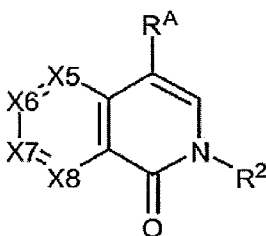


SUMMARY

[0005] The examples of the present disclosure provide for methods and pharmaceutical compositions for treating subjects with cancer and neoplastic disease; such as those with advanced solid tumors, relapsed or refractory non-Hodgkin's lymphomas, glioblastoma multiforme, anaplastic astrocytoma, basal cell carcinoma, or other cancers. At least one example provides a method for treating cancer and neoplastic disease comprising administering to a subject in need thereof a therapeutically effective amount of at least one BET inhibitor and a therapeutically effective amount of at least one chemotherapeutic agent. The chemotherapeutic agent may be an alkylating agent, such as temozolomide, or a mitotic inhibitor such as paclitaxel or paclitaxel protein-bound particles. An exemplary BET inhibitor is 4-[2-(cyclopropylmethylamino)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one. According to the method, administration of a BET inhibitor and chemotherapeutic agent may be concurrent or sequential.

[0005a] In one aspect, the present disclosure refers to a use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor of Formula 1 and at least one chemotherapeutic agent, which does not inhibit BET directly, in the manufacture of a medicament for treating cancer or neoplastic disease, wherein the BET inhibitor has the structure of Formula I:



Formula 1

wherein:

R^2 is CH_3 , CH_2CH_3 , CH_2CF_3 , CH_2F , CHF_2 , CF_3 , CH_2D , CHD_2 , or CD_3 ;

$X5$ is $C-R^5$ or N , wherein

R^5 is hydrogen, halogen, OH , CN , OR^{61} , NHR^{61} , $N(R^{61})_2$, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, in which each R^{61} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

X6 is C-R⁶, or N, wherein

R⁶ is hydrogen, halogen, OH, CN, alkyl, cycloalkyl, cycloalkylalkyl, amino, alkylamino, dialkylamino, cycloalkylalkylamino, alkoxy, or cycloalkylalkoxy;

X7 is C-R⁷ or N, wherein

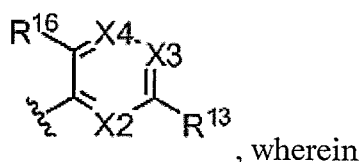
R⁷ is hydrogen, halogen, OH, CN, OR⁶¹, NHR⁶¹, N(R⁶¹)₂, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

X8 is C-R⁸ or N, wherein

R⁸ is hydrogen, halogen, or alkyl;

wherein no more than two of X5, X6, X7, or X8 may be N; and

R^A is:



X2 is N or C-R¹², wherein R¹² is hydrogen, halogen, alkyl, or alkoxy;

R¹³ is Y-Z; wherein Y is selected from a bond, CH₂, CH(C₁-C₄ alkyl); and Z is selected from SO₂R²¹, N(R²²)SO₂R²¹, SO₂N(R²²)₂, N(R²²)SO₂N(R²²)₂, CON(R²²)₂, N(R²²)CO₂R²¹, N(R²²)CON(R²²)₂, N(R²²)COR²¹, COR²¹, OC(O)N(R²²)₂, OSO₂N(R²²)₂, or N(R²²)SO₃R²¹; each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

X3 is N or C-R¹⁴, wherein R¹⁴ is hydrogen, halogen, -CN, alkyl, cycloalkyl, or alkoxy; and

X4 is N or C-R¹⁵, wherein R¹⁵ is hydrogen, halogen, alkyl, CN, or alkoxy;

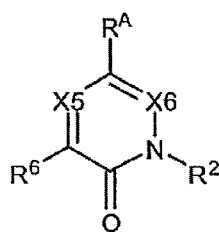
R¹⁶ is hydrogen, halogen, or W-X, wherein W is a bond, O, S, or NH, and

X is selected from alkyl, aryl, aralkyl, cycloalkyl, cyclo-alkylalkyl, alkynyl, cycloalkylalkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl,

or a pharmaceutically acceptable salt thereof.

