-1) to (IIIa-8), (IV), (V), (Va-1) to (Va-11), (VI), or (VIa-1) to (VIa-11), or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, as detailed herein.

DETAILED DESCRIPTION OF THE INVENTION

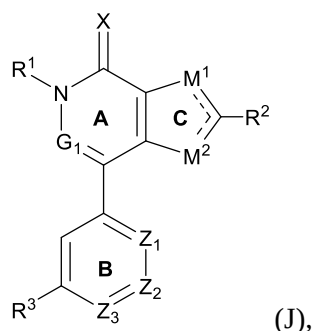
Definitions

[0015] “Alkyl” refers to and includes saturated linear and branched univalent hydrocarbon structures and combination thereof, having the number of carbon atoms designated (*i.e.*, C₁-C₁₀ means one to ten carbons). Particular alkyl groups are those having 1 to 20 carbon atoms (a “C₁-C₂₀ alkyl”). More particular alkyl groups are those having 1 to 8 carbon atoms (a “C₁-C₈ alkyl”), 3 to 8 carbon atoms (a “C₃-C₈ alkyl”), 1 to 6 carbon atoms (a “C₁-C₆ alkyl”), 1 to 5 carbon atoms (a “C₁-C₅ alkyl”), or 1 to 4 carbon atoms (a “C₁-C₄ alkyl”). Examples of alkyl include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0016] “Alkenyl” as used herein refers to an unsaturated linear or branched univalent hydrocarbon chain or combination thereof, having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and having the number of carbon atoms designated (*i.e.*, C₂-C₁₀ means two to ten carbon atoms). The alkenyl group may be in “cis” or “trans” configurations, or alternatively in “E” or “Z” configurations. Particular alkenyl groups are those having 2 to 20 carbon atoms (a “C₂-C₂₀ alkenyl”), having 2 to 8 carbon atoms (a “C₂-C₈ alkenyl”), having 2 to 6 carbon atoms (a “C₂-C₆ alkenyl”), or having 2 to 4 carbon atoms (a “C₂-C₄ alkenyl”).

CLAIMS

1. A compound of Formula (J):



or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

each --- is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G₁ is CR^a or N, wherein:

R^a is hydrogen, halogen, or C₁-C₄ alkyl;

Z₁ is C-W₁-R^c; wherein:

each W₁ is independently -O- or -NR^{w1}-, wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently C₃-C₆ cycloalkyl, 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z₂ is C-W₂-R^d or N, wherein:

W₂ is -O-, -NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo,

-OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

Z₃ is C-R^e or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

M¹ is S or CR^{1a};

M² is S or CR^{2a}, provided that

(1) when M¹ is S, then the ---- adjacent to M¹ is a single bond and the ---- adjacent to M² is a double bond,

(2) when M² is S, then the ---- adjacent to M² is a single bond and the ---- adjacent to M¹ is a double bond, and

(3) either M¹ or M² is S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹ or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁰, -NR¹⁰R¹¹, -C(O)OR¹⁰, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹, each of which is independently optionally substituted by R¹²;

R³ is -(CH₂)_mNR¹³S(O)₂R¹⁴ wherein m is 0, 1, 2 or 3; C₃-C₆ cycloalkyl optionally substituted by halogen, oxo, -CN, or -OH; C₁-C₄ alkyl substituted by halogen, oxo, -CN, or -OH; or C₁-C₆ alkynyl;

R¹⁰ and R¹¹ are each independently hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene)C₃-C₆ cycloalkyl, -(C₁-C₃ alkylene) 3- to 6-membered heterocyclyl, -(C₁-C₃ alkylene) C₆-C₁₄ aryl, -NR¹⁵R¹⁶, or -C(O)R¹²,

wherein each of R^{10} and R^{11} is independently optionally substituted by halogen, oxo, -CN, -CF₃, -OH, -NR¹³R¹⁴, -C(O)NR¹³R¹⁴, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, -CF₃, or -OH,

or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -CF₃, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH;

each R^{12} is independently halogen, cyano, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -OR¹⁵, -NR¹⁵R¹⁶, -C(O)NR¹⁵R¹⁶, -NR¹⁵C(O)R¹⁶, -S(O)₂R¹⁵, -NR¹⁵S(O)₂R¹⁶, -S(O)₂NR¹⁵R¹⁶, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl, each of which is independently optionally substituted by halogen, oxo, -CF₃, -CN, -OH, -NR¹³R¹⁴, or -NR¹³C(O)R¹⁴;

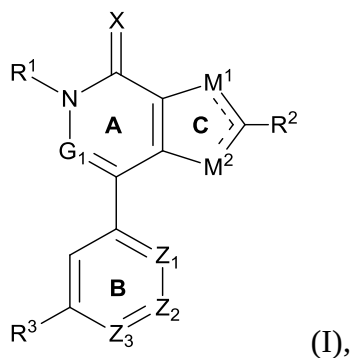
R^{13} and R^{14} are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R^{13} and R^{14} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

each R^{15} and R^{16} are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R^{15} and R^{16} are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH.