[0005b] In another aspect, the present disclosure refers to a use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor comprising 4-[2-(cyclopropylmethylamino)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, or a pharmaceutically acceptable salt thereof, and at least one chemotherapeutic agent, which does not inhibit BET directly, in the manufacture of a medicament for treating cancer or neoplastic disease.

[0005c] In another aspect, the present disclosure refers to a use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor of Formula 2 and at least one chemotherapeutic agent, which does not inhibit BET directly, in the manufacture of a medicament for treating cancer or neoplastic disease, wherein the BET inhibitor of Formula 2 is:



Formula 2

wherein:

R² is alkyl, cycloalkyl, cycloalkylalkyl, heterocyclalkyl, aralkyl, or heteroarylalkyl;

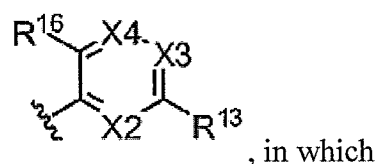
X5 is C-R⁵ or N; wherein

R⁵ is hydrogen, halogen, OH, CN, OR⁶¹, NHR⁶¹, N(R⁶¹)₂, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, wherein each R⁶¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

X6 is C-H or N, provided that if X6 is N, then X5 is C-R⁵, and if X5 is N, then X6 is CH;

R⁶ is hydrogen, halogen, OH, CN, alkyl, cycloalkyl, cycloalkylalkyl, amino, alkylamino, dialkylamino, cycloalkylalkylamino, alkoxy, S-alkyl, cycloalkylalkoxy, heterocycl, aralkoxy, heteroaryloxy, aryloxy, alkynyloxy, or N(H)COalkyl;

R^A is:



X₂ is N or C-R¹², wherein R¹² is hydrogen, halogen, alkyl, or alkoxy;

R¹³ is -Y-Z; wherein Y is selected from a bond, -CH₂-, or -CH(C₁-C₄ alkyl)-, and Z is selected from -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹; each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl; and each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

X₃ is N or C-R¹⁴, wherein R¹⁴ is hydrogen, halogen, -CN, alkyl, cycloalkyl, or alkoxy;

X₄ is N or C-R¹⁵, wherein R¹⁵ is hydrogen, halogen, alkyl, -CN, or alkoxy; and

R¹⁶ is hydrogen, halogen, N(H)COX, or W-X, wherein W is a bond, O, S, or NH, and X is selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, alkynyl, cycloalkylalkynyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

provided that when X₆ is N, then R⁵ and R⁶ are not hydrogen, or a pharmaceutically acceptable salt thereof.

[0006] In at least one example, a BET inhibitor and chemotherapeutic agent of the combination therapy may be administered in a single pharmaceutical composition. Some examples provide a composition comprising a pharmaceutically effective amount of a BET inhibitor and temozolomide, formulated in a pharmaceutically acceptable carrier. Some examples provide a composition comprising a pharmaceutically effective amount of a BET inhibitor and protein-bound paclitaxel, formulated in a pharmaceutically acceptable carrier. In one example, BET inhibitor and chemotherapeutic agent of the combination therapy may exist as separate pharmaceutical compositions administered either concurrently or sequentially. In another example, BET inhibitor and chemotherapeutic agent are independent pharmaceutical compositions that are admixed before administration (i.e., admixed in a pharmaceutically

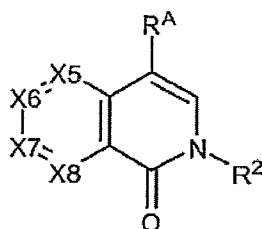
acceptable solution for injection or infusion). In still another example, BET inhibitor and chemotherapeutic agent are disposed as separate pharmaceutical compositions that are packaged together for administration (e.g., a blister-pack containing oral formulations, or packaging comprising an oral dosage form and an injectable dosage form).

[0007] In at least one embodiment, administering the BET inhibitor and the chemotherapeutic agent results in a synergistic inhibition of cell proliferation or increased cell death (e.g., tumor cell death) compared with administration of either the BET inhibitor or the chemotherapeutic agent alone. The chemotherapeutic agent can be an anti-proliferative or pro-apoptotic compound, and can be selected so as to show a synergistic anti-proliferative or pro-apoptotic effect when co-administered with a BET inhibitor. Combinatorial treatment with a BET inhibitor and a chemotherapeutic agent can result in a synergistic anti-cancer effect or can

CLAIMS

We claim:

1. Use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor of Formula 1 and at least one chemotherapeutic agent, which does not inhibit BET directly, in the manufacture of a medicament for treating cancer or neoplastic disease, wherein the BET inhibitor has the structure of Formula I:



Formula 1

wherein:

R^2 is CH_3 , CH_2CH_3 , CH_2CF_3 , CH_2F , CHF_2 , CF_3 , CH_2D , CHD_2 , or CD_3 ;

$X5$ is $C-R^5$ or N , wherein

R^5 is hydrogen, halogen, OH , CN , OR^{61} , NHR^{61} , $N(R^{61})_2$, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, in which each R^{61} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

$X6$ is $C-R^6$, or N , wherein

R^6 is hydrogen, halogen, OH , CN , alkyl, cycloalkyl, cycloalkylalkyl, amino, alkylamino, dialkylamino, cycloalkylalkylamino, alkoxy, or cycloalkylalkoxy;

$X7$ is $C-R^7$ or N , wherein

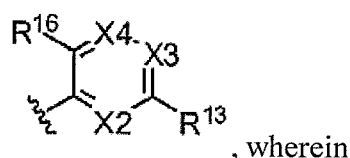
R^7 is hydrogen, halogen, OH, CN, OR^{61} , NHR^{61} , $N(R^{61})_2$, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl;

X8 is $C-R^8$ or N, wherein

R^8 is hydrogen, halogen, or alkyl;

wherein no more than two of X5, X6, X7, or X8 may be N; and

R^A is:



X2 is N or $C-R^{12}$, wherein R^{12} is hydrogen, halogen, alkyl, or alkoxy;

R^{13} is Y-Z; wherein Y is selected from a bond, CH_2 , $CH(C_1-C_4 \text{ alkyl})$; and Z is selected from SO_2R^{21} , $N(R^{22})SO_2R^{21}$, $SO_2N(R^{22})_2$, $N(R^{22})SO_2N(R^{22})_2$, $CON(R^{22})_2$, $N(R^{22})CO_2R^{21}$, $N(R^{22})CON(R^{22})_2$, $N(R^{22})COR^{21}$, COR^{21} , $OC(O)N(R^{22})_2$, $OSO_2N(R^{22})_2$, or $N(R^{22})SO_3R^{21}$; each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

X3 is N or $C-R^{14}$, wherein R^{14} is hydrogen, halogen, $-CN$, alkyl, cycloalkyl, or alkoxy; and

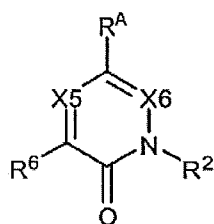
X4 is N or $C-R^{15}$, wherein R^{15} is hydrogen, halogen, alkyl, CN, or alkoxy;

R^{16} is hydrogen, halogen, or W-X, wherein W is a bond, O, S, or NH, and

X is selected from alkyl, aryl, aralkyl, cycloalkyl, cyclo-alkylalkyl, alkynyl, cycloalkylalkynyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, or a pharmaceutically acceptable salt thereof.

2. Use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor comprising 4-[2-(cyclopropylmethylamino)-5-methylsulfonylphenyl]-2-methylisoquinolin-1-one, or a pharmaceutically acceptable salt thereof, and at least one chemotherapeutic agent, which does not inhibit BET directly, in the manufacture of a medicament for treating cancer or neoplastic disease.