2. The compound of claim 1, wherein the compound is a compound of Formula (I):



or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

each --- is independently a single bond or double bond;

X is O or S;

R¹ is hydrogen, C₁-C₃ alkyl, -(C₁-C₃ alkylene)OH, C₁-C₃ haloalkyl, or C₃-C₄ cycloalkyl;

G₁ is CR^a or N, wherein:

R^a is hydrogen, halogen, or C₁-C₄ alkyl;

Z₁ is C-W₁-R^c; wherein:

each W₁ is independently -O- or -NR^{w1}-, wherein:

R^{w1} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^c is independently 4- to 6- membered heterocyclyl, C₆-C₁₄ aryl, or 5- or 6-membered heteroaryl, each of which is independently optionally substituted by R^{c1}, wherein each R^{c1} is independently halogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, 3- to 6-membered heterocyclyl, cyano, oxo, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, -OR¹⁰, -NR¹⁰R¹¹, -C(O)NR¹⁰R¹¹, -NR¹⁰C(O)R¹¹, -S(O)₂R¹⁰, -NR¹⁰S(O)₂R¹¹, or -S(O)₂NR¹⁰R¹¹;

Z₂ is C-W₂-R^d or N, wherein:

W₂ is -O-, -NR^{w2}-, or a bond, wherein:

R^{w2} is hydrogen, C₃-C₆ cycloalkyl, or C₁-C₄ alkyl optionally substituted by oxo, -OH, or halogen, and

R^d is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

Z₃ is C-R^e or N, wherein:

R^e is independently hydrogen, halogen, cyano, 3- to 6-membered heterocyclyl, or C₁-C₄ alkyl;

M¹ is S or CR^{1a};

M² is S or CR^{2a}, provided that

(1) when M^1 is S, then the --- adjacent to M^1 is a single bond and the = adjacent to M^2 is a double bond,

(2) when M^2 is S, then the --- adjacent to M^2 is a single bond and the = adjacent to M^1 is a double bond, and

(3) at least one of M^1 and M^2 is not S;

R^{1a} and R^{2a} are each independently hydrogen, halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-\text{OR}^{10}$, $-\text{NR}^{10}\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $-\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$ or $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, each of which is independently optionally substituted by R^{12} ;

R^2 is halogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-(C_1-C_3 \text{ alkylene})$ 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, cyano, oxo, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-\text{OR}^{10}$, $-\text{NR}^{10}\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $-\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$, or $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, each of which is independently optionally substituted by R^{12} ;

R^3 is $-(\text{CH}_2)_m\text{NR}^{13}\text{S}(\text{O})_2\text{R}^{14}$, C_3 - C_6 cycloalkyl, or C_1 - C_4 alkyl substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$, wherein m is 0, 1, 2 or 3;

R^{10} and R^{11} are each independently hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkenyl, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, $-(C_1-C_3 \text{ alkylene})C_3$ - C_6 cycloalkyl, $-(C_1-C_3 \text{ alkylene})$ 3- to 6-membered heterocyclyl, $-\text{NR}^{15}\text{R}^{16}$, or $-\text{C}(\text{O})\text{R}^{12}$, wherein each of R^{10} and R^{11} is independently optionally substituted by halogen, oxo, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, $-\text{CN}$, $-\text{CF}_3$, or $-\text{OH}$,

or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1 - C_4 alkyl optionally substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$;

each R^{12} is independently halogen, cyano, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-\text{OR}^{15}$, $-\text{NR}^{15}\text{R}^{16}$, $-\text{C}(\text{O})\text{NR}^{15}\text{R}^{16}$, $-\text{NR}^{15}\text{C}(\text{O})\text{R}^{16}$, $-\text{S}(\text{O})_2\text{R}^{15}$, $-\text{NR}^{15}\text{S}(\text{O})_2\text{R}^{16}$, $-\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{16}$, C_3 - C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or C_1 - C_4 alkyl, each of which is independently optionally substituted by halogen, oxo, $-\text{CF}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, or $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$;