3. Use of a therapeutically effective amount of at least one bromodomain and extra-terminal protein (BET) inhibitor of Formula 2 and at least one chemotherapeutic agent, which does not inhibit BET directly, in the manufacture of a medicament for treating cancer or neoplastic disease, wherein the BET inhibitor of Formula 2 is:



Formula 2

wherein:

R² is alkyl, cycloalkyl, cycloalkylalkyl, heterocyclalkyl, aralkyl, or heteroarylalkyl;

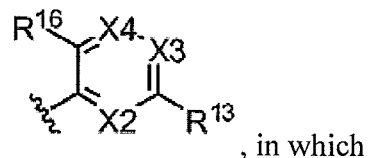
X5 is C-R⁵ or N; wherein

R⁵ is hydrogen, halogen, OH, CN, OR⁶¹, NHR⁶¹, N(R⁶¹)₂, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclalkyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl, wherein each R⁶¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclalkyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

X6 is C-H or N, provided that if X6 is N, then X5 is C-R⁵, and if X5 is N, then X6 is CH;

R⁶ is hydrogen, halogen, OH, CN, alkyl, cycloalkyl, cycloalkylalkyl, amino, alkylamino, dialkylamino, cycloalkylalkylamino, alkoxy, S-alkyl, cycloalkylalkoxy, heterocyclalkyl, aralkoxy, heteroarylalkoxy, aryloxy, alkynyloxy, or N(H)COalkyl;

R^A is:



X₂ is N or C-R¹², wherein R¹² is hydrogen, halogen, alkyl, or alkoxy;

R¹³ is -Y-Z; wherein Y is selected from a bond, -CH₂-, or -CH(C₁-C₄ alkyl)-, and Z is selected from -SO₂R²¹, -N(R²²)SO₂R²¹, -SO₂N(R²²)₂, -N(R²²)SO₂N(R²²)₂, -CON(R²²)₂, -N(R²²)CO₂R²¹, -N(R²²)CON(R²²)₂, -N(R²²)COR²¹, -COR²¹, -OC(O)N(R²²)₂, -OSO₂N(R²²)₂, or -N(R²²)SO₃R²¹; each R²¹ is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl; and each R²² is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

X₃ is N or C-R¹⁴, wherein R¹⁴ is hydrogen, halogen, -CN, alkyl, cycloalkyl, or alkoxy;

X₄ is N or C-R¹⁵, wherein R¹⁵ is hydrogen, halogen, alkyl, -CN, or alkoxy; and

R¹⁶ is hydrogen, halogen, N(H)COX, or W-X, wherein W is a bond, O, S, or NH, and X is selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, alkynyl, cycloalkylalkynyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroarylalkyl;

provided that when X₆ is N, then R⁵ and R⁶ are not hydrogen, or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1-3, wherein administration of the BET inhibitor and the chemotherapeutic agent results in a synergistic reduction in cell proliferation in a tumor of a patient or a synergistic increase in apoptosis in a tumor of the patient as compared with administration of either the BET inhibitor or the chemotherapeutic agent alone.

5. The use of any one of claims 1-3, wherein the therapeutic effective amount for both the BET inhibitor and chemotherapeutic agent when administered together can be at least 50% lower than that when the BET inhibitor and chemotherapeutic agent are used individually.
6. The use of any one of claims 1-3, wherein the chemotherapeutic agent is selected from the group consisting of temozolomide, romidepsin, and protein-bound paclitaxel.
7. The use of any one of claims 1-3, wherein the medicament comprises the BET inhibitor in an amount to enhance the therapeutic effect of the chemotherapeutic agent.
8. The use of any one of claims 1-3, wherein the chemotherapeutic agent is temozolomide.
9. The use of any one of claims 1-3, wherein the chemotherapeutic agent is romidepsin.
10. The use of any one of claims 1-3, wherein the chemotherapeutic agent is protein-bound paclitaxel.
11. The use of any one of claims 1-3, wherein the cancer or neoplastic disease is glioblastoma.
12. The use of any one of claims 1-3, wherein the cancer is temozolomide-resistant.