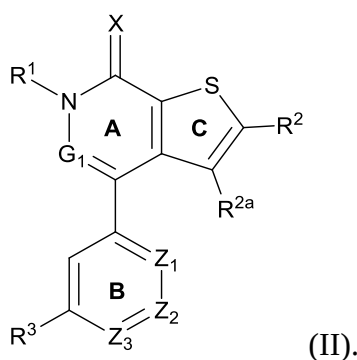
R^{13} and R^{14} are independently hydrogen, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, $-\text{CN}$, or $-\text{OH}$,

or R¹³ and R¹⁴ are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH; and

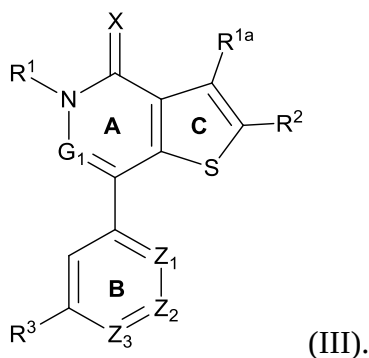
each R¹⁵ and R¹⁶ are independently hydrogen, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, or 3- to 6-membered heterocyclyl, each of which is independently optionally substituted by halogen, oxo, -CN, or -OH,

or R¹⁵ and R¹⁶ are taken together with the atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen, oxo, -CN, -OH, or C₁-C₄ alkyl optionally substituted by halogen, oxo, -CN, or -OH.

3. The compound of claim 1 or 2, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of Formula (II),



4. The compound of claim 1 or 2, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of Formula (III),

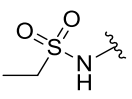


5. The compound of any one of claims 1-4, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is O.

6. The compound of any one of claims 1-5, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein G₁ is CH.

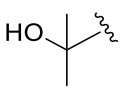
7. The compound of any one of claims 1-6, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z^1 is $C-W_1-R^c$ and R^c is C_6-C_{14} aryl optionally substituted by R^{c1} .
8. The compound of claim 7, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^c is phenyl optionally substituted by halogen or C_1-C_4 alkyl.
9. The compound of any one of claims 1-8, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z_2 is CH.
10. The compound of any one of claims 1-9, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Z_3 is CH.
11. The compound of any one of claims 1-10, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is C_1-C_3 alkyl.
12. The compound of any one of claims 1-11, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $-C(O)NR^{10}R^{11}$, 5- to 10-membered heteroaryl, $-(C_1-C_3 \text{ alkylene})_3$ - to 6-membered heterocyclyl, or C_1-C_4 alkyl, each of which is independently optionally substituted by R^{12} .
13. The compound of claim 12, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $-C(O)NR^{10}R^{11}$ which is optionally substituted by R^{12} , wherein R^{10} and R^{11} are each independently hydrogen, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl, or R^{10} and R^{11} are taken together with the atom or atoms to which they are attached to form a 3- to 6-membered heterocyclyl ring optionally substituted by halogen.
14. The compound of claim 12, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5- to 10-membered heteroaryl optionally substituted by R^{12} .
15. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$ or C_1-C_4 alkyl substituted by halogen, oxo, -CN, or -OH.
16. The compound of any one of claims 1-15, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is $-(CH_2)_mNR^{13}S(O)_2R^{14}$.

17. The compound of any one of claims 1-16, or a tautomer or stereoisomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, wherein R³ is .

18. The compound of any one of claims 1-15, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is C₁-C₄ alkyl substituted by -OH.

19. The compound of claim 18, or a tautomer or stereoisomer thereof, or a pharmaceutically

acceptable salt of any of the foregoing, wherein R³ is .

20. The compound of any one of claims 1 and 4-19, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{1a} is hydrogen.

21. The compound of any one of claims 1, 2, 3 and 5-19, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^{2a} is hydrogen.

22. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of the compounds in Table 1.

23. A pharmaceutical composition comprising the compound of any one of claims 1-22, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier.

24. A ~~method of treating disease mediated by bromodomain and extraterminal domain (BET) in an individual in need thereof comprising administering to the individual a therapeutically effective amount of the~~ compound of any one of claims 1-22, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, for use in therapy.

25. Use of a compound of any one of claims 1-22, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for A-~~method of treating cancer in an individual in need thereof comprising administering to the individual a therapeutically effective amount of the compound of any one of claims 1-22, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.~~

26. A compound of any one of claims 1-22, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing for method of inhibiting bromodomain and

extraterminal domain (BET) in a cell, ~~comprising administering the compound of any one of claims 1-22, or a tautomer or isomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, to the cells.~~

27. Use of the compound of any one of claims 1-22, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treatment of a disease mediated by bromodomain and extraterminal domain (BET).

28. A kit comprising the compound of any one of claims 1-22, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.